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EARLY DIAGNOSIS AND EVOLUTION OF SERONEGATIVE RHEUMATOID ARTHRITIS

321.04 – RHEUMATOLOGY

Summary of Doctor of Medical Sciences Thesis

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The thesis was developed at the Discipline of Rheumatology and Nephrology

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CONTENT

CONCEPTUAL MARKINGS OF THE RESEARCH

The actuality and significance of the topic. Some researchers consider that rheumatoid arthritis (RA) is not a single disease, but rather a collection of diseases. It could also be a disease with many different causes. However, RA is ultimately defined based on two main subtypes in adults: seropositive and seronegative. In seropositive RA, serological tests demonstrate high levels of antibodies called anti-cyclic citrullinated peptides (anti-CCP) and rheumatoid factor (RF). These are specific markers for RA and can appear long before overt symptoms of the disease. About 60% to 80% of people diagnosed with RA have anti-CCP and RF. By definition, people with seronegative RA do not have these antibodies and complexes in their serum, although this is controversial.

The development of RA is accompanied by polyclonal activation of B cells and hyperproduction of autoantibodies, which, through the activation of the complement system and lymphocytes (directly or through the formation of immune complexes), induce inflammation and damage to body tissues [1, 3, 7]. In the serum and synovial fluid of patients with RA, a wide range of organ-specific autoantibodies are detected: rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPAs), RA-33/hnRNP-A2, immunoglobulin-binding protein Bip/p68, glucose-6-phosphate isomerase, calpastatin, type II collagen, HMG1/2 non-histone chromosomal proteins, carbamylated proteins [2, 9, 19]. The most important in the laboratory diagnosis of RA are serological tests related to the determination of RF and ACPAs. RF and antibodies to cyclic citrullinated peptide (anti-CCP) in serum are included in the new classification criteria for the diagnosis of RA – ACR/EULAR 2010 [8, 14, 22].

In this regard, RF and anti-CCP have been considered as markers of RA and are used as evidence to justify intensive treatment in patients with seropositive RA (SPRA) [1, 4, 5, 17, 25]. However, it is not known whether patients with SPRA show more severe disease progression compared to patients with seronegative RA (SNRA) in other than radiological disease activity scores. Studies have reported greater disease severity and functional impairment in patients with SPRA both during disease presentation and after treatment with disease-modifying anti-rheumatic drugs (DMARDs) [6, 18, 24]. In contrast, other studies reported that patients with SNRA had more severe inflammatory activity compared to SPRA assessed clinically and by joint ultrasonography [5, 9, 21] and that patients with SNRA had a worse radiographic outcome compared to SPRA [10, 16, 27]. This divergence may be attributable to differences in the selected patient samples, the inclusion criteria, and the disease activity scores between studies. In this study, we investigated and compared the clinical presentations and evolutionary outcomes of patients diagnosed with SPRA and SNRA.

Currently, there are ACPA-positive and anti-CCP negative subtypes of RA, which differ in molecular mechanisms of pathogenesis, severity of disease progression, and therapeutic approaches [7, 11, 15, 27]. ACPA-positive RA is characterized by an accelerated radiological progression of destructive joint lesions, severe disease evolution with an increase in overall mortality, and more frequent development of comorbid conditions. However, the data on the relationship of ACPA with clinical and laboratory indicators of the activity of the pathological process, the presence of systemic manifestations, the severity of destructive joint lesions in RA remain contradictory and need to be clarified [6, 12, 16, 18].

An important problem of RA immunodiagnosis is the insufficient standardization of ACPA determination methods [3, 6, 10, 13, 20].

Recently, new tests for the detection of ACPAs have been developed - an electrochemiluminescent (ECL) method for the detection of anti-CCP in patient serum and a semi-quantitative immunochromatographic analysis of anti-CCP and anti-MCV in whole blood serum using test strips [11, 14, 19, 26]. These methods of determining ACPAs significantly expand the possibilities of laboratory diagnosis of RA, but their clinical significance has not been sufficiently studied. Therefore, the urgent task of standardizing laboratory studies in RA in the post-analytical stage is a comparative analysis of the indicators of the content of clinical information from different methods of determining ACPAs with the calculation of sensitivity and specificity, which makes it possible to identify the optimal test systems for diagnosis RA which currently remains seronegative [15, 17, 22, 23, 27].

This study demonstrates that SNRA patients had a more active disease at onset but a more benign course. This study recruited patients in several rheumatology clinical departments.

The purpose of the study: evaluation of clinical characteristics at presentation and clinical-evolutionary and radiographic outcome in patients with seronegative rheumatoid arthritis, with the determination of prognostic factors for disease progression.

Based on the purpose of the study, there were completed the following **objectives**:

1. Assessment of the triggering factors associated with seronegative rheumatoid arthritis;
2. Comparative evaluation of the particularities of the joint syndrome in seronegative rheumatoid arthritis and in those seropositive at the onset and in the manifest clinical stage of the disease;
3. Delineation of the particularities of extra-articular involvement in the evolution of rheumatoid arthritis in seronegative and seropositive evolution;
4. Study of the clinical-evolutionary profile and its correlation with the clinical, biochemical, immunological and radiological data of seronegative rheumatoid arthritis.
5. Comparative analysis of quality of life and prognosis in patients with seronegative rheumatoid arthritis

Scientific research methodology. The type of study carried out is clinical and analytical. Inclusion and exclusion criteria were used to select patients for the study. The patient groups studied were homogeneous and comparable. Data accumulation was of the "case-control" type. According to the requirements of ethical attachment, the study did not include any elements of human experimentation, and the evaluation criteria did not change throughout the study. The analysis of the obtained data was performed at the end of the study. Considering the presence in the statistical examination of groups with several types of variants (nominal and scaling), they were processed separately. The obtained data were analyzed statistically by statistical data processing: linear regression analysis, cluster variance with multiple scans, ANOVA (modified after Welch) to calculate mean values (M), standard error (ES) and standard deviation (DS), of correlations (r). Differences in means were compared using Welch's t-test. Methodological support was provided by the use of the methods presented in the works of well-known specialists in the field [9, 13].

Scientific novelty and originality

Following the study, we were able to quantify the value of anti-CCP in the clinical manifestation of RA, so that the presence of autoantibodies and RF reflect a specific clinical picture and a more severe evolution of the disease. However, the results confirmed that the absolute

value of the amount of anti-CCP and RF is not of primary importance in the expression of clinical severity. In the same way, the triggering factors associated with the onset of seronegative rheumatoid arthritis were highlighted - acute viral respiratory infections, intense physical stress and mental stress, as well as prolonged exposure to hypothermia. The quality of life certified on the basis of the HAQ questionnaire, which directly targeted motor and functional joint ability, revealed more favorable values for SNRA, compared to SPRA. At the same time, definite inverse correlations of this index with the markers of the acute phase, the radiological stage of joint damage, were also demonstrated. Thus, we conclude that humoral autoimmunity represents the important link in the onset, evolution and clinical presentation of RA.

The scientific aspects solved in the thesis

The joint syndrome from the onset of rheumatoid arthritis in SNRA presents itself as a mono- or oligoarthritis, with the predilection involvement of the large and medium joints of the lower limbs, which later evolves into a polyarthritis that also affects the areas of the small joints. The radiological evolution of joint involvement in SNRA is more pronounced in the lower limbs versus the upper ones ($p<0.05$). The analysis of the prognostic factors of the rapid-progressive evolution at SNRA highlighted the following ones: insidious onset, triggered after the age of 60; onset through polyarthritis with symmetrical involvement of the interphalangeal joints of the plantar region or through monoarthritis with asymmetrical radiocarpal joint damage; the presence of extra-articular manifestations and smoking.

The theoretical significance of the work

Rheumatoid arthritis is a pathology with an autoimmune component, with a severe and progressive evolution which, although it shows a predilection for seropositive evolution, it evolves seronegative just as severely and due to its particularities of the evolution of articular and extra-articular manifestations, severely impairs the motor and functional abilities of seronegative patients , producing an adverse impact on the quality of life.

The applicative value of the work

The study of extra-articular manifestations in rheumatoid arthritis established the presence of clinical dimorphism depending on the patients' seronegativity and seropositivity. Seronegative patients have a reduced rate for vascular, gastrointestinal, and hepatic manifestations (manifested by gastroduodenal ulcer and fatty degeneration of the liver), metabolic pathology (both with active smoking status and nontraditional factors determined by the underlying pathology), and a reduced predisposition for the association of chronic bronchial infections and renal damage compared with seropositive rheumatoid arthritis

The scientific problem solved in the thesis consists in the assessment of clinical and paraclinical characteristics in patients with seronegative rheumatoid arthritis, therefore determining prognostic factors in these patients.

Implementation of results. The obtained data will be applied in the activity of the Discipline of Rheumatology and Nephrology, of PMSI RCH "Timofei Moșneaga", Chisinau, Republic of Moldova.

Approval of scientific results. The results of the thesis were discussed, approved and recommended for support at the meeting of the Discipline of Rheumatology and Nephrology of IP SUMPh "Nicolae Testemițanu" (minutes no. 3 of 19.09.2023), at the 321 Scientific Profile Seminar, specialty 321.04 - Rheumatology (minutes no. _____ from _____) and within the University Senate (minutes no. ____ from _____).

The study materials were reflected in 9 scientific publications, 4 articles in accredited national scientific journals, in B category journals – 3 articles in: *Moldovan Journal of Health Sciences /Revista de Ştiinţe ale Sănătăţii din Moldova 2022*, and 1 article in *Arta Medica 2023*. 5 abstracts/theses in the works of national and international scientific conferences – 2 in *Public Health, Economics and Management in Medicine (Sănătate Publică, Economie şi Management în Medicină)*. 2017, 1 in Scientific and practical rheumatology *Научно-практическая ревталогия (Научно-практическая ревматология)in* 2017, 1 in *International Journal of Medical Dentistry*. Apr-Jun 2020, and 1 in T*heses of the Congress "Congress dedicated to the 75th anniversary of the founding of the State University of Medicine and Pharmacy "Nicolae Testemiţanu"*, Chişinău, Moldova, 2020.

Presentations and abstract communications at 16 international and national scientific conferences.

Summary of compartments. The thesis is presented on 101 basic text pages and includes the following sections: introduction, 4 chapters, conclusions, practical recommendations, a bibliographic index with 191 sources. The iconographic material includes 32 tables and 28 figures.

Key words: rheumatoid arthritis, seronegative, early diagnosis, seropositive, rheumatoid factor, anti-CCP, citrullinated proteins, joints, HAQ, acute phase markers.

The positive opinion of the Research Ethics Committee was obtained for the study on 17.06.2016, no. 61, Department of Rheumatology and Nephrology, "Timofei Moșneaga" Republican Clinical Hospital.

THESIS CONTENT

1. SERONEGATIVITY OF RHEUMATOID ARTHRITIS - DIFFICULTIES IN CLINICAL-PARACLINICAL ASSESSMENT

1.1 Rheumatoid arthritis – some clinical-evolutionary aspects of seronegativity

The heterogeneity of the pathogenetic mechanisms of RA is reflected in the existence of a wide range of phenotypes and endotypes of the disease, which allows us to consider it not as a "single disease", but as a clinical and immunological syndrome, which can evolve seropositive or seronegative [1 -3, 12, 16, 25]. RA is a frequent immunoinflammatory disease and one of the most severe, which determines the great medical and socio-economic significance of this pathology [7, 11, 17, 21]. The prevalence of RA among the adult population in different geographical areas of the world varies from 0.5 to 2% [4, 9, 24]. The disease occurs in all age groups, but the peak incidence falls on the most active age – 40-55 years.

In the absence of effective therapy, the impact on life expectancy of patients with RA is 3 years less in women and 7 years less in men, primarily due to the increased risk of developing comorbid diseases - cardiovascular pathology, osteoporosis, severe infections, lung diseases interstitial, oncological diseases [6, 8, 13, 18]. In many patients with RA, the prognosis is considered as poor as in lymphogranulomatosis, type 2 diabetes, trivascular lesions of the coronary arteries, and stroke. RA causes persistent function loss (disability) in half of patients within the first 3–5 years of disease onset, and after 20 years, one third of patients become completely disabled.

