RESEARCH ARTICLE

Association between serological, hematological and biochemical status and cardiac involvement in rheumatic connective tissue diseases

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Introduction: Rheumatic connective tissue diseases (RCTDs) are chronic systemic autoimmune disorders frequently complicated by cardiovascular involvement, which represents a major cause of morbidity and mortality. Subclinical cardiac manifestations may remain unrecognized and may be associated with systemic inflammation and laboratory abnormalities.

Objective: To evaluate the prevalence and characteristics of cardiac manifestations in patients with RCTDs and to assess their association with serological status and selected hematological and biochemical parameters.

Methods: This observational study included 110 adult patients hospitalized and treated for rheumatic connective tissue diseases over a one-year period. Patients were classified into seropositive and seronegative groups based on autoantibody profiles. All participants underwent clinical evaluation, electrocardiography, and transthoracic echocardiography. Hematological, inflammatory, biochemical, electrolyte, enzyme, and serum protein parameters were analyzed.

Results: Cardiac involvement was more frequently observed in seropositive patients and increased significantly with age. Ventricular hypertrophy and atrioventricular or intraventricular conduction disturbances were the most common abnormalities in this group. Seropositive patients showed significantly lower hematocrit, hemoglobin, calcium, and albumin levels, as well as higher erythrocyte sedimentation rate, fibrinogen, triglycerides, lactate dehydrogenase, and serum urea levels. In the seropositive group, demonstrated significant negative correlations with hematocrit, hemoglobin, albumin, and calcium.

Conclusion: Seropositive rheumatic connective tissue diseases are associated with a higher prevalence of subclinical cardiac involvement and distinct laboratory abnormalities reflecting chronic inflammation and myocardial remodeling. Integrated cardiovascular assessment combined with laboratory evaluation may facilitate early detection of cardiac involvement in this patient population.

Keywords: Rheumatic connective tissue disorders, serological status, cardiac involvement.

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Introduction

Rheumatic connective tissue diseases (RCTDs) comprise a heterogeneous group of chronic systemic inflammatory disorders characterized by autoimmune-mediated tissue damage, multi-organ involvement and overlapping pathogenesis and clinical features [1].

Cardiovascular involvement is a well-recognized complication and a major contributor to morbidity and mortality among this diverse group of diseases [2].

Chronic systemic inflammation plays a central role in vascular dysfunction, thereby accelerating cardiovascular comorbidities and immune-mediated myocardial injury, particularly in seropositive connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and mixed connective tissue disease [3, 4]. In these conditions, all structures of cardiovascular system may be affected, including the pericardium, myocardium, cardiac valves, conduction system and vasculature [5].

Although cardiovascular involvement has been documented across individual RCTDs, data comparing cardiac manifestations between seropositive and seronegative patient populations remain inconsistent. Differences in immunological profiles may influence the pattern and severity of cardiac involvement; however, they are not fully clarified in routine clinical practice, particularly when it is about serological status and subclinical myocardial remodeling, functional impairment, and associated laboratory abnormalities.

The aim of this study was to evaluate the prevalence and

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characteristics of cardiac manifestations and their association with laboratory parameters according to serological status in patients with rheumatic connective tissue diseases.

Materials and methods

This observational study was conducted at the Clinical Center of the University of Sarajevo, Department of Cardiology, Vascular Diseases, and Rheumatology. Patients hospitalized and treated for rheumatic connective tissue diseases during a one-year period were included.

A total of 110 patients of both sexes, aged 18 - 86 years, were enrolled.

Inclusion and exclusion criteria

Inclusion criteria were age ≥18 years, documented and a diagnosis of RCTD according to the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria [6-8]. Exclusion criteria included age<18 years, documented cardiac disease prior to the rheumatic disease diagnosis, and incomplete clinical or laboratory data.

Data and sample collection

Demographic characteristics, disease duration, and routine laboratory parameters were collected from medical records. Disease duration was defined as the time from initial diagnosis to study inclusion.

Laboratory analyses included complete blood count, inflammatory markers, lipid profile, serum proteins, parameters of renal function, electrolytes, non-specific tissue markers (LDH, CK), and immunological markers.

Immunological assessment

Patients were classified according to serological status based on immunological testing results.

