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THE IMPORTANCE OF DEPRESSION MANAGEMENT IN RHEUMATOID ARTHRITIS

ABSTRACT OF THE DOCTORAL THESIS

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General Section

Rheumatoid arthritis (RA) is a chronic inflammatory, immune-mediated disease, affecting the synovial joints, leading to early and progressive irreversible osteoarticular damage, with a significant negative impact on patients' functionality, ultimately resulting in severe impairment of their quality of life. RA is associated with multiple extra-articular manifestations, contributing to increased patient mortality through various complications, and is also linked to diverse comorbidities. Among the comorbidities frequently associated with RA, depression is one of the most prevalent, contributing to a negative long-term prognosis for RA patients due to its significant adverse effects on pain perception, disease activity, the likelihood of achieving remission, and patients' quality of life.

The current therapeutic management of RA is guided by the principles of "treat to target" and "tight control." Given the significant negative impact of depression on disease activity, it becomes clear that this psychiatric condition limits the goals of RA management guidelines, making the addressing of depression essential.

Considering the major impact of mental health, particularly depression and anxiety, on RA patients, this work emphasizes the importance of managing psychological factors in this category of patients by analyzing the prevalence and effects of depression in a cohort of RA patients from Romania.

The research hypothesis of this study is that depression is a frequently encountered comorbidity in RA patients in Romania. RA patients with associated depression will exhibit higher disease activity, as measured by the Disease Activity Score, using 28 joint counts and CRP (DAS28) and by its subjective and objective components. Additionally, RA patients with comorbid depression will have a lower probability of achieving remission, according to the composite DAS28 index. Similarly, anxiety is prevalent in RA patients, and its presence exerts negative effects on disease progression.

This study had multiple general objectives, including evaluating the prevalence of depression in three distinct cohorts of RA patients using retrospective and cross-sectional methodologies, and assessing the prevalence of anxiety in a cohort of RA patients in a cross-

sectional manner. Differences caused by the presence of depression on disease activity, evaluated through the DAS28 score and its subjective and objective components—tender joint count (TJC), swollen joint count (SJC), patient global assessment (VAS), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)—were analyzed. Similarly, differences caused by the presence of anxiety on disease activity, evaluated through the DAS28 score and its components, TJC, SJC, VAS, CRP, and ESR, were analyzed.

Using self-assessment screening questionnaires for depression and anxiety—the Patient Health Questionnaire-9 (PHQ-9) and the Hospital Anxiety and Depression Scale (HADS)—the possible prevalence of these psychiatric conditions in RA patients was determined to analyze differences between subgroups with negative and positive screenings concerning disease activity, evaluated through the DAS28 score and its components, TJC, SJC, VAS, CRP, and ESR. Additionally, correlations between the severity of depressive and anxious symptoms with the DAS28 score and its components, TJC, SJC, VAS, CRP, and ESR, were performed.

The prevalence of depression is 2–3 times higher in RA patients compared to the general population. A 2013 meta-analysis reported a 16.8% prevalence of major depressive disorder in RA patients. Since 2014, the COMORA cross-sectional study reported depression as the most frequent comorbidity associated with RA, with a prevalence of 15%. Subsequently, in 2022, a systematic review and meta-analysis related to the prevalence of comorbidities in RA patients observed that the three most common pathologies associated with RA are anxiety, hypertension, and depression, with a prevalence of 32.1%.

Methodological differences among studies, socio-cultural characteristics of study populations, multiple used definitions of depression, and screening methods employed in its detection lead to a high variability in the reported prevalence of depression in studies, ranging from 14% to 48%.

Diagnosing depression in RA patients is extremely challenging, leading to frequent underdiagnosis. Firstly, RA is a debilitating chronic disease dominated by pain and severe functional impact, making it difficult to differentiate between a normal reaction to illness and depressive symptomatology. Multiple reasons contribute to the underdiagnosis of depression, such as attributing certain symptoms to a somatic pathology rather than a mood disorder, the

stigma of psychiatric illnesses, and the lack of consultation time available to thoroughly analyze patients' psychological aspects.

RA patients exhibit multiple constitutional symptoms such as fatigue, weight loss, insomnia, and loss of appetite, which are common symptoms of depression. Therefore, in multiple analyses of depression prevalence in RA patients, researchers have eliminated certain symptoms that could be erroneously attributed to RA, such as fatigue or sleep quality.

