MEDICAL UNIVERSITY - SOFIA

DEPARTMENT OF RHEUMATOLOGY

CARDIOVASCULAR RISK IN PATIENTS WITH PSORIATIC ARTHRITIS

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ABSTRACT

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SOFIA
2024

For obtaining a PhD in higher education
7. "Health and Sport" by professional field
7.1. "Medicine", scientific specialty "Rheumatology"

The dissertation is written on 202 pages, illustrated with 57 figures and 13 tables. The bibliography contains 316 titles. In connection with the dissertation 3 publications, 3 participations in scientific forums and 2 scientific projects have been realized.

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Date of defence: 25.04.2024 at 14:00 in Aula, University Hospital "St. Ivan Rilski" EAD - Sofia, ul. "Academician Ivan Evstratiev Geshov" 15

LIST OF ABBREVIATIONS USED

AH: Arterial Hypertension
anti-CCP: Antibodies to Citrullinated Peptide
ASAS: Assessment of SpondyloArthritis international Society
ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-CRP
ASQoL: Ankylosing Spondylitis Quality of Life
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BMI: Body Mass Index
BSA: Body Surface Area
BSAPs: Body Surface Area Psoriasis
Chol: Cholesterol
CHI3L1, YKL-40: Chitinase-3-like protein 1
Crea: Creatinine
CRP: C-reactive Protein
DAPSA: Disease Activity in Psoriatic Arthritis
DAS28: Disease Activity Score 28 joints C-reactive protein
DLQI: Dermatology Life Quality Index
DPAS: Dijon Physical Activity Score
EG: Endothelial Glycocalyx
EU GDPR: European Union General Data Protection Regulation
FER: Ferritin
FRS: Framingham Risk Score
GGT: Gamma-Glutamyl Transferase
GLS: Global Longitudinal Strain
Glu: Glucose
HbA1C: Glycated Haemoglobin
HAQ-DI: Health Assessment Questionnaire Disability Index
HDL: High-Density Lipoprotein
HLA-B27: Human Leukocyte Antigen B27
HOMA-IR: Homeostatic Model Assessment for Insulin Resistance
HPSE: Heparanase
HYAL: Hyaluronidase
IL-17: Interleukin 17
IMT: Intima-Media Thickness
INS: Insulin
LDI: Leeds Dactylitis Index
LEI: Leeds Enthesitis Index
LMR: Lymphocyte to Monocyte Ratio
LDL: Low-Density Lipoprotein
Lp-PLA2: Lipoprotein-associated phospholipase A2
LYM#: Lymphocytes count
MDA: Minimal Disease Activity
MetS: Metabolic Syndrome
MONO#: Monocytes count
MPV: Mean Platelet Volume
MPVLR: Mean Platelet Volume to Lymphocyte Ratio
MDS: Mediterranean Diet Score
mNAPSI: Modified Nail Psoriasis Severity Index
NEUT#: Neutrophils count
NLM: Neutrophil to Lymphocyte Ratio
OMERACT: Outcome Measures in Rheumatology
PASI: Psoriasis Area Severity Index
PECAM-1 or **CD31**: Platelet Endothelial Cell Adhesion Molecule-1
PGA: Physician Global Assessment
PLR: Platelet to Lymphocyte Ratio
PLT: Platelets
PMR: Platelet to Monocyte Ratio
PtGA: Patient global assessment
PtPAIN: Patient pain scale
PsAID: Psoriatic Arthritis Impact of Disease

PsAQoL: Psoriatic Arthritis Quality of Life
QUICKI: Quantitative Insulin Sensitivity Check Index
RAQoL: Rheumatoid Arthritis Quality of Life Questionnaire
RDW: Red Cell Distribution Width
RF: Rheumatoid Factor
RPR: Red cell Distribution Width to Platelet Ratio
SF-36: Short Form Health Survey
SYND1 or **CD138**: Syndecan-1
TG: Triglycerides
TNFα: Tumour Necrosis Factor Alpha
U: Urea
UA: Uric Acid
VAS: Visual Analogue Scale
VCAM1: Vascular Cell Adhesion Molecule 1
VLDL: Very Low-Density Lipoprotein

CONTENTS

I. INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous, chronic inflammatory disease that primarily affects the joints, tendons, entheses and skin. In recent decades, scientific literature has shown that PsA patients face an increased risk of cardiovascular disease (CVD), highlighting the systemic nature of the condition. The need for a comprehensive understanding of this relationship has never been more pressing, as the association of inflammatory arthritis and CVD poses both clinical challenges and opportunities for intervention.

In this dissertation, we use a multifaceted approach to elucidate the cardiovascular risks associated with PsA. By using a wide range of indices of disease activity and metabolic state, innovative serum markers, and diagnostic imaging techniques such as cardiac and carotid ultrasound, we aim to provide a holistic understanding of the cardiovascular consequences of PsA. This expanded methodology offers a deeper insight into the systemic nature of the disease, laying the foundation for a more targeted therapeutic approach. Large cohort epidemiologic studies suggest that inflammatory joint disease is associated with increased CVD morbidity and mortality, yet the mechanisms and details of the relationship between inflammation and CV complications remain unclear. Evidence from the literature suggests, through the use of risk algorithms and adjustment for traditional CVD risk factors, that it may be inflammation rather than a specific nosological entity that is responsible for the severity of CVD. In order to investigate the comparative characteristics and establish the cardiovascular risk of typical synovial and typical enthesopathic inflammation, we decided to extend the scope of the study and add a group of patients with rheumatoid arthritis (RA).

PsA and RA are diseases with high social relevance, significant comorbidity, which are associated with increased costs for the healthcare system and the patient. In addition to tissue-specific local inflammatory responses, significant nonspecific systemic inflammation is also present in PsA and RA. The presence of different underlying mechanisms and a variable inflammatory burden leads to a diverse pathognomonic manifestation of CVD.

The inflammatory process inherent in PsA not only causes joint and skin manifestations, but also has a wide-ranging impact on various organs and systems. The vascular endothelium, a dynamic monolayer of cells covering the interior of blood vessels, serves as a critical interface between circulating blood and underlying tissues. Disturbances in its function, largely caused by inflammatory processes, play a major role in the pathogenesis of atherosclerosis and subsequent cardiovascular complications.

The endothelial glycocalyx (EG), a thin gel-like layer that covers the luminal side of the vascular endothelium, has recently been identified as a central player in these interactions. EG acts as a barrier modulating cell adhesion, coagulation and vascular permeability. In states of chronic inflammation, such as PsA, EG is compromised, leading to its degradation, a phenomenon that contributes significantly to endothelial dysfunction. Understanding the molecular mechanisms, including the involvement of shaddase enzymes such as heparanase and hyaluronidase, may provide new insights into disease pathogenesis and potential therapeutic targets. The roles of specific markers in this regard remain to be elucidated. EG is indicative of the earliest phases of atherosclerosis and this may revolutionize the way we approach, diagnose and potentially treat the cardiovascular consequences of chronic inflammatory conditions.

Our aim was to analyze the impact of disease assessed by different serological biomarkers and ultrasonographic methodologies, such as intima-media thickness (IMT) and speckle-tracking echocardiography (STE), on the structure and function of the SS complex in patients with prototypical representatives of inflammatory joint diseases such as PsA and RA to differentiate between different nosological entities. The manifestation of SS varies among different patients with arthritis, dictated by their unique pathophysiological characteristics. For example, the metabolic syndrome that predisposes to CVD is more prevalent in PsA than in other inflammatory arthritides. Such nuances highlight the need to tailor cardiovascular risk assessment and management strategies for patients with arthritis.

We aim to uncover complex interrelationships, offering a comprehensive overview of the current understanding of cardiovascular risk in PsA comparing it with RA and healthy controls. Because multiple risk factors contribute to the onset and progression of CVD, recent advances in rheumatology have shed light on the complex relationship between chronic inflammatory conditions such as PsA and cardiovascular health. The findings not only highlight the systemic nature of these conditions but also suggest a shared pathogenetic basis. This potential overlap between the chronic inflammation characteristic of rheumatic diseases and the pathological changes seen in atherosclerosis is fundamental, promoting the notion of an intertwined pathogenesis.

Beyond the realm of inflammation, the role of the immune system, encompassing both innate and adaptive immunity, has emerged as a key player. Proinflammatory cytokines and other immune mediators demonstrate the ability to accelerate endothelial injury, thereby acting as potential accelerators in the development of CVD. The intertwined relationship between chronic inflammatory conditions and cardiovascular disease is not new. For decades, researchers have explored how conditions such as PsA extend their impact beyond joint inflammation. The systemic effects of these conditions, particularly on cardiovascular health, have become a major focus of numerous studies.

CVD being a dominant global health problem, understanding all potential risk factors, including those arising from conditions such as PsA, are of paramount importance. If a causal link is established, this may pave the way for new therapeutic interventions targeting the very genesis of cardiovascular risk.

II. AIM AND OBJECTIVES

Purpose of making famous

The aim of this thesis is to conduct a comprehensive analysis of cardiovascular risk factors in PsA patients. This analysis is placed in the context of a comparison with a group of patients suffering from RA as well as with a control group composed of healthy individuals. The comparative approach allows us to identify potential differences in cardiovascular risk profiles and associated pathophysiological mechanisms between these two nosological entities. We also detail the role of specific biomarkers, clinicodiagnostic tools, and physiological parameters in the assessment of cardiovascular involvement and structural changes in the endothelial glycocalyx among these patient populations.

Tasks

In order to achieve the above objective, the following tasks were formulated:

1. To investigate the relationships between disease activity and key clinical and laboratory indicators characterizing the inflammatory process and metabolism.
2. To analyze the impact of quality of life, physical activity and diet on disease activity and cardiovascular involvement.
3. To investigate potential correlations with changes in cell ratios between the different groups studied, using this approach as an innovative and easily accessible method to assess the condition of patients with inflammatory joint disease.
4. To assess cardiovascular involvement by carotid artery ultrasonography to measure IMT and echocardiography to determine GLS.
5. To calculate cardiovascular risk using the validated QRISK3 calculator, followed by correlation and predictive analysis to assess the association between risk profile and clinical outcomes in patients with inflammatory joint disease.
6. To determine the serum concentrations, statistically significant correlations and predictive value of key experimental biomarkers - YKL-40, SYND-1, HYAL, HPSE, VCAM1, PECAM in patients with PsA and to compare them with those in healthy controls and patients with RA.

III. MATERIALS AND METHODS

3.1. Inclusion and exclusion criteria

3.1.1. Inclusion criteria:

1. Men and women over the age of 18;
2. Confirmed diagnosis of PsA according to CASPAR classification criteria (2006);
3. Different duration and activity of the disease;
4. Patients treated with different therapeutic regimens according to the standard of care for the respective disease;

3.1.2. Exclusion criteria:

1. Age 65+;
2. Current active acute or chronic infection, including acute or chronic viral hepatitis B and C, HIV infection, or tuberculosis;
3. History of cancer in the last 5 years;
4. Diagnosed inflammatory disease other than PsA and RA, including and not limited to sarcoidosis, systemic lupus erythematosus, and reactive arthritis (individuals diagnosed with chronic ulcerative colitis or Crohn's disease are allowed to participate in the study);
5. Significant comorbidity (cardiovascular, neurological, renal, hepatic, metabolic, pulmonary, gastrointestinal, hematological, immunological, etc.) - unstable or uncontrolled acute or chronic disease;
6. Other illnesses, including mental illness, which in the opinion of the investigator are inappropriate for inclusion of the patient in the study;

3.2. Approach of the study

1. Prospective recruitment of suitable patients from 2018 to 2023.
2. Provide detailed study information to potentially eligible patients. Provide time for reflection and consultation with a GP or family. Signing of informed consent by the patient and medical researcher. Two copies of the consent, one for the research team and one for the patient.
3. Collection of comprehensive clinical data on the patients included in the study, which was properly coded and accessible only to the research team (complying with the General Data Protection Regulation - EU GDPR).

4. Conduct venipuncture to collect peripheral venous blood for analysis. Storage of serum at -80°C within 60 minutes of sample separation.
5. Coordinating with the cardiology team to perform speckle-tracking echocardiography.
6. Perform ultrasonography of carotid arteries to determine IMT.
7. Calculation of individual scores from completed questionnaires, indices and SAC.
8. Serum analysis by the immunology team.
9. Statistical data processing

3.3. Survey design

Demographic characteristics, clinical indicators of disease activity, including synovitis, enthesitis, and dactylitis, and physical function of patients were analyzed as part of the cross-sectional study. In addition, the patients' dietary habits were assessed using specialized questionnaires. Laboratory results including traditional and innovative biomarkers such as TNF, VCAM, PECAM, YKL-40, IL17, HPSE, Lp-PLA2, SYND-1 and HYAL were also integrated into the study. Cardiovascular risk assessment was conducted using specialized calculators including ultrasonography. All these data were synthesized and aggregated into a custom-designed study protocol. Baseline data for all participants (n=99) were pooled and subjected to cross-sectional analysis. Additionally, a comparative analysis of target biomarkers was performed in 60 patients from the study cohort and 20 healthy individuals to determine any difference in serum concentrations of these markers between individual nosological entities and healthy participants.

3.4. Evaluation methods and tools used in the study

3.4.1. Clinical methods

3.4.1.1. History and status

In the clinical examination process, particular attention was paid to the collection of anamnestic data for each patient - in-depth information on the duration of the disease, as well as available complications, treatment and comorbidities. A detailed musculoskeletal and skin status was taken on all patients for the detection of active synovitis, enthesitis, tenosynovitis and spinal involvement.

3.4.1.2. Assessment tools for disease activity

- **Joint Count 68/66 - 66/68-swollen and tender joint count (SJC66/TJC68):** This is a key assessment tool for the study of rheumatic diseases and measures 66 swollen and 68 painful joints. The maximum value can reach 134, where higher values indicate greater disease

activity. It has been validated by OMERACT and developed in accordance with filter 2.1 (1).

- **Psoriasis Area Severity Index (PASI): the** index can range from 0 to 72. It combines factors such as erythema, induration and desquamation, multiplying them by the percentage of the affected area. Higher values indicate more severe psoriasis (2).
- **Body Surface Area Psoriasis (BSAP) is measured as a** percentage, with 100% meaning that all the skin is affected. Reference values can vary, but generally higher values indicate increased skin involvement (2).
- **The Leeds Enthesitis Index (LEI)** is a dichotomous scale from 0 to 6, where 0 is 'painless' and 1 is 'painful' for 6 specific anatomical sites. Higher values indicate more severe enthesitis (2).
- **Leeds Dactylitis Index (LDI): a** fingerstick is used to measure the circumference and soreness of the fingers. The index can be complex, covering also the contralateral fingers for comparison (2).
- **Modified Nail Psoriasis Severity Index (mNAPSI):** 7 characteristics are assessed for each nail. Although there is no strict maximum value, higher values are associated with more severe disease (3).
- **Physician Global Assessment (PGA):** assessed on a visual analog scale (VAS), usually from 0 to 100 mm, where higher values indicate a more severe clinical picture (3).
- **VAS for Musculoskeletal Manifestations (PhysMSK)** and **VAS for Dermatologic Manifestations (PhysSk): both** are scored on a VAS scale from 0 to 100 mm. GRAPPA recommends separate assessment of skin and joint manifestations as they may vary (3).
- **Disease Activity Score 28 joints C-reactive protein (DAS-28-CRP): the** scale usually ranges from 0 to 10, where values above 5.1 indicate high disease activity (3).
- **ASAS criteria for inflammatory-type low back pain (2009).):** 1) Age at onset less than 40 years; 2) Improvement on movement; 3) Nocturnal pain or awakening from pain second half of the night: 4) Unexpected/hidden onset of pain; 5) No improvement from rest;
  When four of these five criteria are present, the likelihood that it is inflammatory back pain is considered high with a sensitivity of 79.6% and specificity of 72.4%(4)
- **Disease Activity in Psoriatic Arthritis (DAPSA): the** DAPSA is calculated using the TJC68 and SJC66 scores, the patient's global and VAS pain scores, and the C-reactive protein (CRP) level. A DAPSA score ≤14 represents a state of low disease activity, and a score ≤4 represents remission, 15-28 moderate, >28 high disease activity (3).

- **ASDAS-CRP** is an index that is used to assess the activity of ankylosing spondylitis and other related diseases. The scale and reference values may vary. We assessed disease activity status by calculating the Ankylosing Spondylitis Disease Activity Score (ASDAS) index using C-reactive protein (CRP) according to a standard formula using an online calculator (https: //www.asasgroup .org). It was interpreted as inactive disease/low disease activity ASDAS-CRP <2.1 or high/very high disease activity ASDAS-CRP ≥2.1 (5,6).
- **Minimal Disease Activity (MDA):** contains 7 criteria and a patient is considered MDA if they meet 5 of them. This index is used to assess minimal disease activity (7).
- **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI):** on a scale of 0 - 10 measures discomfort, pain and fatigue (0 is no problem and 10 is the worst problem) in response to six questions asked of the patient relating to the five main symptoms of axial spondyloarthritis. Includes 6 questions related to typical symptoms of the disease (back pain, fatigue, peripheral joint and enthesitis pain, stiffness - severity and duration). The level was interpreted as an inactive disease with BASDAI < 4 and the presence of disease activity when the magnitude of the parameters was above the indicated threshold value (8)**.**
- **Patient pain scale (PtPAIN) : a** visual analogue scale to assess patient pain. From 0-100mm (9).
- **Patient global assessment (PtGA) : a** global assessment of the patient's disease. From 0-100mm (9).

3.4.1.3. Cardiovascular risk assessment

- **Metabolic syndrome (MetS)** is a complex of conditions including obesity, insulin resistance, hypertension, and dyslipidemia. According to the International Diabetes Federation, the diagnosis requires a BMI above 30 kg/m2 or waist circumference ≥ 102 cm in men and ≥ 88 cm in women, plus two of the following five other components: ; Triglycerides ≥ 1.7 mmol/L; HDL < 1.03 mmol/L in men; < 1.29 mmol/L in women; Blood pressure ≥ 130/85 mm Hg ; Fasting blood glucose ≥ 5.6 mmol/L (10).
- **QRISK®3** is a validated algorithm developed to estimate the risk of cardiovascular disease over the next 10 years. Risk is expressed as a percentage, with a higher percentage indicating a greater risk. This assessment tool is widely applicable in clinical practice and is used to identify high-risk individuals who may benefit from preventive measures, such as lifestyle modification or drug treatment. QRISK®3 combines various parameters including age, gender, BMI, GCS treatment, presence of arthritis or systemic lupus, blood

pressure, cholesterol levels, conditions such as diabetes to provide a summary risk assessment. One of the most comprehensive validated cardiovascular risk calculators (11).

- **Body Mass Index (BMI)**, measures body mass in relation to height. High BMI is associated with greater cardiovascular risk. According to the WHO - Normal weight: BMI between 18.5 and 24.9; Overweight: BMI between 25 and 29.9; Obese grade I: BMI between 30 and 34.9; Obese grade II: BMI between 35 and 39.9 Obese grade III: BMI 40 or more; These values are generally accepted standards and are widely used in medical practice to assess the risk of various diseases, including cardiovascular disease. It is important to note that BMI does not take into account body fat distribution or muscle mass, and therefore cannot be used alone as an absolute indicator of an individual's health status.
- **Arterial hypertension (AH)** is characterized by persistently elevated blood pressure. Systemic pressure ≥ of 130 and/or diastolic pressure ≥ of 85 mm Hg is considered hypertension.
- **Body Surface Area (BSA)** is used to normalize various cardiac parameters. Reference values for BSA vary but are usually measured in square meters.