The seropositive group was defined as patients with the presence of at least one autoantibody associated with connective tissue diseases, including antinuclear antibodies (ANA), anti-cyclic citrullinated peptide antibodies (aCCP), rheumatoid factor (RF), anti-double-stranded DNA antibodies (anti-dsDNA), anti-Sm, anti-Jo-1, anti-Scl-70, anti-Ro (anti-SSA) or anti-La (anti-SSB).

The seronegative group was defined as patients without detectable autoantibodies associated with connective tissue diseases.

For descriptive purposes, underlying diagnoses were also recorded, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and mixed connective tissue disease (MCTD) which were classified as seropositive connective tissue diseases, as well as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), which were classified as seronegative conditions.

Importantly, serological classification was based on autoantibody status rather than underlying diagnosis.

Electrocardiographic and echocardiographic assessment

All patients underwent a standard 12-lead electrocardiogram using a Schiller AT-1 electrocardiograph (Switzerland). ECG parameters included heart rate, conduction disturbances, ectopic rhythm disturbances, and ischemic changes.

Transthoracic echocardiography was performed using a Philips Affiniti 50 system in B-mode, M-mode, and color Doppler mode.

Assessed parameters included diameter of the aortic root, left atrial diameter, interventricular septal thickness, posterior wall thickness, left ventricular ejection fraction, early (E) and late (A) diastolic filling velocities, and maximal flow velocities.

Statistical analysis

Data were analyzed using descriptive and inferential statistical methods. Continuous variables were expressed as mean with standard deviation or median with interquartile range, depending on distribution. Normality was assessed using the Shapiro-Wilk test. Group comparison was performed using Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were analyzed using the chi-square test or Fischer's exact test. Correlations were assessed using Spearman's rank correlation coefficient. A p-value <0.05 was considered statistically significant.

Ethical statement

This study had a cross-sectional design and was conducted retrospectively using anonymized data. In accordance with institutional and national regulations, ethical approval was not required. The study was conducted in compliance with the principles of the Declaration of Helsinki.

Results

Baseline characteristics of the study population

A total of 110 patients were included in the study, of whom 21 (19.1%) were male and 89 (80.9%) were female.

According to serological status, 95 patients (86.4%) were classified as seropositive and 15 patients (13.6%) as seronegative. In the seropositive group, females predominated, with 82 women (86.3%) and 13 men (13.7%). In contrast, the seronegative group showed a more balanced sex distribution, with 8 men (53.3%) and 7 women (46.7%). The difference in sex distribution between the seropositive and seronegative groups was statistically significant (χ^2=13.065, p<0.01), indicating a statistically significant association between serological status and sex. Rheumatoid arthritis was the most prevalent diagnosis (n=72; 65.45%), followed by the mixed connective tissue disease with systemic lupus erythematosus (n=16, 14.54%), psoriatic arthritis (n=9, 6.37%), systemic sclerosis (n=7, 6.36%), and ankylosing spondylitis (n=6, 2.73%). The distribution of rheumatic connective tissue diseases differed signifi-

cantly between sexes (p=0.017). Rheumatoid arthritis and MCTD and SLE were more prevalent in female patients, whereas ankylosing spondylitis was more frequently observed in male patients.

Seropositive patients were predominantly older, with the highest proportions in the 51-60 and 61-70-year age groups, whereas seronegative patients were more frequently observed in younger age groups, particularly between 31 and 40 years.

No statistically significant difference was observed in disease duration between seropositive and seronegative patients (χ^2=2.02, p=0.567). In both groups, the majority of patients had a disease duration of 1-5 years. Seropositive patients most frequently had a disease duration of 1-5 years (56.7%), followed by 6-10 years (17.6%) and more than 15 years (17.6%). A similar distribution was observed among seronegative patients, with 46.7% having disease duration of 1-5 years and 33.7% of 6-10 years. The lowest proportion of patients in both groups had disease duration between 11 and 15 years.