The essence of the pathological process in RA is a systemic autoimmune inflammation, which affects the synovial membrane of the joints with maximum intensity. The evolution of RA includes several stages of sequential (or discrete) development: "preclinical", which is transformed

into "symptomatic", culminating in the formation of a complex of early and then extensive clinical and laboratory symptoms characteristic of RA [13, 19-21 , 25]. It is assumed that the development of "subclinical" synovitis is already observed in the "preclinical" stage of RA and is associated with local microtrauma, joint damage, activation of the complement system and/or the pathogenic effect of autoantibodies (or immune complexes) that determine the activation of periarticular osteoclasts expressing citrullinated proteins that cause bone destruction, the synthesis of "pro-inflammatory" mediators that induce the development of pain and inflammation. In the synovial tissue in RA, massive infiltration by "immune" cells (T-lymphocytes, B-lymphocytes, plasma cells, macrophages, mast cells, activated stromal cells and synovial fibroblasts), the nature of the interaction between them and the synthesis profile of "pro-inflammatory" mediators are detected ” varies significantly depending on the stage of the disease [4, 9, 12, 16, 21].

Seronegative rheumatoid arthritis is characterized by the fact that the patient does not have RF or anti-CCP, but this does not affect the progression of the disease. The disease does not start as acutely as other forms, and the evolution and symptoms are less pronounced [7, 18-20, 27]. The onset of symptoms begins with the involvement of one or more joints, but they are not characterized by symmetry [5, 14, 17]. Large joints are involved in the process more often, finger joints - less frequently [1, 5, 23-25].

Seronegative rheumatoid arthritis, the prognosis of which is more favorable compared to other forms of pathology, develops against the background of exposure to the following factors: hereditary predisposition; difficult environmental situation and living conditions; viral diseases; diseases of the endocrine system; stress; mechanical damage to the elements of the musculoskeletal system; alergic reactions; infectious diseases; overload [3, 15, 19, 23]. The risk group includes the elderly (from 40 years old).

Clinically pronounced joint lesions in patients with seronegative RA may be preceded by a prodromal period lasting from several weeks to several months. During this period, the patient may be bothered by increased fatigue, weight loss, arthralgias, subfebrile body temperature [6-9, 15, 18, 21].

The onset of the disease is characterized by diversity, the following options for the onset of seronegative RA are conditionally distinguished [9-11, 24]:

- symmetrical polyarthritis with a gradual increase (over several months) of pain and stiffness, mainly in the small joints of the hands (in half of the cases);
- mono-oligoarthritis of the knee or shoulder joints with subsequent rapid involvement of the small joints of the hands and feet in this process;
- acute monoarthritis of large joints, similar to septic or microcrystalline arthritis;
- recurrent bursitis and tenosynovitis, especially often of the hand joints;
- acute polyarthritis in the elderly: multiple lesions of small and large joints, severe pain, diffuse edema and limitation of joint mobility.
- generalized myalgia, stiffness, depression, bilateral carpal tunnel syndrome, weight loss. Usually seen in the elderly. It resembles polymyalgia rheumatica. The characteristic clinical signs of RA develop later [5, 8, 21-24].

When attesting the particularities of the joint syndrome, the scientists found differences, a more frequent involvement of the metatarsal and talo-crural joints in SNRA at the onset of the condition, while in SPRA the small joints of the hands and radiocarpal joints are more frequently involved. The latter also found that the symmetry of the affect was registered somewhat more often in SPRA, and the morning recovery more prolonged in SNRA. Some scientists, studying the

peculiarities of RA in 787 patients, came to the conclusion that at the onset of the SNRA pathology, the middle and large joints of the upper limbs - humerus and elbows - are more frequently affected, which is in great contradiction with the majority of studies carried out for this purpose, which demonstrate a prevalence at the onset of the large and medium joints of the lower limbs. Scholars' opinions differ on the radiological manifestations and their degree of progression in patients with SPRA and SNRA. Thus, some authors [11, 13, 15, 19] report a reduced expression of joint damage in SNRA. Opponents, however, declare a relatively rapid progression of joint changes in SPRA predominantly at a young age and with a high frequency of erosive evolution. Thus, in the literature there are no unanimously accepted opinions regarding the nature of the radiological changes in patients with SNRA and SPRA. The contradictions could be explained by the inhomogeneity of the patient groups. The vast majority of studies note a greater activity of inflammation and immunopathological reactions to SPRA compared to SNRA. Therefore, studies on important series of patients with mainly articular manifestations with different age periods, reported a high activity of the immuno-inflammatory process in SPRA [6, 18, 23].

The analysis of the indicators of the immunopathological status highlighted the reduction by consumption of the serum complement fractions regardless of the RA type, with a more pronounced tendency in SPRA. Among the indicators were mentioned: within SPRA, the increase in the level of G and M immunoglobulins, the circulating immune complexes, is specific, showing a severe evolution. In the same way, a direct correlation was determined between SNRA and anti-keratin antibodies, with important specificity for RA, noting the increase of CRP in SNRA, with insignificant statistical significance. Thus, the lack of a consensus on the specifics of the immuno-inflammatory process in patients with SPRA and SNRA, confirms the need for further research with the aim of elucidating the immunoserological and evolutionary clinical-management particularities in patients with RA [2, 5, 16, 19, 22].

Research on the extra-articular systemic manifestations of SNRA is very limited. There is an increased tendency of SPRA to manifest extra-articularly, but there are some sporadic reports, which do not declare significant differences in the frequency of systemic manifestations regardless of the serological results of RF and anti-CCP [3, 9, 12, 16, 22].

The review of the data from the specialized literature directed our opinion about a small number of publications with reference to extra-articular affections of the SNRA. One of the most important systemic manifestations of SNRA is vascular disease, which occurs in approximately 2.5% of patients. According to some scientists, the severe forms of rheumatoid vasculopathy are more frequently found in SPRA, at an age over 55 years, with a high frequency of extra-articular damage and argue for the development of pro-inflammatory dyslipidemia and vasculopathy [4, 11, 19, 26].

It needs to be mentioned that dyslipidemia can induce vasculopathy in patients with SNRA. Respectively, the aspects regarding SNRA 's particularities remain to this day not definitively elucidated. This equally refers to the assessment of systemic manifestations, including rheumatoid vasculitis and amyloidosis and the degree of their progression, a phenomenon that to some extent can be linked to a non-rigorous preselection of patients for the study [3-5, 16 , 21]. No works have been carried out with the clinical-paraclinical description of SNRA and with the simultaneous assessment of the indicators, which characterize the functional state of the pituitary-gonadal system. Starting from the above, the study of various clinical aspects, paraclinical features and the function of the immune system in SNRA presents a problem of important scientific and practical value, as an element to reduce morbidity, disability and mortality, to establish effective therapeutic strategies and improving the quality of life of patients with SNRA [12, 16, 25, 27].

1.2 Clinical significance of antibodies to citrullinated proteins in rheumatoid arthritis

To date, a sufficient amount of data has been accumulated to allow us to consider anti-CCP to be the most effective marker for the diagnosis of RA. Development of ELISA using PCC2 as antigen achieved sensitivity = 91% and specificity = 98% [1, 6, 7, 11, 19]. The high diagnostic potential of anti-CCP2 is confirmed by their detection in 34-69.3% of RF IgM seronegative patients with RA [3, 6, 8, 16, 19]. It should be noted that the sensitivity of ACPA2 determination at the onset of RA (<2 years) is insignificantly lower than in established RA [1-5]. In general, for the diagnosis of early RA, the sensitivity of this test is 78-97% and the specificity is 66-81% [2, 9, 13, 27].

In clinical and laboratory practice, test systems for ELISA are also used, using the third generation antigen. It allows the simultaneous determination of antibodies of the IgA and IgG isotypes, but they do not exceed their ACPA2 diagnostic value [3, 18, 24]. In addition, in the specialized literature [6, 17, 25], by comparing the sensitivity and specificity of IgA, IgG and IgM isotypes in RA, it was demonstrated the advantage of determining ACPA IgG. A generalized analysis of the results of ACPA detection in different rheumatic diseases showed higher sensitivity of this marker in the diagnosis of RA compared to RF IgM [14, 18, 21].

The role of ACPA as a predictor of the development of a more pronounced degree of joint destruction and a much more severe clinical picture of the disease is actively discussed, while it is proven that its prognostic value in relation to the development of a severe erosive process increases significantly when it is determined jointly with HLA BQV1 * 0101, 0104, 0404 [8, 12-15]. The combined determination of anti-CCP2 and RF is optimal for predicting the nature of RA evolution in the group of patients with early synovitis [5, 11, 18, 24, 27].

Anti-CCP is a more stable serological marker of RA compared to RF IgM, less likely to undergo seroconversion during the course of the disease and does not depend on age, while the frequency of detection of RF in healthy people increases with age, reaching 10-30% [10, 13, 17, 23]. An increase in RF concentration reliably correlates with acute phase indicators (ESR, CRP) and reflects inflammation activity to a greater extent than ACPA [6, 14, 19, 23].

In the diagnosis of RA, anti-MCV represents fairly informative parameters (sensitivity: 69.5-82%; specificity: 91-97%) [3, 16, 20, 26]. At the onset of RA, anti-MCV demonstrates a lower specificity (67%) than during progression, which shows a similar sensitivity (71%) [7, 12, 17, 22]. A number of studies have observed the relationship between the concentration of anti-MCV and ESR and the number of swollen joints [4, 8, 11, 17]. Various authors provide conflicting data regarding the relationship of anti-MCV level with disease activity. On a small sample of patients, a correlation was detected between the concentration of anti-MCV and DAS28 (r=0.404), while other research did not find such a relationship [1, 6, 23]. It is noted that the simultaneous totalization of anti-MCV, anti-CCP and RF IgM test results is accompanied by an increase in specificity to 78%-100% [1, 9, 22].

In the diagnosis of RA, AKA demonstrates high sensitivity (95-97%) with intermediate specificity (36-59%) [4, 7, 12, 18]. All studies observed an association between AKA positivity in disease severity and joint destruction severity [1, 19, 22, 25]. In addition, the determination of AKA can be a useful serological test for the differential diagnosis of RA with polyarthropathy associated with hepatitis C [2, 8, 10, 11, 26].

Thus, an important feature of RA as a systemic autoimmune disease is the hyperproduction of a wide range of organ-specific antibodies, among which RF and ACPA are of the greatest clinical importance.

2. CLINICAL-STATUS CHARACTERISTICS AND RESEARCH METHODOLOGY OF SERO-NEGATIVE RHEUMATOID ARTHRITIS

2.1. The clinical-status characteristics of the study group

In order to achieve the proposed goal and objectives, a sample of 100 patients was selected, with the diagnosis of RA confirmed by the ACR/EULAR 2010 diagnostic criteria - 50 patients with seropositive RA and 50 patients with seronegative RA. The study was carried out in the clinic of the Discipline of Rheumatology and Nephrology of the Department of Internal Medicine of SUMPh "Nicolae Testemițanu", the rheumatology and arthrology sections of PMSI RCH "Timofei Moșneaga" and MSPI MCH "Sfânta Treime" in the years 2015-2019. Being interested in comparing the clinical features of seropositive and seronegative RA, the study group was divided into 2 categories of patients depending on the presence of RF and anti-CCP - group 1 SNRA and group 2 – SPRA. Patients in the studied groups underwent thorough evaluations according to the developed design.

Criteria for inclusion in the study:

- Definite diagnosis of RA according to the ACR/EULAR 2010 criteria;
- Age >20 years;
- Inclusion of patients of different disease duration (minimum number of 5 for each age subgroup)
- Patient acceptance to participate in the study

Exclusion criteria:

- Patients who, due to severity, receive GCs in a cumulative dose > 20 mg/24 h;
- Concomitant chronic decompensated pathologies: DM, liver cirrhosis, TB, etc.

The diagnosis of RA was defined based on the ACR/EULAR 2010 criteria. Thus, based on these criteria, the diagnosis of RA is confirmed in the presence of at least 4 of the 7 criteria. Criteria 1-4 must persist for at least 6 weeks.

