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DOCTORAL THESIS

DOCTORAL THESIS
Particularities of Respiratory Involvement in Rheumatoid Arthritis
THESIS SUMMARY

Thesis Supervisor:
Prof. Univ. Dr. Habil. Oana-Cristina Arghir

PhD Candidate:
Iulia-Tania Andronache

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Contents

Key words: Rheumatoid Arthritis, Extraarticular Manifestations, Interstitial Lung Disease, Bronchiectasis

Abbreviation	Meaning
AR	Rheumatoid Arthritis
FR	Rheumatoid Factor
MTX	Methotrexate
IMC	Body Mass Index
TNF	Tumor Necrosis Factor Alpha
DMARD	Disease Modifying Antirheumatic Drug
LEF	Leflunomide
AZA	Azathioprine
HCQ	Hydroxychloroquine
CCP	Cyclic Citrullinated Peptide
UIP	Usual Interstitial Pneumonia
NSIP	Non-Specific Interstitial Pneumonia
OP	Organizing Pneumonia
COP	Cryptogenic Organizing Pneumonia
DAD	Diffuse Alveolar Damage
DIP	Desquamative Interstitial Pneumonia
RB-BPI	Respiratory Bronchiolitis-Associated Interstitial Lung Disease
LIP	Lymphoid Interstitial Pneumonia
IPF	Idiopathic Pulmonary Fibrosis
DAS28	Disease Activity Score 28
PCR	C-Reactive Protein
VSH	Erythrocyte Sedimentation Rate
AINS	Non-Steroidal Anti-Inflammatory Drug
IL	Interleukin
NAD	Number of Painful Joints
NAT	Number of Swollen Joints
VAS	Visual Analogue Scale
HAQ	Health Assessment Questionnaire
EULAR	European League Against Rheumatism
HRCT	High-Resolution Computed Tomography
HTP	Pulmonary Arterial Hypertension
SDRA	Acute Respiratory Distress Syndrome
FVC	Forced Vital Capacity
FEV1	Forced Expiratory Volume in 1 Second
FEV1/FVC	Ratio of FEV1 to FVC
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide

General Data

Rheumatoid arthritis (RA) is an inflammatory, multisystemic, polymorphic, and heterogeneous disease due to its extra-articular manifestations. Extra-articular respiratory manifestations in rheumatoid arthritis, such as interstitial lung disease (ILD), bronchiectasis, and pleural effusion, significantly contribute to morbidity and mortality and have an impact on reducing survival and quality of life. The pulmonary manifestations of rheumatoid arthritis, especially ILD and bronchiectasis, are often underdiagnosed. ILD is the second leading cause of mortality (after cardiovascular diseases) in patients with rheumatoid arthritis, accounting for 7% of RA-associated deaths. Patients with RA-ILD have a threefold higher risk of death compared to those without pulmonary involvement.

Despite their clinical significance, respiratory manifestations are frequently underdiagnosed by specialists and underestimated by patients due to their subtle presentation and overlapping musculoskeletal symptoms, which may be confused with other respiratory conditions, such as tuberculosis.

Personal Contribution

In this thesis, we aimed to address the pulmonary manifestations in RA from an epidemiological perspective, analysing risk factors such as smoking and disease activity, and the therapeutic approach based on the immunosuppressive medication used. We also collected data on factors that may influence the clinical and socio-economic impact of the disease. Since traditional diagnostic techniques such as chest X-ray and spirometry have limited value in detecting early pulmonary changes and impaired ventilatory function, we aimed to evaluate imaging patterns through complex investigations (CT/HRCT) to detect early, subclinical pulmonary changes such as ground-glass opacities and reticular patterns and to demonstrate early impairment of carbon monoxide diffusion across the alveolar-capillary membrane (DLCO).

The information provided in this doctoral research will serve as a starting point for the development of clinical guidelines for better multidisciplinary monitoring of RA patients with pulmonary manifestations.

Research Objectives

To assess the prevalence of major respiratory manifestations in patients with rheumatoid arthritis.

To evaluate the clinical, imaging, and ventilatory features of respiratory involvement in RA patients, considering exposure to certain endogenous and/or exogenous risk factors.

To identify clinical, imaging, and functional expression patterns and their correlations with the activity stage of RA and therapy.

To identify a phenotype of RA patients susceptible to pulmonary involvement and to establish an early diagnostic algorithm for pulmonary manifestations.

General Methodology

The studied cohort includes patients with rheumatoid arthritis over 18 years of age, registered with the Rheumatology Department – Medical Clinic II of the Clinical County Emergency Hospital "St. Andrew the Apostle" Constanța, evaluated between January 2016 and December 2019. The cohort includes both patients already registered with the department and newly diagnosed cases during this period. The diagnostic criteria used were those established by ACR/EULAR in 2010.

The clinical evaluation of the patients was performed by rheumatology specialists in the clinic. Information obtained from medical history, clinical examination, and paraclinical investigations (biological and imaging) was recorded on the same date. Data were collected from both the records of patients hospitalized bot on an inpatient and outpatient basis.

A. Inclusion Criteria:

Diagnosed with rheumatoid arthritis according to ACR/EULAR 2010 criteria;

Age ≥ 18 years;

Patient’s signed informed consent.

B. Exclusion Criteria:

Unconfirmed/uncertain diagnosis of rheumatoid arthritis.
Underage patients.
Patient refusal to participate in the study.
Lack of patient cooperation in performing respiratory tests.
Respiratory infections at the time of examination.
History of major chest surgery or radiotherapy.

Materials and Methods

We collected the following types of data: demographic data, including name, place of origin (urban/rural), sex, age, smoking status, and occupation. The evaluation of smoking history was done through self-report and anamnesis. This included questions about the age at which the person started smoking, the type of tobacco products used, smoking intensity (quantified in pack-years), and the duration of tobacco exposure. The anthropometric data collected included height, weight, and body mass index (BMI). Disease-related data included seropositivity for RF and anti-CCP, history of DMARD medication and any adverse reactions to DMARDs, seropositivity for other autoantibodies (ANA, anti-Ro, La, ± ANA-blot profile), presence of erosions and ankylosis, VAS score, ESR, CRP, disease activity scores, year of onset, year of diagnosis, the interval between onset and diagnosis (in months), number of painful joints, number of swollen joints, history of extra-articular manifestations, and smoking exposure (measured in pack-years). We also recorded information on current and previous DMARD therapy, including biological therapies, and any adverse effects experienced by patients, documented in medical records as well as mentioned during anamnesis. Pulmonary function tests were performed in collaboration with the Pneumology Dispensary in Constanța. These tests included spirometry, measuring forced expiratory volume in one second (FEV1), forced vital capacity (FVC), Tiffeneau index (FEV1/FVC), and DLCO (diffusing capacity of the lung for carbon monoxide). Chest X-rays were performed for all patients included in the study.

Statistical Methods Used
The socio-demographic, anthropometric, clinical, laboratory, and imaging data from the study files were processed into a database and analyzed using IBM SPSS version 20.0. The intermediate results of the research were presented at various international congresses and published in specialized literature starting in 2018. For the descriptive analysis of score-type variables, we used the following central tendency indicators: mean and standard deviation for normally distributed variables, and median and mean deviation for abnormally distributed variables. The Mann Whitney U test was used to compare quantitative data, while the Chi-square test was used to compare frequencies. The Student's T-test was used to compare quantitative data with a normal distribution. For situations where there was a low frequency of certain variables, Fisher's exact test was used (processed only for 2x2 tables).

STUDY 1. SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE COHORT
1.1 Objectives:
To determine the socio-demographic distribution and clinical characteristics (disease forms, medical history) of patients with rheumatoid arthritis in Constanţa County.

1.2 Materials and Methods:
The cohort includes a total of 466 patients with rheumatoid arthritis who were consecutively evaluated in a cross-sectional observational study. We collected the following types of data: demographic data, smoking history, and disease-related data, including medical history.