Table 1. Laboratory parameters according to serological status

Parameter	Seropositive values (N=95)	Seronegative values (N=15)	p value	Significance
RBC (1012/l)	4.27 (±0.50)	4.87 (±0.60)	0.840	NS
WBC (109/l)	6.88 (5.74-8.22)	8.33 (±2.56)	0.088	NS
PLT (109/l)	302.5 (236.00-78.00)	290.00 (±73.22)	0.618	NS
Hct (%)	37.26 (±4.76)	41.02 (±4.63)	0.018	*
Hgb (g/l)	122.00 (110.00-130.00)	126.00 (119.50-148.50)	0.006	**
Sodium (mmol/L)	140.00 ± 23.17	139.0 ± 3.07	0.298	NS
Potassium (mmol/L)	4.10 (3.80–4.30)	4.20 (3.90–4.45)	0.351	NS
Chloride (mmol/L)	102.00 (100.00–103.00)	99.6 ± 3.24	0.040	*
Calcium (mmol/L)	2.24 (2.17–2.33)	2.33 (2.30–2.72)	0.000	**
AST (U/L)	16.00 (13.00–20.00)	15.00 (13.50–18.00)	0.890	NS
ALT (U/L)	13.00 (9.10–17.00)	17.00 (11.50–24.50)	0.137	NS
LDH (U/L)	315.00 (256.00–389.00)	240.30 ± 83.71	0.012	*
CK (U/L)	54.00 (37.00–91.00)	79.00 (58.00–93.00)	0.116	NS
Creatinine (µmol/L)	66.0 (55.00–76.50)	69.30 ± 23.10	0.768	NS
Urea (mmol/L)	5.10 (4.25–6.00)	4.30 (3.60–5.25)	0.018	*
Bilirubin (µmol/L)	6.10 (4.50–7.80)	6.00 ± 4.60	0.120	NS
Total protein (g/L)	73.00 (70.00–77.00)	76.10 ± 5.70	0.098	NS
Albumin (g/L)	35.00 (32.00–38.00)	37.80 ± 5.10	0.048	*
Globulin (g/L)	38.00 (33.00–41.00)	38.40 ± 4.60	0.786	NS
ESR (mm/h)	42.00 (21.50-64.50)	21.00 (9.50-62.00)	0.117	NS
CRP (mg/l)	13.100 (4.90-31.00)	17.60 (3.00-35.65)	0.415	NS
Fibrinogen (g/l)	4.50 (3.30-5.50)	5.10 (4.30-7.90)	0.712	NS
Cholesterol (mmol/l)	5.10 (4.20-5.70)	4.40 (4.20-4.75)	0.112	NS
Triglycerides (mmol/l)	1.50 (1.22-1.92)	1.10 (0.91-1.71)	0.001	**

Continuous variables are presented as mean ± standard deviation or median (interquartile range), depending on data distribution within each group.
NS, not significant. * $p < 0.05$; ** $p < 0.01$.
Abbreviations: N, number of patients; RBC, red blood cells; WBC, white blood cells; PLT. Platelets; Hct, hematocrit; Hgb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase, ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

Biochemical and laboratory differences according to serological status

We observed significant differences for hematocrit (Hct) and hemoglobin (Hgb) values between seropositive and seronegative patients. Seronegative patients had significantly higher median values of hematocrit (41.02 ±4.63%) compared to seropositive patients (37.26±4.76%). Similarly, hemoglobin levels were significantly higher in the seronegative group (median 126.0 g/L, IQR 119.5-148.5) compared to seropositive group (median 122.0 g/L, IQR 110-130), p=0.0069.

Serum chloride levels were significantly lower in seronegative patients compared with seropositive patients (p=0.040), while serum calcium levels were significantly lower in the seropositive group (p<0.01). Lactate dehydrogenase (LDH) levels were significantly higher in seropositive patients compared with seronegative patients (p=0.012).

Serum urea concentrations were significantly higher in seropositive patients compared with seronegative patients (p=0.018). In contrast, serum albumin levels were significantly lower in the seropositive group (p=0.048). Seropositive patients showed higher median levels of triglycerides compared to seronegative group (p=0.001) (Table 1).

In the seropositive group, we observed significant associations between selected laboratory parameters and the presence of cardiac manifestations, including: erythrocyte count (p=0.013), hemoglobin levels (p=0.005), platelet count (p=0.044), triglycerides (p=0.003), calcium levels (p=0.014), urea (p=0.018), albumins (p=0.046).