3.4.1.4. Quality of life and burden of disease

- **The Psoriatic Arthritis Impact of Disease (PsAID) :** This validated questionnaire is specifically designed to assess disease burden in patients with psoriatic arthritis. The questionnaire covers various aspects of the patient's life that may be affected by the disease, including physical activity, emotional and psychological state, work capacity and social interactions. The assessment is performed by collecting and averaging the responses to all questions, and the result is used to assess the patient's general condition. It includes 12 questions with answers ranging from 0-10 (0 being no problem and 10 being the worst problem) (12).
- **RAQoL (Rheumatoid Arthritis Quality of Life Questionnaire)** : The questionnaire is specific to rheumatoid arthritis and assesses how the disease affects various aspects of the patient's daily life, including physical activity, emotional state, and social interactions (13).
- **The Psoriatic Arthritis Quality of Life (PsAQoL) :** specific to psoriatic arthritis, this questionnaire focuses on how the disease affects a patient's daily life, including physical activity and social interactions (14).
- **Ankylosing Spondylitis Quality of Life (ASQoL) :** This questionnaire is also used in patients with axial involvement in psoriatic arthritis and assesses the impact of the disease

on quality of life. Reference values depend on the context and population, but higher values usually indicate poorer quality of life (15).

- **Dermatology Life Quality Index (DLQI) :** This questionnaire measures the impact of skin disease on quality of life and includes ten questions that relate to symptoms and feelings, activities and personal relationships. Reference values: 0-1 (no effect), 2-5 (mild effect), 6-10 (moderate), 11-20 (severe), 21-30 (very severe) (3).
- **The Health Assessment Questionnaire Disability Index (HAQ-DI) focuses on** daily activities and tasks that may be impeded by arthritic conditions. The questionnaire includes various categories such as independence in the home, walking and grasping objects. Reference scores depend on the population and context, but higher scores generally indicate poorer functional status (16).
- **The Short Form Health Survey (SF-36) :** this universal quality of life assessment tool measures eight domains including physical function, emotional function, energy, and general health. The reference values can be used for comparison with normative data for the relevant age group and sex. a set of common, coherent, and easily applicable quality of life measures (17).

3.4.1.5 Physical activity and diet

- **The Mediterranean Diet Score (MDS)** assesses adherence to a Mediterranean diet, which is associated with reduced cardiovascular risk. The MDS scale ranges from 0 to 9, with higher scores indicating better diet adherence. It is one of the most studied and validated diet questionnaires worldwide (18,19).
- **Dijon Physical Activity Score (DPAS)** : a validated physical activity questionnaire. This questionnaire was developed to measure an individual's physical activity, taking into account various aspects such as duration, intensity and frequency of physical exercise or activity (20).
- **Short frequency questionnaire (SfdietQuest)** : a short validated questionnaire on diet and habits constructed by the University of Leeds (21).

3.4.2 Ultrasonographic imaging diagnostics

3.4.2.1. Speckle tracking echocardiography

Global Longitudinal Strain (GLS) is a parameter measured by speckle tracking echocardiography that provides information about myocardial deformation or shortening of the heart muscle in the

longitudinal direction. This parameter is extremely sensitive to early changes in cardiac function and is considered one of the most predictive markers of cardiomyopathies and other heart diseases. Speckle tracking echocardiography is a technology that uses "speckles," or small, clearly identifiable areas in the echogenic structure of the myocardium, to monitor the movement of the heart muscle through the cycle of contraction and stretch. This allows extremely precise assessment of various aspects of cardiac function, such as GLS. Reference values for GLS vary depending on measurement methodology and instrumentation, but normal values are generally considered to be between -18% and -22%. Values that are higher (closer to zero or positive) are usually an indicator of impaired cardiac function. In the context of cardiovascular risk, measuring GLS can provide early signals of myocardial ischemia, cardiomyopathy, or other conditions that can affect cardiac function and increase the risk of cardiovascular events, such as heart attack or stroke. Therefore, GLS is an important parameter to integrate into an overall cardiovascular risk management strategy (22). The study was conducted by experienced cardiology specialists at the University Hospital of Alexandrovska and University Hospital of St. Petersburg. Ivan Rilski with a General Electric sonograph (GE E95).

3.4.2.2 Carotid artery ultrasonography

Intima-media thickness is a parameter measured by carotid artery ultrasonography that is used as a biomarker for atherosclerosis and cardiovascular risk. IMT represents the thickness of the two main layers of the artery wall, the intima and the media. High IMT values are associated with an increased risk of cardiovascular disease, such as coronary disease, stroke, and peripheral arterial disease (23). We used a high-frequency 15 Mhz linear probe and ESAOTE's specialized quality IMT (qIMT) software (MyLab 70), which automatically measures carotid artery intima media thickness, calculating standard deviation and verifying the value.

3.4.3. Laboratory tests

Patients' blood samples were collected in the morning on an empty stomach after a 12-hour fast by an experienced clinical laboratory technician. Some of the samples were sent to the clinical and immunological laboratory of UMHAT “St. Ivan Rilski” EAD. After distribution of the separated serum, in equal portions in individual vials, it was frozen within 60 minutes of sample collection in a freezer at -80°C for storage until the examination.

3.4.3.1. Cellular, immunological and biochemical analysis

In the present study, we used flow cytometry as our main methodological approach to quantify hematological markers. This technique offers high precision and reproducibility. Below are the markers of interest:

- **Leukocytes (WBC): the** reference range is between 3.50 - 10.80 x 10^9/L;
- **Platelets (PLT):** reference range 112 - 330 x 10^9/L;
- **Lymphocytes (LYM#):** reference range 1.00 - 4.50 x 10^9/L;
- **Monocytes (MONO#):** reference range 0.40 - 1.10 x 10^9/L;
- **Neutrophils (NEUT#):** reference range 2.00 - 7.00 x 10^9/L;
- **Red cell distribution width (RDW): this** parameter indicates the variability in red cell size. Reference range 11.50 - 14.00 %
- **Mean platelet volume (MPV):** This gives an idea of the size of the platelets, which can be an indicator of platelet function and the body's ability to form clots. Increased MPV often correlates with increased platelet activation. Reference range 6.2 - 10.6 femtolitres (fm)

Various hematological ratios were calculated for additional detail in the analysis. These ratios provide additional information that cannot be obtained by individual parameters alone. The following ratios were estimated:

- **Neutrophil to lymphocyte ratio (NLM):** this ratio serves as an inflammatory marker and varies in different pathological conditions. Reference range: 1.5-3.0 (24);
- **Platelet to lymphocyte ratio (PLR):** commonly used as a prognostic factor in various cancers, this ratio also plays a role as an inflammatory marker. Reference range: 100-200 (25);
- **Lymphocyte-to-monocyte ratio (LMR):** this ratio provides additional information about the state of the immune system and is often considered in infectious diseases and malignancies. Reference range: 2.0-5.0 (26);
- **Platelet to monocyte ratio (PMR):** This less commonly used ratio provides another perspective on systemic inflammation. Reference range;
- **Red cell distribution width ratio (RDW) to platelet distribution width ratio (RPR):** usually a higher RPR ratio may indicate underlying chronic disease or inflammation. Reference range;

- **Mean platelet to lymphocyte volume ratio (MPVLR):** this ratio is being studied for its possible implications in inflammatory conditions and cancer. Reference range: not yet standardized;

The following markers relevant to cardiovascular risk and disease activity were also examined by laboratory analysis of the samples:

- **Erythrocyte sedimentation rate (ESR):** reference range varies by age and sex, usually < 22 mm/hr for males and < 29 mm/hr for females;
- **C-reactive protein (CRP):** reference range <6 mg/L;
- **Creatinine (Crea):** reference ranges up to 134.00 µmol/l in men and up to 96 µmol/l in women;
- **Urea (U):** Reference range up to 60.00 U/L;
- **Uric acid (UA): the** reference range is 200.00 - 420.00 µmol/l in men and 142.00 - 340.00 µmol/l in women;
- **Gamma-glutamyl transferase (GGT): the** reference range is 0-30 U/L;
- **Ferritin (FER): the** reference range is 24-336 ng/mL for men and 11-307 ng/mL for women;
- **Glucose (Glu):** reference range 3.50 - 6.10 mmol/l;
- **Glycated haemoglobin (HbA1C)** is an indicator widely used to assess the average blood glucose level over the past 2-3 months. HbA1C testing is considered robust and reliable and is used in both clinical practice and research. Reference values: Normal levels: 4-5.6% Prediabetes: 5.7-6.4% Diabetes: 6.5% or more;
- **Insulin (INS): the** reference range is 3-17 mkIU/mL;

HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) and **QUICKI (Quantitative Insulin Sensitivity Check Index)** are two widely used methodologies to assess insulin resistance and insulin sensitivity. These two indices are calculated based on blood glucose and insulin concentrations and provide information on the metabolic state of an individual.

- HOMA-IR Formula: HOMA-IR = (Plasma glucose [mmol/l] x Insulin [µU/ml]) / 22.5 Reference range: < 2.5 (normal insulin sensitivity), > 2.5 (insulin resistance) (27)

- QUICKI Formula: QUICKI = 1 / [log(Insulin [µU/ml]) + log(Glucose [mg/dl])] Reference range: > 0.33 (normal insulin sensitivity), < 0.33 (reduced insulin sensitivity) Both

measurements are widely used in research and clinical practice to identify individuals at increased risk of developing type 2 diabetes or other metabolic conditions (27).

The HOMA-IR is one of the most widely used indices to assess insulin resistance in clinical and epidemiological studies. Its advantages include its simple and robust calculation methodology, and the large number of publications in which it has been used. QUICKI, on the other hand, has been proposed as a more accurate indicator of insulin sensitivity and has been shown to correlate slightly better with standard insulin sensitivity tests compared with HOMA-IR(28).

- **Total cholesterol (Chol)** has normal values less than 5.2 mmol/L, elevated between 5.2-6.2 mmol/L and high above 6.2 mmol/L;
- **High-density lipoprotein (HDL)** is normal above 1.55 mmol/L and low below 1.04 mmol/L;
- **Low-density lipoprotein (LDL)** is optimal below 2.6 mmol/L, intermediate between 3.4-4.1 mmol/L and high above 4.9 mmol/L;
- **Very low-density lipoprotein (VLDL)** normal range of 0.13 to 0.52 mmol/L;
- **Triglycerides (TG)** are normal below 1.7 mmol/L, elevated between 1.7-2.3 mmol/L and high above 2.3 mmol/L;
- **The Chol/HDL ratio** is one indicator used to assess the risk of cardiovascular disease. A lower value is considered better and indicates a lower risk. Typically, target values for this index are lower for women compared to men. Normal values can vary, but usually target values are: Chol/HDL below 5: considered normal or low risk. Chol/HDL ratio above 5: indicates increased risk of cardiovascular disease (29).
- **Human leukocyte antigen B27 (HLA-B27)** examined by flow cytometric immunophenotyping (30)
- **Rheumatoid factor IgM (RF)** by ELISA. Measured in IU/mL, the reference value is >20;
- **Antibodies against cyclic citrullinated peptides (anti-CCP)** by ELISA. Also measured in U/mL, where values above 20 U/mL are considered pathological;

3.4.3.2. Experimental biomarkers

The biomarker study was conducted by experienced specialists in the Clinical Immunology Laboratory at St. Ivan Rilski EAD, following the manufacturer's instructions. A solid-phase immunoenzymatic method using commercial *ELISA* kits was applied for biomarker determination.

- **Lipoprotein-associated phospholipase A2 (Lp-PLA2)** : commercial *ELISA* kit *HUMAN Lp-PLA2/PLA2G7/PAF-AH Lp-PLA2* (*ThermoFisher Scientific*); *Cat.No:EH304RB* was

used for quantification of Lp-PLA2 in serum. Analytical sensitivity 8.1 ng/mL. Assay range 8.19-2000 ng/mL;

- **Heparanase (HPSE) :** *Human Heparanase ELISA* kit *(Abbexa) Cat.no:abx151795* with analytical sensitivity <13.3 pg/mL was used for quantification of serum heparanase concentration. Assay range 31.2 - 2000 pg/mL;
- **Hyaluronidase (HYAL) : A** *Human Hyaluronidase ELISA kit (Abbexa) Cat.no: abx350613* with an analytical sensitivity of 1.88 ng/mL was used for quantification of serum hyaluronidase concentration. Assay range 3.13 - 200 ng/mL;
- **Vascular Cell Adhesion Molecule 1 (VCAM1) :** *Human VCAM1 ELISA kit (ELK Biotechnology); Cat.No.: ELK1256* with analytical sensitivity 0.29 ng/mL; Assay range 0.79 - 50 ng/mL was used for quantification of serum VCAM1 concentration;
- **Platelet endothelial cell adhesion molecule-1 (PECAM-1 or CD31) : A** *HUMAN PECAM CD31 ELISA kit (Abbexa) Cat.no.: abx250160* with an analytical sensitivity of 18.8 pg/mL was used to quantify the serum concentration of PECAM-1. Assay range 31.2 - 2000 pg/mL;
- **Tumor necrosis factor alpha (TNFα) :** *Diaclone Human TNFα ELISA* Kit *Cat.No.: 950.090.090* with an analytical sensitivity of 8 pg/mL. Assay range 25 - 800 pg/mL;
- **Interleukin 17-A (IL-17A) : A** *Human IL-17A ELISA kit (Diaclone) Cat.#:850.940.096* with an analytical sensitivity of 2.3 pg/ml was used to quantify serum IL-17A concentration. Assay range: 3.125-1000 pg/ml;
- **Chitinase-3-like protein 1 (CHI3L1 or YKL-40) :** *HUMAN Chitinase-3-like Protein 1 (CHI3L1) ELISA kit (Abexxa) Cat.no:abx575447* with analytical sensitivity 37.5 pg/mL was used for quantification of serum Chitinase-3-like protein 1 concentration. Assay range 62.5 - 4000 pg/mL;
- **Syndecan-1 (SYND1 or CD138)** : *HUMAN sCD138 (Syndecan-1) (Diaclone) ELISA kit Cat.no:950.640.096* with analytical sensitivity of 4.94 ng/mL was used to quantify the serum concentration of Syndecan-1. Assay range 8 - 256 ng/mL;

3.4.3. Statistical methods

Basic descriptive statistics such as mean, median, standard deviation, and frequency tables with absolute and relative frequencies were calculated. The results are presented graphically by bar, box-plot and pie charts as well as heat maps. Means with SDs and percentages were calculated to describe the clinical and laboratory characteristics of the subjects. Between-group comparisons were performed by analysis of variance (Kruskal-Wallis test) and Mann-Whitney U test. Proportional differences were tested using χ-

squared (χ^2) and Fisher's exact test. Spearman's correlation coefficients were calculated to assess univariate correlation between the different parameters examined. The correlation relationships between the different variables were examined using Spearman's correlation coefficients.

Data processing was performed using the statistical packages SPSS versions 26.0 and 22.0 (IBM, SPSS Inc., Chicago, IL, USA) and the Python programming language. The Python libraries Pandas for data preprocessing, Scipy for statistical analyses, and Seaborn for graphical visualizations were used. For all analyses used, differences were considered statistically significant at a significance level of $p < 0.05$, with the corresponding null hypothesis rejected for results showing p-values less than 0.05.

IV. RESULTS

4.1. Summary of key indicators in the study cohort

We enrolled a total of 99 individuals in the study, 49 with PsA, 30 with RA, and 20 healthy controls. For the PsA group, 25 were male (51%) and 24 were female (49%). The mean age (mean ± SD) of the patients was 49.93 ± 11.31 (28 - 65 years). The mean body mass index (BMI) was 28.17 ± 6.05 (18.91 - 48.44). Mean body surface area (BSA) was 1.91 ± 0.24 (1.50 - 2.43 m^2). The mean duration of psoriasis was 19.66 ± 12.66 (3 - 54 y). The mean duration of arthritis was 9.82 ± 9.09 (0 to 36 y). Regarding therapy, 15% of the patients were on biologic disease-modifying antirheumatic drug (bDMARD), 38.46% were on conventional synthetic disease-modifying antirheumatic drug (ccDSMARD), 31.71% were on glucocorticosteroid (GCS) treatment, and 24.39% were on nonsteroidal anti-inflammatory drugs (NSAIDs).

For comparative analysis, we used a cohort of RA patients diagnosed based on the ACR/ EULAR classification criteria (2010). The sex distribution of this group was: 7 males (23%) and 23 females (77%). The mean age of RA patients was 50.47 ± 8.97 (24 to 63). BMI was 24.17 ± 3.93 (18.04 to 34.01). BSA was 1.79 ± 0.21 (1.39 to 2.20 m2). The mean duration of arthritis was 10 ± 10.05 (0 to 42 y). Regarding therapy, 6.67% of patients were on bDMARDs, 55.17% were on csDMARDs, 58.62% were on GCS and 26.67% were on NSAIDs. In addition, a comparison was made with 20 healthy subjects, 5 males and 15 females, aged 28 to 65 years, mean age 45.9 ±12.4 years, BMI 21.3 ± 4.2. Participants were sex-age matched. Among patients with PsA, only 8.16% were identified as HLA-B27 positive.