1.3 Results:
The analyzed cohort consists of 466 patients, predominantly female (396 patients, 85%), most of whom were from urban areas, with a mean age of 61.6 ± 12.25 years. The average body mass index (BMI) was 26.97 ± 5.15 kg/m². (Table 12)

Table 12: Socio-demographic Characteristics of the Analyzed Cohort

Variable	Number (%)	Mean Value and Standard Deviation
Female sex	396 (85%)	
Urban area	369 (79.2%)	
Age		61.6 ± 12.25 years
Retired	318 (68.2%)	
BMI		26.97 ± 5.15 kg/m²
Smoking history	152 (32.6%)	

The majority of the patients were overweight or obese at the time of evaluation (Figure 2). No significant differences regarding obesity were identified between sexes (p=0.08).

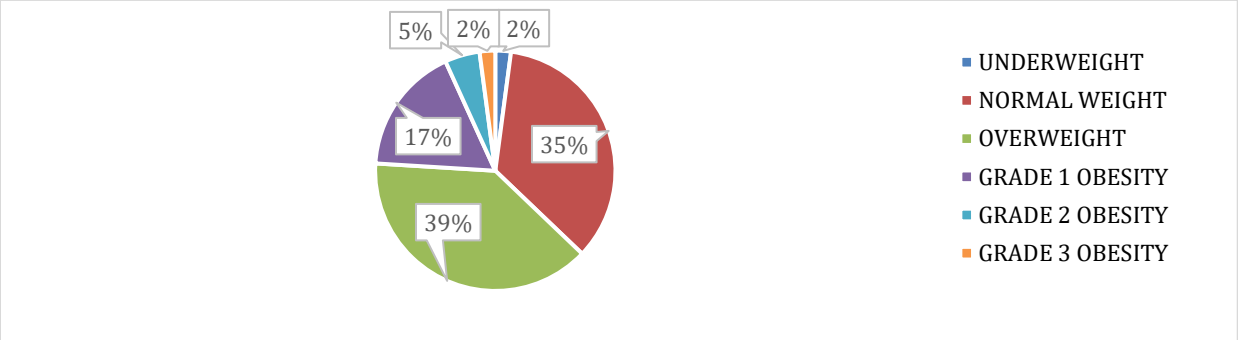

Figure 2. Obesity in RA patients

One-third of patients with a smoking history (n=49; 32.3%) had an exposure of over 20 pack-years. The smoking cessation rate was 59.9% (n=91/152). At the onset of the disease, patients had an average tobacco exposure of 13.84 pack-years, and at the time of evaluation, it was 14.98 ± 13.96 pack-years (Figure 4, Table 14). There were statistically significant differences regarding smoking history and intensity of smoking exposure between the sexes (p<0.001) (Table 14).

Table 14. Smoking Exposure Based on Sex

Variable	Total (466)	Women (396)	Men (70)	p-value
Smoking history	152 (32.6%)	106 (26.8%)	46 (65.7%)	p<0.001
Smoker at disease onset	103 (22.1%)	75 (18.9%)	28 (40.0%)	p<0.001
Current smoker	61 (13.1%)	49 (12.4%)	12 (17.1%)	p=0.335
Smoking >20 pack-years	49 (10.5%)	21 (5.3%)	28 (40%)	p<0.001

Patients reported that 91.8% (n=428) had a work history, but at the time of evaluation, 10 patients (2.1%) were unemployed, and 52 female patients (11.2%) were housewives.

Rheumatoid arthritis has a socio-economic impact on patients. Although most are retired (n=318; 68.2%), 23.4% (n=109) retired for medical reasons and are registered with the regional Work Capacity Expertise Commissions. Additionally, 161 patients from the studied cohort (36.5% of the total group) have a disability certificate.

The age of patients at the onset of rheumatoid arthritis was 50.93 ± 14.35 years, with 6 cases being juvenile onset (before 16 years of age). The average disease duration at the time of enrolment in the study group was 10.66 ± 9.71 years, with a statistically significant difference between the sexes. Rheumatoid arthritis onset occurs approximately 5 years earlier in women than in men (50.18 ± 13.89 years vs. 55.2 ± 16.16 years), and this difference is statistically significant (p=0.017) (Table 17). The interval between the onset of the disease and the confirmation of the diagnosis for the entire study group was over 1 year, with an average duration of 15.57 ± 24 months.

Table 17: Differences Between Sexes Regarding Disease Onset

Variable	Men	Women	p-value
Age at onset (years)	55.2 ± 16.16	50.18 ± 13.89	0.017
Disease duration (years)	8.57 ± 10.88	11.03 ± 9.46	0.056
Onset-diagnosis interval (months)	18.19 ± 27.38	14.64 ± 22.36	0.245
Onset-DMARD interval (months)	19.19 ± 27.33	19.25 ± 34.89	0.989

Rheumatoid factor (RF) was identified in 373 patients (80%), present in high titers (over 3 times the upper limit of normal) in 54.9% of cases (n=256), with a higher prevalence (68.6%) among highly seropositive patients (Table 18). Anti-CCP antibodies were identified in 339 patients, present in high titers in 62.4% of the analyzed cohort, with a higher prevalence (n=207; 74.2%) among patients seropositive for anti-CCP antibodies.

The diagnosis of rheumatoid arthritis was established late, more than 1 year after symptom onset, with the cohort being characterized by a mean onset-diagnosis interval of 15.5 ± 24.00 months (Table 19).

Table 19: Differences Regarding Diagnosis Timing Based on Rheumatoid Factor

Variable	Total cases	Men (RF positive)	Men (RF negative)	Women (RF positive)	Women (RF negative)
Onset-diagnosis interval (months)	15.57 ± 24	13.61 ± 19.68	18.14 ± 28.01	18.35 ± 26.23	15.15 ± 23.29
Onset-DMARD interval (months)	20.53 ± 36.45	14.1 ± 19.79	19.13 ± 27.97	19.35 ± 26.11	20.76 ± 37.71

Similarly, regarding the initiation of therapy, there is a delay of more than 1 year: the average duration from symptom onset to the initiation of disease-modifying treatment (DMARD) was 20.53 ± 36.45 months (Table 19)., with significant differences between sexes (table 20).

Table 20: Differences Regarding Diagnosis Timing in Anti-CCP Positive Patients

Variable	Men	Women	p-value
Age at onset (years)	54.33 ± 13.45	49.11 ± 13.00	0.009
Onset-diagnosis interval (months)	21.13 ± 31.35	14.13 ± 21.09	0.05
Onset-DMARD interval (months)	22.16 ± 31.35	20.05 ± 37.76	0.979

Table 21: Immunological Cohort Features Based on Smoking Exposure

Variable	Patients with smoking history (152)	Patients without smoking history (314)	p-value
RF positive	125 (82.2%)	248 (79%)	0.459
RF > 3x ULN	95 (62.5%)	161 (51.3%)	0.023
Anti-CCP antibodies positive	118 (77.6%)	221 (70.4%)	0.12
Anti-CCP antibodies ≥ 3x N	110 (72.4%)	181 (57.6%)	0.002
RF and anti-CCP antibodies positive	102 (67.1%)	168 (53.5%)	0.007
RF and anti-CCP antibodies >3xN	80 (52.6%)	109 (37.4%)	<0.001

Smoking history does not correlate with a significantly higher rate of autoantibody positivity (RF, anti-CCP antibodies), but it does correlate with high titers of these antibodies. RF values are over 3 times the upper limit of normal in 62.5% of smokers (n=95; p=0.023), and the same is true for anti-CCP antibodies (n=110; 74.2%; p=0.002).

More than half of the patients who are positive for both biomarkers (RF and anti-CCP) and highly positive are smokers, with the differences being highly statistically significant (p=0.007; and p<0.001, respectively) (Table 21).