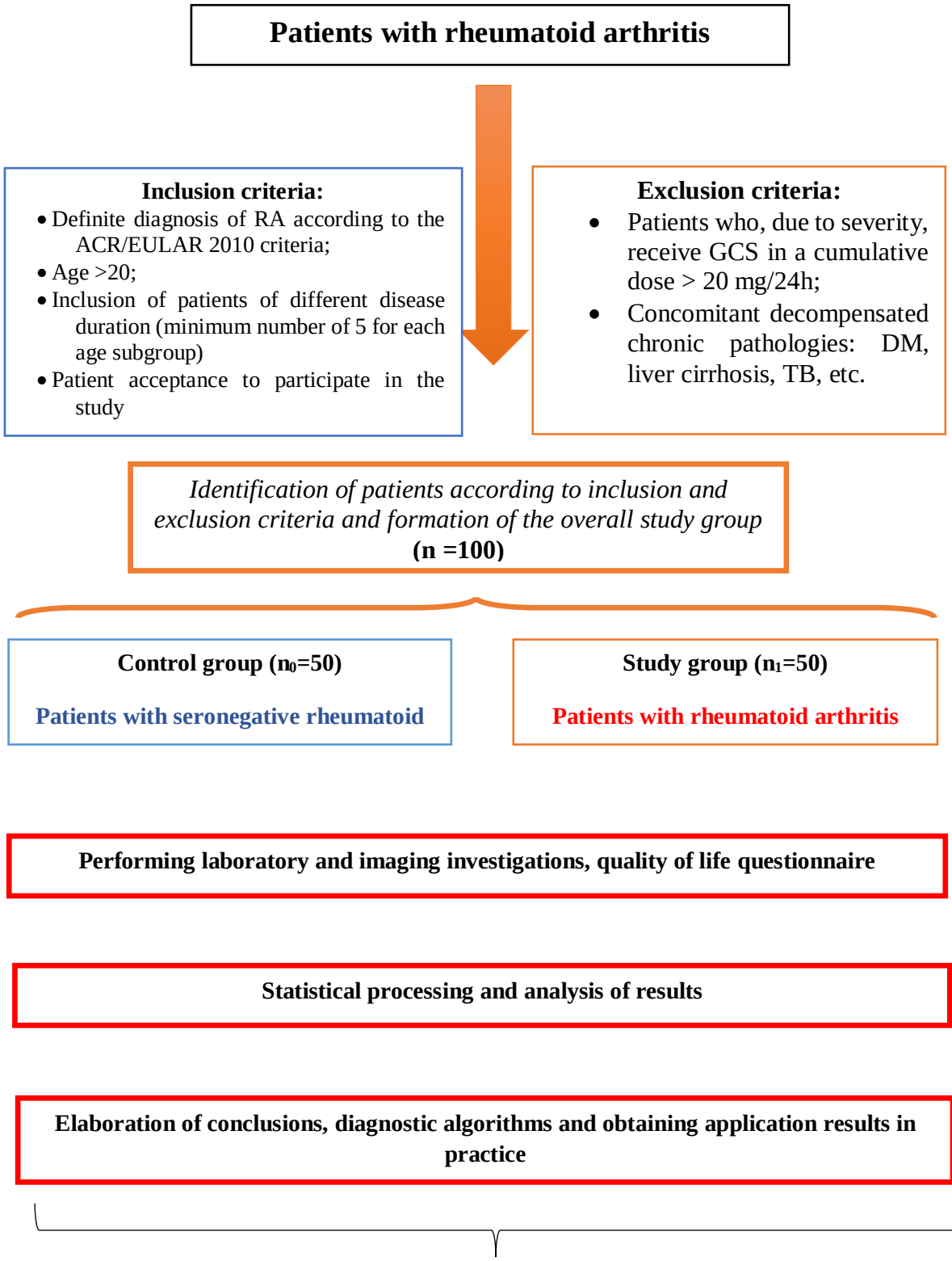

Figure 4. **Study design**

We mention that the studied groups were homogenized by age (SNRA, average age is 53.4±1.71; [26.7; 1.234] and for SPRA it is 52.3±1.14 [27.1; 1.314]) and by duration of disease (SNRA - 88.1±9.5 months and SPRA - 98.4±10.2 months; p>0.05).

The clinical characteristics attested based on the RA classification criteria in the study groups are shown in Table 4.

Table 4. **Clinical characteristics of patients in the study group, %**

Evaluation criteria	**Total group (RA) n=100**	**χ^2, df**	**p**
Disease evolution:		(df=1)	
Slow progression	84 (84%)	2,491	0.037
Fast progression	16 (16%)	2,349	
Activity degree:		(df=2)	
low (DAS28)	12 (12%)	1,378	0.042
moderate (DAS28)	44 (44%)	3,324	0.078
high (DAS28)	44 (44%)	1,981	0.081
RF/anti-CCP		(df=1)	
Positive	50 (50%)	2,347	0.039
Negative	50 (50%)	2,619	
Radiological status (Steinbrocker, 1949)		(df=3)	
I	2 (2%)	2,179	0.033
II	48 (48%)	1,058	0.069
III	46 (46%)	2,034	0.071
IV	4 (4%)	2,089	0.021
Functional class (Steinbrocker, 1949)		(df=3)	
I	2 (2%)	2,597	0.019
II	69 (69%)	3,187	0.078
III	23 (23%)	2,169	0.044
IV	3 (3%)	2,654	0.023

Note: χ^2 – correspondence coefficient; df – degrees of freedom.

2.2. Algorithms and principles of patient examination

In order to define the clinical particularities of RA in seronegative and seropositive clinical presentation, especially the joint syndrome and extra-articular manifestations, the patients in study groups I and II were examined according to a clinical and paraclinical program illustrated in the study design. The joint syndrome as the main clinical expression of the disease was examined by using complementary scores for the assessment of joint damage, which included: the joint index 28, Ritchie and Lee index, with the performance of the radiological joint examination, which included the evaluation of the palmar and plantar joints at 100 patients with the aim of determining the manifestations of osteo-articular damage expressed by: pinching of the joint space, juxta-articular osteoporosis, the presence and number of erosions, ankylosis and osteo-articular deformations), with staging according to Steinbrocker. In the presence of indications, radiographs of other joint areas were also performed. The evaluation of the disease activity was carried out by analyzing the blood count with ESR, CRP (mmol/l) and fibrinogen (g/l) with the assessment of the DAS-28 index. Immunological evaluation: the detection of RF in the serum and synovial fluid

of patients was related by the latex-test method authorized by Refa-Dac, which is based on the ability of RF not to agglutinate latex particles sensitized by native human IG and anti-CCP antibodies by the chemiluminescent method (Eleksys-2010 automated analyzer, manufacturer: F. Hoffman-La Roche Ltd, Switzerland). To assess the quality of life, the HAQ (Health Assessment Questionnaire) questionnaire was used, validated for patients with RA, completed individually by each of the 100 patients with RA from the study. In the same way, in order to achieve the proposed objectives, we performed: the assessment of extra-articular manifestations, lipid metabolism, the respiratory system, the digestive system and the status of the renal system.

2.3. Methods of statistical examination

All the values obtained as a result of the conducted study were processed statistically in the statistical program STATISTICA ver. 7.0 **(StatSoft, USA)**. For the statistical analysis of small values, non-parametric methods were used, in which the significance was analyzed in each group using Welch's modified t-test (adapted for abnormal distributions and asymmetric groups), and for categorical variables frequency differences were assessed by the $\chi 2$ criterion with Yates correction and, in cases of 2x2 contingency tables – according to Fisher's exact test.

According to the data on the Republic of Moldova, seronegative rheumatoid arthritis at the ages included in the study has the lowest frequency for RA, on average in a proportion of 0.17% and P_0=0.0017, so that the minimum group was assessed according to this nosology. Thus, in the research group the incidence must be three times higher P_1=0.0051; P= (P_1+ P_0):2 =0.0034. Entering the data into the formula, we obtained that the required number of patients is 20.5 (≈21), so 50 patients were accepted in each study group. In the case of the presence of variables in the statistical examination, the correlative analysis was performed using the χ^2 criterion and the correlation coefficient (r). The correlation coefficient of a and b values is determined by: $r(\xi,\eta) = \mu 1.1(\xi,\eta) \div (\sigma(\xi) \times \sigma(\eta))$. Data exploration through box-plots allowed the distribution of the max-min values, the median and the standard deviation, and the cluster method highlighted the similarity (dendrograms), with three-dimensional multiple scanning. The ANOVA analysis established the interaction of the factors.

3. CLINICAL-PARACLINICAL, EVOLUTIONARY AND PROGNOSTIC CHARACTERISTICS IN PATIENTS WITH SERONEGATIVE RHEUMATOID ARTHRITIS

3.1Clinical, laboratory and radiological peculiarities of seronegative rheumatoid arthritis

The clinical-status characteristics of the patients in the studied groups demonstrate their homogeneity (Table 5) - thus having the possibility to characterize the evolution of the disease by age groups and depending on the duration of the disease with the assessment of the onset and evolution depending on the serological status.

Table 5. **General characteristics of the subjects in the study group**

General data	**SNRA** n=50	**SPRA** n=50	**p (CI)**	**χ^2, df**
Age, yrs (M±m)	51,2±1,93	50,5±1,66	0.089 (44,0-59,0)	1,596
Age at RA onset, yrs (M±SD)	44,9±1,87	41,0±1,75	0.071 (38,0-49,0)	1,348
Disease duration, months (M±SD)	89,9±11,66	112,8±12,24	0.044 (72,0-125,0)	2,018
Age groups at the onset AR,%				(df=4)
• < 30 yrs	16,0	18,0	0.059 (14,0-19,0)	2,676
• 31-40	22,0	24,0	0.057 (20,0-25,0)	2,318
• 41-50	32,0	40,0	0.049 (31,0-42,0)	3,018
• 51-60	18,0	10,0	0.048 (8,0-20,5)	2,089
• > 60 yrs	12,0	8,0	0.051 (7,0-14,0)	3,077
Groups based on disease duration,%				(df=3)
1. < 1 yr	14,0	2,0	0.007 (1,0-16,0)	2,037
2. 1-5 yrs	38,0	46,0	0.049 (32,0-49,0)	3,078
3. 6-15 yrs	38,0	28,0	0.038 (24,0-40,0)	1,268
4. > 15 yrs	12,0	24,0	0.041 (8,0-26,0)	1,249

Note: t - the value of the coefficient (Welch test); χ^2 – correspondence coefficient; df – degrees of freedom.

In order to facilitate comparability, the study groups were created from an equal number of people. According to the data in the table, the subjects in the studied groups were comparable according to the average age ($p>0.05$), the average age of onset ($p>0.05$) as well as the average duration of the disease ($p>0.05$). If we refer to the age of RA onset, in seronegative cases, a relatively uniform distribution of onset was observed for all age groups, perhaps with a more pronounced tendency for the 4th decade of life (32%). In seropositive cases, however, an agglomeration was observed up to the age of 50 for the onset, with peaks recorded for 31-40 years age group(24%) and maximally for 41-50 years age group (40%), the period where the maximum incidence of disease activity lies.

Thus, we can note the fact that for the studied patients, the age at RA onset in seronegative and seropositive patients follows the same regularities.

Hereditary predisposition was attested anamnestically in the evaluated patients, thus 84% of the patients in the study group did not present familial aggregation for RA. According to the data in Table 6 - 12% of seronegative cases and 8% of seropositive cases mentioned the presence of RA in first-degree relatives and 4% of seronegative cases and 4% of seropositive cases noted the presence of the disease in second-degree relatives.

Table 6. **Genetic predisposition distributed by study groups, %**

Heredo-collateral anamnesis	SNRA **n=50**	SPRA **n=50**	**P (χ^2)**	**χ^2, df=1**
Unaggravated heredity, %	84	88	0.061 (37.0-44.0)	2,037
RA in first degree relatives, %	12	8	0.063 (6,0-12,0)	3,045
AR in 2nd degree relatives, %	4	4	0.388 (4,0-4,0)	1,987

Note: χ^2 – correspondence coefficient; df – degrees of freedom.

The role of the triggering factors, determined anamnestically, which immediately preceded the onset of AR, was analyzed and are shown in Table 7.