Features	PsA	RA
Age (years) (mean ± SD)	49.93 ± 11.31 (28-65)	50.47 ± 8.97 (24-63)
Gender (male, n (%))	25 (51%)	7 (23%)
Gender (female, n (%))	17 (49%)	23 (77%)
Duration of arthritis (years) (mean ± SD)	9.82 ± 9.09 (0-36)	10.00 ± 10.05 (0-42)
BMI (mean ± SD)	28.17 ± 6.05 (18.91 - 48.44)	24.17 ± 3.93 (18.04 - 34.01)
BSA (m2) (mean ± SD)	1.91 ± 0.24 (1.50 - 2.43)	1.79 ± 0.21 (1.39 - 2.20)
Therapy		
bBMARL (%)	15%	6.67%
ccBMARL (%)	38.46%	55.17%
GCS (%)	31.71%	58.62%
NSAIDS (%)	24.39%	26.67%

Table 1. Main demographic characteristics and therapy in patients with PsA and RA

BMI body mass index; **BSA** body surface area; **bBMARD** biologic disease-modifying antirheumatic drugs; **ccBMARD** disease-modifying antirheumatic drugs; **GCS** glucocorticosteroids; **NSAID** nonsteroidal anti-inflammatory drugs; **SD** standard deviation;

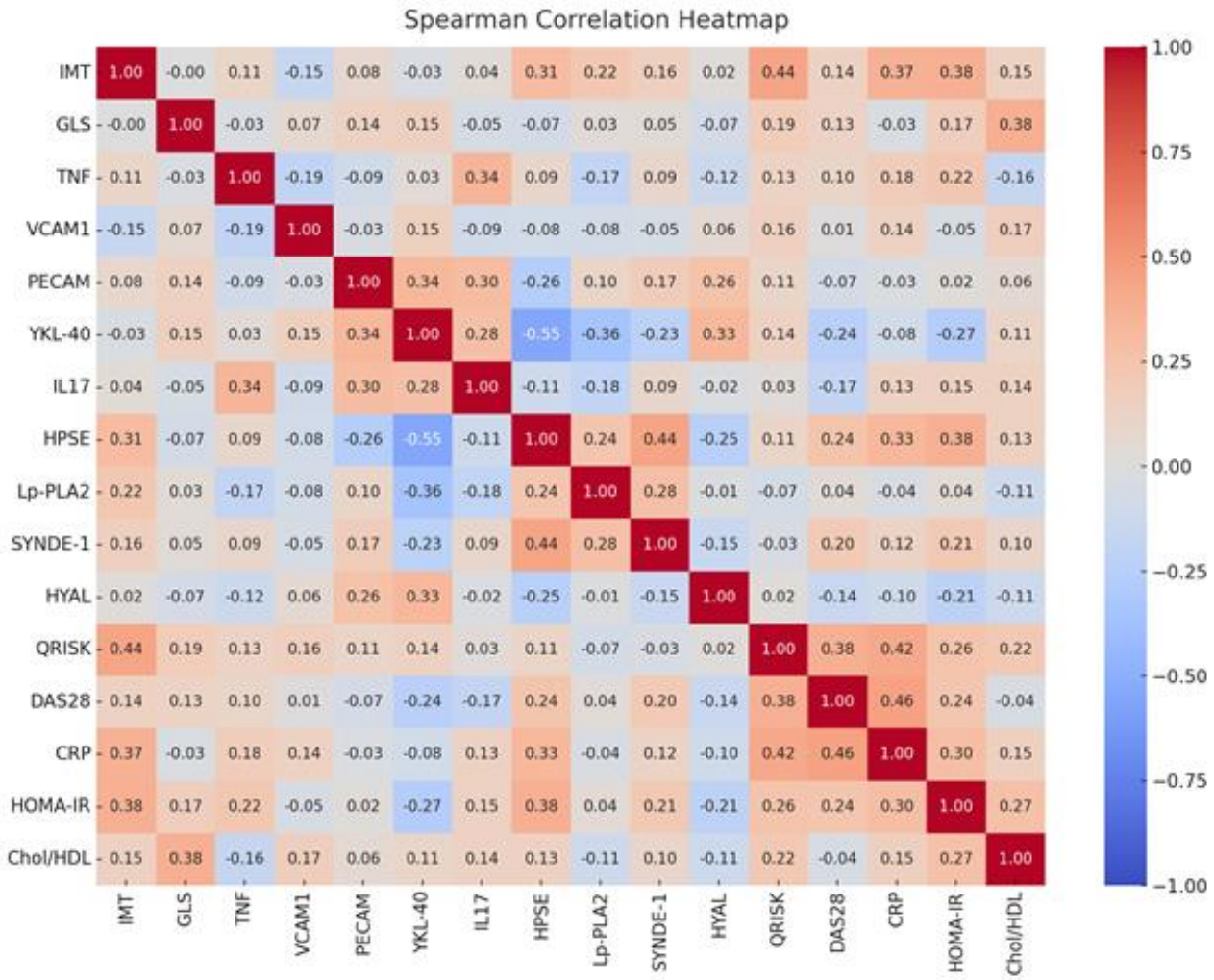


Figure 1. Spearman correlation matrix (Heat Map) depicting the main correlations between the studied biomarkers

4.2 Clinico-laboratory evaluation of the examined patients in terms of disease activity

4.1.1. Disease duration

Arthritis age was 9.83 ± 9.09 (0 - 36 years). In the RA group, it was 10 ± 10.05 (0 - 42 y) (Figure 3).

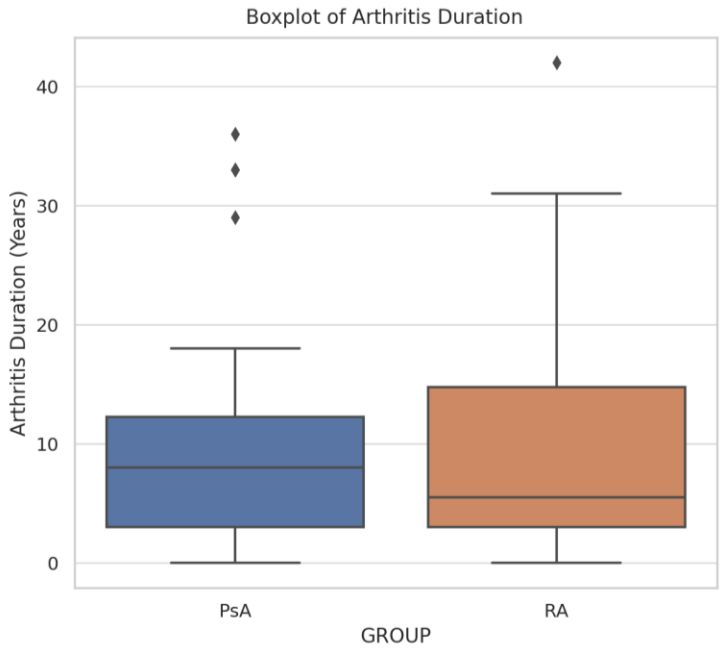


Figure 3. Box-plot depicting the duration of arthritis in the PsA and RA groups

In the dataset covering PsA and RA patients, there were notable correlations between disease duration and other key variables such as SF-36, triglycerides (TG) and GLS. For arthritis duration, we observed a moderate negative correlation with the SF-36 quality of life measure, r(66) = -.34, p<.001. In addition, there were moderate positive correlations with TG, r(66) = .30, p=.020, and GLS, r(66) = .34, p=.01. Similarly, for psoriasis age, there was a moderate negative correlation with SF-36, r(31) = -.39, p = .030, and a weak positive correlation with TG, r(32) = .20, p = .25, and a moderate positive correlation with GLS, r(14) = .39, p = .15.

Arthritis duration showed a weak positive correlation with the DAS28 disease activity score, r(62) = .14, p = .29. On the other hand, duration of psoriasis showed a moderate positive correlation with DAS28, r(32) = .36, p = .043. While the correlation between arthritis duration and DAS28 was not statistically significant, the correlation between psoriasis duration and DAS28 was statistically significant p < .05.

4.1.2. Clinical indicators

Patient-reported pain (ptPAIN) had a mean of 56.45 (SD = 22.53), and patient global assessment (ptGA) M = 57.56 (SD = 19.04). The number of painful joints based on 68 joints (TJC68) had a mean of 11.07 (SD = 10.28) and the number of swollen joints based on 66 joints (SJC66) weret 2.91 (SD = 3.71). For the physician musculoskeletal score (PhysMSK), the mean was 35.61 (SD = 24.04), and for the physician skin score (PhysSk), the mean was 21.88 (SD = 24.43). Physician Global Assessment (PhysGA) had a mean of 36.25 (SD = 22.44).

Specifically, for PsA patients, the Psoriasis Area and Severity Index (PASI) was 3.86 (SD = 6.34), and the mean body surface area (BSA) was 6.44% (SD = 11.99). Inflammatory type back pain (IBP) was experienced by 40% and dactylitis by 17% of patients with PsA.

The results of Mann-Whitney U-tests between PsA and RA showed the following. For ptPAIN, the result was not statistically significant ($z = -1.17$, $p = .244$). The same was true for ptGA, which also showed no significant difference between groups ($z = -0.86$, $p = .395$). TJC68 also showed no significant difference ($z = -0.68$, $p = .499$). However, there was a significant difference SJC66 ($z = -1.98$, $p = .043$). Physician Global Assessment (PhysGA) showed no significant difference between the two groups ($z = -0.38$, $p = .709$). These results suggest that the PsA and RA groups were largely similar with respect to the clinical markers examined, with the exception of SJC66 (Figure 4).

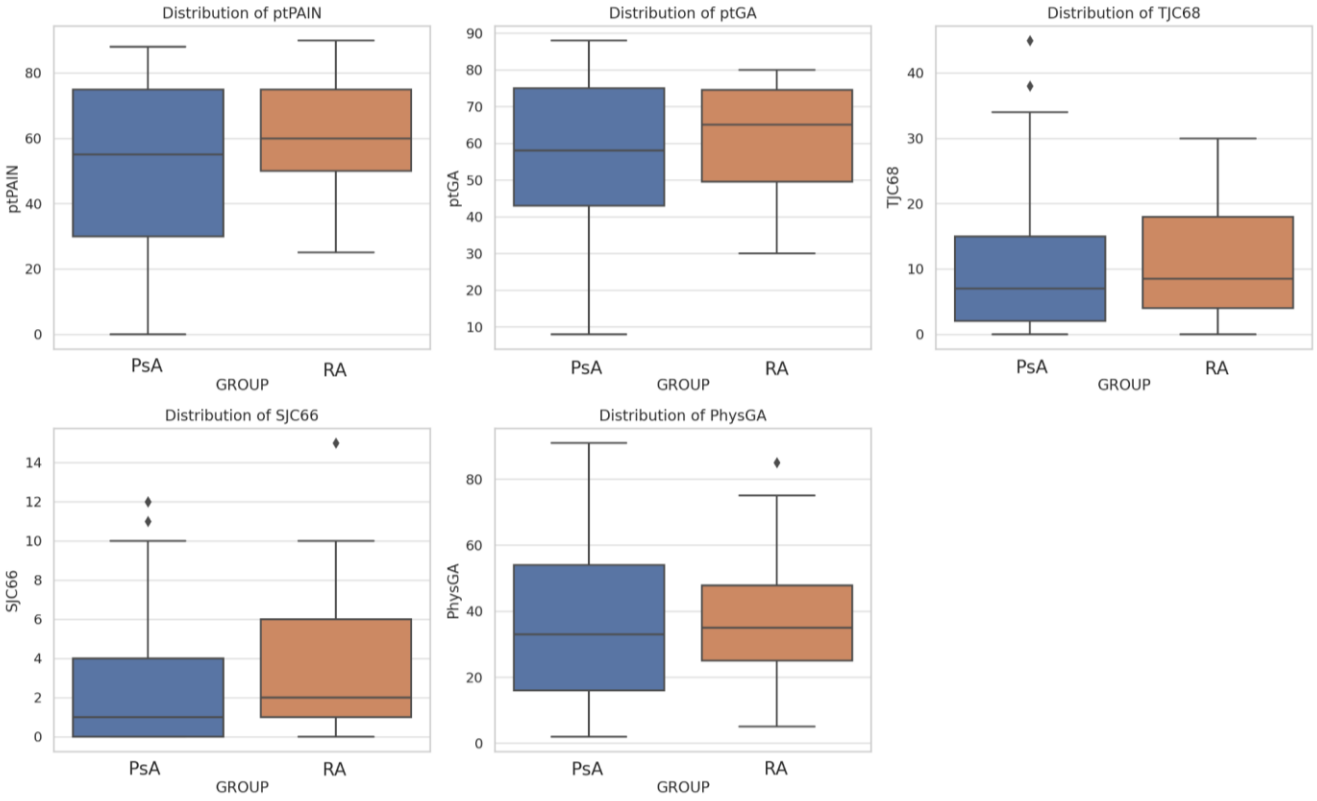


Figure 4. Box-plot depicting the distribution of clinical indicators reported pain(ptPAIN), patient global assessment (ptGA), number of painful joints based on 68 joints (TJC68), number of swollen joints based on 66 joints (SJC66), physician global assessment (PhysGA) in PsA and RA patients.

Cliff's Delta is a nonparametric measure of effect size that quantifies the degree of overlap between two distributions. In the analysis of SJC66, the value of Cliff's Delta was approximately -0.14, 95% CI [-0.26, -0.01]. This effect size, although small in magnitude, suggests a slight tendency for the RA group to have a higher number of edematous joints compared with the PsA group.

Strong correlations between ptPAIN and ptGA were observed in both groups. Specifically, in PsA, the correlation between ptGA and the Disease Activity Index in Psoriatic Arthritis (DAPSA) was very strong ($r = .90$, $p < .001$), as were the correlations between ptPAIN and ASDAS-CRP ($r = .83$, $p < .001$), ptGA and ptPAIN ($r = .82$, $p < .001$), and ptPAIN and Psoriatic Arthritis Impact of Disease (PsAID) ($r = .80$, $p < .001$). Similarly, in RA, the correlation between ptGA and ptPAIN was also very strong ($r = .74$, $p < .001$), as was the strong correlation between ptGA and DAS28 ($r = .55$, $p = .003$) and ptPAIN and Rheumatoid Arthritis Quality of Life (RAQoL) ($r = .54$, $p = .003$).

4.1.3. Laboratory indicators

4.1.3.1. Ostrophase indicators

In the PsA group, 16 of 49 patients had SUE levels above the sex-specific cutoff values, representing 32.65% of the cohort. In addition, 14 patients (28.57%) had elevated CRP levels. In the control group, none of the 20 participants had SUE levels above the sex-specific limits. Similarly, only 2 of the 20 participants (10.00%) had elevated CRP levels. In the RA group, 10 out of 30 patients (33.33%) had elevated SUE levels above the gender specific limits. Meanwhile, 13 of 30 patients (43.33%) had CRP levels above the threshold of 6 mg/L. These results suggest that a significant proportion of patients in the PsA and RA groups had elevated ESR and CRP levels, indices typically associated with disease activity and inflammation (Figure 6).

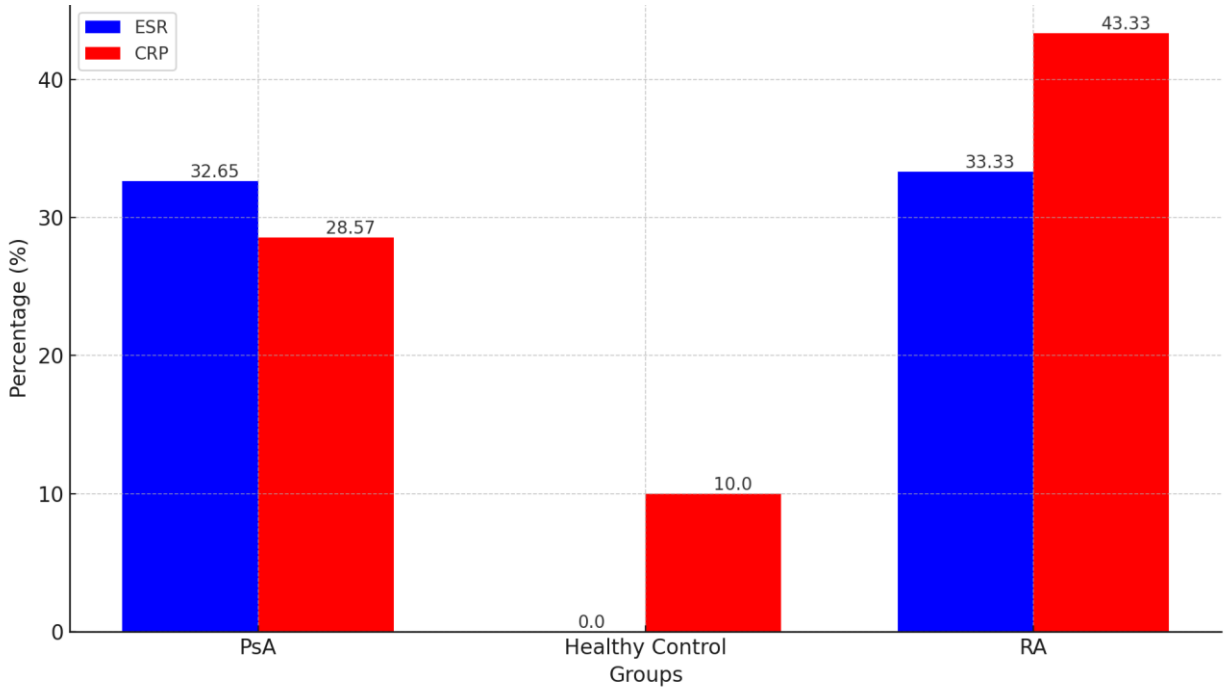


Figure 6. The bar graph illustrates the percentage of patients in each group who exceeded the ESR and CRP cutoffs.

ESR : erythrocyte sedimentation rate; **CRP :** C reactive protein

4.1.3.2. Lipid profile and metabolic syndrome

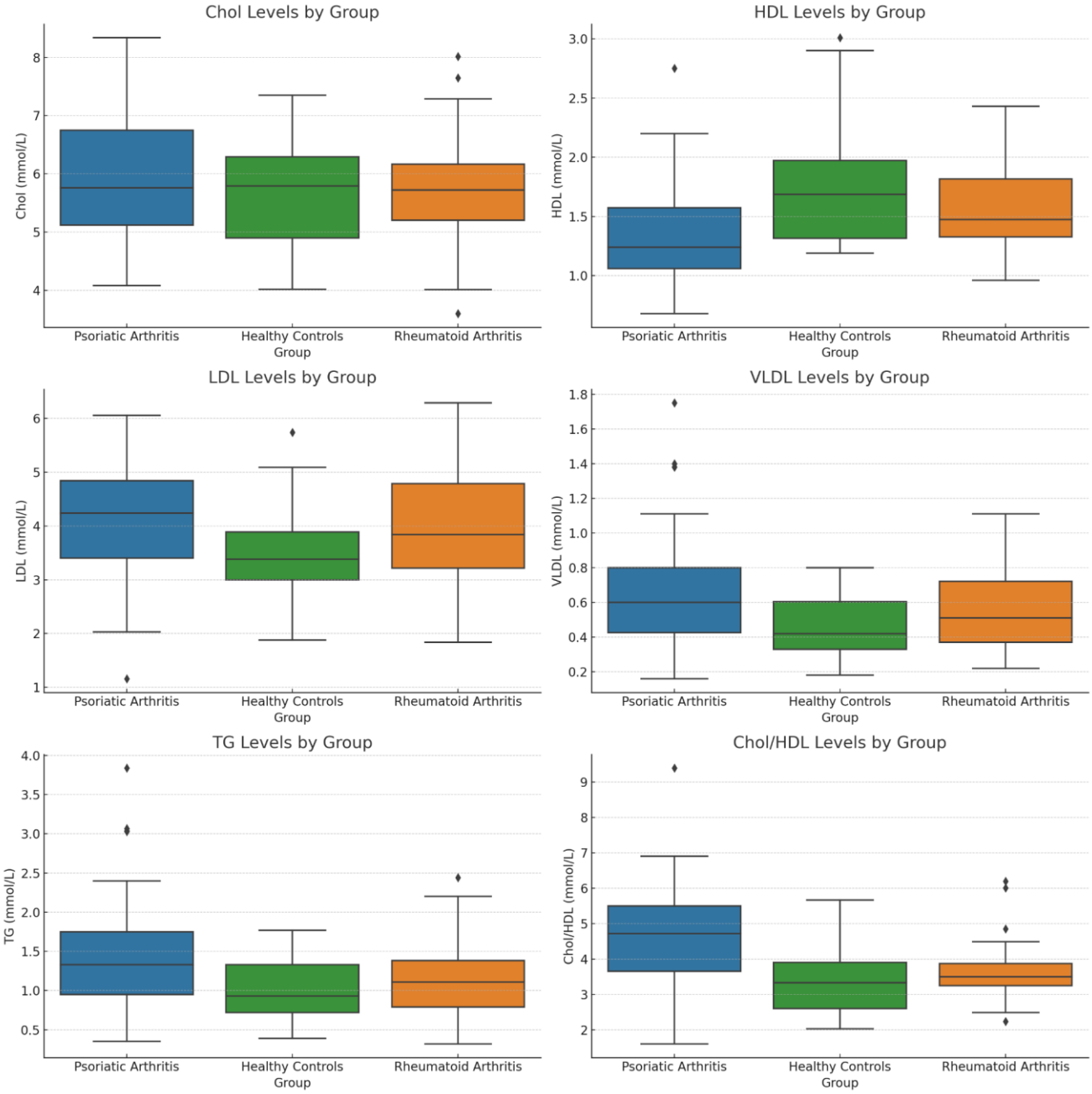


Figure 8. Boxplots visually representing the distribution of each lipid profile component for the three groups. Each boxplot shows the median, interquartile range, and all potential outliers for the groups

Chol: total cholesterol; **HDL**: High-Density Lipoprotein; **LDL**: Low-Density Lipoprotein; **VLDL**: Very Low-Density Lipoprotein; **TG**: Triglycerides; **Chol/HDL**: Cholesterol to HDL ratio.