Smoking exposure at the onset of the disease is significantly associated with the positivity of RF and anti-CCP antibodies, both when analyzed as individual biomarkers or cumulatively, regardless of their titers, but especially at values over 3 times the normal limit (p<0.001) (Table 22).

Table 22: Immunological Cohort Features Based on Smoking Exposure at Disease Onset

Variable	Smoker at onset (103)	Non-smoker at onset (363)	p-value
RF positive	91 (88.3%)	282 (77.7%)	0.017
RF > 3x N	73 (70.9%)	183 (50.4%)	<0.001
Anti-CCP antibodies positive	85 (82.5%)	254 (70%)	0.007
Anti-CCP antibodies ≥ 3x N	79 (76.7%)	212 (58.4%)	0.001
RF and anti-CCP antibodies positive	74 (71.8%)	196 (54.0%)	<0.001
RF and anti-CCP antibodies highly positive	60 (58.3%)	129 (35.5%)	<0.001

Due to the late detection of the disease, with symptoms and clinical signs lasting for more than one year, the cohort is characterized by a high incidence of erosive changes, reported in 70.4% of patients (n=328). Erosive disease with severe joint destruction and ankylosis was found in 30% of cases, i.e., in 140 patients. Women had erosive changes in 72.2% of cases, more often than men (60%), and this difference is statistically significant (p=0.047). The positivity of anti-CCP antibodies significantly reduces the sex difference: in the sub-group of patients positive for anti-CCP antibodies (n=339), erosions were identified in 78.8% of women and 64.7% of men (p=0.032). The presence of rheumatoid factor (RF) is also associated with a high incidence of erosions, identified in 73.7% (n=275) of RF-positive patients and in 77.7% (n=199) of those with high RF titers (Table 23).

Table 23: Erosive Changes and Autoantibodies

Variable	Erosive changes present (328)	No erosive changes (138)	p-value
RF positive (N=373)	275 (83.8%)	98 (71%)	0.001
RF > 3x N (N=256)	199 (60.7%)	57 (41.3%)	<0.001
Anti-CCP antibodies positive (N=339)	260 (79.3%)	79 (57.2%)	<0.001
Anti-CCP antibodies > 3x N (N=291)	227 (69.2%)	64 (46.4%)	<0.001
RF and anti-CCP antibodies positive (N=270)	218 (66.5%)	52 (37.7%)	<0.001
RF and anti-CCP antibodies highly positive	151 (46.0%)	38 (27.5%)	<0.001

The most important parameter associated with the presence of erosive changes is disease duration. Patients with erosions had an average disease duration of 13.09 ± 9.43 years, almost three times longer than that of patients without these changes (4.50 ± 7.46 years), and this difference is statistically significant (p<0.001). The interval between disease onset and therapy initiation is more important than the interval between onset and diagnosis. Patients with erosive changes had an average delay of 9 months in therapy initiation (p=0.002) (Table 24).

Table 24. Relationship Between Erosive Changes and Therapy Delay

Variable	Erosions Present (324)	Erosions Absent (128)	p-value
Age at onset	49.34 ± 13.55	54.73 ± 15.48	0.058
Onset-diagnosis interval (months)	16.52 ± 23.74	11.79 ± 21.43	0.071
Onset-DMARD interval (months)	21.94 ± 37.22	12.40 ± 21.72	0.002
Disease duration	13.09 ± 9.43	4.5 ± 7.46	<0.001

The history of extra-articular manifestations was recorded over time in 296 patients from the study cohort. Extra-articular manifestations at the time of disease diagnosis were polymorphic: a high incidence of anaemia (n=180;

38.64%) was observed, with a low incidence of rheumatoid nodules (n=45; 12.5%). Thrombocytopenia was present in 15 cases (3.21%), and leukopenia in 10 patients (2.14%). Neurological involvement was noted in 5.36% of cases, represented by polyneuropathy (n=15; 3.21%) and carpal tunnel syndrome (n=10; 2.14%).

Intrathoracic manifestations were heterogeneous: 13 cases (2.78%) of rheumatoid lung nodules, 10 cases of pulmonary fibrosis (2.14%), 7 cases of pleurisy (1.5%), and 4 cases of pericarditis (0.85%). Sicca syndrome was present in 14 patients (3%), and keratoconjunctivitis sicca in 3 patients. Additionally, 5 cases of generalized lymphadenopathy, 5 cases of Raynaud's syndrome, 4 cases of cutaneous vasculitis, and cases of prolonged febrile syndrome, episcleritis, erythema pernio, and myopathies were reported. These manifestations were not isolated and could coexist (31 cases of co-occurrence of extra-articular manifestations were identified).

Extra-articular manifestations were more common in patients with established disease; the majority (97%) were identified in patients (n=287) with disease duration over 1 year ($p<0.001$). The frequency of these manifestations increases in patients with erosive disease, being identified in 75% of patients (n=246).

Patients reported an average of 8.23 ± 7.99 painful joints and 2.77 ± 4.09 swollen joints. The number of painful joints does not seem to be influenced by sex (men reported an average of 9.17 ± 8.08 painful joints, while women reported 8.06 ± 7.98, $p=0.286$), but the number of swollen joints with synovitis is higher in men (4.19 ± 4.78) compared to women (2.52 ± 3.91) ($p<0.001$).

Heavy smoking status influences the number of painful joints. Heavy smokers reported an average of 10.39 ± 8.7 painful joints, while women with the same tobacco exposure reported an average of 5.62 ± 5.38 painful joints ($p=0.006$). Similarly, the number of swollen joints is significantly higher ($p=0.049$) in men with more than 20 pack-years of exposure (4.68 ± 5.53 joints) compared to women with similar exposure (3.57 ± 4.15 joints). Analysing the sub-group of smokers at the time of evaluation, the difference between the two sexes remains, with men having more swollen joints (5 ± 5.36) than women (2.73 ± 3.43) ($p=0.012$) (Table 26).

Table 26: Smoking and Joint Involvement

Variable	Swollen Joints			Painful Joints		
	Men	Women	P	Men	Women	P
Study cohort	4.19±4.78	2.52±3.91	<0.001	9.17±8.08	8.06±7.98	0.587
Exposure >20 pack-years (n=49)	4.68±5.53	3.57±4.15	0.049	10.39±8.7	5.62±5.38	0.006
Current smokers (61 patients)	5.00±5.36	2.73±3.43	0.012	10.42±7.14	7.51±6.64	0.477

Pain intensity evaluation was performed using the visual analogue scale (VAS): patients reported a VAS score of 51.95 ± 26.15 mm. Men and women reported similar pain intensity (54.64 ± 26.27 mm vs. 51.48 ± 26.14 mm, $p=0.89$). High titers of anti-cyclic citrullinated peptide antibodies (anti-CCP) were associated with a more severe perception of pain (52.44 ± 27.02 mm) compared to patients with low titers of these autoantibodies (51.14 ± 24.70 mm) ($p=0.042$).