Tabelul 7. **The share of triggering factors that preceded the onset of RA, %**

Trigger factors	SNRA n=50	SPRA n=50	**p**	**χ^2**	**χ^2, df=1**
ARVI	30	22	0.029	22.0-38.0	1,548
Physical stress or intense physical exertion	17	12	0.051	8.0-22.0	2,147
Acute mental stress	15	14	0.054	12.0-16.0	2,315
Prolonged exposure to cold and hypothermia	12	8	0.049	6.0-16.0	2,614
Joint trauma	4.0	6	0.061	3.0-6.0	2,919
Exacerbation of chronic infections	2.0	6	0.058	1.0-6.0	2,316
Age-specific hormonal disturbances	9	16	0.002	1.0-16.0	2,347
Births, abortions	8	16	0.0034	0.0-16.0	1,988

Note: χ^2 – correspondence coefficient; df – degrees of freedom.

According to the data presented in Table 7, the maximum weight as a trigger factor, for both groups, went to ARVI, but at the same time SNRA presents a statistical value clearly superior to that obtained in SPRA ($p<0.05$). The next important triggering factor, by weight, for SNRA, was intense physical over-exertion, followed equally by mental stress and prolonged exposure to cold. In SPRA, births, abortions and age-specific hormonal changes, as well as the psycho-emotional factor, had an important share. RA presents different forms of onset: acute, subacute and insidious (Figure 5).

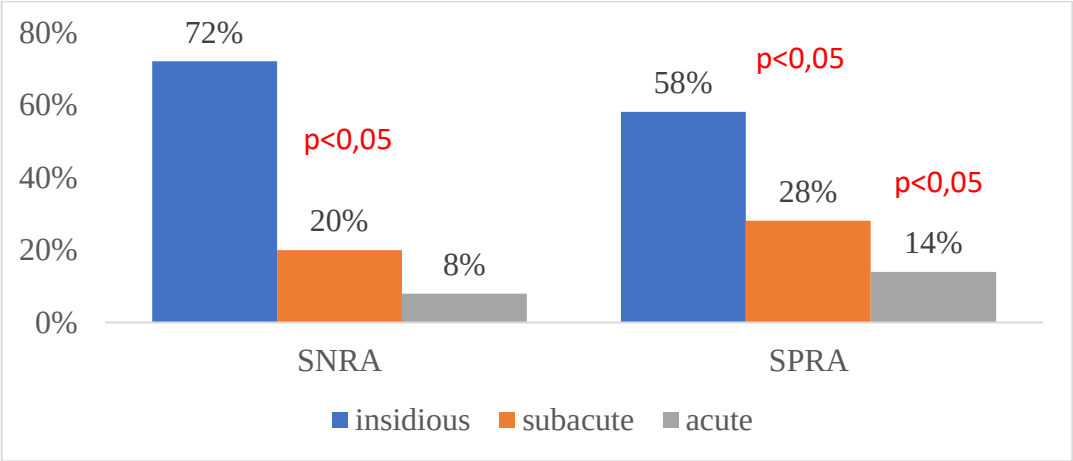

Figure 5. **Distribution of RA onset among subjects in the study group,%**

Most patients were registered with insidious onset, SNRA - 72%, and for SPRA - 58% ($p<0.05$). Likewise, the acute/subacute onset did not reveal statistically significant differences ($p<0.05$), but an increased rate was recorded in the case of SPRA (14% acute onset and 28% subacute onset) compared to SNRA (8% and 20 %).

The onset of RA in the vast majority of cases is predominantly articular, presenting as monoarthritis, oligoarthritis or polyarthritis. The patients in the study groups presented the following picture of the onset of the joint syndrome shown in Figure 6. Thus, we find that SNRA more frequently started with monoarthritis (56%) and oligoarthritis (16%), while SPRA presented a monoarticular onset in 36% cases and oligoarticular in 10% cases. For monoarticular onset, the difference between the groups is statistically significant ($p<0.05$). At the same time, SPRA is characterized by a symmetrical polyarticular onset of RA, mentioned in 54% of cases, compared to 28% of SNRA that indicated a polyarticular onset, the difference being statistically significant ($p<0.05$).

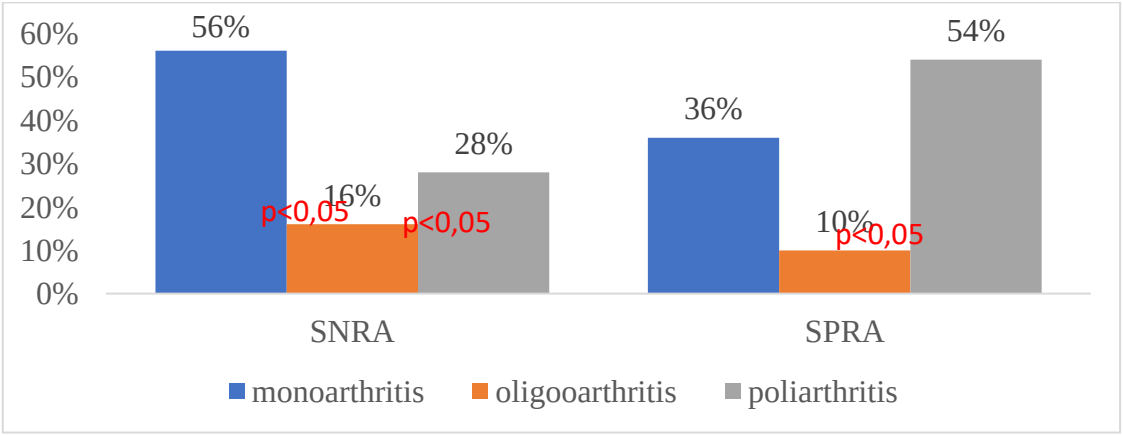

Figure 6. **The character of the joint syndrome at the onset of RA in the subjects of the study group,%**

The radiological examination of the hands and feet was performed in all 100 patients in the study group. Additionally, radiological images of other joints were selected that showed a marked joint deformity or a manifest functional disability. The obtained results are presented in Table 10.

Table 10. **Radiological evaluation of the joint syndrome in the patients of the study group, %**

Radiological space	SNRA **n=50**	SPRA **n=50**	**p**	**95 %CI**	**χ^2, df**
Small joints of the hands:					(df=3)
• Stage I	2,0	0,0	0,179	0,0-1,8	2,017
• Stage II	48,0	52,0	0,237	46,7-51,2	2,134
• Stage III	46,0	30,0	0,038	32,1-44,2	1,954
• Stage IV	4,0	18,0	0,012	3,5-13,5	1,746
The small plantar joints:					(df=3)
• Stage I	4,0	0,0	0,184	0,0-3,3	2,033
• Stage II	46,0	78,0	0,018	33,4-61,0	2,098
• Stage III	48,0	18,0	0,024	12,4-31,8	1,234
• Stage IV	2,0	4,0	0,053	1,5-3,3	1,649
Joint erosions:					
• Unique	18,0	28,0	0,052	14,5-23,6	1,647
• Multiple	14,0	42,0	0,013	11,0-37,5	1,239

Note: χ^2 – correspondence coefficient; df – degrees of freedom.

The analysis of the radiological changes in the joints of the hands highlighted particularities for SNRA and for SPRA with obvious statistical significance ($p<0.05$). In case of SNRA, a more benign evolution of joint damage was established, only 4% of them reached the advanced stage of joint destruction, the majority presenting radiological stage II and III. In the SPRA study group, 52% presented stage II and the other half presented radiological stage III and IV, the latter having a share of 18.0%.

The radiological changes of the plantar joints also indicate statistically significant differences between the groups. SNRA is characterized by a more advanced stage of radiological changes in the small joints of the legs, 48% of them indicated radiological stage III compared to 18% of SPRA who presented the same stage. The majority of SPRA (78%) on the radiography of the small joints of the legs showed changes corresponding to the radiological stage II ($p<0.05$).

Analyzing advanced joint evolutions, depending on the duration of RA, in these patients we found that joint destruction develops in the first 5 years of the disease, a phenomenon valid for both groups.

For a more objective assessment and a more accurate quantification of joint damage, we applied the calculation of joint indices. For joint index 28, the number of painful joints and the number of swollen joints were determined separately. The data are presented in Table 11.

Table 11. Evaluation of joint indices in SNRA and SPRA

Indicii articulari	**SNRA n=50**	SPRA **n=50**	**p (95 %CI)**
Ritchie Index, (M±SD)	28,40 ±1,53	32,86±1,54	0,024 (24,15-33,95)
Articular index 28 for painful joints, (M±m)	14,80±1,30	19,30± 0,96	0,0097 (11,08-22,9)
Articular index 28 for swollen joints, (M±m)	20,12±1,28	23,46±0,76	0,037 (18,5-24,67)

Graphical analysis of the relationships of these indicators for seronegative RA reiterated a state generally similar to seropositive RA (Figure 7).

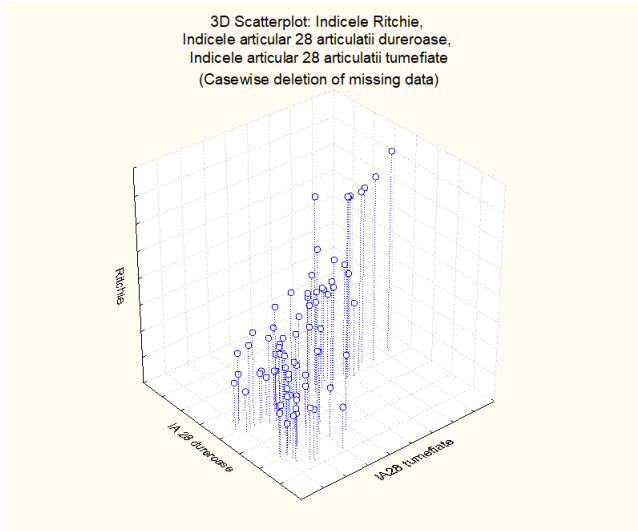

Figure 7. **Graphical presentation of the relationship of mean values of joint indices in patients with SNAR**

The calculation of joint indices revealed statistically significant differences between SNRA and SPRA ($p<0.05$) according to the Ritchie index and the Joint Index 28 calculated for swollen joints as well as the Joint Index 28 calculated for painful joints ($p<0.01$), in all cases SNRA demonstrating more moderate figures of joint involvement.

The evaluation of the joint syndrome was performed by assessing the non-specific inflammation markers CRP and ESR. Their presence in large amounts in the serum, the presence of prolonged osteo-articular healing, indicates high activity of the inflammatory process at the level of the synovium with the presence of joint destruction. Another objective and complex index, which denotes disease activity in RA patients that we determined in the study group, was DAS 28. The results obtained are presented in Table 12.

Table 12. **The average values of markers of the acute phase of inflammation in SNRA and SPRA**

Acute phase markers	**SNRA n=50**	**SPRA n=50**	**p (t)**	**95 %CI**
CRP, mmol/l (M±SD)	24.02±3,276	19,16±3,803	0,052 (1,229)	11,35-25,08
ESR, mm/h (M±SD)	35,84±2,122	34,68±2,07	0,145 (1,974)	21,3-39,7
Fibrinogen, g/l (M±SD)	5.17±0,24	4,60±0,28	0,072 (2,347)	2,07-5,33
DAS28 (M±SD)	6,781±0,190	7,249±0,994	0,047 (2,266)	4,21-8,52
Morning stiffness, minutes (M±SD)	134,8±7,576	156,60±11,85	0,059 (3,001)	74,0-168,5

Given the fact that the patients were in the rheumatology clinic with exacerbation of the pathology, the non-specific markers of inflammation presented high values. Although without statistical differences between groups regarding the acute phase indicators, with the exception of

the DAS28 index, SNRA showed an increase in CRP and ESR, while SPRA had a prolongation of morning stiffness.

Through the multiple correlational analysis, we evaluated the degree of correlation between the number of painful joints determined by the joint index 28 and markers of disease activity. In the result, we found a moderate positive correlation, with the morning wakefulness of r = 0.304, with the number of erosions of r = 0.308, with the Lee index of r = 0.423 and with the quality of life index - r = 0.365. At the same time, a strong correlation was highlighted with the DAS28 score. The number of swollen joints also calculated by the joint index 28 demonstrated moderate positive correlations with the HAQ and Lee indices and a substantial correlation with the DAS28 score of 0.804. The described correlations refer equally to SNRA and SPRA (Figure 9).