The Mann-Whitney U test was used in the comparative analysis of lipid profiles of PsA and RA patients There were no significant differences in total cholesterol, c (U = 664 and p = .568), or LDL levels (U = 664, p = .560). Similarly, VLDL (U = 690, p = .181) and TG (U = 756, p = .102) were not significantly different. In contrast, HDL levels showed a significant difference (U = 351, p = .003), as did Chol/HDL, (U = 882, p < .001) (Figure 8).

The Mann-Whitney U test comparing the presence of metabolic syndrome (MetS) between the PsA group and the RA group had a score of U = 905.5 and p = .009. The p value was less than .05, indicating a statistically significant difference in MetS status between the two groups (Figure 9).

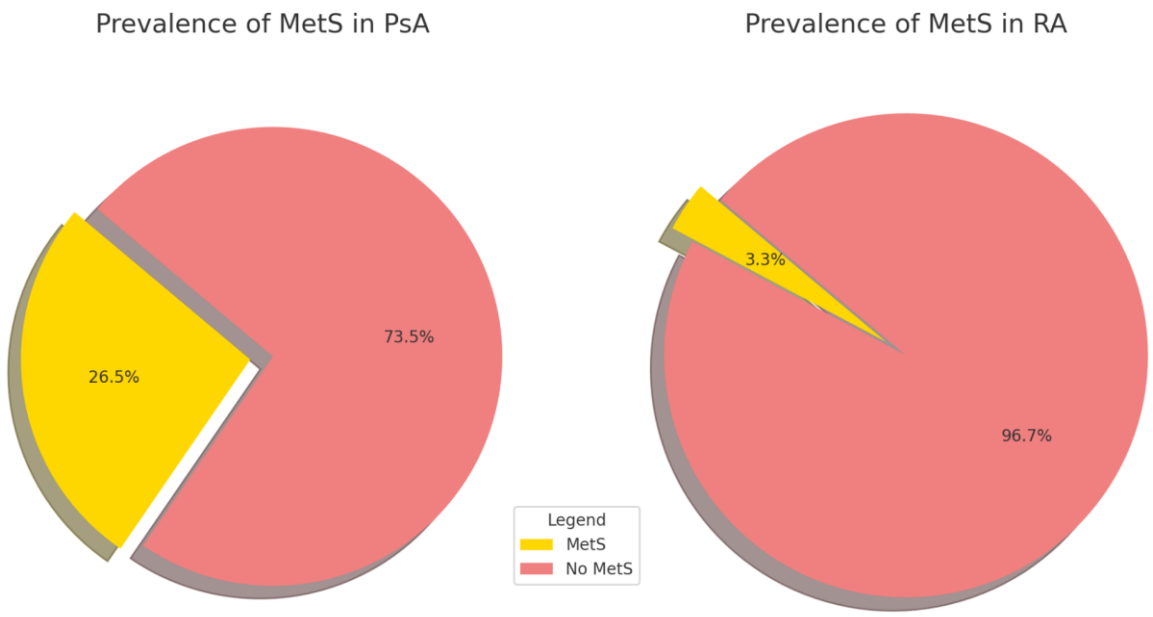


Figure 9. Pie-chart representing percentage prevalence of metabolic syndrome (MetS) in patients with PsA and RA.

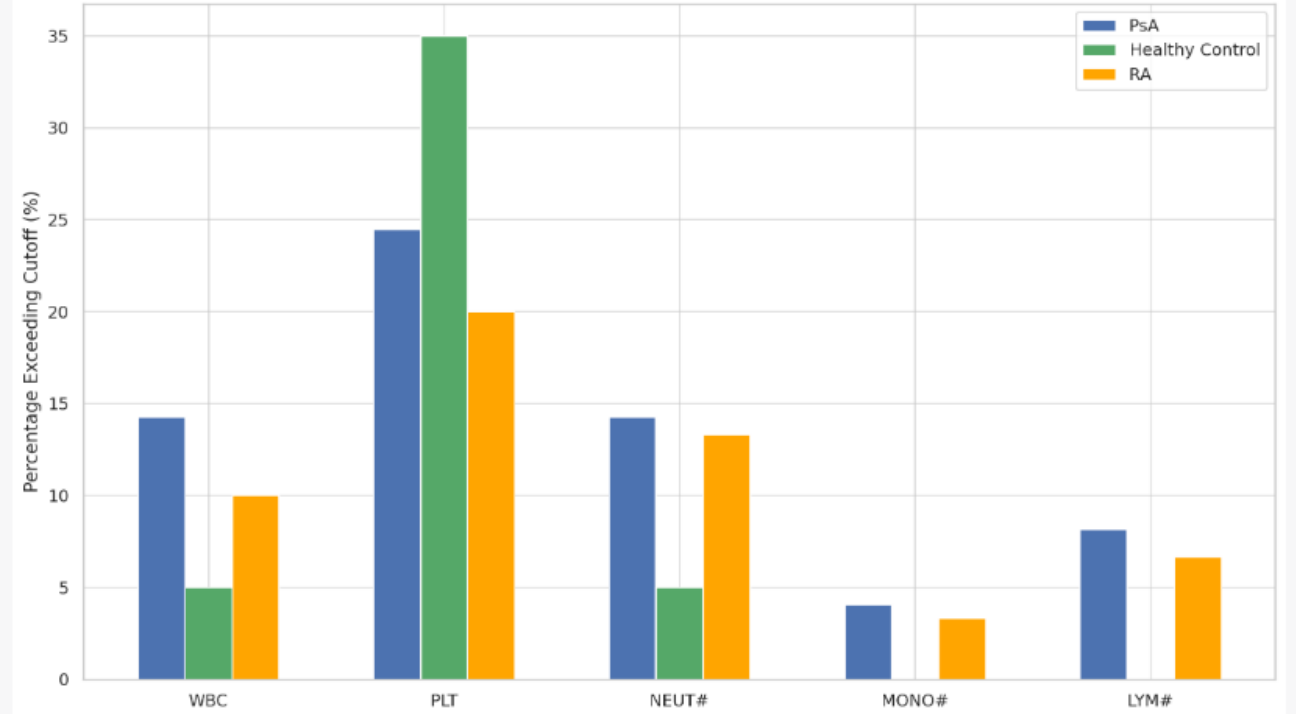
4.1.3.3. Cell markers

In terms of both the mean values and the percentages exceeding the established cut-off values for specific cell lines, different patterns emerged in the three groups. For WBC, the PsA group not only showed the highest mean value of 9.20, but also had the highest percentage of patients (14.29%) exceeding the

cutoff value. Similar trends were observed for NEUT#, where the PsA group had the highest mean at 5.46 and the highest percentage of patients (14.29%) exceeding the cutoff value. In the context of MONO#, the RA group stands out with a mean of 0.82 and 3.33% of patients exceeding the cutoff value.

Interestingly, the healthy control showed the highest percentage of patients (35%) exceeding the cutoff value for PLT, despite having a lower mean value of 295.00 compared to the PsA and RA groups. Finally, for LYM#, the PsA group had both the highest mean value of 2.71 and the highest percentage of patients (8.16%) falling outside the normal range (Figure 10).

Figure 10. Percentage distribution of patients by groups exceeding the reference values of cell parameters



WBC: White Blood Cell count; **PLT**: Platelet count; **NEUT#**: Neutrophil count; **MONO#**: Monocyte count; **LYM#**: Lymphocyte count.

4.1.3.4. Serum levels of RF and anti-CCP

A distinct pattern was present for both rheumatoid factor (RF) and anti-anti-cyclic citrullinated peptide (apti-CCP) levels. For RF, the PsA group had 4 individuals above the cutoff, the 2 healthy controls had 2 above the cutoff, whereas the RA group had 21 seropositive individuals. Chi-square test showed a highly significant difference in the distribution of RF levels across groups ($\chi^2 = 39.64$, $p < .001$). Similarly, for the apti-CCP, PsA had 2 individuals with values above the reference cutoff, In the healthy contralateral, all 20 individuals were below the cutoff, and RA had 25 positives. The chi-square test also showed a highly

significant difference in the distribution of anti-CCP levels in these groups (χ^2 = 68.32, p < .001). These results suggest a strong association between disease groups and elevated levels of both RF and anti-CCP. In particular, the RA group had a higher proportion of individuals with levels above cutoff values, which is consistent with the diagnostic criteria and pathophysiology of rheumatoid arthritis.

Moderate and statistically significant correlations were found between RF and anti-CCP and other variables. Specifically, Spearman's rank correlation showed that RF had a statistically significant relationship with RAQoL (rs = .46, p = .014), Insulin (r = .43, p < .001), and SJC66 (rs = .46, p < .001). On the other hand, anti-CCP showed a statistically significant association with Insulin (r = .44, p < .001), HOMA-IR (r = .40, p < .001), TNF (r = .50, p < .001), HPSE (r = .46, p < .001), and CRP (r = .33, p = .002).

4.1.3.5 Serum levels of IL-17 and TNF-α

The serum concentrations of the cytokines studied and the comparison between the groups - PsA, RA patients and healthy controls are presented in Table 3.

Table 3. Serum concentrations of cytokines in PsA, RA patients and healthy controls

Цитокини	ПсА (n = 32)	РА (n = 30)	Здрави контроли (n = 20)	P
TNF-α (pg/ml)				
mean ± SD	8.53 ± 32.47	11.14 ± 24.69	4.11 ± 13.79	0.001
(range)	(0.97-172.25)	(0.97-127.01)	(0.97-62.71)	
% над 95 персентил (n)*	6.3% (2)	33.3% (10)	5% (1)	0.006
IL-17 (pg/ml)				
mean ± SD	7.89 ± 6.71	9.37 ± 6.90	4.56 ± 3.81	0.023
(range)	(0.33-36.04)	(0.01-24.20)	(0.01-12.76)	
% над 95 персентил (n)*	12.5% (4)	23.3% (7)	5% (1)	0.185

TNF-α = Tumor Necrosis Factor; IL = Interleukin

* Процент на болни и контроли със стойности съответно на: TNF-α > 5.97 pg/ml, IL-17 > 12.76 pg/ml

Kruskal–Wallis test

Significantly higher serum levels (mean ± SD) of TNF-α were measured in RA patients, 11.14 ± 24.69 pg/ml, compared to healthy controls (4.11 ± 13.79 pg/ml, p = 0.005) and PsA patients (8.53 ± 32.47 pg/ml, p = 0.002). Among patients with PsA, levels of this cytokine were numerically but nonsignificantly higher relative to healthy controls (p = .569). Mean serum IL-17 concentrations in patients with PsA (7.89 ± 6.71) and RA (9.37 ± 6.90) also showed significantly higher values compared with healthy subjects (4.56 ± 3.81) (p = .039 and p = .008, respectively), with no significant difference between the two inflammatory arthropathies (p = .398). In both patients with the two inflammatory joint diseases and in healthy subjects as a whole, serum concentrations of the two cytokines showed an irregular distribution, varying widely across individual blood samples. When patients and controls were divided into subgroups based on the 95th

percentile of the mean cytokine values in healthy controls, 33.3% of RA patients and 6.3% of those with PsA had TNF-α values higher than the 95th percentile compared with 5% of healthy controls (p = .006), 23.3% of patients with RA and 12.5% of those with PsA had IL-17 values higher than the 95th percentile compared with 5% of healthy controls (p = .185). For better understanding, the ratio of mean serum cytokine concentrations in patients with PsA and RA versus healthy individuals is presented as an index/calculated ratio (Figure 12).

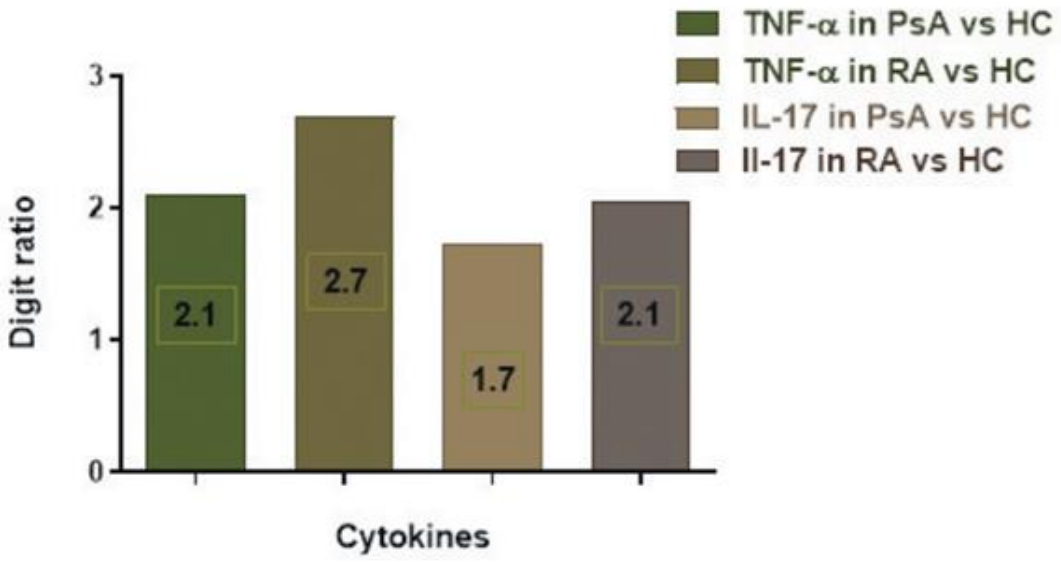


Figure 12. Numerical ratio of mean serum concentrations of the two cytokines in PsA and RA compared to healthy subjects

Comparison of serum cytokine concentrations according to the level of clinical disease activity (DAS28-CRP ≥ 3.2 versus < 3.2). The two cytokines tested showed no significant difference in serum concentrations according to disease activity status: inactive disease or low disease activity (DAS28-CRP < 3.2) versus moderate and high disease activity (DAS28-CRP ≥ 3.2) in both PsA and RA (Table 4).

Table 4. Mean serum cytokine concentrations stratified according to disease activity

The association of changes in circulating cytokine levels with disease activity (DAS28-CRP, SUE,

PsA (n = 32)	**DAS28-CRP < 3.2**	**DAS28-CRP ≥ 3.2**	
	Mean ± SD	Mean ± SD	P value *
TNF-α (pg/ml)	1.05 ± 0.29	14.24 ± 42.79	0.658
IL-17 (pg /ml)	8.64 ± 5.20	7.37 ± 7.67	0.186
RA (n = 3 0)	DAS28-CRP < 3.2	DAS28-CRP ≥ 3.2	
	Mean ± SD	Mean ± SD	P value *
TNF-α (pg /ml)	3.56 ± 5.18	12.30 ± 26.33	0.361
IL-17 (pg /ml)	11.23 ± 6.96	9.09 ± 6.99	0.583

*Mann-Whitney U test

CRP) was investigated. Spearman correlation coefficients were calculated and showed no association of TNF-α and IL-17 with any of the disease and inflammatory activity parameters ($p > .05$ for all).

4.1.4. Clinical indices of disease activity

4.1.4.1. BASDES

In the PsA group, 27 patients had a BASDAI ≥ 4, representing about 55.1% of the total number of patients in this group. This significant percentage indicates that more than half of the patients in the PsA group had high disease activity.

In the present study, statistically significant moderate correlations were found between BASDAI and HLA-B27 ($r = 0.371$, $p = .020$), SJC66 ($r = 0.448$, $p = .004$), and PhysGA ($r = 0.335$, $p = .035$). Similarly, statistically significant strong correlations were also found between BASDAI and HAQ-DI ($r = 0.700$, $p < .001$), ASQoL ($r = 0.731$, $p < .001$), PsAQoL ($r = 0.728$, $p < .001$), PsAID ($r = 0.882$, $p < .001$), TJC68 ($r = 0.542$, $p < .001$), DAS28 ($r = 0.619$, $p < .001$), PhysMSK ($r = 0.547$, $p < .001$), DAPSA ($r = 0.678$, $p < .001$), and ASDAS-CRP ($r = 0.679$, $p < .001$) (Figure 14).

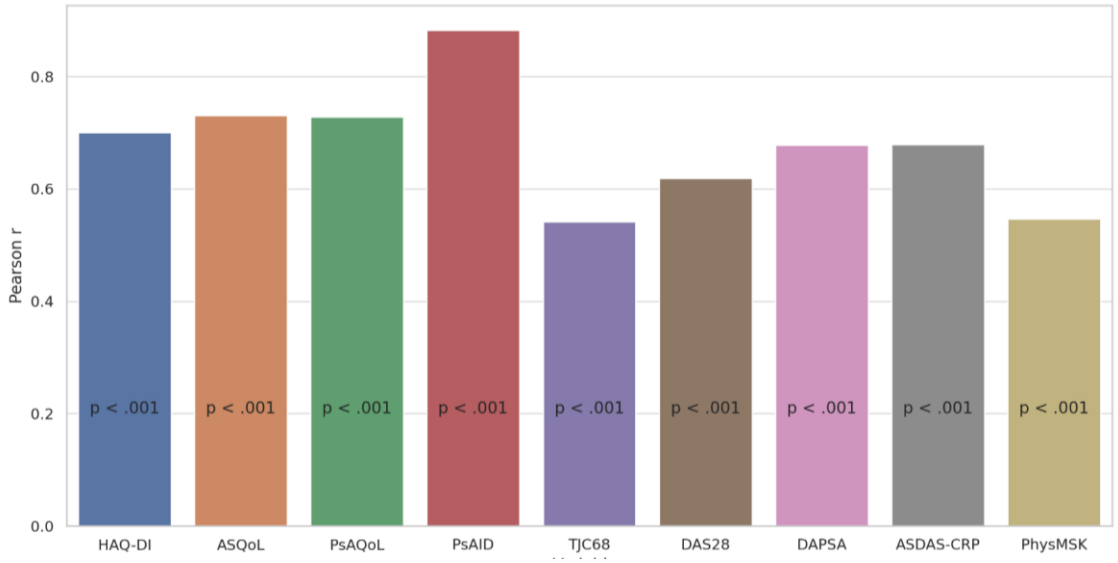


Figure 14. Statistically significant strong correlations with BASDAI by Pearson

Point-biserial correlation analysis was used to assess the relationship between a BASDAI threshold value >4, indicating high disease activity, and other variables. Several statistically significant correlations were identified as a result of the analysis. Specifically, strong positive correlations were found between a high BASDAI value and ptPAIN ($r = .804$, $p < .001$), ptGA ($r = .621$, $p < .001$), HAQ-DI ($r = .655$, $p < .001$), and PsAID ($r = .714$, $p < .001$). These correlations indicate that with increasing BASDAI value there is a significant increase in ptPAIN, ptGA, HAQ-DI, and PsAID. In addition, there was a moderate positive correlation between a high BASDAI value and MONO# ($r = .377$, $p = .040$).