The gold standard for diagnosing depression is the clinical interview and psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) criteria, which are time-consuming, costly, and difficult to perform in a busy hospital setting. This is why clinical studies investigating the prevalence of depression in RA patients most often use self-assessment screening questionnaires, which are quicker, easier to complete, and more cost-effective.

The association between immune-mediated inflammatory diseases and depression is well recognized, with immune-mediated inflammation affecting neuroendocrine activity and neuroplasticity. Recent literature describes in detail the interaction between the immune system and the central nervous system (CNS).

It is hypothesized that some psychiatric illnesses, including depression, are closely associated with systemic inflammation and modulation by pro-inflammatory cytokines. Multiple meta-analyses have found elevated levels of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α), characteristic of RA, in the peripheral blood of patients with depression compared to controls. The role of these cytokines is supported by the similarity between cytokine-induced sickness syndrome symptomatology and depression, such as behavioral inhibition, anorexia, weight loss, anhedonia, psychosomatic symptoms, anxiety, and neurocognitive symptoms.

Pro-inflammatory cytokines reach the CNS via two pathways: a humoral route and a neural route. Pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, involved in the pathogenesis of depression, are also implicated in the pathogenic mechanisms of pain and fatigue.

The primary manifestations of RA—pain and fatigue—can indirectly lead to depressive pathology.

It is well known that RA activity correlates with elevated levels of C-reactive protein (CRP), which, according to a 2019 study by Chamberlain *et al*., correlates with the severity of depressive symptoms and lack of response to antidepressants, and CRP was proposed as a biomarker for depression. The correlation of increased CRP levels with treatment-resistant depression could explain the lower susceptibility of RA patients to respond to antidepressant treatments.

Persistent chronic pain caused by RA acts as a stressor that stimulates the nervous system, producing changes in synaptic plasticity and ultimately contributing to depression. The level of serotonin, a neurotransmitter involved in depression, is altered by inflammatory processes through the activation of the indoleamine 2,3-dioxygenase enzyme, which decreases the availability of tryptophan, the precursor of serotonin, or through increased expression of the serotonin transporter, mediated by TNF. The degradation products of tryptophan can have both neuroprotective and neurotoxic effects, but the presence of inflammation tilts the balance toward neurotoxic effects. Indoleamine activation increases the level of kynurenine, a catabolite of tryptophan, which is subsequently transformed into 3-hydroxykynurenine and quinolinic acid, leading to increased glutamate production, heightened response to oxidative stress, inhibition of GABAergic control, resulting in apoptosis in the hippocampus and prefrontal cortex.

Pro-inflammatory cytokines affect neuroplasticity and neurogenesis by decreasing the expression of brain-derived neurotrophic factor (BDNF), an important molecule in neurotransmission and neuroprotection.

In RA patients, depression is associated with a poor long-term prognosis. Multiple studies have demonstrated that RA patients with depression exhibit higher levels of pain, fatigue, and functional deficits. The presence of depression decreases treatment compliance, leads to more comorbidities, and increases mortality, partially through a higher suicide rate. Additionally, it increases the utilization of medical services and raises healthcare costs both directly through the number of hospitalizations and indirectly through decreased workplace productivity. Lastly,

depression significantly reduces the quality of life in RA patients, as reflected in all the domains of quality-of-life questionnaires.

Beyond reduced treatment adherence, psychological distress impacts other behaviors with implications for general health, such as smoking and physical activity. It is well known that smoking can induce disease flares in RA patients, and decreased physical activity leads to deconditioning, loss of natural endorphins, and increased pain levels.

Multiple studies have shown a clear correlation between the severity of depression and RA activity. High depression scores are associated with RA activity, but since the studies conducted were observational, causality or the direction of the effect could not be established.

Most RA activity scores are based on subjective components, which can be affected by the patient's psychological state, thereby influencing disease activity assessment. In most studies conducted, depression is associated with higher disease activity through the modulation of subjective components included in the activity index, such as TJC and VAS, but there is also evidence regarding the association of depression with objective components, such as SJC or even inflammatory markers, ESR and CRP. Most likely, depression and RA activity have a bidirectional relationship, considering that in early RA, a higher number of involved joints is associated with a higher prevalence of depression at 6 months.