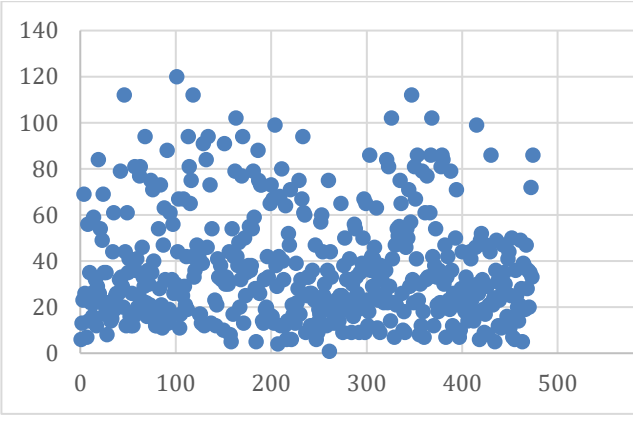

Figure 11: ESR value distribution in AR patients

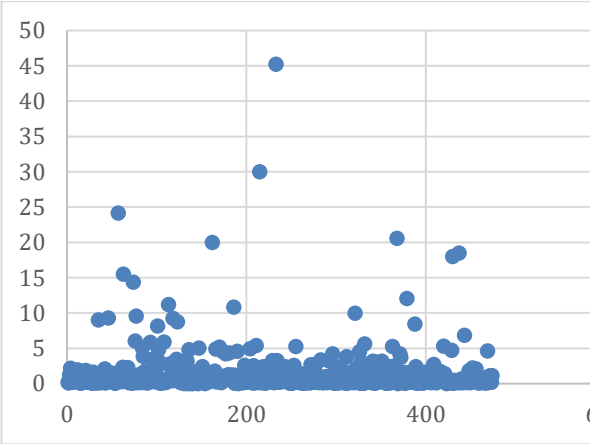

Figure 12: CRP value distribution in AR patients

Patients showed elevated levels of acute phase reactants, with a mean ESR value of 36.48 ± 32.82 mm/h. The mean C-reactive protein (CRP) value was more than 3 times the upper limit of normal: 1.63 ± 3.56 mg/dl. Men had almost double the CRP values (2.82 ± 4.27 mg/dl) compared to women (1.42 ± 3.39 mg/dl) (p=0.002 (table 27).

Table 27. Acute Phase Reactants and Immunological Changes

Variable	ESR (mm/h)	p-value	CRP (mg/dl)	p-value
Men	39.65 ± 27.88	0.228	2.82 ± 4.27	0.002
Women	35.92 ± 23.01		1.42 ± 3.39	
RF positive	38.69 ± 24.69	<0.001	1.73 ± 3.69	0.211
RF negative	27.56 ± 17.36		1.22 ± 2.96	
Anti-CCP positive	38.44 ± 24.31	0.004	1.8 ± 3.81	0.1
Anti-CCP negative	31.27 ± 21.63		1.19 ± 2.77	
Erosions present	38.74 ± 23.83	0.001	1.64 ± 3.03	0.938
Erosions absent	31.13 ± 22.95		1.61 ± 4.60	

Rheumatoid arthritis activity was evaluated using composite indices. The SDAI had a mean value of 22.61 ± 15.79 for the studied cohort. The cohort reported a mean CDAI value of 20.97 ± 14.71. The mean DAS28-ESR score was 4.74 ± 1.61, with the therapeutic target being reached in less than one-fifth of the cohort (19.6%). The mean DAS28-CRP score was 4.41 ± 1.8. In this parameter, the therapeutic target was reached in 32.8% of patients (Table 28). Erosive changes were consistently associated with elevated values of these composite indices.

Table 28: Disease Activity in Rheumatoid Arthritis

Activity Level	SDAI	CDAI	DAS28-ESR	DAS28-CRP
Remission	5.8%	6%	8.2%	19.4%
Low activity	20.9%	18.9%	11.4%	13.4%
Moderate activity	36.1%	34.6%	40.1%	38.1%
High activity	37.2%	40.4%	40.3%	29.1%

Most patients in the studied cohort had a complex medication history. Regarding conventional disease-modifying antirheumatic drugs (DMARDs), most patients had a history of at least three DMARDs (269 patients, 57.77%). A sub-group of five patients had six DMARDs, including less commonly used drugs (cyclosporine, gold salts, azathioprine) added to conventional therapy regimens.

Most patients in the cohort (412 patients, 88.4%) had a history of methotrexate use, and currently, almost half of the patients (241 patients, 51.7%) are using this DMARD. Methotrexate inefficacy was reported by 74 patients (15.87%). Most patients treated with methotrexate reported adverse effects (215 patients, 46.6%). Non-responder status to methotrexate is correlated with the presence of juxta-articular erosions (p<0.001), but not with immunological changes such as high titres of anti-CCP antibodies (p=0.307) or rheumatoid factor (p=0.098).

Data on the history of leflunomide use were collected from 455 patients. Most patients (287, 63.1%) had a history of this DMARD, with 135 patients continuing therapeutic regimens that include this agent. Among the patients who used this DMARD over time, 73 reported therapy inefficacy, and 120 (26.37%) reported adverse effects.

A history of sulfasalazine use was reported by 267 patients in the cohort, with 113 patients continuing therapy with this DMARD at the time of examination. Adverse reactions to this treatment were reported by 114 patients, representing 42.69% of those treated with this therapeutic agent, and therapy inefficacy was noted in 94 patients (35.2% of patients with a history of sulfasalazine use).

Hydroxychloroquine was used over time by nearly half of the patients (243 patients, 52.1%) in the analyzed cohort, and at the time of evaluation, 109 patients (23.4%) were still using this disease-modifying drug. A quarter of the patients (62, 25.51%) exposed to hydroxychloroquine reported adverse effects and therapy inefficacy was noted in 84 patients (34.56%).

Biological therapy was necessary for 156 patients in the analysed cohort, representing 33.5% of the studied group. Access to biological therapies appears to be similar regardless of the patient's living environment: 34.1% for urban patients and 30.9% for rural patients (p=0.62).

Patients receiving biological therapy more frequently had high anti-CCP antibody titres (70.5%) compared to those currently undergoing conventional treatment (58.4%) ($p=0.01$). Patients who received biological therapy also had a higher proportion of erosive changes (84.6%) compared to 63.2% ($p<0.001$).

The history of corticosteroid therapy was identified in 326 patients, and currently, 172 patients (36.9%) are undergoing corticosteroid treatment. The total duration of corticosteroid treatment was 3.54 ± 3.67 years (range 0.1–22 years).

Of the 422 patients who agreed to be tested for these infections, 14 patients (3.31%) were HBsAg positive, and 27 patients (6.39%) tested positive for anti-HCV antibodies. Most patients in the studied cohort had cardiovascular risk factors: 232 (49.8%) were hypertensive, 180 (38.62%) were diagnosed with dyslipidaemia, and 51 (10.9%) were diabetic. A history of myocardial infarction was documented in 9 patients (1.9%) in the analyzed group, and 20 patients (4.3%) had a personal history of stroke (including transient ischemic attacks). Most patients reported the use of non-steroidal anti-inflammatory drugs (NSAIDs) (376 patients), with an average NSAID requirement of 14.07 ± 7.55 days per month.

STUDY 2: THE EVALUATION OF PULMONARY IMAGING CHANGES IN PATIENTS WITH RHEUMATOID ARTHRITIS

2.1 Objectives:
To evaluate the spectrum of respiratory manifestations in patients with rheumatoid arthritis.

2.2 Materials and Methods:
The evaluated cohort consists of 92 patients with rheumatoid arthritis. The patients were diagnosed according to the ACR/EULAR 2010 criteria. All patients were recruited from the "St. Apostle Andrew" Clinical Emergency County Hospital in Constanța, from January 2017 to December 2019. All patients underwent postero-anterior (P-A) chest radiography and high-resolution computed tomography (HRCT) of the chest. HRCT images were independently evaluated by a radiologist, rheumatologist, and pulmonologist.

2.3 Results:
The imaging cohort consisted of 92 patients, predominantly female (79.3% women, 20.7% men), mostly Caucasian (92.4%), and living in urban areas (69.6%), with a mean age of 63.77 ± 11.56 years. Most patients were overweight or obese, with an average body mass index (BMI) of 29.53 ± 28.07 (table 30).

Table 30: Demographic Data of Rheumatoid Arthritis Patients

Variable	Number (%)	Mean Value and Standard Deviation
Current age (years)		63.77 ± 11.56
Female	73 (79.3%)	
Caucasian	85 (92.4%)	
Urban	64 (69.6%)	
Ever smokers	39 (42.9%)	
Current smokers	15 (16.3%)	
Pack-years at onset		20.43 ± 17.89
Current pack-years		18.19 ± 17.26
BMI (Kg/m²)		27.19 ± 5.17

Smoking history was identified in 42.9% of patients, with 16.3% still smoking at the time of evaluation. For patients with a smoking history, tobacco exposure at the time of evaluation was 18.19 ± 17.26 pack-years. At disease onset, smoking patients had an exposure of 20.43 ± 17.89 pack-years.