Cardiac manifestations in patients with rheumatic connective tissue diseases

In the overall study population, cardiac manifestations were identified in 38 out of 110 patients (34.5%). Among sero-

positive patients, 34 individuals (35.8%) exhibited at least one cardiac manifestation, whereas 61 patient (64.2%) had no evidence of cardiac involvement. In the seronegative group, cardiac manifestations were observed in 4 patients (26.7%), while the majority, 11 patients (73.3%), showed no cardiac manifestations. Although a higher proportion of seropositive patients showed cardiac manifestations compared to seronegative patients, the difference did not reach statistical significance (p>0.05).

Cardiac manifestations were analyzed across age groups (Table 2) and showed a statistically significant association in seropositive patients (p=0.043), with the highest prevalence in the 51-60 and 61-70 year age groups. In these age groups, ventricular hypertrophy and atrioventricular/intraventricular conduction disturbances were the most commonly identified cardiac abnormalities. In contrast, seronegative patients largely showed no cardiac manifestations across all age categories (p>0.05).

The analysis of cardiac manifestations in relation to disease duration revealed different patterns between seropositive and seronegative patients. In the seropositive group, the prevalence of cardiac manifestations did not differ significantly across the disease duration (χ^2=2.686, p=0.487). In seronegative group of patients, a statistically significant association was observed between disease duration and the occurrence of cardiac manifestations (χ^2=8.846, p=0.031), that were more frequent in patients with longer disease duration, particularly after more than 10 years. These results should be interpreted with caution due to limited sample size in seronegative group.

Rheumatoid factor (RF) demonstrated a statistically significant association with hemodynamic valvular abnormalities (p=0.023), atrioventricular and intraventricular conduction disturbances (p=0.007), and ischemic heart disease (p=0.042). Furthermore, RF showed a strong overall association with the presence of any cardiac manifestation (p<0.001) (Table 3).

A statistically significant difference was found for the left ventricular end-diastolic diameter (LVEDD), which was higher in seropositive compared with seronegative patients (p=0.037) (Table 4).

In the seropositive group, statistically significant negative correlations were observed between LVDD and hematological and biochemical parameters, including hematocrit

Table 2. Association between age groups and cardiac manifestations according to serological status

Serological status	Age group (years)	No cardiac manifestations N (%)	Hemodynamic disorders N (%)	Ventricular hypertrophy N (%)	AV/IV conduction disturbances N (%)	Ectopic arrhythmias N (%)	Ischemic heart disease N (%)
Seropositive	18–30	3 (3.16)	1 (1.05)	0 (0)	0 (0)	0 (0)	0 (0)
	31–40	4 (4.2)	0 (0)	0 (0)	2 (2.1)	0 (0)	0 (0)
	41–50	9 (9.4)	2 (2.1)	3 (3.16)	2 (2.1)	1 (1.05)	1 (1.05)
	51–60	21 (24.5)	4 (4.2)	1 (1.05)	2 (2.1)	1 (1.05)	1 (1.05)
	61–70	18 (18.4)	0 (0)	4 (4.2)	2 (2.1)	0 (0)	2 (2.1)
	>70	6 (6.3)	0 (0)	1 (1.05)	4 (4.2)	0 (0)	2 (2.1)
Seronegative	18–30	2 (13.3)	0 (0)	0 (0)	2 (2.1)	0 (0)	0 (0)
	31–40	6 (5.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	41–50	1 (1.05)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	51–60	1 (1.05)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	61–70	1 (1.05)	0 (0)	1 (1.05)	0 (0)	0 (0)	1 (1.05)
	>70	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: AV, atrioventricular; IV, intraventricular; χ^2, chi-square test.
Seropositive group: χ^2=11.916, df=5, p=0.043. Seronegative group: χ^2=7.265, p=0.064.