Depression has a significant impact on achieving remission in RA patients by affecting treatment adherence, modulating pain perception, and through underlying biological mechanisms. Multiple studies have demonstrated that RA patients with depression have a lower probability of achieving remission, regardless of the activity scores used, compared to patients without depression.

Promoting early psychological well-being during the course of the disease could prove to be a cost-effective measure to prevent high levels of disease activity later on, thus utilizing less aggressive therapeutic strategies.

The interaction between psychological distress and physical disability creates a vicious cycle that worsens both conditions and hinders a good long-term prognosis for RA patients with

depression. Multiple studies have emphasized the importance of managing depression in RA, considering its effect on the degree of disability. Any improvement in depressive symptoms will lead to an amelioration of patients' functional status.

A Danish study observed that fluctuations in depression levels are associated with fluctuations in the functional status of RA patients. The degree of functional disability at one year after RA diagnosis is predicted, among other factors, by depression, and among the predictive factors for depression in multiethnic cohorts of RA patients, higher HAQ scores wore associated with depression.

Depression in RA leads to an increased use of healthcare services, resulting in high healthcare expenses, both for health insurance providers and for patients and their families. Depression is associated with a higher number of medical consultations due to amplified symptom perception and psychological stress. Moreover, patients with RA and comorbid depression are at greater risk of hospitalizations caused by RA complications, and these hospital stays tend to be longer.

Furthermore, patients with depression more frequently use analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and antidepressants, but poor adherence to disease-modifying antirheumatic drugs (DMARDs) leads to suboptimal disease control.

The burden of depression carries significant socio-economic costs, both direct—such as those listed above—and indirect, related to work absenteeism due to functional disability and depressive symptomatology.

Considering the involvement of inflammatory mechanisms in both RA and depression, and the results of multiple studies that have observed a bidirectional relationship between the severity of depression and RA activity or functional disability, further research has been developed to investigate depression as a potential risk factor for the development of RA.

Currently, mechanisms are still being studied through which central inflammation seen in depression may generate a systemic inflammatory response, which could ultimately favor the development of an autoimmune disease such as RA.

It has been suggested that a possible connection between psychological stress and immune-mediated diseases lies in neurotransmitter imbalances and dysfunctional intracellular signaling. Chronic exposure to a negative mood state leads to dysfunction of the hypothalamic-pituitary axis, with peripheral release of glucocorticoids (GCs), which—together with increased activation of the sympathetic nervous system and decreased activation of parasympathetic branches of the autonomic nervous system—induce the expression of inflammatory markers that contribute to the initiation and progression of autoimmune diseases. Moreover, pro-inflammatory cytokines mediate the activation of the hypothalamic-pituitary axis in response to potential imbalance in homeostatic regulation, thus potentially playing a key role in the development of major depressive disorder.

Anxiety is a more frequent comorbidity in RA patients than in the general population, and the reported prevalence rates in RA vary. Using the Generalized Anxiety Disorder 7-item scale (GAD-7), 25.1% of RA patients screened positive for anxiety.

Despite the fact that the prevalence of anxiety in RA patients may be even higher than that of depression—reaching up to 89%—anxiety is less studied, and there are very few data available on the common biological mechanisms shared between anxiety and RA.

Both depression and anxiety in RA are associated with higher levels of pain, fatigue, disease activity, disability, decreased quality of life, and increased use of healthcare services. Additionally, they reduce medication adherence and lead to higher reports of subjective symptoms, such as joint pain and the degree of disability.

Original Research

This paper includes three studies conducted on three different cohorts of patients: two retrospective longitudinal studies and one cross-sectional study. All studies were carried out at the “Dr. Ion Stoia” Clinical Center for Rheumatic Diseases, in Bucharest. All patients included in the studies signed written informed consent at each visit regarding medical management and the scientific use of their medical data. The studies were conducted in accordance with the Declaration of Helsinki and were approved by the ethics committee of the CCBR.

The first study, a pilot retrospective longitudinal study conducted between 2019 and 2020, included 203 patients with rheumatoid arthritis (RA), whose data were collected at three different time points. The goal was to estimate the prevalence of depression, based on patients’ known medical history, and to analyze the correlations between the presence of depression and the DAS28 score and its components.

All patients diagnosed with RA, aged 18 or older, who had at least three consecutive visits no more than 6 months apart were selected. The RA diagnosis was established by each patient's attending physician—either a specialist or consultant rheumatologist—meeting the 2010 classification criteria of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR).