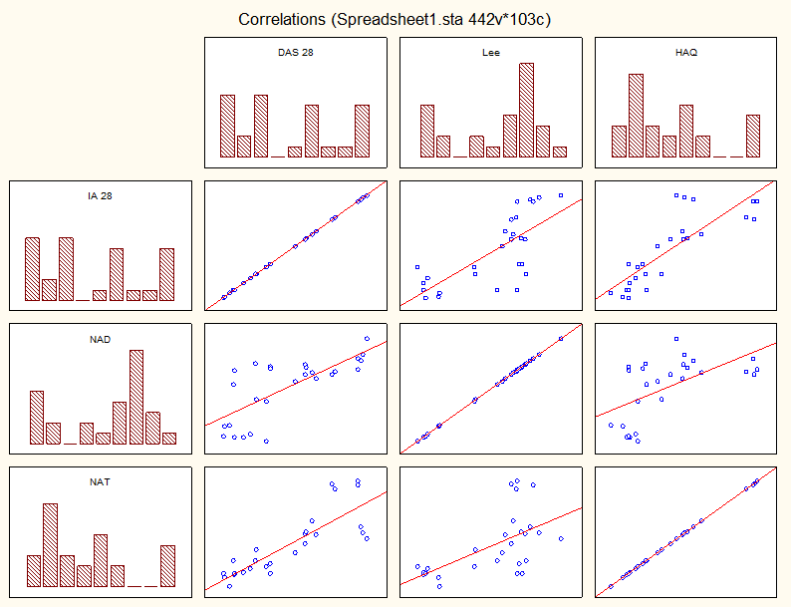

Figure 9. Correlation matrix of joint and cumulative index values (DAS28, Lee, HAQ) in patients with SNRA

Another point that deserves attention in the evaluation of patients with rheumatoid arthritis is the determination of the degree of functional disability in these patients, achieved by calculating the Lee index and, at the same time, the assessment of the quality of life based on a questionnaire validated for RA, the HAQ questionnaire. Both indicators are used to highlight the motor disability of patients with RA and are followed as criteria for remission of the disease, for the evaluation of treatment. The results of these assessments are presented in Table 13.

Table13 Evaluation of Lee functional index and HAQ quality of life index in patients with RA in study groups I and II

Indices	SNRA n=50	SPRA n=50	p (t)
Lee Index, score (M±SD)	15,46±0,91	20,18±0,76	0,0028 (2,007)
HAQ Index, score (M±SD)	1,68±0,08	1,92±0,07	0,0271 (1,088)

Note: χ^2 – correspondence coefficient; df – degrees of freedom.

The calculation of these indices at SNRA and SPRA revealed statistically significant differences between the groups. In conclusion, we can mention the fact that in SNRA, functional disability due to illness is less affected than in SPRA ($p<0.01$), at the same time, the quality of life has more favorable indicators compared to those determined in SPRA ($p<0, 05$).

Later, having these data available, we were interested in evaluating the correlation between the parameters characteristic of the inflammatory process in RA and the radiological stage of joint damage in these patients, the results obtained are shown in table 14.

Table 14. The inter-relationship between the radiological stage and inflammation markers in SNRA and SPRA

Indices		**Radiological stage I**	**Radiological stage II**	**Radiological stage III**	**Radiological stage IV**
Morning stiffness, min (M±SD)	SNRA	77±3,43	113,75±7,44	156,08±11,90	180,0±60,0
	SPRA	-	132,69±13,12	146,0±18,48	243,33±32,57
ESR, mm/h (M±SD)	SNRA	44,1±7,4	34,95±3,30	37,00±3,05	29,00±7,0
	SPRA	-	29,46±2,53	38,33±3,93	43,66±6,35
CRP, mmol/l (M±SD)	SNRA	12,2±2,4	20,54±4,75	27,13±4,98	36,00±12,00
	SPRA	-	10,62±2,21	19,73±7,02	42,88±14,40
DAS28 (M±SD)	SNRA	5,03±1,3	6,24±0,29	7,34±0,20	7,55±0,54
	SPRA	-	6,93±0,20	7,40±0,19	7,90±0,28
Lee Index (M±SD)	SNRA	8,0±1,71	12,41±1,66	18,30±1,18	23,00±1,00
	SPRA	-	18,23±0,60***	20,46±1,28	25,33±2,65
HAQ Index (M±SD)	SNRA	0,87±0.09	1,48±0,12	1,87±0,12	2,31±0,06
	SPRA	-	1,67±0,08	2,11±0,07	2,32±0,22

Note: ***p<0,001

Based on the data presented in this table, we can underline the correlation that stands out between the degree of disease activity and the advancement of the radiological stage. In both SNRA and SPRA, a positive correlation trend was observed between the more advanced radiological stage and the higher average values of the acute phase markers such as: duration of the morning stiffness, ESR, CRP, DAS-28. At the same time, the presence of correlation indexes between the joint radiological stage and the values of the Lee functional index as well as with the values of the HAQ quality of life index was noted.

3.2. Comparative onset characteristics of seronegative rheumatoid arthritis

When collecting the anamnesis of the disease, the patients were asked to mention precisely which joint or which joints were affected at the onset. The results obtained in this chapter are shown in Figure 11.

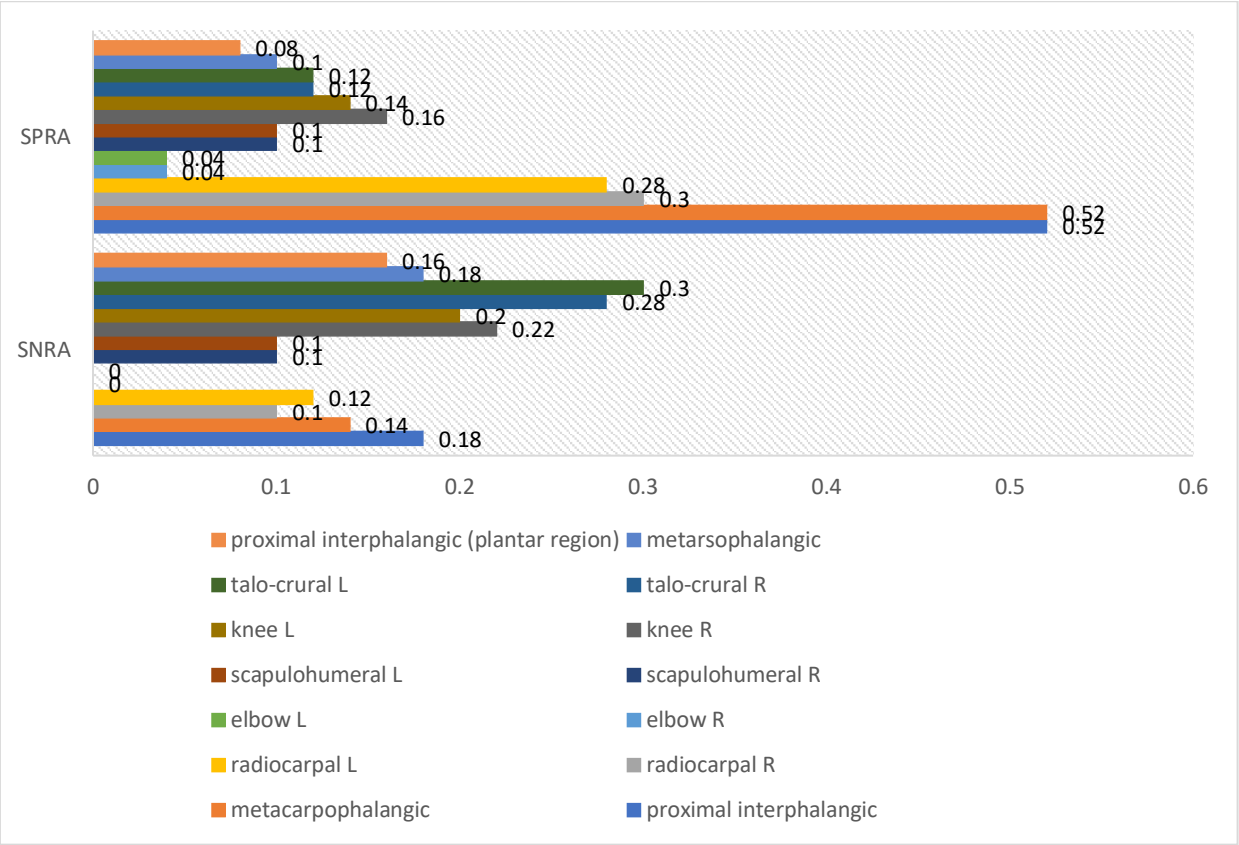

Figure 11. **Topographical distribution of the joint syndrome for the onset of RA in the subjects of the study group, %**

SNRA at RA onset showed a notable predilection for the large and medium joints of the lower limbs. The most frequent SNRA mentioned the damage at the onset of talocrural joints (30% left talocrural and 28% right talocrural), with a statistically significant difference compared to SPRA ($p<0.05$). Also, in SNRA, during the onset period, a tendency to affect knee joints was observed (22% right knee and 20% left knee) compared to patients with SPRA (16% and 14% respectively). When the onset of RA was achieved through polyarthritis of the small joints, no differences were noted in SNRA for the upper or lower limbs. In SPRA, however, the most frequent RA started with polyarthritis of the small joints of the hands compared to the small plantar joints ($p<0.01$), also noting statistically significant differences compared to the damage to these joints at the onset of RA in seronegative cases ($p< 0.01$). Involvement of the radiocarpal joints at the onset of the pathology was less frequently observed in SNRA than in SPRA ($p<0.05$). The onset of joint syndrome by affecting the humeral joints is absolutely identically distributed in the two groups.

During the objective examination of the patients in the study group, joint pain and joint swelling were attested by compression of the joint areas.

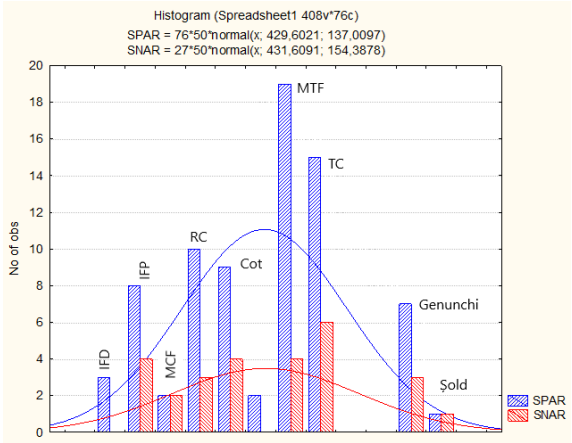

Figure 12. **Distribution of swollen joints of the upper limbs depending on the study group**

In the expressed stage of the disease, the joint syndrome acquires a generalized character, with polyarticular involvement. At the identification of joint pain in the subjects of group I and group II of the study, a predilection for the small joints of the hands and soles was observed (Figure 12). In SNRA, these joint areas were affected in relatively uniform proportions, while SPRA demonstrated a significant predilection for the small joints of the hands, with statistically significant differences compared to the damage of these joints in SNRA ($p<0.05$). SPRA also presents statistically significant differences in affecting the small joints of the hands and soles, the hands being more frequently involved. At the same time, SNRA statistically significantly less frequently presented pain in the radiocarpal joints bilaterally ($p<0.01$) (Figure 13). Another statistically demonstrated difference was presented by the damage to the shoulder joints, the predilection for these joints being manifested in SPRA ($p<0.01$).