Table 3. Association between autoantibody profiles and cardiac manifestation in patients with rheumatic connective tissue diseases

Autoantibody	Hemodynamic abnormalities	Ventricular hypertrophy	AV/IV conduction disorders	Ectopic Rhythm disorders	Ischemic heart disease	Overall cardiac manifestations
ANA	NS	NS	NS	NS	NS	NS
aCCP/RF	NS	NS	NS	NS	NS	NS
RF	p = 0.023	NS	p = 0.007	NS	p = 0.042	p < 0.001
Anti-dsDNA	NS	NS	NS	NS	NS	NS
Anti-Sm	NS	NS	NS	NS	NS	NS
Anti-Scl-70	NS	NS	NS	NS	NS	NS
Anti-Jo-1	NS	NS	NS	NS	NS	NS
Anti-Ro/SSA	NS	NS	NS	NS	NS	NS
Anti-La/SSB	NS	NS	NS	NS	NS	NS

Abbreviations: ANA – antinuclear antibodies; RF – rheumatoid factor; aCCP – anti-cyclic citrullinated peptide; NS – not significant (p > 0.05).

Table 4: Comparison of echocardiographic parameters according to serological status

Parameter	Seropositive	Seronegative	p value
Ao (cm)	3.10 (2.85–3.30)	3.10 (2.95–3.30)	0.725
LA (cm)	3.63 ± 0.40	3.60 (3.30–3.70)	0.562
LVEDD (cm)	4.83 ± 0.50	4.45 (4.20–4.85)	0.037*
IVSd (cm)	1.10 (1.00–1.20)	1.10 (0.90–1.20)	0.393
LVPWd (cm)	1.08 (0.90–1.20)	1.10 (0.88–1.20)	0.385
EF (%)	60 (55–62)	60 (58–62)	0.809
E/A ratio	0.90 (0.70–1.20)	0.90 (0.80–1.10)	0.836

Values are presented as mean ± standard deviation or median (interquartile range), as appropriate.
Abbreviations: Ao, aortic root diameter; LA, left atrium diameter; LVEDD, left ventricular end-diastolic diameter; IVS, Interventricular septum thickness at end-diastole; EF, ejection fraction; E/A, left ventricular diastolic filling by comparing early (E) to late/atrial (A) mitral flow velocities * $p < 0.05$.

(r=-0.347, p=0.016), hemoglobin (r=-0.246, p=0.017), serum calcium (r=-0.234, p=0.025) and serum albumin levels (r=-0.316, p<0.01). These findings indicate that lower values of these parameters were associated with larger left ventricular end-diastolic diameter.

Electrocardiographic parameters, including heart rate and PQ interval, did not differ significantly between the two groups, with values remaining within the reference range in the majority of patients.

Discussion

Cardiovascular manifestations are a major contributor to long-term morbidity and mortality in patients with rheumatic connective tissue diseases, often remaining clinically silent until advanced stages [5].

In our study, cardiac involvement was observed in approximately one-third of patients with RCTDs, without a significant difference in overall prevalence between seropositive and seronegative groups. These findings are consistent with previous reports indicating that cardiac involvement may occur across the spectrum of inflammatory rheumatic diseases, regardless of serological status [5, 9].

Rheumatoid factor positivity was significantly associated with specific cardiac manifestations, including valvular hemodynamic abnormalities, atrioventricular and intraventricular conduction disturbances, ischemic heart disease, and overall cardiac involvement. Rheumatoid factor is a well-established marker of chronic systemic inflammation and increased cardiovascular risk, contributing to cardiovascular disease through multiple pathophysiological mechanisms, including endothelial dysfunction [4]. Circulating immune complexes containing RF directly interact with vascular endothelium, causing endothelial activation, expression of adhesion molecules, and impaired nitric oxide bioavailability. This leads to reduced vasodilatory capacity, increased arterial stiffness, and microvascular dysfunction [10]. Rheumatoid factor positivity has also been implicated in accelerated atherosclerosis, mainly through elevated pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). It contributes to plaque formation and its instability, increasing the risk for ischemic heart disease [11]. Large cohort studies have shown that seropositive patients may exhibit a more severe disease phenotype with earlier cardiovascular involvement [12, 13], although cardiovascular risk appears to be comparable between seropositive and seronegative individuals [14]. Our findings support the existing evidence suggesting that RF positivity reflects a more aggressive systemic inflammatory phenotype associated with increased cardiovascular risk [12, 13].