The Kendall's coefficient for the correlation between high BASDAI and MONO# values was $r_\tau = .341$, $p = .028$, indicating a moderate and statistically significant relationship between the two variables. This result indicates that there is a significant and statistically reliable relationship between elevated BASDAI values, which indicate high disease activity, and blood monocyte levels.

A simple linear regression was performed to assess the predictive value of BASDAI for MONO# levels in the sample (Figure 15). The model explained approximately 11.4% of the variance in MONO# levels, $R^2 = 0.114$, $F(1, 31) = 3.609$, $p = .068$. The unstandardized regression coefficient for BASDAI was 0.036, but this result was not statistically significant at the 0.05 significance level ($p = .068$). This fact highlights that BASDAI values taken alone do not appear to be strong predictors of MONO# levels.

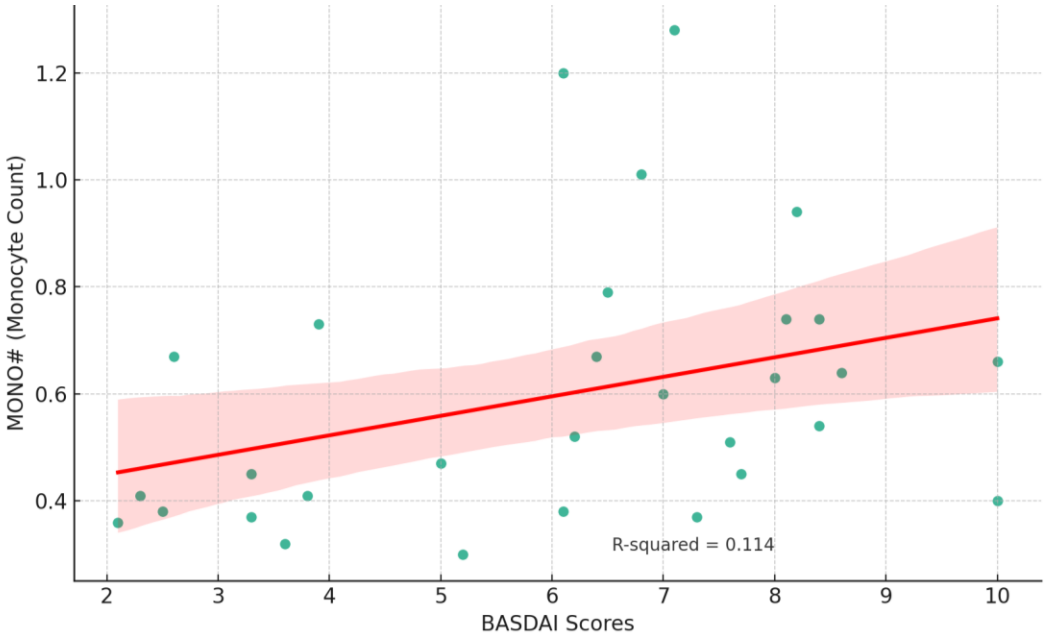


Figure 15. Regression plot of BASDAI scor and MONO#

4.1.4.2 DAS28

For the purpose of the study, DAS28 values were categorized into four different levels:

- Remission: DAS28 < 2.6
- Low disease activity: DAS28 ≥ 2.6 and
- ≤ 3.2 Moderate disease activity: DAS28 > 3.2 and ≤ 5.1
- High disease activity: DAS28 > 5.1

The PsA group was distributed as follows: 21 cases were categorized as High disease activity, 15 as Moderate disease activity, 9 as Low disease activity, and 4 as Remission. For RA, the distribution was as follows: 6 cases with High disease activity, 20 cases with Moderate disease activity, 2 cases with Low disease activity and 2 cases in Remission (Figure 16).

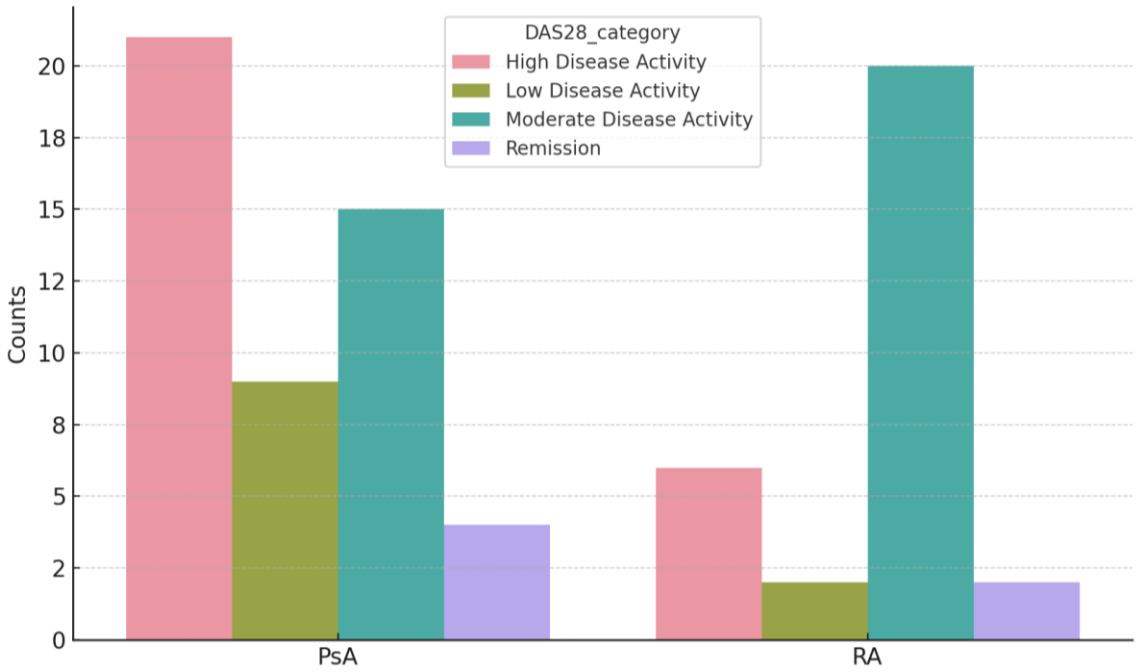


Figure 16. Distribution of DAS28 categories by group

In the "High Disease Activity" category, the PsAID variable exhibited a strong positive correlation with DAS28 values ($r = .71$, $p < .05$). Similarly, RAQoL showed a strong positive correlation with DAS28 values ($r = .95$, $p < .05$). Due to the small sample size, this strong correlation should be interpreted with caution. SYND-1 was also strongly positively correlated with DAS28 ($r = .71$, $p < .05$).

In patients categorized as having "Low disease activity," DLQI showed a strong positive correlation with DAS28 values ($r = .85$, $p < .05$). BMI exhibited a moderate negative correlation with DAS28 values ($r = -.62$, $p < .05$). UA also appeared strongly negatively correlated with DAS28 values ($r = -.68$, $p < .05$). In the Remission category, QUICKI showed a strong positive correlation with DAS28 values ($r = .83$, $p < .05$). Conversely, Glu had a strong negative correlation with DAS28 values ($r = -.94$, $p < .001$), as did IMT, which exhibited a strong negative correlation ($r = -.83$, $p < .0$). HOMA-IR and Insulin also showed strong negative correlations with DAS28 ($r = -.83$, $p < .05$) (Figure 18).

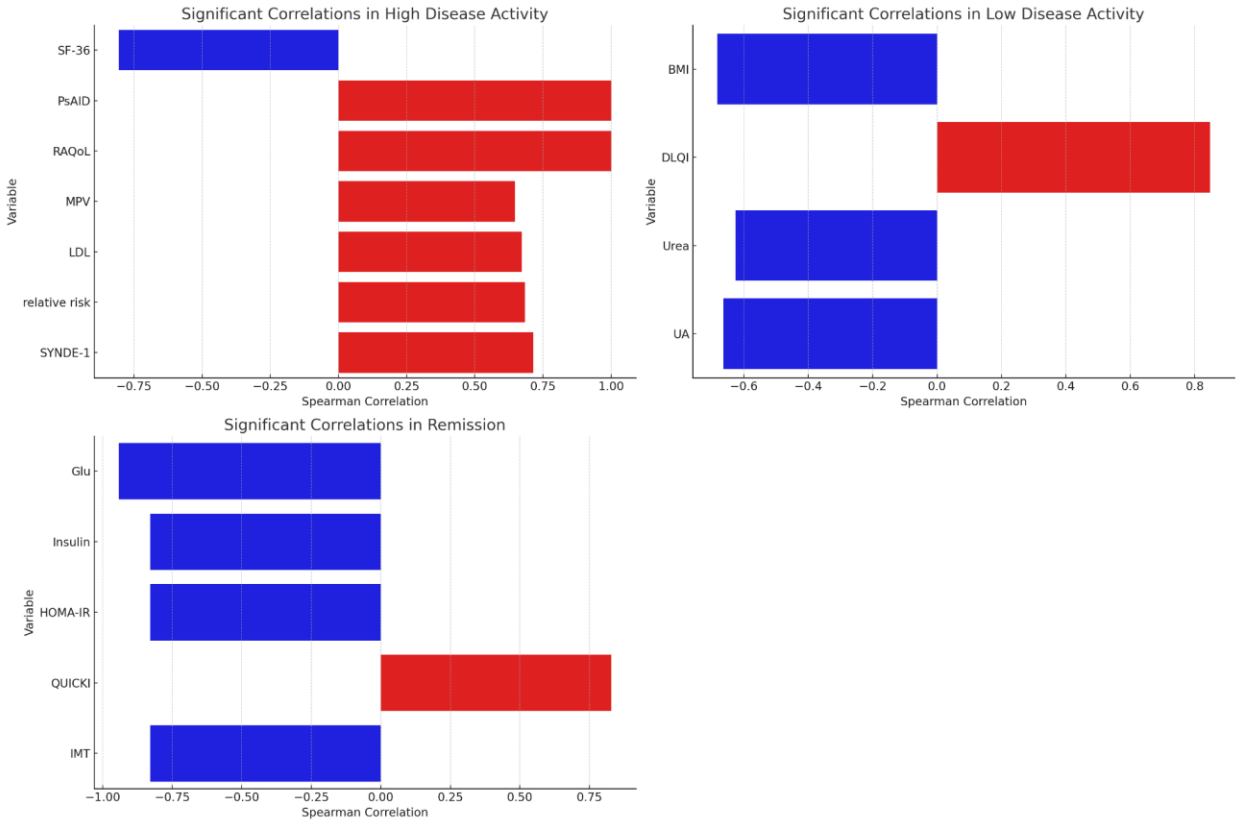


Figure 18. Bar-plots visualizing significant Spearman correlations in patients with high and low disease activity, and in remission, respectively

4.1.4.3. mNAPSI

In the PsA group, we examined mNAPSI to assess the severity of nail changes. A total of 37 observations were recorded for mNAPSI. The mean mNAPSI was 13.76 (SD = 11.73), indicating variability in the severity of nail psoriasis among this group of patients. Values ranged from a minimum of 0, indicating no affected nails, to a maximum of 53, suggesting severe nail psoriasis. The 25th percentile was at a value of 6, the median was at a value of 11, and the 75th percentile was at a value of 16. The range and variability in mNAPSI values indicate that the severity of nail psoriasis was not uniform among PsA patients in this sample. Further research is needed to understand the factors that contribute to this variability.

Several variables showed moderate correlations with mNAPSI. Specifically, PASI exhibited a moderate positive correlation with mNAPSI ($r = .55$, $p < .001$). Similarly, PhysSk also demonstrated a moderate positive correlation with mNAPSI ($r = .53$, $p < .001$). GLS had a moderate negative correlation with mNAPSI ($r = -.54$, $p = .039$).

4.1.4.4 DAPSA

Patients were categorized into four different levels of disease activity: remission (DAPSA ≤ 4), low disease activity (4 < DAPSA ≤ 14), high disease activity (14 < DAPSA ≤ 28), and very high disease activity (DAPSA > 28). After categorization, the distribution of DAPSA results in these defined categories was as follows: 14 cases (34.15%) were in the "Very High Disease Activity" category, 13 cases (31.71%) were categorized as "High Disease Activity," 12 cases (29.27%) were identified as "Low Disease Activity," and only 2 cases (4.88%) were classified as "Remission" (Figure 19).

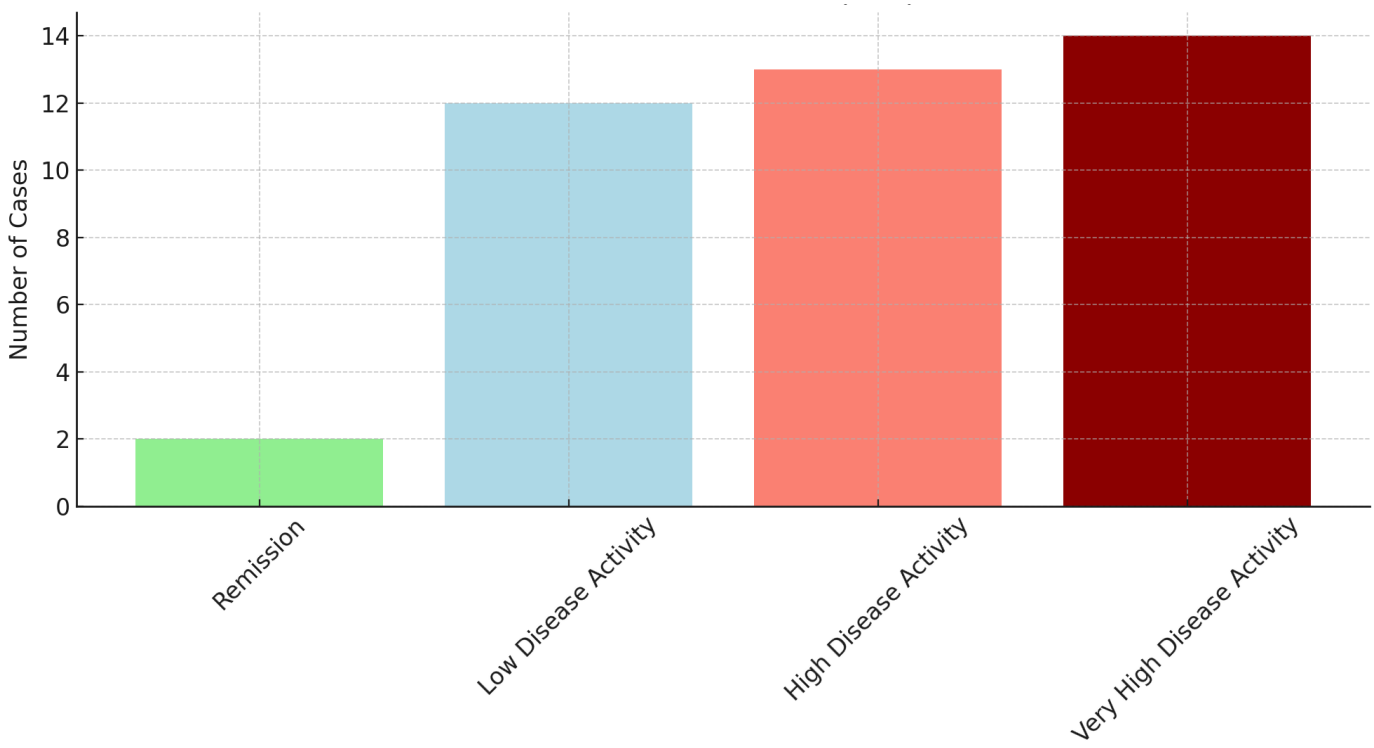


Figure 19. Distribution of DAPSA by levels of disease activity in PsA

4.1.4.5 ASDAS-CRP

The mean ASDAS-CRP level was 7.61 (SD = 3.45). A Shapiro-Wilk test was performed to assess the normality of the distribution of the ASDAS-CRP data. The test yielded a test statistic equal to 0.97 and a p value = 0.252.

Pearson correlation analysis between "ASDAS-CRP" and the other indices in the PsA group revealed relationships of varying degrees of strength (Figure 21). Very strong positive correlations were observed, especially with "ptGA" (r = .954, p < .001), highlighting the strong relationship between patients'

overall score and ASDAS-CRP levels. In the area of strong positive correlations, "DAPSA" (r = .768, p < .001), "ptPAIN" (r = .822, p < .001), and "PsAID" (r = .715, p < .001) were notable, highlighting the utility of ASDAS-CRP as a reliable indicator of disease activity. Additionally, "DAS28" showed a strong positive correlation (r = .736, p < .001). Analysis also revealed moderate correlations, both positive and negative. On the positive side, variables such as "BASDAI" (r = .679, p < .001), "HAQ-DI" (r = .574, p < .001), "SJC66" (r = .562, p < .001), "PsAQoL" (r = .542, p < .001), "ASQoL" (r = 0.545, p < .001), "TJC68" (r = 0.462, p = .0023), "PhysMSK" (r = .489, p = .012), and "CRP" (r = .391, p = .011) showed significant associations with ASDAS-CRP. Negatively, "SF-36" (r = -0.664, p < .001) and "MDA" (r = -.606, p < .001) stood out as significant, indicating that higher ASDAS-CRP values were associated with lower quality of life and less likelihood of reaching minimal disease activity, respectively. "Chol/HDL" also showed a moderate negative correlation (r = -.421, p = .006). "DLQI" had a moderate positive correlation (r = .431, p = .055).