Established disease was identified in 98.9% of patients, with a disease duration of 15.00 ± 11.55 years. The average age at disease onset was 50.7 ± 15.25 years.
Erosive changes were identified in 76.1% of patients, and ankylosis was present in 40.2% of patients (Table 31). The majority of patients (90.2%) were rheumatoid factor positive (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibodies were present in 81.5% of patients. (Table 31)

Table 31: Clinical Data of Rheumatoid Arthritis Patients

Variable	Number (%)	Mean Value and Standard Deviation
Age at onset (years)		50.7 ± 15.25
Disease duration (years)		15.00 ± 11.55
Erosions	70 (76.1%)	
Ankylosis	37 (40.2%)	
RF positive	83 (90.2%)	
Anti-CCP Antibodies Positive	75 (81.5%)	27.19 ± 5.17

More than two thirds (70.7% of patients) presented respiratory symptoms, with exertional dyspnea being the main complaint (64.1%). (Table 33).

Table 33: Respiratory Symptoms in Rheumatoid Arthritis Patients

Variable	Number (%)
Respiratory complaints	65 (70.7%)
Exertional dyspnea	59 (64.1%)
Dry cough	46 (50%)
Productive cough	15 (16.3%)

Radiographic abnormalities were present in 50% of cases, and 71 patients (77.2%) showed changes on chest CT scans. The pulmonary changes identified via CT were correlated with the age at disease onset (p=0.013), radiographic abnormalities, and the presence of symptoms (table 34).

Table 34: Main Characteristics of Patients with CT Changes

Variable	CT (+) (n=71)	CT (-) (n=21)	p-value
Female	55 (77.5%)	18 (85.7%)	0.547
Age	64 ± 11.43	63 ± 12.24	0.73
Smoking history	31 (43.7%)	8 (38.1%)	0.776
Disease duration (years)	13.8 ± 9.88	19.00 ± 15.59	0.071
RF positive	65 (91.7%)	18 (85.7%)	0.42
Active disease (moderate/high)	44 (62%)	12 (57.1%)	0.69
Erosions	54 (76.1%)	16 (76.2%)	0.9
Methotrexate	40 (56.3%)	10 (47.6%)	0.481
Respiratory symptoms	59 (83.1%)	6 (28.6%)	<0.001
Thoracic radiographic abnormalities	44 (62.0%)	2 (9.5%)	<0.001

The most common pulmonary CT abnormalities are observed in the lung parenchyma, with linear attenuation, ground-glass opacities, air-space consolidation, honeycomb pattern, and architectural distortion being structural abnormalities characteristic of interstitial lung disease (ILD) (Table 35 and Table 36).
These are followed by CT changes suggestive of airway disease (bronchial dilation and bronchial wall thickening). Pleural changes were identified in 28 patients (39.43%), as follows: 21 cases showed pleural thickening, 2 patients had isolated pleural effusion, and in 5 cases, these changes coexisted. The positive findings of high-resolution computed tomography (HRCT) are presented in the table below (Table 35).

Table 35. Main Types of Identified Lesions

Type of Lesion (%)	N=71
Linear attenuation (reticular)	52%
Nodular attenuation	39.43%
Bronchial dilation (bronchiectasis)	33.8%
Bronchial wall thickening	11.26%
Pleural abnormalities	39.43%
Enlarged lymph nodes	29.57%
Emphysema	28.16%
Ground-glass opacity	9.85%
Air-space consolidation	8.45%
Honeycomb pattern	7.04%
Architectural distortion	5.63%
Air trapping	-

Table 36. Main Causes of Pulmonary Lesions (N=71)

Type of Involvement	Imaging Changes	Percentage
Interstitial Lung Disease (ILD)	Ground-glass opacity	9.85%
	Reticular pattern	52%
	Honeycomb pattern	7.04%
	Consolidation	8.45%
	Architectural distortion	5.63%
Airway Disease (AD)	Bronchiectasis	33.8%
	Bronchial wall thickening	11.26%
Nodular Lesions	Nodular pattern	39.43%
Others	Pleural thickening	36.6%
	Pleural effusion	9.8%
	Emphysematous lesions	28.16%
	Enlarged lymph nodes	29.57%

Pulmonary fibrosis is correlated with disease duration (p=0.012), erosive disease (p=0.045), and the presence of respiratory complaints (p=0.023), including cough (p=0.003) and exertional dyspnea (p=0.026), without a correlation with pulmonary radiographic changes (Table 38).

Table 38: Characteristics of Patients with Rheumatoid Arthritis and Pulmonary Fibrosis (N=37)

Variable	Fibrotic Changes Present	Fibrotic Changes Absent (N=55)	p-value
Female sex	30 (81.1%)	43 (78.2%)	0.789
Ever smoked	16 (43.2%)	23 (41.8%)	0.531
Smoker at onset	14 (38.7%)	15 (27.3%)	0.361
Current smoker	4 (10.8%)	11 (20.4%)	0.388
RF positive	34 (91.9%)	49 (89.1%)	0.736
Anti-CCP antibodies	31 (83.8%)	44 (80.0%)	0.780
Erosions	32 (86.5%)	38 (69.1%)	0.045
Ankylosis	16 (43.2%)	21 (38.2%)	0.669
Respiratory symptoms	31 (83.8%)	65 (70.7%)	0.035
Dry cough	26 (70.3%)	20 (36.4%)	0.003
Exertional dyspnea	29 (78.4%)	30 (54.5%)	0.026
Normal chest X-ray	14 (37.8%)	32 (58.2%)	0.088

Pleural changes are also associated with respiratory complaints (p=0.002) and the coexistence of other lesions: nodular scars (p=0.012), fibrotic tuberculous sequelae (p<0.001), and bronchiectasis (p=0.015) (Table 39).
Our study showed that patients with RA had significant changes on chest HRCT, in larger or similar proportions compared to other studies investigating HRCT findings in patients with long-standing RA (Table 40, 41) (68,69, 70)..

Table 40: Clinical and Demographic Characteristics of RA Patients with CT Abnormalities

Variable	Andronache, 2021	Remy-Jardin, 1994	Cortet, 1997	Youssef, 2012	Shawky, 2020	Tanaka, 2020
Patients evaluated (HRCT)	92	77	64	36	82	208
Age (years)	63,77 ± 11,56	57 ± 9	58,8 ± 10,6	48,5 (median)	59,43 ± 3,68	59,25 ± 13,16
Disease duration (years)	15,00 ± 11,55	12 ± 8	12 ± 9,2	8 (median)	6,01 ± 2,02	7,94 ± 9,31
RF positive	83 (90,2%)	NA	76,5%	28 (77,8%)	64 (78,8%)	175 (84,1%)
Smoking history	39 (42,9%)	8 (10,38%)	23,5%	0	16 (19,5%)	97 (46,8%)
Respiratory symptoms	65 (70,7%)	27 (35,06%)	-	NA	35 (42,7%)	21 (10,1%)
CT findings	71 (77,2%)	38 (49%)	55/68 (80,9%)	17 (47,2%)	47 (57,3%)	146 (70,2%)

In our study, linear attenuation (reticulation), a sign of interstitial lung disease, was the most frequently encountered CT finding (52%). Among the 71 patients with HRCT abnormalities, the most prevalent feature in our patients was nodular attenuation, identified in 45 patients (63.38%). However, 14 (19.71%) cases of pulmonary nodules had apical localization and were associated with fibrotic changes, thus considered tuberculous sequelae. Reticulation was another prevalent feature, identified in 37 patients (52%), followed by pleural involvement (pleural effusion or thickening) (39.43%) and bronchiectasis (33.8%).