The lack of significant associations between other autoantibody profiles and specific cardiac manifestations can be explained at least in part by the relatively small number of patients with other seropositive diseases compared to rheumatoid arthritis. Also, cardiac involvement in RCTDs is multifactorial, influenced by inflammation, vascular changes, disease duration, and traditional cardiovascular risk factors [15]. These findings are consistent with heterogeneous reports in the literature, indicating that the association between specific autoantibodies and cardiac involvement is inconsistent and disease-specific. Cardiovascular assessment in patients with RCTDs should be guided primarily by the overall clinical context rather than serological profile [16, 17].

Cardiac involvement was more prevalent in seropositive patients older than 50 years, highlighting age as an important risk factor and emphasizing the cumulative effect of chronic inflammation and age-related cardiovascular changes [9, 17, 18].

Despite previous reports, disease duration did not differ significantly between seropositive and seronegative patients, and its association with cardiac involvement remains inconsistent across studies [19, 20]. In our study, association regarding disease duration and cardiac involvement in the seronegative group should be interpreted cautiously due to the small sample size. Previous studies on seronegative inflammatory spondyloarthropathies observed clinically significant cardiovascular manifestations in patients with long-standing disease, suggesting that disease duration and cumulative effects of prolonged inflammation impact cardiovascular involvement, rather than serological status by itself [21].

Our findings of significantly larger LVEDD in the seropositive compared to the seronegative group, are consistent with existing literature reporting that left ventricular diastolic dysfunction (LVDD) is a common and often subclinical manifestation in patients with rheumatoid arthritis and other inflammatory rheumatic diseases [22]. Diastolic

dysfunction may act as a precursor to heart failure with preserved ejection fraction. The low-grade systemic inflammation acts as a key mechanism driving this process.

Pro-inflammatory cytokines, particularly TNF-α, and IL-6 contribute to impaired myocardial relaxation, cardiomyocyte dysfunction, myocardial fibrosis and remodeling [23]. Left ventricular diastolic dysfunction has been recognized not only in RA, but also in other seropositive rheumatic connective tissue diseases, including systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease and inflammatory myopathies [22, 24]. These findings emphasize the value of transthoracic echocardiography as a sensitive tool for detecting early structural changes that may precede overt cardiac dysfunction.

Only seropositive patients exhibited significant negative correlations between selected LVEDD and hematocrit, hemoglobin, serum albumin, and calcium levels, suggesting that lower values of these parameters are associated with greater left ventricular dilatation in seropositive rheumatic connective tissue diseases.

Reduced hemoglobin and hematocrit values may reflect anemia of chronic disease. Anemia leads to increased minute volume and left ventricular volume load. In the long term, this leads to remodeling and dilation of the left ventricle [25].

Hypoalbuminemia is a marker of persistent systemic inflammation and has previously been associated with adverse cardiovascular outcomes [26]. Similarly, alterations in calcium homeostasis may contribute to impaired myocardial contractility, relaxation, and diastolic function [27]. These results additionally support the concept that systemic inflammatory and metabolic disturbances in seropositive rheumatic diseases contribute to subclinical cardiac remodeling, particularly affecting left ventricular dimensions [28].

Analyzing complete blood count and blood parameters, we observed significantly lower hemoglobin and hematocrit levels in seropositive patients compared with seronegative patients. This finding is consistent with the anemia of chronic disease, which is frequently seen in seropositive rheumatoid arthritis and other seropositive RCTDs, caused by persistent inflammation but also by iron deficiency, usually due to medication side effects [29, 30].

Although erythrocyte count, mean corpuscular volume (MCV), leukocyte count, and platelet count did not differ significantly between seropositive and seronegative groups overall, further analysis demonstrated that in seropositive patients only, the presence of cardiac involvement was significantly associated with erythrocyte count, hemoglobin levels, and platelet count. Our results suggest that hematological abnormalities in seropositive diseases may reflect greater systemic inflammatory burden and subclinical cardiac involvement, especially since available data show that blood platelets and red blood cell indices are associated with disease activity, especially in rheumatoid arthritis [31]. The complete blood count, specifically evaluating RBCs, Hb, and platelet, are very important, widely available tool for assessing cardiac risk and monitoring patients with cardiac involvement [32].