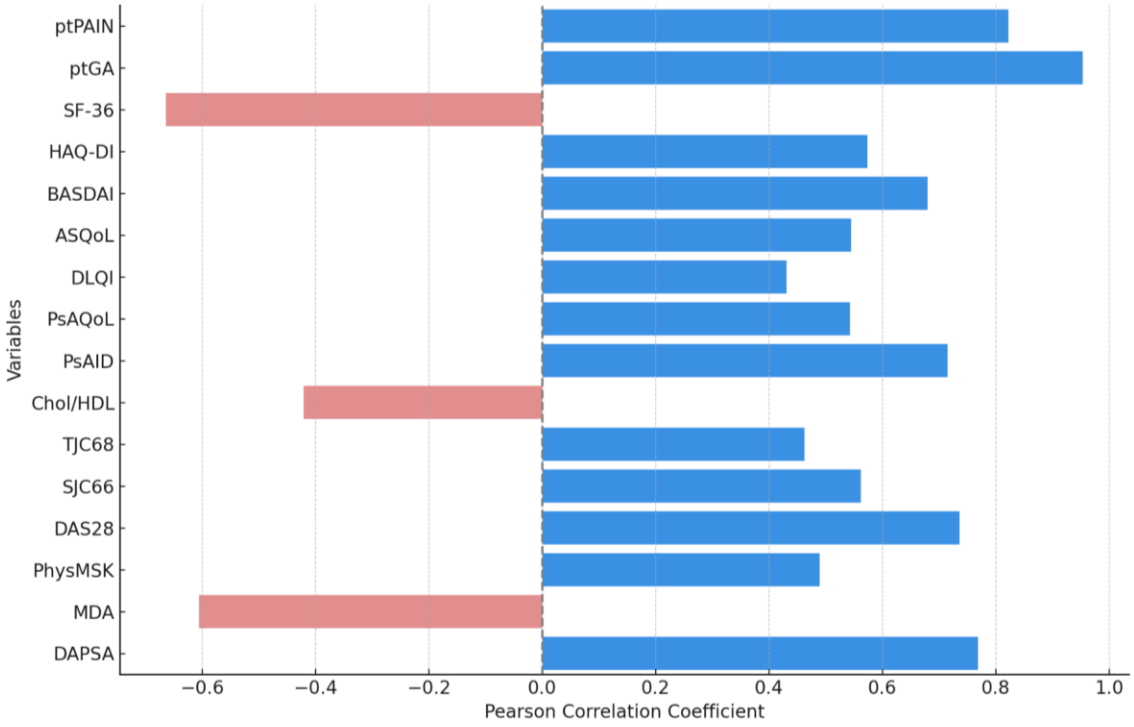


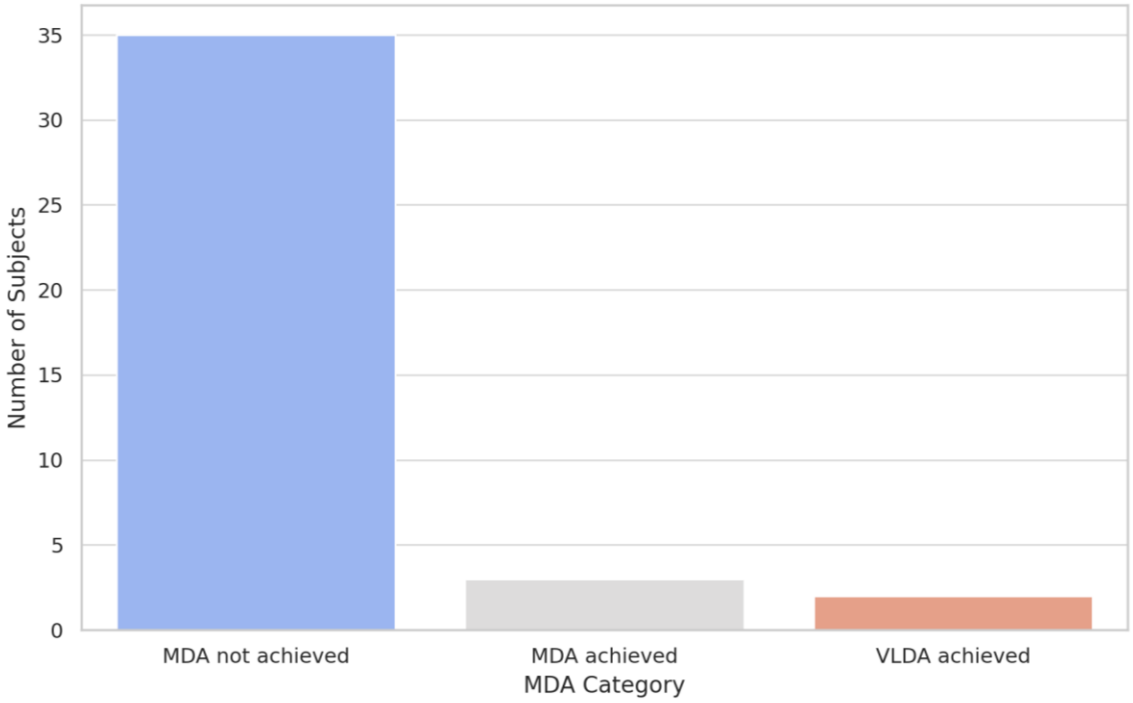
Figure 21. Bar-plot depicting statistically significant Pearson correlations with ASDAS-CRP in patients with PsA

4.1.4.6 MDA

Minimal Disease Activity (MDA) scores were categorized into three different groups in the PsA group: 'MDA not achieved (score < 5)', 'MDA achieved (score between 5 and 6)' and 'Very low disease

activity (VLDA) achieved (score 7)'. The categorization showed that out of 40 people, 35 did not achieve MDA, 3 achieved MDA, and 2 achieved VLDA. The bar chart visually shows these results, providing a clear depiction of the distribution of disease activity (Figure 22).

Figure 22. Categorization of MDA scor in PsA



In the group with minimal disease activity not reached (MDA < 5), several clinical and laboratory variables showed significant correlations. TJC68 exhibited a strong negative correlation ($r = -.633$, $p < .001$). SJC66 exhibited a strong negative correlation with MDA scores ($r = -.605$, $p < .001$). PhysMS) showed a strong negative correlation ($r = -.648$, $p < .001$). DAPSA) also had a negative correlation with MDA scores ($r = -.610$, $p < .001$), ASDAS-CRP ($r = -.620$, $p < .001$). In addition, PhysGA had a strong negative correlation ($r = -.480$, $p = .004$), HAQ-DI ($r = -.432$, $p = .009$). ASQoL also showed a strong

negative correlation (r = -.443, p = .008). LDI showed moderate negative correlation (r = -.339, p = .047) (Figure 23).

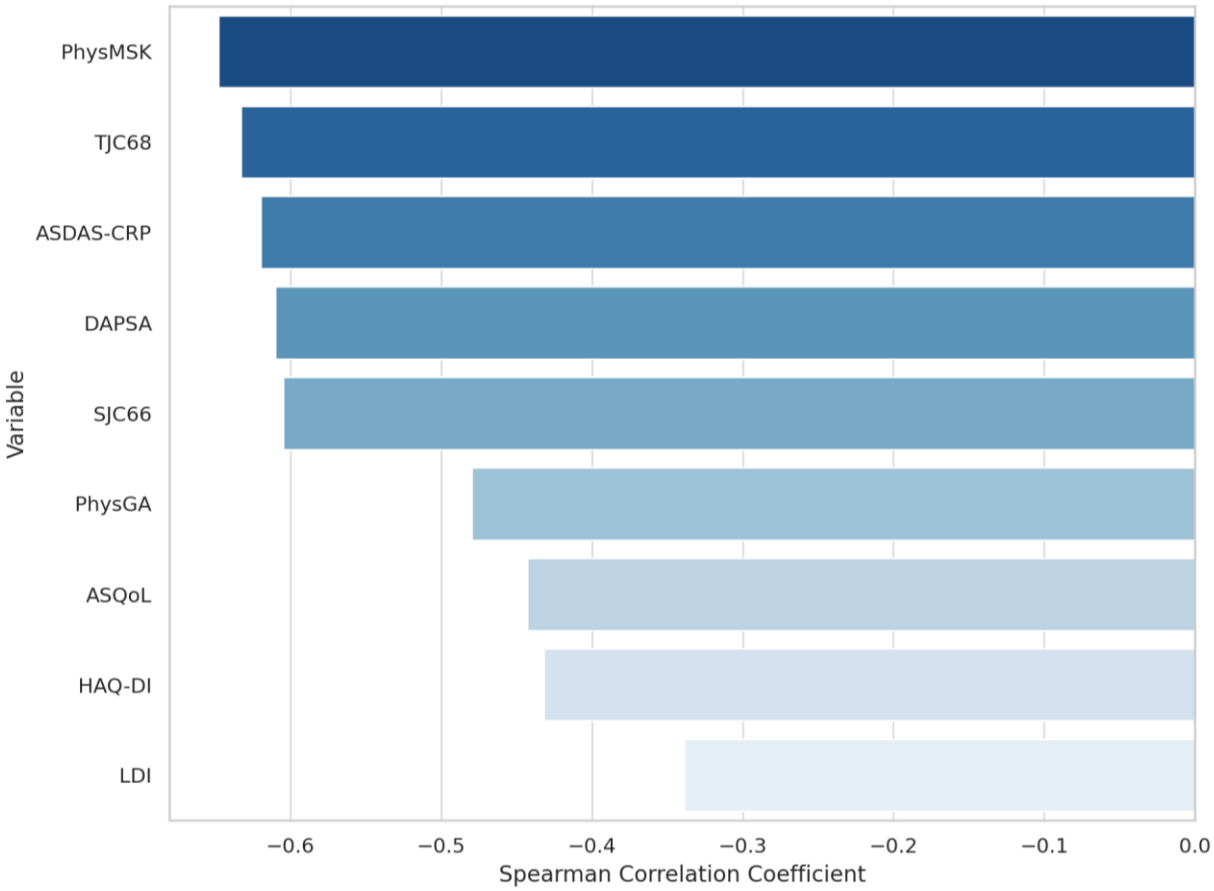


Figure 23. Significant Spearman correlations in patients with PsA who did not reach MDA <5

4.2 Analysis of quality of life, physical activity and diet

4.2.1. Comparative analysis

Various variables related to quality of life, physical activity, and diet were analyzed among patients with PsA, RA, and healthy controls (Table 6). For PsA, the mean SF-36 score was 411.19 (SD = 137.94), HAQ-DI was 0.93 (SD = 0.61), and DPAS was 15.48 (SD = 5.09). BMI was 28.17 (SD = 6.05). In terms of disease-specific quality of life indices, the mean ASQoL score was 8.12 (SD = 5.37), DLQI was 5.50 (SD = 5.53), PsAQoL was 8.00 (SD = 5.36), and PsAID was 4.61 (SD = 2.12) (Table 7). Healthy controls served as the reference point for some analyses. For RA, the mean SF-36 score was 417.38 (SD = 182.84), HAQ-DI was 0.94 (SD = 0.55), and DPAS was 16.72 (SD = 5.40). Mean age for this group was 50.47 years (SD = 8.97), and BMI was 24.17 (SD = 3.93). The mean disease-specific RAQoL score was 11.10 (SD = 7.18) (Table 8).

Table 6: Compared mean and SD of common RA and PsA indices

Variable	PsA Mean ± SD	Healthy Control Mean ± SD	RA Mean ± SD	p - value
SF-36	411 ± 137	679 ± 134	417 ± 182	.004
HAQ-DI	0.93 ± 0.61	0 ± 0	0.94 ± 0.55	.001
DPAS	15.47 ± 5.09	22.57 ± 3.55	16.72 ± 5.40	.006
MDS	4.24 ± 1.95	5.50 ± 2.12	4.59 ± 1.84	.606
BMI	28.17 ± 6.05	21.328 ± 4.21	24.17 ± 3.93	.001
BSA	1.91 ± 0.24	1.66 ± 0.19	1.79 ± 0.21	.013

SF-36, Short Form 36; **HAQ-DI**, Health Assessment Questionnaire-Disability Index; **DPAS**, Dijon Physical Activity Score; **MDS**, Mediterranean Diet Score; **BMI**, Body Mass Index; **BSA**, Body Surface Area;

Table 7: Specific indices for PsA

Variable	Mean ± SD
ASQoL	8.12 ± 5.37
DLQI	5.50 ± 5.53
PsAQoL	8.00 (± 5.36)
PsAID	4.61 (± 2.12)

ASQoL, Ankylosing Spondylitis Quality of Life; **DLQI**, Dermatology Life Quality Index; **PsAQoL**, Psoriatic Arthritis Quality of Life; **PsAID**, Psoriatic Arthritis Impact of Disease;

Table 8: RA specific indices

Variable	**RA** **Mean ± SD**
RAQoL	11.10 ± 7.18

RAQoL - Rheumatoid Arthritis Quality of Life;

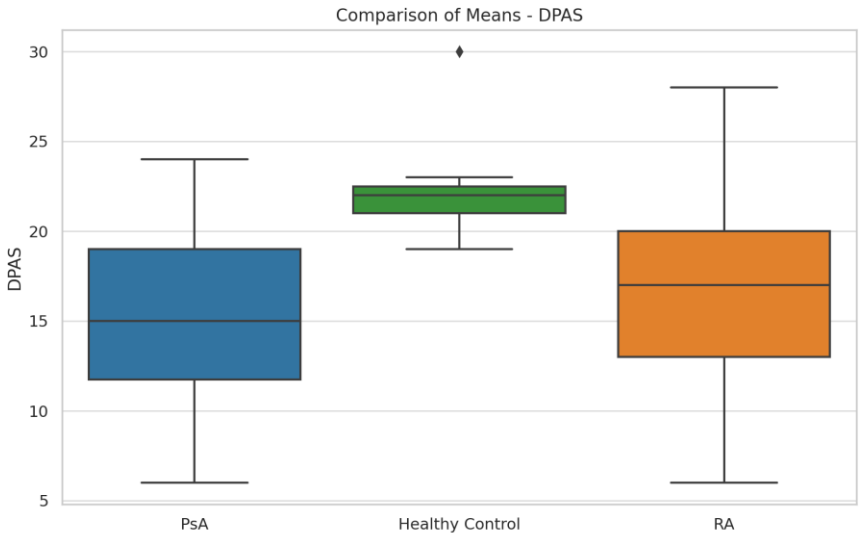


Figure 24. Box-plot showing the distribution of DPAS values

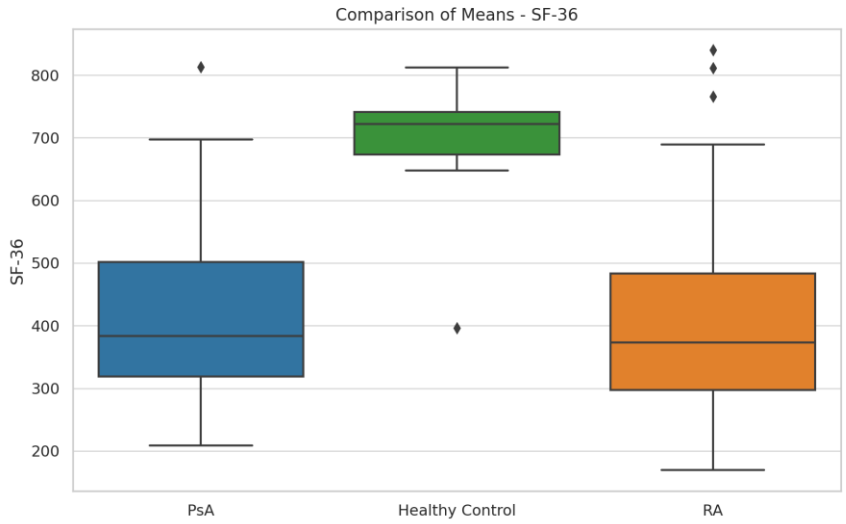


Figure 27. Box-plot showing the distribution of SF-36 values

Independent t-tests were performed to compare means between PsA and RA. For DPAS, no significant difference was found between group 1 and group 3 (t = -1.15, p = .257). Similarly, for the MDS, the difference was not significant (t = -0.74, p = .460). For the DPAS, the groups were also not significantly different (t = -0.98, p = .330).

4.2.2. Correlation analysis

Correlation analyses were performed to examine the relationships between measures of quality of life, diet, and physical activity across groups. For PsA, a moderate negative correlation was noted between the SF-36 and the HAQ-DI (r = -.47, p = .010), indicating that higher levels of disability were associated with poorer quality of life. Also, the SF-36 was positively correlated with the MDS (r = .41, p = .028), indicating that higher diet scores were associated with better quality of life. However, no significant correlations were found between the SF-36 and BMI or BSA. For specific measures of PsA, there were positive correlations between ASQoL and PsAQoL (r = .83, p < .001), and between ASQoL and PsAID (r = .69, p < .001). The MDS showed no significant correlation with either BMI (r = -.32, p = .090) or BSA (r = -.23, p = .223).

Additionally, a moderate negative correlation was found between DAS28 and DPAS (r = -.45, p = .015), suggesting that higher disease activity was associated with lower levels of daily physical activity. However, DAS28 did not show significant correlations with other variables such as SF-36, BMI, BSA, or MDS. Specifically, the relationships between DAS28 and SF-36 (r = -.29, p = .129) and between DAS28 and MDS (r = -.29, p = .130) were not statistically significant.

There was a negative correlation between ptGA and DPAS (r = -.45, p < .001), indicating that a higher DPAS score was associated with a lower score by the patient on their overall disease assessment. Positive correlation with SF-36 (r = .48, p < .001), indicating that higher DPAS scores are associated with better quality of life. Negative correlation of RAQoL with MDS (r = -.42, p = .022). Negative correlation with smoking duration and DPAS (r = -.48, p = .027), indicating that longer smoking duration is associated with lower DPAS scores (Figure 28). Positive correlation with MDA and DPAS (r = 0.43, p = .007), indicating that higher scores on DPAS were associated with better disease control.

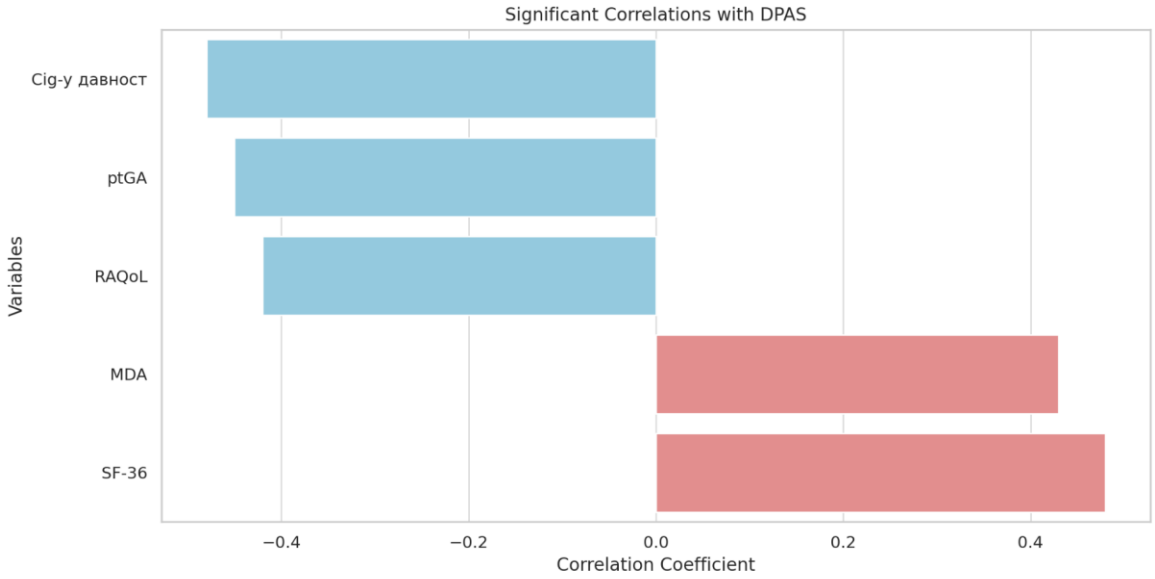


Figure 28. Significant correlations with DPAS

4.2.3. Regression analysis

Regression analysis showed that DPAS score was a significant predictor of MDA in patients with PsA, even after controlling for age, sex, and BMI. The model explained approximately 37.2% of the variance in MDA, as indicated by an R^2 value of 0.372, F(4, 31) = 4.595, p = .005. Specifically, for every one-unit increase in DPAS, there corresponds a 0.179-unit increase in MDA when all other variables are held constant (t(31) = 3.539, p = .001). Age and gender did not emerge as significant predictors in the model (p = .316 and p = .420, respectively). Conversely, BMI was a significant negative predictor (t(31) = -2.423, p = .021), indicating that higher BMI values were associated with lower MDA levels.