To quantify the prevalence of depression in RA patients, the patients’ medical history or medication records were evaluated from their electronic medical records. Additionally, the diagnosis of depression was confirmed either by an ICD-10 code recorded in the electronic file (all codes were entered by psychiatrists who diagnosed the depression) or by the use of specific antidepressants (namely: tricyclic antidepressants, atypical antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, serotonergic-noradrenergic antidepressants, serotonin modulators/stimulators, serotonin reuptake inhibitors/antagonists, and monoamine oxidase inhibitors).

Exclusion criteria included: fibromyalgia, another chronic autoimmune inflammatory disease, a current or recent cancer diagnosis, other psychiatric disorders (e.g., schizophrenia,

bipolar disorder), experimental treatments for RA, alcohol or substance addiction, cognitive disorders, or pregnancy. All retrospectively selected patients had completed at least three visits to our clinic over the 24-month study period, each visit spaced six months apart.

From the electronic records, the following data were extracted: demographic data (age, sex, smoking status), RA clinical variables (disease duration, TJC – tender joint count, SJC – swollen joint count, VAS – visual analog scale for global disease activity), Steinbrocker functional classes, current medication (GCs, csDMARDs, bDMARDs, tsDMARDs), laboratory data obtained using standard commercial kits (rheumatoid factors [RF, normal range 0–30 IU/mL], anti-cyclic citrullinated peptide antibodies [anti-CCP, ELISA normal range: 0–20 IU/mL], CRP [normal: 0–5 mg/L], ESR [normal: 0–30 mm/h]), DAS28 score, and Steinbrocker radiographic stages.

At all three evaluation visits, patients with RA and comorbid depression had significantly higher DAS28 scores than those without depression. At the first visit, the mean DAS28 score in the depression subgroup was 5.2 ± 1.5 compared to 4.6 ± 1.5 in the non-depressed subgroup ($p = 0.045$); at the second visit, the mean DAS28 was 4.8 ± 1.4 vs. 4.1 ± 1.4; and at the third visit, it was 4.7 ± 1.7 vs. 3.9 ± 1.4 ($p < 0.001$).

At each reevaluation visit, the values of the DAS28 components—excluding TJC—were significantly higher in the RA subgroup with associated depression. This includes both subjective measures (VAS) and objective measures (SJC, inflammatory markers ESR and CRP), compared to the RA subgroup without associated depression.

An analysis of active smokers between the RA subgroup with associated depression and the RA subgroup without associated depression, revealed that depression was associated with a higher rate of active smoking: 8.1% in the depressed group vs. 1.8% in the non-depressed group, with a statistically significant difference ($p = 0.041$).

The second retrospective longitudinal study, conducted on a larger cohort of 400 patients, was carried out after the pilot study confirmed the research hypothesis, aiming to increase the statistical power of the results. This study followed the same methodology as the pilot study.

At both the second and third evaluations, patients with RA and comorbid depression again showed higher DAS28 averages compared to those without depression. Specifically, at the second visit, the mean DAS28 in the depression subgroup was 4.5 ± 4.2 vs. 4.1 ± 3.9 ($p = 0.045$), and at the third visit: 4.4 ± 1.6 vs. 4.0 ± 1.3 ($p = 0.038$).

At each reevaluation visit, all DAS28 components—TJC, SJC, VAS, ESR—were statistically higher in the depressed subgroup, with the exception of CRP, which showed no significant difference.

Similarly, the percentage of active smokers was higher in the depressed group: 8.0% vs. 2.8% in non-depressed patients ($p = 0.032$).

The analysis of the data collected in the second longitudinal retrospective study, conducted on an extended cohort, reproduced the results obtained in the pilot study, with minor exceptions. Regarding the differences in the values of the DAS28 score components, stratified by subgroups—patients with RA and depression versus patients with RA without depression—all were significantly higher in the subgroup with depression, except for the TJC (Tender Joint Count) in the first study and CRP in the second study.

The third study, a cross-sectional study conducted between September and November 2024, included 209 RA patients, who completed two self-assessment screening questionnaires, PHQ-9 and HADS. The prevalence of depression and anxiety was estimated based on patients' medical history and the potential prevalence according to the questionnaire scores. Correlations were then made between DAS28 values and its components between subgroups with positive and negative screening results for depression and anxiety.