Among inflammatory markers, erythrocyte sedimentation rate (ESR) and fibrinogen levels showed significant differences exclusively within the seropositive group. Elevated ESR and fibrinogen are well-established markers of chronic inflammation and are closely linked to increased cardiovascular risk, based on endothelial dysfunction, hypercoagulability, and accelerated atherosclerosis [33].

Interestingly, CRP did not differ significantly between seropositive and seronegative groups, although the majority of seropositive patients in our study had RA. In RA, CRP is strongly associated with disease activity and acts as an active mediator for atherosclerosis, enhancing endothelial dysfunction, inflammation, plaque instability, and thrombosis [34]. In the 2015/16 EULAR recommendations, CRP and ESR are acknowledged as markers of systemic inflammatory burden. Effective suppression of inflammation by reduction in CRP and ESR is as an integral component of cardiovascular risk management in RA [35]. Our findings suggest that CRP may fluctuate with disease activity and treatment, whereas fibrinogen and ESR may better reflect long-term inflammatory exposure in chronic autoimmune disease [36].

Triglyceride levels were significantly associated with seropositivity, whereas total cholesterol did not differ significantly between groups. Partially, it can be explained by the so-called “lipid paradox” observed in inflammatory rheumatic diseases, where systemic inflammation alters lipid metabolism, leading to qualitative rather than quantitative lipid abnormalities that contribute to cardiovascular risk. It is an inflammation-mediated impact on lipid metabolism, caused by pro-inflammatory cytokines that false lowers levels of lipid during active disease. Triglycerides are mainly increased as a direct effect of inflammation through the inhibition of lipoprotein lipase and insulin resistance [37].

Although electrolyte imbalances have been noticed in patients with chronic rheumatic diseases, they are considered indicators of systemic inflammation, renal involvement, or therapy side effects, rather than having a direct cause-and-effect relationship [38]. Serum levels of chloride and calcium showed significant differences between seropositive and seronegative patients, but with values mainly within the reference range.

Lactate dehydrogenase (LDH) levels were significantly higher in seropositive patients, suggesting increased tissue turnover or systemic inflammatory activity. Elevated LDH is recognized as a nonspecific marker of cellular damage and inflammation and has been associated with disease severity and adverse outcome in various inflammatory and connective tissue diseases [39].

Seropositive patients demonstrated significantly lower serum albumin levels and higher urea concentrations compared with seronegative patients. Hypoalbuminemia is a recognized negative acute-phase reactant and reflects

chronic inflammation, increased vascular permeability, and poor nutritional status, all of which are associated with adverse cardiovascular outcomes [40].

Taken together, our findings indicate that seropositive RCTDs are characterized by hematological and biochemical abnormalities reflecting chronic inflammation and altered metabolic homeostasis. These changes are associated with increased cardiovascular vulnerability and may lead to cardiac manifestations detectable by echocardiography and electrocardiography.

An important limitation of this study is the imbalance between the study groups, with a substantially smaller number of patients in the seronegative RCTD group. This, together with the overall small sample size, may have reduced the statistical power and limited the ability to detect differences between groups. Therefore, findings related to the seronegative group should be interpreted with caution. Additionally, treatment-related factors, comorbidities and traditional cardiovascular risk parameters were not included in the analysis and may have influenced the observed results.

Conclusion

Our findings indicate that seropositivity, particularly the presence of rheumatoid factor, is associated with increased risk of cardiac involvement in patients with RCTDs. Echocardiographic abnormalities suggest early structural cardiac changes in seropositive patients, while age and selected hematological parameters further reflect the impact of chronic systemic inflammation and disease burden. These results highlight the importance of routine cardiac assessment, including electrocardiography and echocardiography, to enable early detection of subclinical cardiac involvement and improve long-term cardiovascular outcomes.

Authors' Contributions

EH (Conceptualization; Data curation; Methodology; Writing – review & editing, Supervision), AI (Writing – original draft, Formal analysis; Investigation; Methodology); NČ (Writing – original; Visualization; Writing – original draft;); JS (Investigation; Methodology; Formal analysis); AZČ (Formal analysis, Validation, Visualization); DS (Investigation, Software, Visualization); MM (Supervision, Writing – review & editing, Methodology).

Conflict of interest

None to declare.

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