The regression analysis model for SF-36 and DPAS shows a significant positive relationship between the two variables (Figure 29). Specifically, the normalized regression coefficient for "SF-36" was β = 0.015 (p < .001). This means that for every one point increase in SF-36 scores, DPAS is predicted to increase by approximately 0.015 units. The model intercept was β = 9.979 (p < .001), suggesting that when

the SF-36 score is zero, the predicted DPAS score would be approximately 9.979. For R^2 , the model value was 0.228, indicating that 22.8% of the variability in DPAS scores could be explained by SF-36 scores. Although the model was significant with F(1,71) = 20.93, p < .001, the relatively modest value of R^2 suggests that other factors likely influence DPAS scores. Therefore, although the SF-36 is a significant predictor, it explains only part of the variability in DPAS scores.

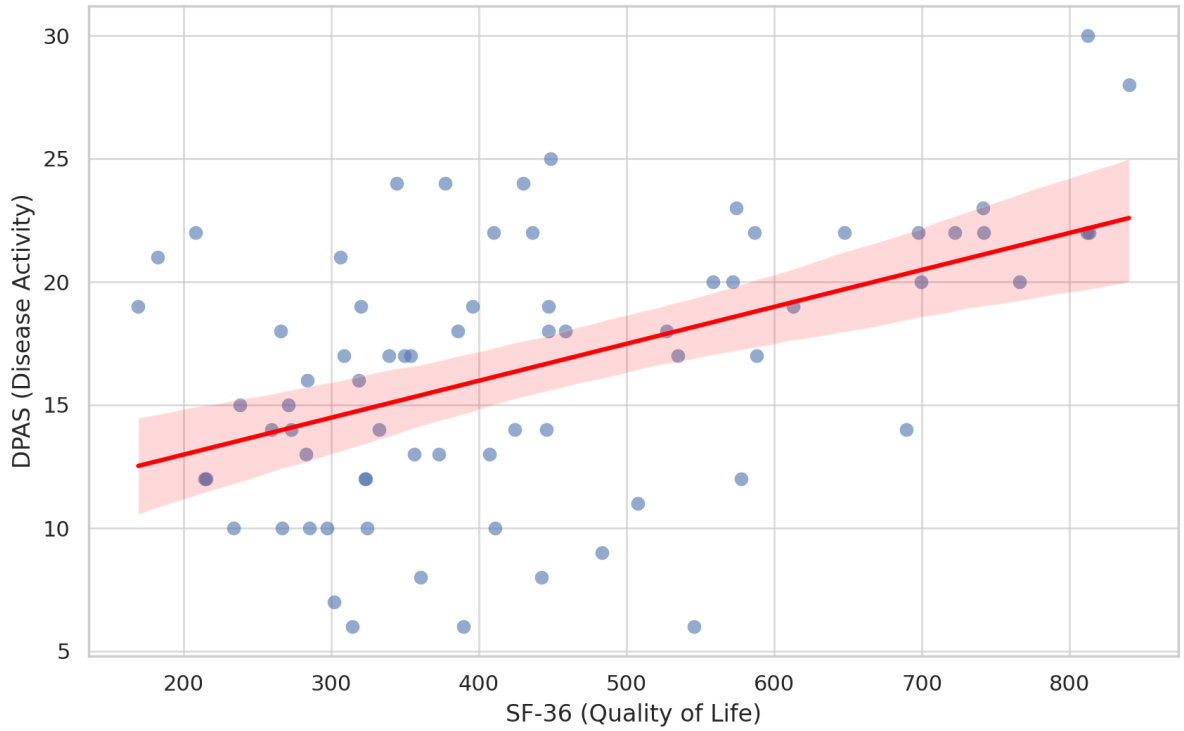


Figure 29. Regression analysis of SF-36 and DPAS

4.3 Cell ratios

4.3.1. Descriptive statistics

Mann-Whitney U tests showed different levels of significance between different cell ratios when compared between the PsA, RA, and Healthy control groups (Figure 30).

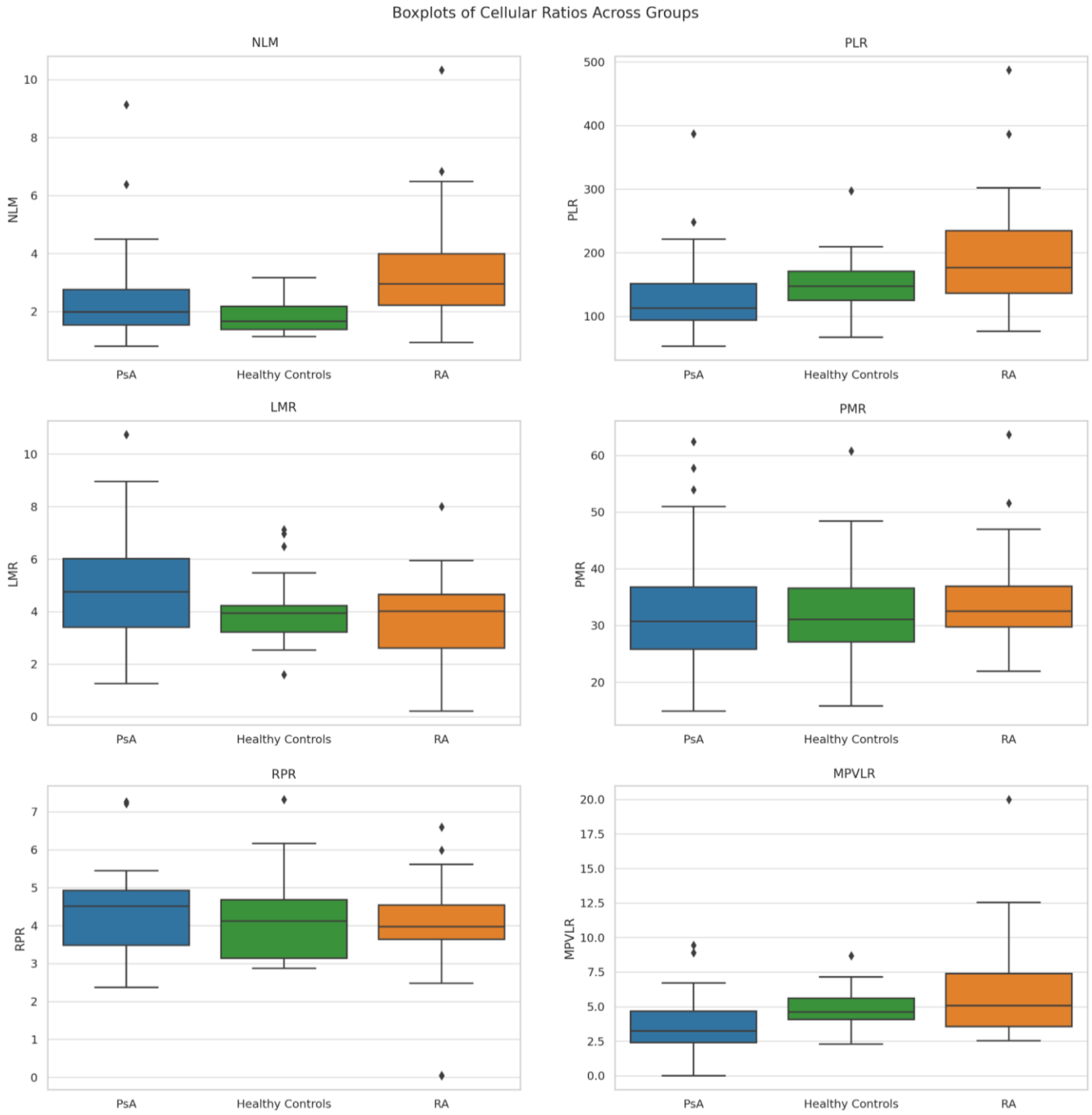


Figure 30. Boxplots depicting the distribution of cell ratios between groups. **NLM**: Neutrophil-to-Lymphocyte Ratio **PLR**: Platelet-to-Lymphocyte Ratio **LMR**: Lymphocyte-to-Monocyte Ratio **PMR**: Platelet-to-Monocyte Ratio **RPR**: Red Blood Cell Distribution Width-to-Platelet Ratio **MPVLR:** Mean platelet volume-to-lymphocyte ratio

For the NLM ratio, significant differences were found between the PsA and RA groups ($U = 359.0$, $p = .004$) and between the Healthy Controls and RA groups ($U = 119.0$, $p < .001$). However, no significant difference was found between the PsA and Healthy Controls groups ($U = 481.0$, $p = .207$). Similarly, for the Platelet to Lymphocyte Ratio (PLR), significant differences were observed between the PsA and Healthy Controls groups ($U = 193.0$, $p = .025$) and between the PsA and RA groups ($U = 223.0$, $p < .001$). No significant difference was found between the Healthy Controls and RA groups for PLR ($U = 211.0$, $p = .080$).

4.3.2. Correlation analysis

Spearman correlation analysis revealed several interesting relationships between cell ratios of interest and other important variables (Figure 31). For example, LMR exhibited a strong negative correlation with PsO-dur ($r = -.54$, $p < .001$), suggesting that higher LMR values may be associated with shorter psoriasis duration. Also, LMR showed a strong positive correlation with RAQoL ($r = .49$, $p = .01$), indicating that LMR may be associated with quality of life in patients with rheumatoid arthritis.

MPVLR showed a strong negative correlation with WBC ($r = -.45$, $p < .001$), suggesting that lower MPVLR values may be associated with higher white blood cell counts. PMR had a strong positive correlation with PsAQoL ($r = .45$, $p = .01$), indicating its role on quality of life in patients with psoriatic arthritis. LMR also showed a strong negative correlation with LDI ($r = -.44$, $p = .01$) and BASDAI ($r = -0.39$, $p = .03$), indicating its potential role in disease activity indices. MPVLR showed a moderate positive correlation with DPAS ($r = .39$, $p < .001$) and a negative correlation with Chol/HDL ($r = -.35$, $p < .001$), further highlighting its association in cholesterol metabolism and physical activity.

NLM showed a moderate positive correlation with anti-CCP ($r = .35$, $p < .001$), which highlights its importance in the context of RA. RPR had a moderate positive correlation with GLS ($r = .34$, $p = .03$), which may suggest an association between with cardiac function. NLM also showed moderate positive correlations with CRP ($r = .34$, $p < .001$) and ESR ($r = .32$, $p < .001$), highlighting its role in inflammatory conditions. Finally, PMR had a moderate positive correlation with SJC66 ($r = 0.31$, $p = .01$), suggesting its potential role on the number of edematous joints.

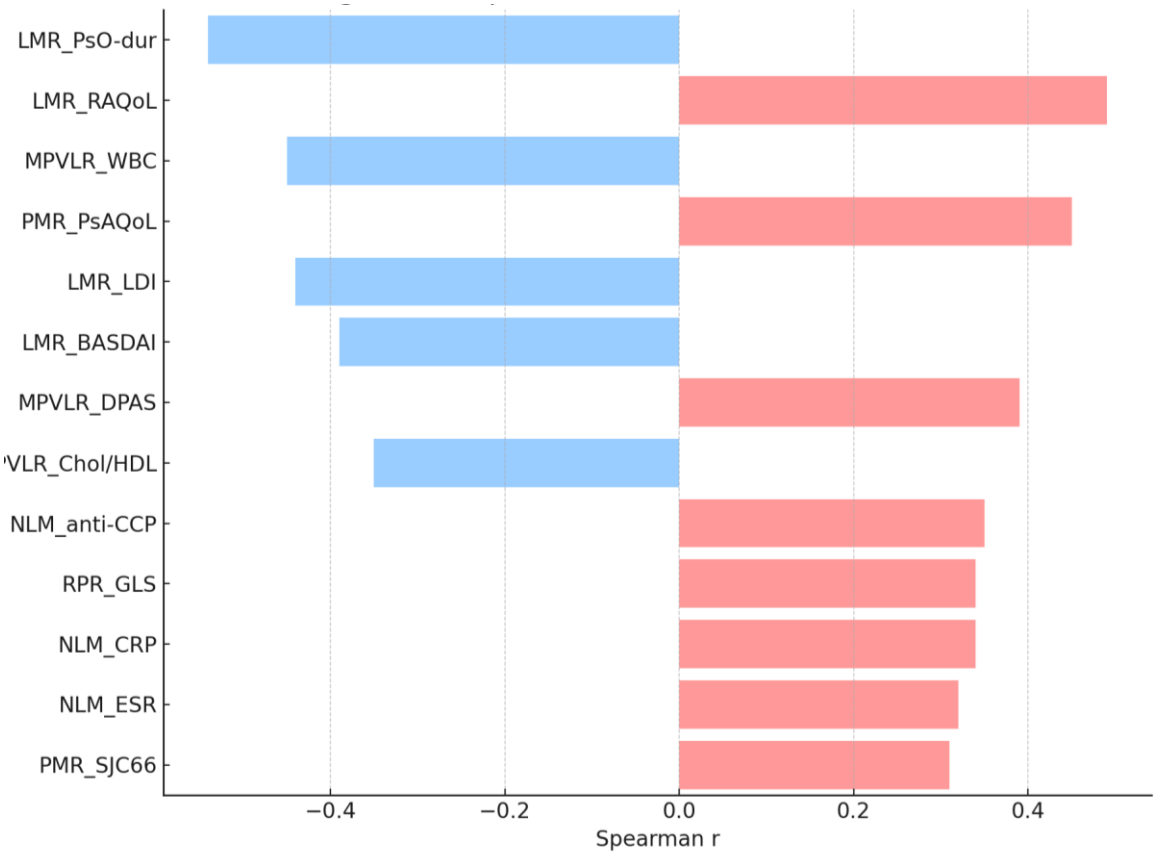


Figure 31. Statistically significant Spearman correlations between cell ratios and other markers.

4.4. Ultrasonographic studies

4.4.1 IMT analysis

The measured IMT of the left carotid artery (IMT-L) in PsA had a mean value of 566.76 (SD = 109.86), whereas for RA3 it was 575.37 (SD = 83.21). The IMT of the right carotid artery in PsA (IMT-R), had a mean value of 554.07 (SD = 118.96), whereas for RA it was 527.77 (SD = 113.82). The composite thickness of the two arteries (composite IMT) was 560.41 (SD = 106.50) for PsA and 551.57 (SD = 87.14) for RA. The mean GLS was -19.24 (SD = 3.06) for PsA and -20.42 (SD = 1.64) for RA.

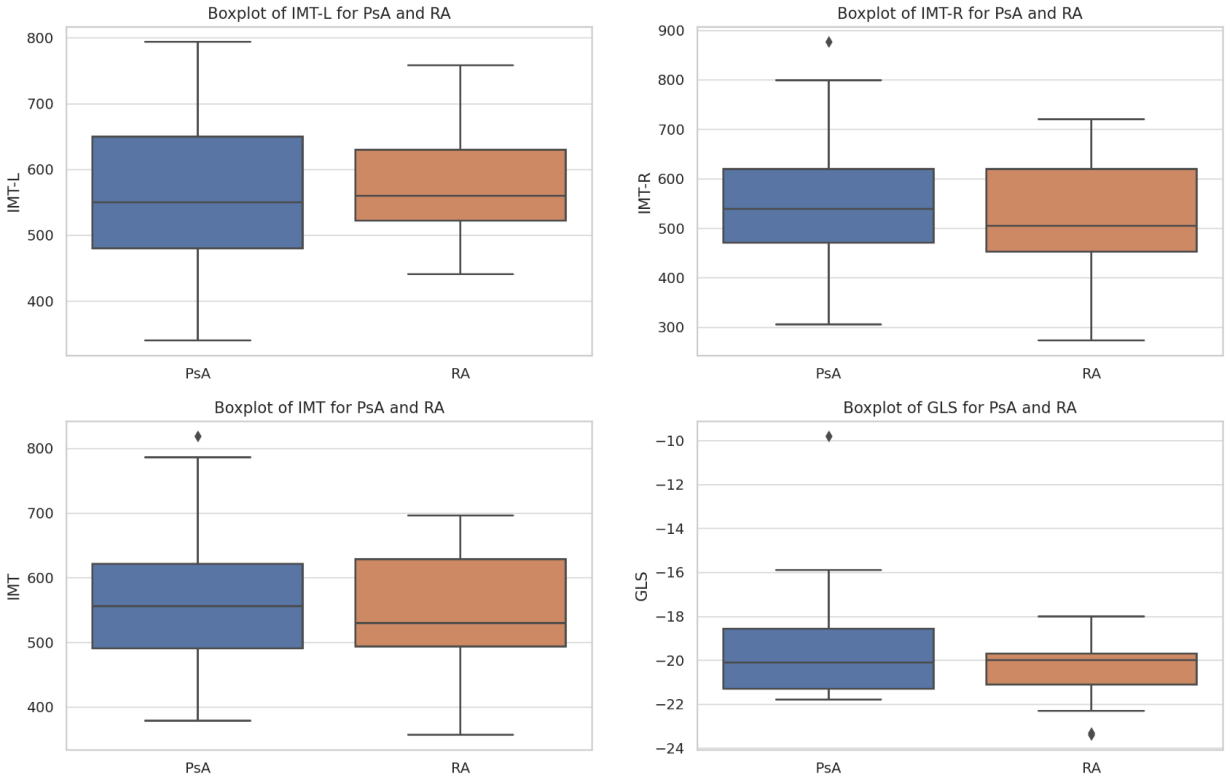


Figure 32. Boxplots showing the distribution of IMT, IMT-L, IMT-R and GLS in patients with PsA and RA

For IMT-L in the PsA group, the 25th percentile was 480.0, the median (50th percentile) was 550.0, and the 75th percentile was 650.0. For the RA group, these values were 521.75, 560.0, and 630.0, respectively. For IMT-R in the PsA group, the percentiles were 490.0 (25th), 539.0 (50th), and 597.0 (75th); for the RA group, they were 505.0, 505.0, and 580.0. For total intima-media thickness (composite IMT), the 25th, 50th, and 75th percentiles for the PsA group were 500.0, 556.0, and 621.5, respectively, whereas for the RA group they were 525.5, 529.75, and 628.75, respectively. Finally, for GLS, the PsA group had percentiles of -21.3 (25th), -20.1 (50th), and -18.575 (75th), while the RA group had -21.1, -20.0, and -19.7, respectively.

Using cut-off values defined by the European Society of Cardiology (ESC) at the 75th percentile and age, the percentages of pathological left and right cartesian values (IMT-p-L and IMT-p-R) were calculated (31). For IMT-p-L, 37.5% of the PsA group and 30.0% of the RA group were categorized as pathological. For IMT-p-R, the percentages were higher, with 50.0% of the PsA group and 40.0% of the RA group falling into the pathological category (Figure 33).