Table 41: Chest CT Abnormalities in Patients with Rheumatoid Arthritis

Type of Lesion (%)	Andronache 2021 (n=71)	Remy-Jardin 1994 (n=77)	Cortet 1997 (n=68)	Tanaka 2004 (n=63)	Mori 2008 (n=61)	Youssef 2012 (n=36)	Shawky 2020 (n=82)	Tanaka 2020 (n=146)
Bronchial dilation (bronchiectasis)	33,8%	30%	30,5%	75%	49,2%	36,1%	12,2%	41,3%
Bronchial wall thickening	11,26%	-	-	-	18%	-	17,1%	-
Nodular attenuation	39,43%	22%	28%	49%	47,5%	11,1%	29,2%	21,6%
Linear attenuation (reticulation)	52%	18%	-	98%	13,1%	22,2%	-	20,2%
Ground-glass opacity	9,85%	14%	17,1%	90%	26,2%	11,1%	24,2%	6,3%
Honeycomb pattern	7,04%	10%	2,9%	60%	9,8%	5,6%	12,2%	6,7%
Air-space consolidation	8,45%	6%	-	35%	4,9%	-	8,5%	7,7%
Architectural distortion	5,63%	6%	-	62%	0	-	-	-
Emphysema	28,16%	5%	-	24%	-	5,6%	-	-
Air trapping	-	-	25%	43%	-	-	-	-
Enlarged lymph nodes	29,57%	9%	-	20%	-	-	-	-
Pleural abnormalities	39,43%	16%	1,5%	29%	-	5,6%	-	-

The pressence of bronchiectasis was identified in 24 patients (26.1%). The presence of bronchiectasis is correlated with dry cough (p=0.031), productive cough (p=0.021), chest pain (p=0.011), pleural changes (p=0.015), the presence of tuberculous sequelae such as nodular scars (p=0.001), and fibrotic sequelae (p=0.02). (Table 42)

Table 42: Characteristics of Patients with Bronchiectasis and Rheumatoid Arthritis

VARIABLE	BRONCHIECTASIS (N=24)	WITHOUT BRONCHIECTASIS (N=68)	p-value
Male	6 (25%)	13 (19.2%)	0.565
Smoking history	8 (33.3%)	31 (45.6%)	0.344
RF positive	21 (87.5%)	62 (91.2%)	0.692
Anti-CCP positive	20 (83.3%)	55 (80.9%)	0.79
Respiratory symptoms	22 (91.7%)	43 (63.2%)	0.009
Dry cough	17 (70.8%)	29 (42.6%)	0.031
Exertional dyspnea	18 (75%)	41 (60.3%)	0.225
Tuberculous fibrotic sequelae	8 (33.3%)	7 (10.3%)	0.020
Pleural involvement	12 (50%)	16 (23.5%)	0.015
Tuberculous nodular scars	17 (70.8%)	21 (30.9%)	0.001

STUDY 3: EVALUATION OF RESPIRATORY FUNCTION TESTS IN PATIENTS WITH RHEUMATOID ARTHRITIS

Objective:
To evaluate respiratory function tests (spirometry, DLCO) in patients with rheumatoid arthritis.

Materials and Methods:
149 patients diagnosed with RA according to the ACR/EULAR 2010 criteria were evaluated. Demographic, clinical, and paraclinical data were collected for all patients included. All patients underwent spirometry and DLCO tests.

Results:
The evaluated cohort consists of 149 patients, the majority of whom were female (85.8%), with an average age of 61.91 ± 11.56 years and a disease duration of 10.35 ± 10.78 years. Smoking history was identified in 37.6% of patients, with 38 patients (25.5%) being smokers at the onset of the disease. (Table 47). At the time of evaluation, 14.9% of patients were still smokers. Heavy smokers (patients with smoking exposure of over 20 pack-years) were identified in 13.4% of the entire cohort.

Table 47: Characteristics of the Studied Cohort

Characteristics	Number (%)
Female	129 (86.6%)
Age	61.88 ± 11.73 years
BMI (Kg/m²)	27.36 ± 4.94
Ever smoked	56 (37.6%)
Current smoker	22 (14.8%)
Smoker at disease onset	38 (25.5%)
Smoking >20 pack-years (heavy smokers)	20 (13.4%)

Most patients (125 patients, 83%) were rheumatoid factor (RF) positive, with high titers (more than 3 times the upper limit of normal) identified in 82 (55%) patients. Anti-cyclic citrullinated peptide antibodies (anti-CCP) were identified in 118 (79%) patients, and 67.1% of patients had high levels of these autoantibodies.
At the time of evaluation, 86 patients were on methotrexate treatment, 41 were on leflunomide treatment, and 52 patients (34.9%) were receiving biological agents. Respiratory symptoms were present in 43 patients, representing 28.9% of the studied cohort. The main reported symptoms were dry cough (27 patients, 18.1%) and dyspnoea (26 patients, 17.4%), followed by productive cough (18 patients, 12.1%).
The spirometry showed a normal pattern in most cases (116 patients, 77.9%), obstruction in 14 patients, a mixed pattern in 12 patients (8.1%), and restriction in 7 patients (4.7%). Restrictive ventilatory dysfunction was identified entirely in women. Obesity is correlated with the presence of restrictive ventilatory dysfunction, p=0.001 (Table 49).

Table 49: Ventilatory Dysfunction and BMI

Variable	BMI (kg/m²) (mean, standard deviation)	p-value
Normal spirometry	27.03 ± 4.68	p<0.001
Restriction	32.19 ± 2.94	
Obstruction	25.31 ± 3.15	
Mixed pattern	12 ± 7.33	

Normal DLCO values were identified in 98 (65.8%) patients, 46 (30.9%) showed a slight decrease in DLCO, and 3.4% had a moderate decrease (Table 51), presenting a heterogeneous distribution with a wide range of values (Figure 15). A decrease in the transfer factor (KCO = DLCO/VA) was recorded in 14 patients (9.4%), with values above 60% in most cases (Figure 16).

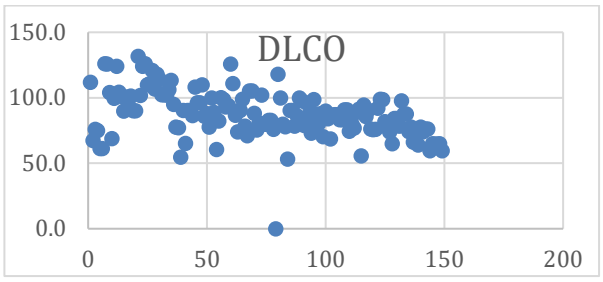

Figura 15: DLCO value distribution

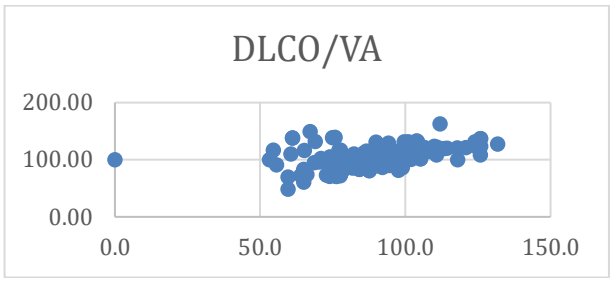

Figura 16. DLCO/VA distribution

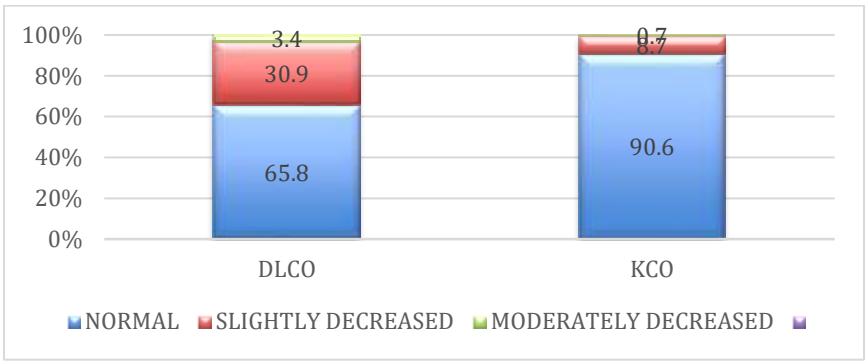

Figura 17: DLCO si KCO la pacienţii lotului studiat;

We identified a sub-cohort of 14 patients who exhibited a decrease in the transfer factor (KCO). These were 14 women with an average age of 55.79 years, all with established disease (disease duration = 11.77 ± 10.28 years), with the majority (9 patients, 64.3%) having active disease and an interval from disease onset to initiation of therapy of nearly 2 years (Table 52).