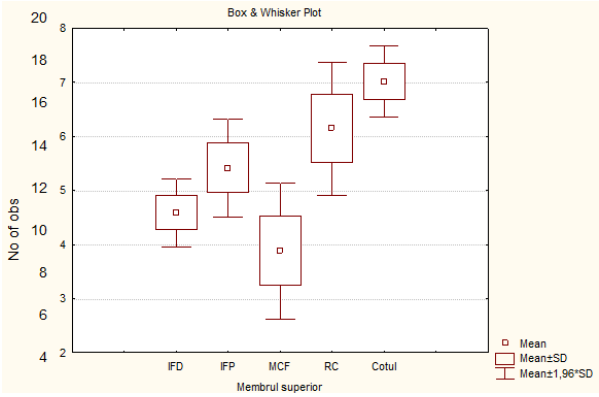

Figure 13. Distribution of upper limb joint involvement in patients with SNRA

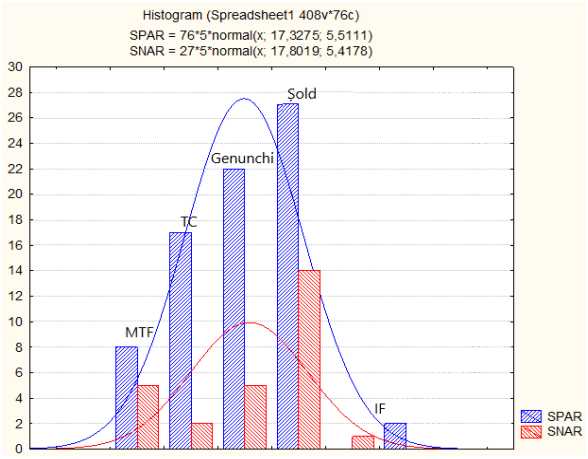

Figura 14. Distribution of painful joints of the lower limbs depending on the study group

ARSP showed swelling of the small joints of the hands, with a significant difference from these joints in ARSN ($p<0.05$), likewise, with a difference from the small joints of the plants ($p<0.01$). In case the exudative process had a localization at the level of large joints, ARSP showed a greater tendency for these areas of the upper limbs. (Figure 14).

3.3 Evaluation of prognostic factors of SNRA evolution

During the retrospective evaluation of the anamnestic data of the patients, we noticed a series of factors that were associated with the character of the RA evolution. Later, these factors were thoroughly processed through discriminant analysis, step by step, and 9 variables were highlighted. Thus, the rapid-progressive evolution of the disease was determined in SNRA in which RA started at an advanced age ($p<0.05$), when at the start the interphalangeal joints of the plants were involved bilaterally or the left radiocarpal joint, in those who at the start they presented more frequently asthenia, also in smokers. The association between smoking and RA is also demonstrated in other clinical studies. At the same time, in the patients in our study, a different evolution of RA was established depending on their nationality, so Moldovan nationality would be a prognostic factor for the slow-progressive evolution compared to Ukrainian and Russian nationality, which was presented as a prognostic factor for the fast-progressive evolution. We find the explanation of the latest data in the fact that most of the studied patients of Moldovan nationality provided services with intense physical involvement, which leads to the continuous functional training of the joints and thus the joint function is maintained at a satisfactory level. The patients of Russian and Ukrainian nationality, evaluated in the study performed more office jobs and lead a more sedentary lifestyle, and thus joint functionality becomes more compromised.

3.4. Peculiarities of extra-articular damage in rheumatoid arthritis depending on seropositivity

3.4.1 Manifestations of vasculopathy in patients with seronegative RA

Rheumatoid vasculitis (RV) is a rare but severe complication of RA.

Table 21. Manifestations of vasculitis in SPRA/SNRA

Forms of vasculitis	Total, %	SPAR/SNAR Ratio	95%CI	χ^2, df=1
Rheumatoid nodules	19,0	1,37:1	11.0-21.0	2,018
Digital arteritis	5,0	1:1,5	3.0-7.0	2,741
Livedo reticularis	11,0	1,75:1	9.0-17.0	2,314
Raynaud's syndrome	19,0	1,71:1	18.0-23.0	2,788
Sensory neuropathy	21,0	1,33:1	18.0-26.0	2,015

Note: χ^2 – correspondence coefficient; df – degrees of freedom.

Thus, we can mention a relatively low incidence of leukocytoclastic vasculopathy, and the detected cases are mostly benign, with an increased tendency for SPRA.

3.4.2. Affected respiratory system in SNRA

If we totalize the respiratory pathologies highlighted by us in the study group, we obtain the following results presented in Table 25.

Table 25. The share of respiratory pathologies in patients with RA distributed according to seronegativity, %

Pulmonary diseases	SNRA n=50	SPRA n=50	95%ÍÎ	p (χ^2, df=1)
No pulmonary pathology	64,0	34,0	33.0-65.0	0.0095 (1,247)
Diffuse interstitial fibrosis	14,0	18,0	13.0-19.5	0.067 (1,245)
Nodular lung	0,0	2,0	0.0-2.5	0.058 (1,335)
Chronic bronchitis	16,0	32,0	14.0-33.6	0.026 (1,118)

Note: χ^2 – correspondence coefficient; df – degrees of freedom.

Thus, with a statistically conclusive difference, respiratory pathology is more frequently associated with SPRA, compared to SNRA, registering a manifest predilection especially for chronic bronchitis ($p<0.05$), while diffuse interstitial fibrosis demonstrated a relatively similar distribution between the two groups.

The detected respiratory dysfunctions were, with a marked predominance, of restrictive type, SPRA demonstrating a more substantial tendency than SNRA, 50% of SPRA and 28% of SNRA, especially for the moderate degree of restriction, but without statistical significance ($p=0.296$) (Figure 15).

We can mention the fact that patients with RA were not characterized by obstructive respiratory dysfunction, and the presented cases are based on another comorbid condition.

3.4.3. Gastrointestinal and liver damage in seronegative RA

76% of the studied patients had specific complaints: anorexia, nausea, discomfort and/or pain in the epigastric region, flatulence, intestinal transit disturbances. Hepatomegaly was determined in 14% men and 8% women. The average values of ALT and AST were relatively normal in the general study group, without statistical differences, but in SPRA, ALT insignificantly exceeded the normal level, in comparison with SNRA.

The investigation of patients through FEGDS demonstrated that SPRA have an increased rate of gastric ulcer, statistically higher than SNRA ($p<0.05$). The aspect of gastroduodenitis has been described similarly for SPRA and SNRA.

The distribution of the digestive pathologies diagnosed in the studied patients according to the duration of the disease did not reveal a predilection for a certain group of duration of the disease neither in SNRA nor in SPRA. At the same time, the digestive and liver pathology associated with patients with RA showed correlations with the age of the patients, being more frequent in older patients, a phenomenon that was observed in both SNRA and SPRA.

3.4.4. Examination of renal diseases in RA

In order to highlight the renal function of the examined patients, renal function tests were performed (Figure 22 and Figure 23), the data are shown in Table 30.

Tabelul 30. Average values of renal function determinations obtained in patients with RA depending on serological status

Lab tests	SNRA n=50	SPRA n=50	p (95%IÎ)	t
Serum creatinine, mmol/l (M±SD)	93.2±13.4	98.4±15.8	0.096 (68.9-99.7)	2,0158
Urine creatinine, g/24h (M±SD)	1,374±0,059	1,942±0,121	0.041 (1.15-1.95)	2,314
Serum urea, mmol/l (M±SD)	6,240±0,216	6,354±0,248	0.088 (5.89-6.44)	1,025
Urine urea,g/24h (M±SD)	23,220±0,295	22,380±0,373	0.067 (20.19-23.67)	1,066
Creatinine clearance, ml/min (M±SD)	124,78±2,462	121,36±2,941	0.078 (91.26-136.4)	1,879

Note: χ^2 – correspondence coefficient; df – degrees of freedom.

The ultrasonographic examination highlighted the following manifestations: dilation of the calyx-pelvis system described in 96% of SNRA and in 100% of SPRA, nephrolithiasis detected in 14% of SPRA and in 4% of SNRA, hyperechoic areas were detected in 4% of SPRA (corresponding to the 2 cases of renal amyloidosis).

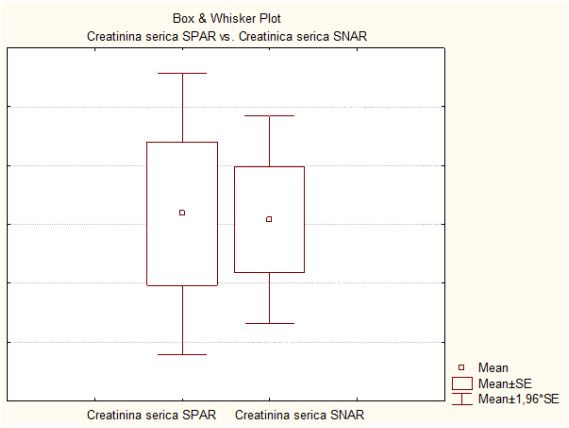

Figure 22. Distribution of serum creatinine values in patients of the studied groups

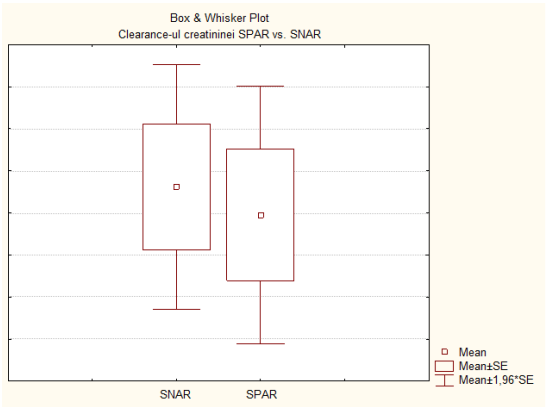

Figure 23. Creatinine clearance in patients with SNRA **and** SPRA

In conclusion, we can emphasize that patients with RA present a relatively frequent association of renal infections, thus chronic pyelonephritis was recorded in 42% of SNRA and in 52% of SPRA with an important susceptibility to infections.

3.4.5 Affected hematopoietic system in RA

In all patients enrolled in the study, the hematopoietic system was analyzed by examining the blood count: the average values of the blood count are shown in Table 31.

Table 31 **Mean values of blood cell indices in patients with RA, (M±SD)**

Blood count indices	**SNRA n=50**	**SPRA n=50**	**p (95%IÎ)**	**t**
Hemoglobin, g/l	125.34±2.498	114.06±2.351	0.074 (98.0-128.7)	2,017
Erythrocytes, $x10^{12}$/l	4.164±0.090	3.96±0.069	0.069 (3.57-4.56)	1,056
Color index	0.88±0.012	0.82±0.012	0.071 (0.80-0.91)	2,048
Platelets, %	335.5±29.68	310.4±47.21	0.062 (307.5-419.1)	2,314
Leukocytes, $x10^9$/l	7.56±0.381	7.00±0.333	0.064 (3.97-7.71)	1,521
Eosinophils, %	2.38±0.360	2.32±0.309	0.071 (2.27-5.41)	1,954
Lymphocytes, %	22.66±1.342	22.50±1.450	0.083 (13.8-23.01)	1785
ESR, mm/h	35.84±2.122	34.68±2.207	0.061 (32.1-36.7)	1,025

Hemoglobin values being below the optimal ones in both SPRA and SNRA – were more frequent in the case of SPRA ($p<0.05$). Leukopenia was found only in the SPRA group ($p<0.05$) – the pathogenesis of leukopenia is uncertain (with a possible contribution of cytostatic treatment) ($p<0.05$).

4. COMPARATIVE ANALYSIS OF QUALITY OF LIFE AND PROGNOSIS IN PATIENTS WITH SERONEGATIVE RHEUMATOID ARTHRITIS

Despite many discoveries that stipulate the massive mechanisms involved in the pathogenesis of RA, the problem of RA remains unsolved until now.

Based on these, we attempted to conduct a clinical study of RA in the two serological groups, with an extensive clinical and paraclinical evaluation, focusing on the investigation of the inflammatory status and its correlation with the joint syndrome and the extra-articular manifestations present.

Early diagnosis and initiation of treatment is crucial to improve RA patient outcomes. According to the results of our study, it quantifies the delay in meeting criteria as well as the delay in initiation of treatment in the seronegative RA population from the time of the first documented joint swelling. The present study demonstrates that among our population, patients with seronegative RA experience a delay in meeting the 1987 and 2010 ACR/EULAR criteria. The median delay was 46 days longer for the 1987 and 14 days longer for the 2010 ones, among seronegative patients. Furthermore, in our study population, seronegative patients perpetuate a longer time to clinical diagnosis of RA as well as to first DMARD treatment with an average of 40 days from the time of first clinically recognized synovitis, compared to 14 days for patients seropositive cases.