The inclusion and exclusion criteria were the same as in the first study. Each patient independently completed the two self-assessment screening questionnaires for depression and anxiety: PHQ-9 and HADS.

PHQ-9 is a widely used tool, validated by Spitzer *et al*. in 1999, designed for screening, monitoring, and assessing the severity of depressive symptoms. It contains 9 items, which at the time corresponded to the 9 criteria included in the DSM-IV for the diagnosis of depressive

disorders. The questions assess symptoms such as 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 between 0–27, categorized as follows: Minimal depression (PHQ-9 = 0–4), Mild depression (PHQ-9 = 5–9), Moderate depression (PHQ-9 = 10–14), Moderately severe depression (PHQ-9 = 15–19), Severe depression (PHQ-9 = 20–27).

The cut-off score used to consider a positive screening for depression was 10 or above, as this is the most commonly used threshold for identifying clinically significant moderate depressive symptoms.

HADS (Hospital Anxiety and Depression Scale) is a validated self-assessment questionnaire used for screening both depression and anxiety symptoms. It was validated in 1983 by Zigmond *et al*., for both screening utility and severity measurement of these emotional disorders. It excludes somatic symptoms to avoid confusion with physical illnesses, which makes it particularly useful in hospital settings or busy outpatient clinics, especially since it is quick and easy to complete.

HADS contains 14 items, divided into two subscales: Depression (HADS-D, 7 items) and Anxiety (HADS-A, 7 items).

Each item is scored from 0 to 3, resulting in subscale scores ranging from 0–21. The overall score indicates severity as: Normal (HADS = 0–7), Borderline abnormal (HADS = 8–10), Abnormal (HADS = 11–21).

In our study, the cut-off values used for positive screening were over 10 for both HADS-D and HADS-A.

Patients who screened positive for depression based on the PHQ-9 score and HADS-D score had higher levels of: disease activity class, DAS28 score, tender joint count (TJC), swollen joint count (SJC), visual analog scale (VAS), functional status class, compared to patients with negative screening for depression. Additionally, patients with possible depression based on HADS-D score, had higher ESR values and more advanced radiographic stages.

Patients with positive screening for anxiety based on HADS-A score, were more frequently female, had a significantly higher TJC, and belonged to higher functional classes.

The PHQ-9 score was significantly higher in female patients and in those with higher disease activity, functional class, and radiographic stage.

Similarly, the HADS-D score was significantly higher among females, patients with higher disease activity and functional class, and those with more advanced radiographic stages. Additionally, it was higher in patients receiving glucocorticoid therapy (GCs).

The HADS-A score was also significantly higher in females, in patients with higher disease activity, and those in higher functional and radiographic classes, similar to the PHQ-9.

In all three studies, the prevalence of depression based on medical history was high: 18.2%, 18.8%, and 10%, which is consistent with existing literature. Additionally, in the cross-sectional study, possible depression based on screening (PHQ-9 and HADS) indicated even higher prevalences than those self-reported by patients: 34.4% based on PHQ-9 and 14.8% based on HADS, compared to only 10% self-reported. Completion of the HADS questionnaire revealed possible anxiety in 32.5% of patients, compared to only 8.1% self-reported. These data emphasize the underdiagnosis and underreporting of psychiatric disorders, a well-documented issue in the medical literature.

Limitations of the first two studies include: the retrospective design, lack of some demographic and socioeconomic variables, reliance on real-life clinical data with unsystematized RA and depression diagnoses, based on expert opinion, methodology that does not allow causal or temporal relationships between RA and depression to be evaluated.

Limitations of the third study include: the cross-sectional design, which prevents establishing causality or temporal relationships between depression, anxiety, and RA, potential bias in self-reported data, due to local cultural variations, fear of stigmatization, or influence on the doctor-patient relationship and the limitations of the screening tools used.

The ideal methodology would involve studies where depression and anxiety are diagnosed through a clinical interview by a psychiatrist. Additionally, our studies did not include certain

confounding factors or variables in the statistical analysis, such as: socioeconomic status, social support, marital status, employment status, coping mechanisms, lifestyle factors.

Selection bias should also be considered, since all cases were recruited from a specialized clinical center.

Future research should aim to address the variability in the prevalence of depression and anxiety in RA patients, to identify optimal screening tools, clarify temporal and causal relationships between RA and depression and to develop optimal pharmacological and non-pharmacological management strategies for depression in RA patients.