Table 52: Characteristics of Patients with Decreased Transfer Factor

Variable	Decreased KCO	Study Cohort
Female	14 (100%)	129 (86.6%)
Age	55.79 ± 10.30 years	61.88 ± 11.73 years
Age at disease onset	44.86 ± 13.26 years	54.8 ± 12.84 years
Interval from onset to DMARD	22.8 ± 21.73 years	20.22 ± 19.21 years

Erosions are correlated with the decrease in the transfer factor (p = 0.032) (Table 53), and among the respiratory manifestations, only dyspnea shows a significant correlation (p = 0.018) (Table 54).

Table 53: Erosive Changes and Transfer Factor in Patients with Rheumatoid Arthritis

Variable	Erosions Present (97)	Erosions Absent (51)	p-value
DLCO	84.91 ± 15.5%	90.03 ± 16.9%	0.032
DLCO/VA (KCO)	99.00 ± 19.11%	106.16 ± 19.29%	

Abnormal DLCO values are correlated with high disease activity (determined by the DAS28-CRP index), predominantly recorded in patients with high and moderate disease activity (p = 0.039); of the 28 patients with DLCO below 75% of the predicted value, 16 (57.1%) had moderate disease activity and 6 (21.4%) had high disease activity.

Regarding obesity, it is correlated with decreased DLCO values: the majority of patients (19 patients, 67.85%) with abnormal values were overweight or obese (p = 0.037). The decrease in the transfer factor is correlated with exertional dyspnea. (Table 54)

Table 54: Transfer Factor in Patients with Rheumatoid Arthritis

Variable	DLCO/VA NORMAL	DLCO/VA REDUCED	p-value
Female	14 (100%)	115 (85.2%)	0.217
Respiratory symptoms	36 (26.7%)	7 (50%)	0.67
Dyspnea	20 (14.8%)	6 (42.9%)	0.018
Dry cough	22 (16.3%)	15 (37.5%)	0.073
History of methotrexate	121 (89.6%)	14%	0.206
Current methotrexate use	76 (56.3%)	10 (71.4%)	0.268
Rheumatoid nodules	26 (19.3%)	4 (28.6%)	0.02

Abnormal DLCO values are correlated with high disease activity (determined by the DAS28-CRP index), predominantly recorded in patients with high and moderate disease activity (p = 0.039); of the 28 patients with DLCO below 75% of the predicted value, 16 (57.1%) had moderate disease activity and 6 (21.4%) had high disease activity.
Regarding obesity, it is correlated with decreased DLCO values: the majority of patients (19 patients, 67.85%) with abnormal values were overweight or obese (p = 0.037).
The decrease in the transfer factor is correlated with exertional dyspnea.
The history of corticosteroid use (medication administered in severe, active forms of the disease) is associated with a decrease in the transfer factor (p=0.049), along with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (p=0.03).
Extra-articular manifestations of rheumatoid arthritis that are correlated with a decrease in the transfer factor include rheumatoid nodules (p=0.02). The decrease in the transfer factor is also correlated with exertional dyspnea (p=0.018).
The KCO transfer factor is correlated with the disability index of patients, being identified in two groups: patients with a low degree of disability or patients with severe disability, with significant limitations in daily activities .

Conclusions

1. The examined cohort is characterized by a longer duration of rheumatoid arthritis (RA), with patients having received complex prior medication regimens. The interval between the onset of the disease and the initiation of therapy is more crucial than the interval between onset and diagnosis, as patients with erosive changes experienced an average therapy delay of 9 months (p=0.002), which significantly influences long-term outcomes.
2. The presence of joint erosions correlates with high disease activity indices, regardless of objective parameters such as ESR or CRP. Smoking is associated with a higher number of painful and swollen joints, especially among men.
3. Chest X-ray findings are frequently nonspecific. Respiratory symptoms may be underreported, as patients with high levels of disability do not report exertional dyspnea. However, when pulmonary involvement is evaluated using HRCT, it is evident in a high percentage of RA patients, even in those without chest X-ray findings or respiratory symptoms. We identified interstitial lung disease (ILD) as the primary cause of lung lesions, followed by airway involvement. Although pleural abnormalities were also common, some of these may be secondary to previous tuberculosis (TB) infection.
4. Respiratory involvement in RA is polymorphic, with multiple types of lesions coexisting. We identified two pulmonary phenotypes among RA patients:
5. A fibrotic phenotype, characterized by exertional dyspnea and dry cough in patients with long-standing RA and erosive changes.
6. A bronchiectatic phenotype, presenting with respiratory symptoms such as dry cough and chest pain, and radiologically associated with tuberculous sequelae.
7. Pulmonary changes in RA patients are not associated with the number of prior DMARDs, or the history of methotrexate or leflunomide use. Restrictive ventilatory dysfunction was identified exclusively in women, and obesity is correlated with its presence (p=0.001).
8. Factors associated with decreased DLCO include obesity and disease activity, quantified using the DAS28-CRP index. A reduction in the transfer factor was recorded in 10% of the cohort, all of whom were women with RA onset 10 years earlier than the rest of the cohort, and with a more aggressive, erosive form of the disease requiring a more aggressive therapeutic approach. All patients with a decreased transfer factor had a history of corticosteroid therapy.
9. We suggest early screening for the phenotype of patients with negative predictive factors: young age at RA onset.
10. delayed initiation of DMARD therapy.
11. All RA patients should be monitored through DLCO and HRCT at the time of diagnosis and therapy initiation. Symptomatic patients should undergo functional respiratory tests and HRCT every 3 months, with a follow-up HRCT at 1 year.
12. The diagnostic algorithm for pulmonary involvement in asymptomatic patients requires two distinct approaches:
    A) Asymptomatic RA patients with normal chest X-rays and CT scans, and normal spirometry results, should undergo annual DLCO evaluations.
    B) Asymptomatic RA patients with imaging or functional test abnormalities should have DLCO testing every 6 months, with imaging reevaluation at 1 year.
13. Screening for TB infection and disease should not be neglected in patients with a history of TB, or in those with suspicious TB lesions, even if they lack a treated history of the disease.

Thesis Originality and Relevance

The originality of this thesis lies in its multidisciplinary approach, integrating perspectives from rheumatology, pulmonology, simple and complex ventilatory functional explorations, and imaging. The thesis explores clinico-imaging-functional, epidemiological, and socio-demographic correlations underlying pulmonary involvement in rheumatoid arthritis (RA).

This holistic approach investigates the interaction between chronic inflammation, autoimmunity, and environmental factors contributing to lung disease. It not only deepens the understanding of pathological processes but also profiles patients with a phenotypic risk for pulmonary manifestations and raises the issue of potential warning signals for identifying therapeutic targets (treat-to-target approach).

Risk factors for severe forms of the disease have been identified, including the statistically significant relationship between smoking and disease activity in male RA patients, as well as the relationship between corticosteroid treatment and a decrease in the transfer constant (KCO).