In our study, the median delay in initiation of DMARD therapy was less than four weeks longer for seronegative patients than for seropositive patients, and despite this delay being shorter

than the window of opportunity described previously, seronegative patients were less likely to achieve remission during the follow-up interval. Although this study did not address the reasons behind treatment delay, it concludes that the delay in meeting classification criteria and receiving a clinical diagnosis of RA may reflect diagnostic uncertainty in the seronegative group and may affect the initiation of DMARD therapy.

Data are heterogeneous with respect to disease activity at diagnosis when comparing seronegative and seropositive RA patients. In our study, seronegative patients had more extensive joint involvement based on meeting the 2010 classification criteria. However, patients did not differ in the prevalence of elevated inflammatory markers, erosive disease, or duration of symptoms before meeting classification criteria, and markers of disease activity such as ESR, CRP, Fibrinogen, HAQ, and DAS28 were comparable between groups over time.

The possibilities of differential diagnosis of seronegative arthritis are extensive. The group of SpA comprises a number of closely related rheumatic diseases, including PAs, nr-axSpA, AS, reactive arthritis and undifferentiated SpA. The clinical presentation is heterogeneous. The group of SpA is one of the differential diagnoses for early SNRA. Our current study supports this view. These results also emphasize the importance of long-term monitoring of patients, which can help reveal the true nature of their disease.

Another important moment, described in patients, from the onset of RA, was the topographical distribution of joint damage. SNRA at the onset showed a notable predilection for the large joints of the lower limbs, maximally involving the talocrural joints, with a statistically conclusive difference compared to SPRA $p<0.05$, being followed by the knee joints and the small plantar joints. Affecting the joints of the upper limbs at SNRA recorded significantly lower frequencies than those attested in SPRA.

In the expressed stage of the disease, SNRA is presented by a quasi-homogeneous topographically distributed polyarticular syndrome, with a moderate character of acute joint processes, with the involvement of the small joints of the hands and soles in almost equal proportions, the damage to the talocrural joints and the joints remains equally important the knees and a substantial share belongs to the radiocarpal joints, the humeral joints and the elbows which are touched within the manifest picture in equal proportions. SPRA shows a marked predilection for MCF joints in a detached manner compared to the other joint areas and statistically significant compared to the damage to these joints in SNRA $p<0.01$, joint synovitis in the framework of exacerbations of the rheumatoid process finds its seat specifically in these joints, a fact also confirmed by other researchers [2, 13, 18].

When comparing the radiological stages of the hands in SNRA and SPRA, we can highlight more advanced stages in SPRA compared to those determined in SNRA, in the sense that 46% of SNRA presented radiological stage III and only 4% stage IV, while SPRA presented 30 % radiological advancement of grade III and 18% stage IV. The situation is different when examining the radiological staging of small plantar joint involvement, where 48% of SNRA presented stage III compared to 18% of SPRA who evaluated at stage III for the small joints of the plantar region. In conclusion, we can emphasize the more advanced nature of the radiological impact in the plantar region, compared to those of the hands at SNRA and an opposite situation found in SPRA. The aggressiveness of joint damage characterized by radiologically highlighted erosions, which are already irreversible joint manifestations, are also the prototype of SPRA, they have a higher weight, which also corresponds to other studies [7, 10, 15, 26].

For a more objective evaluation of the joint syndrome, we applied joint indices, the Ritchie index and the joint index 28 separately for swollen and painful joints. The Ritchie index showed

average values of 28.40±1.53 for SNRA and 32.86±1.54 for SPRA ($p<0.05$), the number of painful joints, according to the joint index 28, in SNRA had a average of 20.12±1.28, compared to 23.46±0.76 at SPRA ($p<0.05$), and the number of swollen joints determined in the same way according to the joint index 28 indicated average values of 14.80± 1.30 for SNRA and 19.30±0.96 for SPRA showing a statistically significant difference $p<0.01$.

When evaluating the indicators of the acute phase of inflammation, the subjects in the study group indicated increased values of these markers of inflammation. Being compared with each other, SNRA indicated trends for higher values of CRP, ESR and morning stiffness, statistically significant differences were observed only for the DAS28 score, which represents a complex index of disease activity assessment ($p<0.05$).

When the laboratory results were superimposed for the determination of the acute phase markers and the stages of radiological advancement, we obtained positive correlation indices, a moment that underlines the importance of inflammatory processes in the production of joint destruction.

The average values of the Lee index at SNRA of 15.46±0.91 compared to those averages in SPRA at 20.18±0.76, $p<0.01$, indicate a greater degree of disability, which presents itself in SPRA compared to SNRA. The quality of life of patients with SNRA is more moderately affected with the average value of the HAQ index of 1.68±0.08 compared to that of the SPRA which indicates more altered quality of life of 1.92±0.07. These data also explain the percentage of invalidity that prevails in SPRA, while SNRA remain in the labor field in a more significant percentage [11, 16, 23].

In this study, 38% of 50 seronegative RA patients had radiographic lesions during the follow-up periods. Presence of erosion and radiological score at onset significantly affect radiographic progression in seronegative rheumatoid arthritis. Age, sex, smoking, morning stiffness and CRP at onset were not associated with radiographic progression in SNRA.

The incidence of radiographic lesions in patients with SNRA in the current study is 38%, which is similar to other studies [6, 12, 17, 25]. In our study 32% of patients with radiographic lesions had joint space narrowing without erosion. Radiographic outcome is one of the most important outcomes in RA patients, as it is directly related to functional capacity and quality of life. However, studies specifically evaluating risk factors for radiographic progression in SNRA are very rare. In addition, our study confirmed that the radiological score at diagnosis is also significantly related to radiographic progression in seronegative patients. These results imply that SNRA is not quite distinct from SPRA in terms of structural damage and related risk factors. Patients with erosions and radiographic lesions at the diagnosis of SNRA should be considered for intensive treatment [1-4, 17, 21].

In several studies on SNRA, the number of inflamed joints or the level of acute phase reactants at baseline did not show statistical significance for clinical outcome scores [12, 17, 20, 22, 27]. Similarly, the number of active synovitis or the level of acute phase reactants as a single parameter was not significantly associated with radiographic progression in the seronegative patients of the current study. A large comparative and prospective study is needed to explore the relationship between these factors and radiographic outcome in SNRA [4, 9, 15, 22].

Along with the articular manifestations, another objective of the study was the delimitation of the particularities of the extra-articular manifestations.

To highlight the respiratory impairments in AR, the results of the study demonstrated that 64% of SNRA present a lung status compared to a much lower percentage of normal images detected in SPRA of 34% $p<0.01$. At SPRA, pulmonary radiological images dominated, which

showed an emphasis on the bronchopulmonary pattern - 48%. Pulmonary fibrosis was attested radiologically in 18% of SPRA and in 14% of SNRA. The determination of a restrictive external ventilation dysfunction was frequently identified among the patients involved in the study [4, 23, 25]. Thus, in 18% of SPRA, a mild restriction was attested and in 32% - the moderate-severe type of pulmonary restriction. At SNRA, these indicators prevailed significantly less often. Thus, such clinical situations were identified in patients with RA, such as diffuse interstitial fibrosis in 18% of SPRA and in 14% of SNRA, multinodular lung being diagnosed in only one case among SPRA. It is important to note the increased association of chronic bronchitis, detected in 32% of SPRA and 16% of SNRA, with a statistically significant difference $p<0.05$. The explanation of this phenomenon would be the increased susceptibility to infections that patients with RA present, due to the immune imbalances that are characteristic of them [5, 8, 11-16].

The evaluation of the digestive system highlighted the following: the characteristic xerostomia in its vast majority SNRA - 38%, gastroduodenitis, confirmed endoscopically, was detected in 20% of SPRA and in 20% of SNRA. The presence of gastric ulcer was also confirmed endoscopically in 18% of SPRA and in 8% of SNRA, the difference being statistically conclusive $p<0.05$. A significant percentage recorded hepatic steatosis at SPRA in 20% of cases compared to 4% of cases at SNRA, and in this case the difference was statistically supported. It should be noted the presence of an impressive number of patients presenting the picture of reactive hepatitis, manifested ultrasonographically by an image of hepatitis and being supported by the increase in the level of liver transaminases, in the conditions of the exclusion of other definite liver pathologies. This was recorded in 16% of SPRA and 24% of SNRA. It would be advisable to carry out a periodic screening, with the inclusion in the treatment of gastroprotective and hepatoprotective medications in line with the administration of foreground treatment [7, 11, 16, 21, 27].

Renal damage is not specific in RA, but once it occurs it precipitates the evolution of the disease. An increased number of renal infections were recorded in 42% SNRA and 52% SPRA. The ultrasound examination highlighted the following manifestations: the dilation of the calyx-basin system was described in most subjects, nephrolithiasis was more frequently associated with SPRA - 14% of the cases. We must mention that the most severe renal damage described in RA is renal amyloidosis, which has a reserved prognosis [6, 10, 14, 23].

Evaluating the systemic manifestations in patients with RA, we can say that today we are witnessing a metamorphosis of the extra-articular clinical presentation of RA, a phenomenon that is probably due to the advanced therapies available to us in recent decades and which we actively apply to patients with RA. On the other hand, precisely these therapeutic successes, along with other factors, have an important percentage of being the cause of the appearance of the new extra-articular manifestations that take shape in patients with RA, equally severe in terms of evolution and prognosis, and which lead us to we are still mobilizing our forces to find new therapies.

Based on the results obtained in the study, we can assume the interference of specific immunopathological reactions in the complex pathogenic processes of rheumatoid immune inflammation, with an impact on the evolution of the disease, on the articular and extra-articular clinical presentation and directly on the quality of life of patients with RA.

CONCLUSIONS

1. Rheumatoid arthritis, being an autoimmune systemic disease, with severe and progressive evolution, which, although it shows a predilection for seropositivity, also evolves

seronegatively through the same osteoarticular and extraarticular manifestations, producing a negative impact on the quality of life.

2. The triggering factors associated with the onset of seronegative rheumatoid arthritis were highlighted: acute viral respiratory infections, physical and mental stress, hypothermia; while, in seropositive rheumatoid arthritis, the major importance returned to the post-infectious recovery periods.
3. The joint syndrome at the onset of seronegative rheumatoid arthritis presented itself as a mono- (56%) or oligoarthritis (16%), with the involvement of the large and medium joints of the lower limbs, which later evolves into a polyarthritis. The radiological evolution of joint damage in seronegative rheumatoid arthritis is expressed in the lower limbs ($p<0.05$).
4. According to the evolutionary profile, the presence of clinical variations in seronegative rheumatoid arthritis was established, correlatively expressed by restrictive external ventilation dysfunctions (32%), the presence of endoscopically confirmed gastroduodenitis (20%) and hepatic steatosis (biochemical and instrumental markers) only in 4% cases. It should be noted the presence of an impressive number of patients with reactive hepatitis (40%), along with an increased number of renal pyelonic infections (42%). Patients with ARSN showed immune disorders through leukocytoclastic vasculitis, with a predisposition in the association of chronic respiratory infections, and in renal damage
5. The quality of life, assessed by the HAQ questionnaire, especially the motor and functional joint functions, revealed more favorable values for seronegative versus seropositive rheumatoid arthritis.
6. The analysis of the prognostic factors of seronegative rheumatoid arthritis highlighted the following: an insidious onset, triggered after the age of 60; onset by polyarthritis with symmetrical involvement of the proximal interphalangeal joints or by monoarthritis with asymmetrical radiocarpal joint involvement; the presence of extra-articular manifestations and smoking.

PRACTICAL RECOMMENDATIONS

1. The delimitation of the particularities of the joint syndrome in SNRA, highlighted in the onset period and in the manifest stage of the disease, are necessary in order to establish a correct diagnosis, even from the early period of the disease and to initiate the appropriate treatment to influence the evolution of the disease and improves the quality of life of the patients.
2. SNRA patients require a continuous monitoring of the risk factors of severe clinical evolution, the implementation of measures to prevent bronchial infections and their complications, a strict supervision of the adverse reactions of the antirheumatoid treatment prescribed for the purpose of gastric and liver protection, with the final objective prevention of associated severe extra-articular manifestations and decrease of the mortality rate in these patients.
3. Patients with SNRA who manifest a more severe activity of the rheumatoid process and more advanced joint damage, require an active and aggressive therapeutic approach in order to improve prognosis, quality of life and treatment effectiveness.