Standardized prevalence studies using self-assessment screening questionnaires with well-defined cut-off points across various populations may help improve estimates of depression prevalence in RA patients. While different screening tools appear to have similar sensitivity, determining optimal thresholds and comparing the results with a psychiatric clinical interview would be necessary.

The temporal, causal, and bidirectional relationship between RA and depression could be better explored through prospective studies, assessing: the impact of high disease activity on depression and the effect of pre-existing depression on RA prognosis.

Dynamic evaluations of acute-phase reactants and proinflammatory cytokines could offer more insight into shared immuno-inflammatory mechanisms. Furthermore, depression should be investigated as a potential risk factor for developing RA.

Interventional studies are also needed to evaluate the effects of depression treatment on RA prognosis, and to identify: effective pharmacologic treatments and types of psychotherapy or other interventions best suited for treating depression in RA.

Some studies already suggest a positive effect of biologic therapies on depressive symptoms. Therefore, exploring the effects of different DMARDs (biologic or targeted synthetic) on depression through randomized clinical trials could potentially lead to individualized treatment for RA patients with comorbid depression.

To achieve optimal RA management outcomes, it is essential to understand the impact of psychiatric conditions on the long-term prognosis of RA patients. A comprehensive treatment approach must be multidisciplinary, involving: a rheumatologist, a psychiatrist, a psychologist, and lifestyle interventions.

Integrating mental health support into the therapeutic management of RA patients can significantly improve disease progression and quality of life. The benefits of such an approach far outweigh the costs related to frequent hospitalizations, disability-related job loss, the burden on families, and societal expenses.

The research hypothesis and general objectives set at the beginning of this paper were achieved, and the results of the three studies conducted were consistent with the international medical literature. These studies represent the first research in our country evaluating the prevalence and impact of depression and anxiety in RA patients.

List of Published Scientific Papers

1. **Ionescu CE**, Popescu CC, Agache M, Dinache G, Codreanu C. Depression in Rheumatoid Arthritis: A Narrative Review-Diagnostic Challenges, Pathogenic Mechanisms and Effects. Medicina (Kaunas). 2022;58(11). IF: 2,4.
https://www.mdpi.com/1648-9144/58/11/1637
(General Part, Chapters 1-4: Prevalence of Depression in Rheumatoid Arthritis, Difficulties in Diagnosing Depression in Patients with Rheumatoid Arthritis, Common Pathogenic Mechanisms of Rheumatoid Arthritis and Depression, Effects of Depression in Patients with Rheumatoid Arthritis, pg. 16-33)
2. **Ionescu CE**, Popescu C, Agache M, Dinache G, Codreanu C. AB0348 DEPRESSION IN RHEUMATOID ARTHRITIS: PREVALENCE AND PHENOTYPIC CHARACTERISTICS - A SINGLE CENTER EXPERIENCE. Annals of the Rheumatic Diseases. 2023;82:1358. IF:20,3.
https://www.sciencedirect.com/science/article/abs/pii/S0003496724653215
(Original Research, Chapter 9: Study 1: Depression in Rheumatoid Arthritis – Prevalence and Effects on Disease Activity – Pilot Study on 203 Patients, pg.58-83)
3. **Ionescu CE**, Popescu CC, Agache M, Dinache G, Codreanu C. Depression in Rheumatoid Arthritis: Prevalence and Effects on Disease Activity. Journal of clinical medicine. 2024;13(7). IF:3,0.
https://www.mdpi.com/2077-0383/13/7/2058
(Original Research, Chapter 10: Study 2: Depression in Rheumatoid Arthritis – Prevalence and Effects on Disease Activity – Extended Study on 400 Patients, pg. 84-114)
4. **Ionescu C-E**, Popescu CC, Codreanu C. Impact and Prevalence of Depression and Anxiety in Rheumatoid Arthritis—A Cross-Sectional Study with Self-Reported Questionnaires. Journal of clinical medicine. 2025;14(5):1718. IF:3,0.
https://www.mdpi.com/2077-0383/14/5/1718

(Original Research, Chapter 11: Study 3: Impact and Prevalence of Depression and Anxiety in Rheumatoid Arthritis – Cross-Sectional Study Using Self-Assessment Screening Questionnaires pg. 115-149)