The analysis of the cohort provides an overview of the RA population in southeastern Romania. The research offers a detailed analysis of the prevalence and impact of bronchiectasis in the study cohort, identifying the coexistence of these manifestations at the bronchial level with post-tuberculous sequelae, in the absence of documented bacillary history. This highlights the need for vigilant monitoring of patients with sequelae.

Furthermore, the thesis sets a precedent for future research. It also raises the issue of the need for a potential prevalence study of tuberculosis infection in RA patients with pulmonary manifestations, not only at the time of initiating biological therapy but also throughout the course of RA.

In Extenso Articles Published As The Result Of Doctoral Research

1. **Andronache IT**, Şuţa VC, Şuţa M, Ciocodei SL, Vladareanu L, Nicoara AD, Arghir OC. *Better Safe than Sorry: Rheumatoid Arthritis, Interstitial Lung Disease, and Medication-A Narrative Review*. Biomedicines. **Jun 2023**;11(6):1755. eISSN: 2227-9059 **IF=4,7;** WOS: 001013948200001; doi: 10.3390/biomedicines11061755. PMID: 37371850; PMCID: PMC10296178. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10296178/*
2. **Iulia-Tania Andronache**, Ioan Anton Arghir, Vladareanu Liliana, Cristina Suta, Laura Babu, Ileana Ion, Arghir Oana Cristina. "Coexistence Of Bronchiectasis Related With Rheumatoid Arthritis And Posttuberculosis Lung Disease -An Ever-Present Issue" ARS Medica Tomitana 2024; 3(30): pag. 91-96 DOI: 10.2478/arsm-2024-0014 https://intapi.sciendo.com/pdf/10.2478/arsm-2024-0014
3. **Iulia Andronache,** Cristina Suta, Sabina Ciocodei, Ionut Bulbuc, Claudia Mihailov, Oana Arghir, Maria Suta. *Pulmonary abnormalities on high-resolution computed tomography in patients with long standing rheumatoid arthritis*. Romanian Journal of Rheumatology, Mar 2020; Vol XXX, No. 1: 15-20; ISSN 1843-0791; e-ISSN 2069-6086; ISSN-L 1843-0791; DOI: 10.37897/RJR.2021.1.3; *https://rjr.com.ro/articles/2021.1/RJR_2021_1_Art-03.pdf*
4. Suta, Cristina, Ciocodei Sabina, **Andronache Iulia-Tania,** Craiu Elvira, and Suta Maria. "The Influence of Environmental Factors on the Onset Of Rheumatoid Arthritis." Romanian Journal of Rheumatology 11, no. 3 (2016). CNCSIS B, BDI, DOI: 10.37897/RJR.2016.3.1 https://rjr.com.ro/articles/2016.3/RJR_2016_3_Art-01.pdf

Oral Presentations In International Events-Published Abstracts -ISI indexed papers

1. **I.-T. Andronache,** M. Suta, C. Suta, O.-C. Arghir. *High-Resolution CT Scan in Rheumatoid Arthritis: Pulmonary Abnormalities.* Poster *Pulmonary Manifestations of Systemic Disease*. Congresul internațional CHEST 2022 Bologna, Italia, 27-29 **Iun 2022**. *Chest,* vol. 161 issue, Supplement: A428; Published in issue: June, 2022; ISSN: 0012-3692; **IF=11,393;** WOS:000821656100414; *https://journal.chestnet.org/article/S0012-3692(21)04904-7/pdf*
   https://journal.chestnet.org/action/doSearch?text1=Arghir&field1=AllField&startPage=&rel=nofollow&Ppub=%5B20220406%20TO%2020220706%5D

2. Suta V, **Andronache I,** Suta M. AB0325 Treat To Target And The Real Life Experience – Data From A Cohort Of Rheumatoid Arthritis Patients In South East Romania (Constanta County)Annals of the Rheumatic Diseases 2017;76:1162 **IF=12.350** https://ard.bmj.com/content/76/Suppl_2/1162.2

Oral Presentations In National Events-Published Abstracts

1. **Iulia Andronache**, Maria Şuţa , Cristina Şuţa , Sabina Ciocodei, Oana Arghir, Pulmonary Involvement In Rheumatoid Arthritis – Imaging Patterns The Romanian National Congress of Physical and Rehabilitation Medicine & Balneology, Timisoara, Romania, 01/09/2023-05/09/2023 Balneo and PRM Research Journal 2023, 14, 3 – Congress Abstracts
2. **Iulia Andronache**, Maria Şuţa, Cristina Şuţa, , Sabina Ciocodei, Liliana Vladareanu Oana Arghir: Treating Rheumatoid Arthritis To Target – Unmet Needs, The Romanian National Congress of Physical and Rehabilitation Medicine & Balneology, Timisoara, Romania, 01/09/2023-05/09/2023 Balneo and PRM Research Journal 2023, 14, 3 – Congress Abstracts
3. **Iulia Andronache**, Cristina Şuţa, Ioan Anton Arghir, Elena Danteş, Oana Cristina Arghir. *Manifestări toracice la pacienţii cu artrita reumatoidă/ Chest involvement in patients with rheumatoid arthritis.* Rezumat publicat in Vol 2 Rezumate comunicari orale pg 10-11; ISBN 978-606-8463-76-6; Al 27-lea Congres Național al Societății Române de Pneumologie, cu participare internațională. "Pneumologia de la știință la multidisciplinaritate și inovație"; 2-6 **Noi 2022**; Sinaia. Organizator Societatea Română de Pneumologie. *https://www.congres-srp.ro/#!fancybox/60ec5bb0*
4. **Iulia-Tania Andronache**, C Şuţa, M. Şuţa, O Arghir. Evaluarea probelor funcţionale respiratorii la pacienţii cu artrită reumatoidă. Congresul Național de Reumatologie editia XXVI; 3-5 Oct. 2019, Poiana Brasov. https://srreumatologie.ro/wp- content/uploads/2020/08/Vol_rezumate_CNR_2019_22sep.pdf
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7. Matei Luminita, Mitroi Adrian, **Andronache Iulia-Tania**, Marinica Mihaela, Suta Maria. „ Glucocorticoizii în practica medicală" (Congresul Naţional de Reumatologie 2015, 23- 26 septembrie 2015, Biblioteca Națională a României, Bucureşti) *Romanian Journal of Rheumatology Vol XXIV, Supplement 2, Year 2015 p26*

Posters -Published Abstracts

1. **Iulia-Tania Andronache,** Liliana Vladareanu, Oana-Cristina Arghir Fumatul și Artrita Reumatoidă - Implicații Clinice /Smoking and Rheumatoid Arthritis - Clinical Implications Al 47-lea Congres Național Anual de Medicină Fizică și de Reabilitare - congres hibrid 16-19 octombrie 2024, Poiana Brașov, Romania
2. **Iulia-Tania Andronache,** Liliana Vladareanu, Oana-Cristina Arghir Artrita Reumatoidă și Bronşiectaziile - Implicații Clinice și Im / Rheumatoid Arthritis and Bronchiectasis – Clinical and Imaging Implications Al 47-lea Congres Național Anual de Medicină Fizică și de Reabilitare - congres hibrid 16-19 octombrie 2024, Poiana Brașov, Romania
3. S. Ciocodei, C. Şuţa, **Iulia-Tania Andronache,** M.Şuţa Artrita reumatoidă și sindrom lupus - like: sindrom overlap sau reacție adversă medicamentoasă? Al XXIII lea Congres Naţional de Reumatologie, Oct 2016,

Biblioteca Națională a României, Bucureşti Romanian Journal of Rheumatology; 2016; Volume XXV, Supplement, p63. https://rjr.com.ro/rjr-vol-xxv-supplement-year-2016/

Oral Presentations

1. **Iulia-Tania Andronache,,** C Şuţa, M. Şuţa, O Arghir Pulmonary Involvement In Rheumatoid Arthritis , ENTeR-chILD the 2nd Conference; European Network for Translational Research in Children and Adult Interstitial Lung Disease Belgrad 1 – 3 November 2018

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