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ADNOTARE

Nistor Alesea „Diagnosticul precoce și evoluția artritei reumatoide seronegative”. Teză de doctor în științe medicale, Chișinău, 2023.

Structura tezei. Lucrarea a fost expusă pe 95 pagini de text electronic și se compartimentează în: introducere, 4 capitole de cercetări, 6 concluzii şi 3 recomandări, indice bibliografic (195 titluri), 28 de figuri, 32 de tabele, 7 anexe. Rezultatele cercetării au fost prezentate în 26 de publicaţii.

Cuvinte-cheie: artrita reumatoidă , factor reumatoid, precoce, seronegativă, diagnostic, indici articulari, prognostic.

Domeniul de studiu: Reumatologie

Scopul studiului: evaluarea caracteristicilor clinice la prezentare și rezultatul clinico-evolutiv și radiografic la pacienții cu artrită reumatoidă seronegativă, cu determinarea factorilor de prognostic pentru progresia bolii.

Obiectivele studiului: 1. Aprecierea factorilor declanşatori, asociaţi artritei reumatoide seronegative; 2. Evaluarea comparativă a particularităţilor sindromului articular în artrita reumatoidă seronegativă și la cei seropozitivi la debut, şi în stadiul manifest al maladiei; 3. Delimitarea particularităţilor afectării extraarticulare în evoluţia artritei reumatoide seronegativă și seropozitivă; 4. Studierea profilului clinico-evolutiv şi corelarea acestuia cu datele clinice, biochimice, imunologice şi radiologice a artritei reumatoide seronegative. 5. Analiza comparativă a calităţii vieţii şi prognosticului la pacienţii cu artrită reumatoidă seronegative

Noutatea şi originalitatea ştiinţifică Rezultatele studiului au cuantificat valoarea AntiCCP în manifestarea clinică a AR, încât prezența autoanticorpilor și FR redau un tablou clinic specific și o evoluție mai severă a bolii. Însă rezultatele au confirmat faptul că valoarea absolută a cantității AntiCCP și FR nu are o importanță primordială în expresia severității clinice. La fel, s-au evidențiat factorii declanșatori, asociați debutului artritei reumatoide seronegative – atât infecțiile respiratorii virale acute, stresul fizic intens și stresul psihic, cât și expunerea îndelungată la hipotermie. Calitatea vieții, atestată în baza chestionarului HAQ, care a vizat nemijlocit abilitatea articulară motorie și funcțională, a relevat valori mai favorabile pentru ARSN, în comparație cu ARSP. Totodată, s-au demonstrat și corelații inverse certe ale acestui indice cu markerii de fază acută, stadiul radiologic de afectare articulară. Astfel, concluzionăm că autoimunitatea umorală prezintă veriga importantă în debutul, evoluția și prezentarea clinică a AR.

Problema ştiinţifică importantă soluţionată în teză. Sindromul articular la debutul ARSN se prezintă drept o mono- sau oligoartrită, cu implicarea de predilecție a articulațiilor mari și medii ale membrelor inferioare care, ulterior, evoluează spre o poliartrită ce interesează și ariile articulațiilor mici. Evoluția radiologică a atingerilor articulare la ARSN este mai pronunțată la nivelul membrelor inferioare v al celor superioare ($p<0,05$).

Semnificaţia teoretică. Artrita reumatoidă este o patologie cu component autoimun, cu evoluţie severă şi progresivă care deşi manifestă o predilecţie pentru evoluție seropozitivă, la fel de sever evoluează seronegativ și, prin particularităţile sale de evoluţie a manifestărilor articulare şi extraarticulare, pereclitează sever abilităţile motorii şi funcţionale ale pacienţilor seronegativi, producând un impact nefast asupra calităţii vieţii.

Valoarea aplicativă. Studiul manifestărilor extraarticulare din cadrul artritei reumatoide a stabilit prezența dimorfismului clinic în funcție de seronegativitatea și seropozitivitatea pacienților. Pacienții seronegativi prezintă o rată redusă pentru manifestările vasculare, gastrointestinale și hepatice, o predispunere redusă pentru asocierea infecțiilor bronșice cronice și afectarea renală comparativ cu artrita reumatoidă seropozitivă.

Implementarea rezultatelor: Rezultatele studiului au fost incluse în Protocolul Clinic Naţional ,,Artrita reumatoidă la adulți”, se aplică în procesul didactic al Departamentului Medicină Internă, în practica Disciplinei reumatologie și nefrologie a IP USMF „Nicolae Testemițanu” și în secțiile clinice de reumatologie, artrologie și nefrologie a IMSP SCR „Timofei Moșneaga” .

SUMMARY

Nistor Alessa "Early diagnosis and evolution of seronegative rheumatoid arthritis". PhD thesis in medical sciences, Chisinau, 2023.

Thesis structure: The work was exposed on 142 pages of electronic text and is divided into: introduction, 4 chapters of research, 6 conclusions and 3 recommendations, bibliographic index (191 titles), 28 figures, 32 tables, 7 annexes. The results of the research were presented in 21 publications.

Keywords: rheumatoid arthritis, rheumatoid factor, early, seronegative, diagnosis, joint indices;

Domain of research: Rheumatology

Aim of the study: Evaluation of the clinical characteristics at presentation and the clinical evolution and radiographic outcome in patients with seronegative rheumatoid arthritis, with the determination of prognostic factors for the progression of the disease.

Study objectives: 1. Assessment of the triggering factors associated with seronegative rheumatoid arthritis; 2. Comparative evaluation of the particularities of the joint syndrome in seronegative rheumatoid arthritis and in those seropositive at the onset and in the manifest stage of the disease; 3. Delimitation of the particularities of extra-articular involvement in the evolution of rheumatoid arthritis in seronegative and seropositive evolution; 4. Study of the clinical-evolutionary profile and its correlation with the clinical, biochemical, immunological and radiological data of seronegative rheumatoid arthritis. 5. Comparative analysis of quality of life and prognosis in patients with seronegative rheumatoid arthritis.

Scientific novelty and originality: The results of the study quantified the value of AntiCCP in the clinical manifestation of RA, so that the presence of autoantibodies and FR reflect a specific clinical picture and a more severe evolution of the disease. But the results confirmed that the absolute value of the amount of AntiCCP and FR is not of primary importance in the expression of clinical severity. In the same way, the triggering factors associated with the onset of SNRA were highlighted - both acute viral respiratory infections, intense physical stress and mental stress, as well as prolonged exposure to hypothermia. Quality of life, attested on the basis of the HAQ questionnaire, which directly targeted motor and functional joint ability, revealed more favorable values for SNRA compared to SPRA. At the same time, definite inverse correlations of this index with the markers of the acute phase, the radiological stage of joint damage, were also demonstrated.

The scientific problem solved in the thesis: The joint syndrome at the onset of the SNRA presents itself as a mono- or oligoarthritis, with the predilection involvement of the large and medium joints of the lower limbs, which later evolves into a polyarthritis that also affects the areas of the small joints. The radiological evolution of joint involvement in SNRA is more pronounced in the lower limbs versus the upper ones ($p<0,05$).

The theoretical significance: RA is a pathology with an autoimmune component, with a severe and progressive evolution that, although it shows a predilection for seropositive RA, also it evolves just as severely in seronegative RA and due to its particularities of the evolution of articular and extra-articular manifestations, severely impairs the motor and functional abilities of these patients, producing an adverse impact on the quality of life.

Application value of the study: The study of extra-articular manifestations in rheumatoid arthritis. Seronegative patients have a reduced rate for vascular, gastrointestinal, hepatic manifestations and a reduced predisposition for the association of chronic bronchial infections and renal damage compared with seropositive rheumatoid arthritis

Results implementation: The results of the study were included in the National Clinical Protocol "Rheumatoid Arthritis in Adults", applied in the didactic process of the Department of Internal Medicine, in the practice of the rheumatology and nephrology discipline of SMPhU "Nicolae Testemițanu" and in the clinical departments of rheumatology, arthrology and nephrology of Republican Clinical Hospital "Timofei Moşneaga".

РЕЗЮМЕ

Нистор Алеся «Ранняя диагностика и эволюция серонегативного ревматоидного артрита». Диссертация на соискание степени доктора медицинских наук, Кишинэу, 2023.

Структура диссертации. Работа представлена на 95 страницах электронного текста и разделена на: введение, 4 глав материала, 6 выводов и 3 практических рекомендации, библиографии (195 источника), 28 рисунков, 32 таблицы, 7 приложений. Результаты исследования были опубликованы в 26 научных работах.

Ключевые слова: ревматоидный артрит, ревматоидный фактор, ранний, серонегативный, диагностика, суставные показатели, прогноз.

Область исследования: Ревматология

Цель исследования: оценка клинических особенностей манифестации, клинико-эволюционного и рентгенологического исхода у больных серонегативным ревматоидным артритом с определением прогностических факторов прогрессирования заболевания.

Задачи исследования: 1. Признание пусковых факторов, связанных с серонегативным ревматоидным артритом; 2. Сравнительная оценка особенностей суставного синдрома при серонегативном ревматоидном артрите и у серопозитивных в дебюте и манифестной стадии заболевания; 3. Выявление особенностей внесуставного поражения в развитии серонегативного и серопозитивного ревматоидного артрита; 4. Изучение клинико-эволюционного профиля и его корреляции с клиническими, биохимическими, иммунологическими и рентгенологическими данными серонегативного ревматоидного артрита. 5. Сравнительный анализ качества жизни и прогноза у больных серонегативным ревматоидным артритом.

Научная новизна: Результаты исследования количественно определили значение АнтиЦЦП в клиническом проявлении РА, так что наличие аутоантител и ФР отражает специфическую клиническую картину и более тяжелое течение заболевания. Но результаты подтвердили, что абсолютное значение количества АнтиЦЦП и ФР не имеет первостепенного значения в выражении тяжести клинической картины. Таким же образом выделены пусковые факторы, связанные с возникновением серонегативного ревматоидного артрита, - как острые вирусные респираторные инфекции, интенсивные физические и психические нагрузки, так и длительное воздействие гипотермии. Качество жизни, подтвержденное на основе опросника HAQ, который непосредственно касался двигательных и функциональных способностей суставов, выявило более благоприятные значения для серонегативного ревматоидного артрита по сравнению с серопозитивным. При этом были продемонстрированы и определенные обратные корреляции этого показателя с маркерами острой фазы – рентгенологической стадии поражения суставов. Таким образом, мы пришли к выводу, что гуморальный аутоиммунитет представляет собой важное звено в возникновении, развитии и клинической картине РА.

Важность решенной научной проблемы. Суставной синдром в дебюте ОРСН проявляется как моно- или олигоартрит с преимущественным поражением крупных и средних суставов нижних конечностей, который в дальнейшем перерастает в полиартрит, поражающий также участки мелких суставов. Рентгенологическая эволюция поражения суставов при ОРСН более выражена в нижних и верхних конечностях ($p<0,05$).

Теоретическая значимость. Ревматоидный артрит патология с аутоиммунным компонентом, с тяжелым и прогрессирующим течением, которое, хотя и проявляет склонность к серопозитивной эволюции, но так же тяжело развивается серонегативно и, в силу особенностей развития суставных и внесуставных проявлений, тяжело ухудшает двигательные и функциональные способности серонегативных больных, оказывая неблагоприятное влияние на качество жизни.

Прикладная значимость. Изучение внесуставных проявлений при ревматоидном артрите установило у серонегативных пациентов снижена частота сосудистых, желудочно-кишечных и печеночных проявлений, снижена предрасположенность на хронические бронхиальные инфекции и поражения почек по сравнению с серопозитивным ревматоидным артритом

Внедрение в практику. Результаты исследования включены в Национальный клинический протокол «Ревматоидный артрит у взрослых», применяемый в учебном процессе кафедры внутренних болезней, в практике дисциплины ревматологии и нефрологии ИП УЗМФ «Николае Тестемицану» и в клинические отделения ревматологии, артрологии и нефрологии ИМСП ЮКР «Тимофей Мошняга».

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