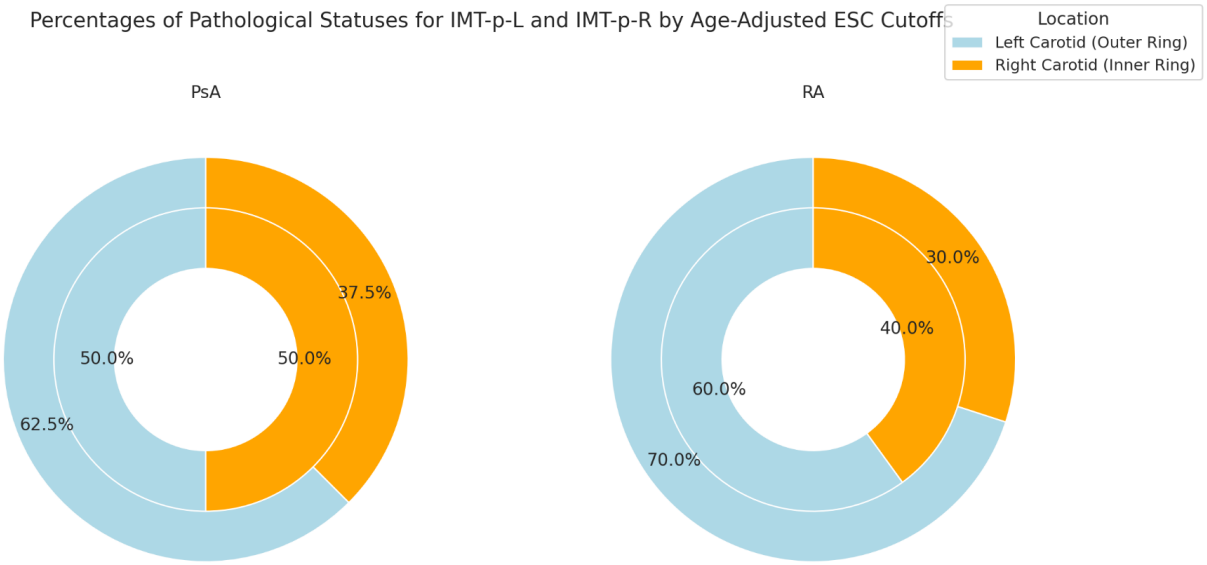


Figure 33. Percentage distribution of pathological IMT of left and right carotid arteries in PsA and RA patients.

A Mann-Whitney test was performed to assess between-group differences. For the IMT-L, the test statistic was 110.5, and the p value was .367. For the IMT-R, the test statistic was 141.5, with a p-value of .857. Similarly, for the composite IMT U=132.0, p = .900. Finally, for the GLS, the test statistic was 157, with a p-value of .460. All p-values were greater than the conventional significance level of .05. For IMT-p-L U = 645 p = .521, and IMT-p-R U = 660 p = .413. All p-values were greater than the conventional significance level of 0.05, indicating that there were no statistically significant differences between the PsA and RA groups with respect to these variables. Therefore, the Mann-Whitney test showed no significant differences between the two groups.

In the analysis, correlations between IMT and years of smoking (r = 0.55, p = 0.015), QRISK (r = 0.52, p < .001), and glucose levels (r = 0.49, p < .001) were found to be moderate in strength. Weak correlations were observed between IMT and HOMA-IR (r = 0.35, p = .003) and QUICKI (r = -0.35, p = .003). Weak negative correlations were found with VCAM1 (r = -0.34, p = 0.008). Steroid use also showed a weak negative correlation with IMT(r = -0.3, p = 0.016). A correlation was noted between IMT and the inflammatory marker CRP (r = 0.34, p = 0.004) as well as with HPSE (r = 0.3, p = 0.021) and AH (r = 0.MetS showed a moderate correlation with IMT(r = 0.4, p < .001) as well as serum urea levels (r = 0.35, p = 0.004) and BMI (r = 0.34, p = 0.005). Weak correlations were observed with PASI (r = 0.33, p = 0.045), age (r = 0.32, p = 0.006), GGT levels (r = 0.32, p = 0.017), and LDL levels (r = 0.32, p = 0.007). Uric acid

(r = 0.28, p = 0.017), HbA1C (r = 0.25, p = 0.044), HDL/LDL ratio (r = 0.25, p = 0.039) and MDS (r = -0.26, p = 0.037) demonstrated weak but statistically significant correlations with IMT (Figure 34).

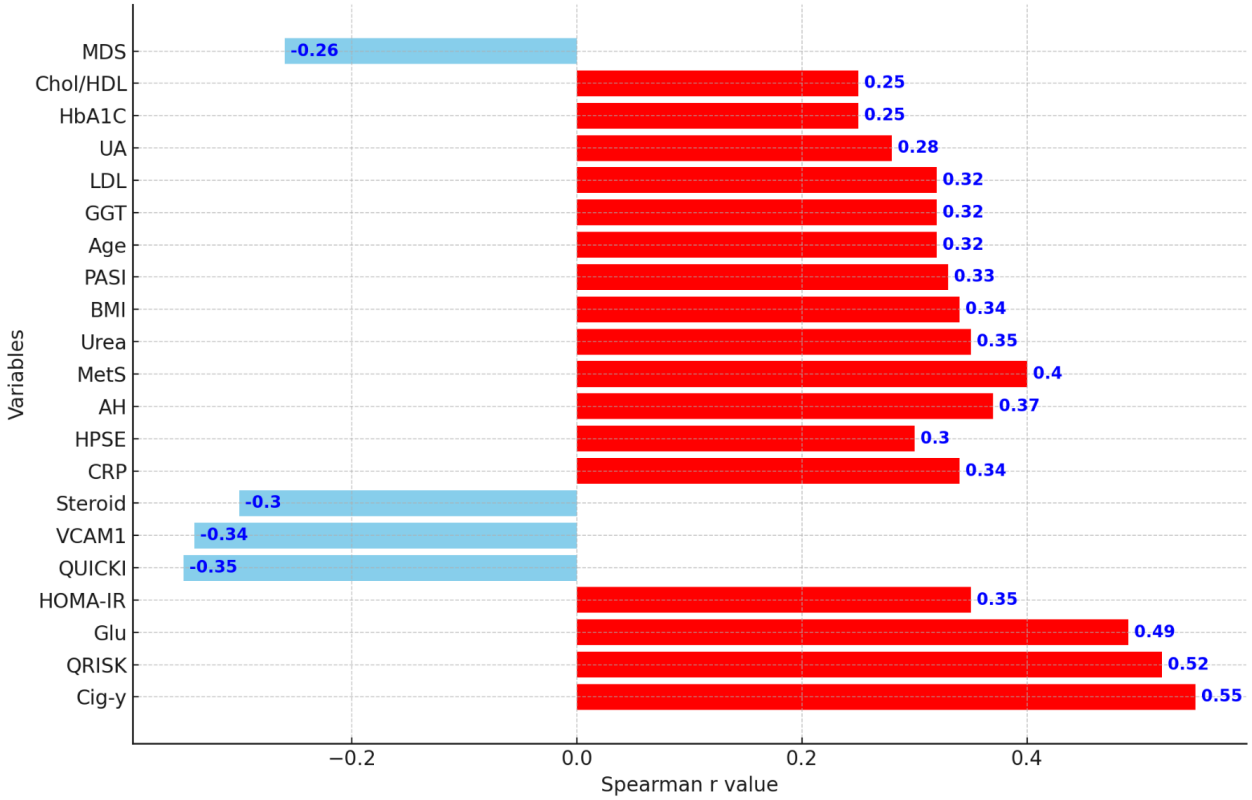


Figure 34. Bar-plot visualizing significant Spearman correlations between IMT and other markers.

4.4.2 Speckle-tracking GLS analysis

Spearman correlation analysis revealed the following results (Figure 36). The coefficient between mNAPSI and GLS was r = -.54 with a p-value of p = .039, indicating a statistically significant inverse relationship. In a clinical context, this means that as mNAPSI scores decreased, which is an indicator of symptom improvement in psoriasis, there was a tendency for GLS values to become less negative, which is usually a sign of worsening cardiac function. This result challenges the conventional understanding that systemic improvement in disease symptoms is usually associated with better cardiac health. A positive and statistically significant correlation was found between Metabolic Syndrome (MetS) and GLS (r = .5, p = .002).

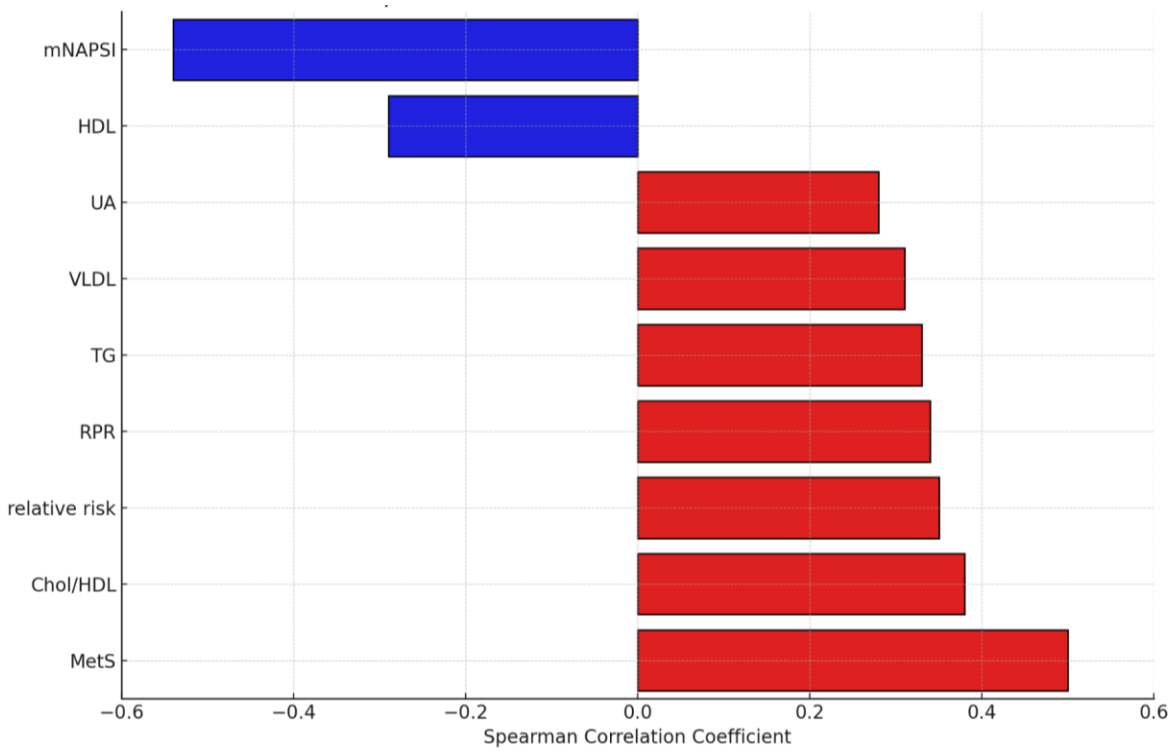


Figure 36. Barplot visualizing Spearman correlation coefficients between GLS and other markers.

The Chol/HDL ratio showed a statistically significant positive correlation with GLS (r = .38, p = .015). This suggests that as this lipid profile increases, cardiac function, as represented by GLS values, deteriorates. In addition, changes in Relative Risk calculated by QRISK (r = .35, p = .052) and the Red cell distribution width to platelet ratio (RPR; r = .34, p = .032) also showed positive correlations with GLS, although the p value for Relative Risk was above the usual significance level. Triglycerides (TG; r = .33, p = .037) and Very Low Density Lipoproteins (VLDL; r = .31, p = .053) also showed a weak positive correlation with GLS Conversely, HDL was negatively correlated with GLS (r = -.29, p = .065), although this was not statistically significant at a level below p = .05. Uric acid (UA; r = .28, p = .075) also showed a positive but statistically insignificant correlation with GLS.

4.5 Cardiovascular risk - QRISK

4.5.1. Descriptive and correlative analysis

Descriptive statistics for QRISK values in PsA showed a mean of 12.66 (SD = 13.22), the range of values was from 0.2 to 57.3. For the group of healthy controls, the mean value was 3.8 (SD = 4.08), with a

range of values from 0.1 to 11.0. For RA, the mean "QRISK" value was 9.6 (SD = 7.94) and the range was 0.1 to 29.0.

The Shapiro-Wilk test was used to assess the normality of the distribution. For PsA, the test showed a significant deviation from normality ($p < .001$). The healthy control group showed no significant deviation from the normal distribution ($p = .236$), whereas the RA group showed a significant deviation ($p = .002$). Significant differences were found between PsA and healthy controls ($p = .030$) and between healthy controls and RA ($p = .040$). However, PsA and RA showed no significant differences in their "QRISK" values ($p = .717$).

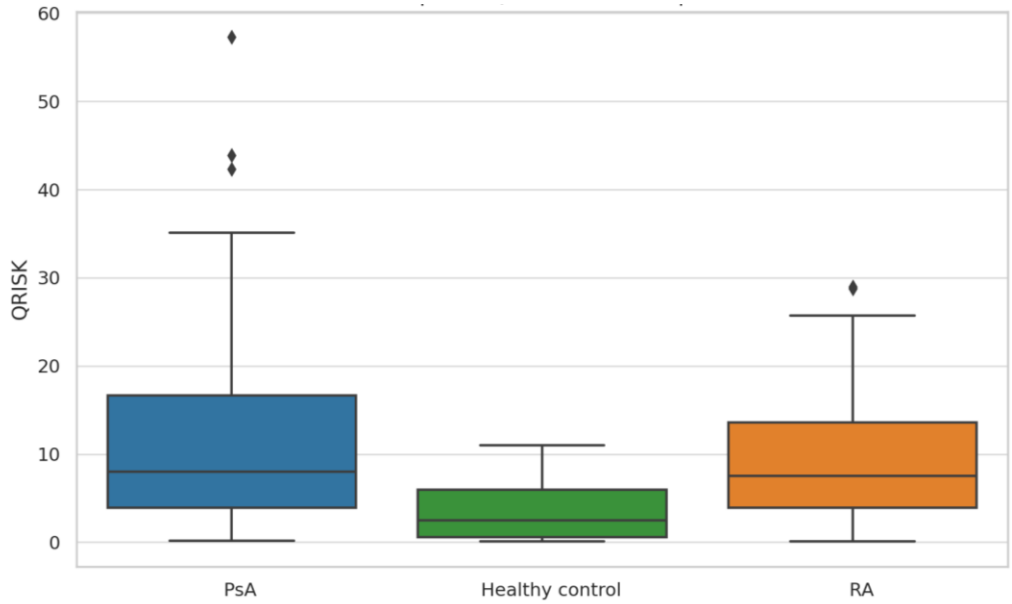


Figure 37. Box-plot for the distribution of QRISK between groups

Age showed a very strong and statistically significant correlation with "QRISK" ($r = .80$, $p < .001$). Similarly, arterial hypertension also demonstrated a very strong and statistically significant correlation with QRISK ($r = .66$, $p < .001$). Years of smoking had a strong and statistically significant correlation with "QRISK" ($r = .59$, $p = .004$). Similarly, active smoking ($r = .54$, $p < .001$) and right carotid IMT ($r = .52$, $p < .001$) also showed strong and statistically significant correlations. Strong and statistically significant correlations with QRISK were observed for SUE ($r = .45$, $p < .001$), composite IMT ($r = .44$, $p < .001$), Urea ($r = .42$, $p < .001$), "CRP" ($r = .42$, $p < .001$), and Ferritin ($r = .41$, $p = .005$). Moderate but statistically significant correlations were observed for the variables DAS28 ($r = .38$, $p = .003$), "NEUT#" ($r = .37$, $p < .001$), UA ($r = .36$, $p < .001$), MetS ($r = .35$, $p = .002$), WBC ($r = .34$, $p = .004$), waist circumference ($r = .33$, $p = .007$), and VLDL ($r = .31$, $p = .007$), BMI ($r = .30$, $p = .010$) (Figure 38).

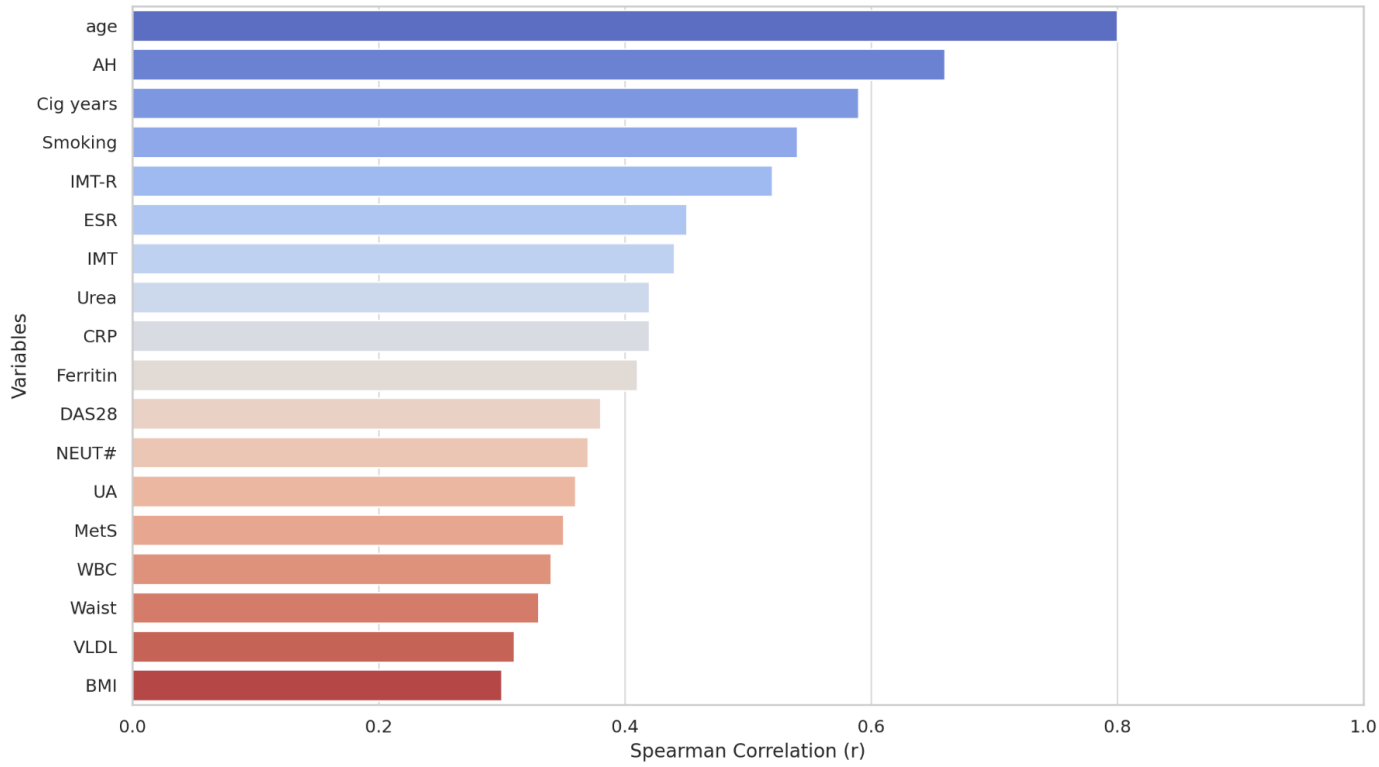


Figure 38. Barplot depicting correlations between QRISK and other variables.

4.5.2. Regression analysis

In the analysis including DAS28 and QRISK from 61 patients, the regression model fitted to predict QRISK (R^2 = .105, p = .011) (Figure 39). That is, the model explained 10.5% of the variance in QRISK scores, and the F-statistic (F(1, 59) = 6.947, p = .011) confirmed the statistical significance of the model. The coefficient for DAS28 was 3.17 and was statistically significant (t = 2.636, p = .011). Although the explanatory power of the model is moderate it provides a deeper understanding of their relationship, confirming that DAS28 alone is a significant predictor of QRISK.

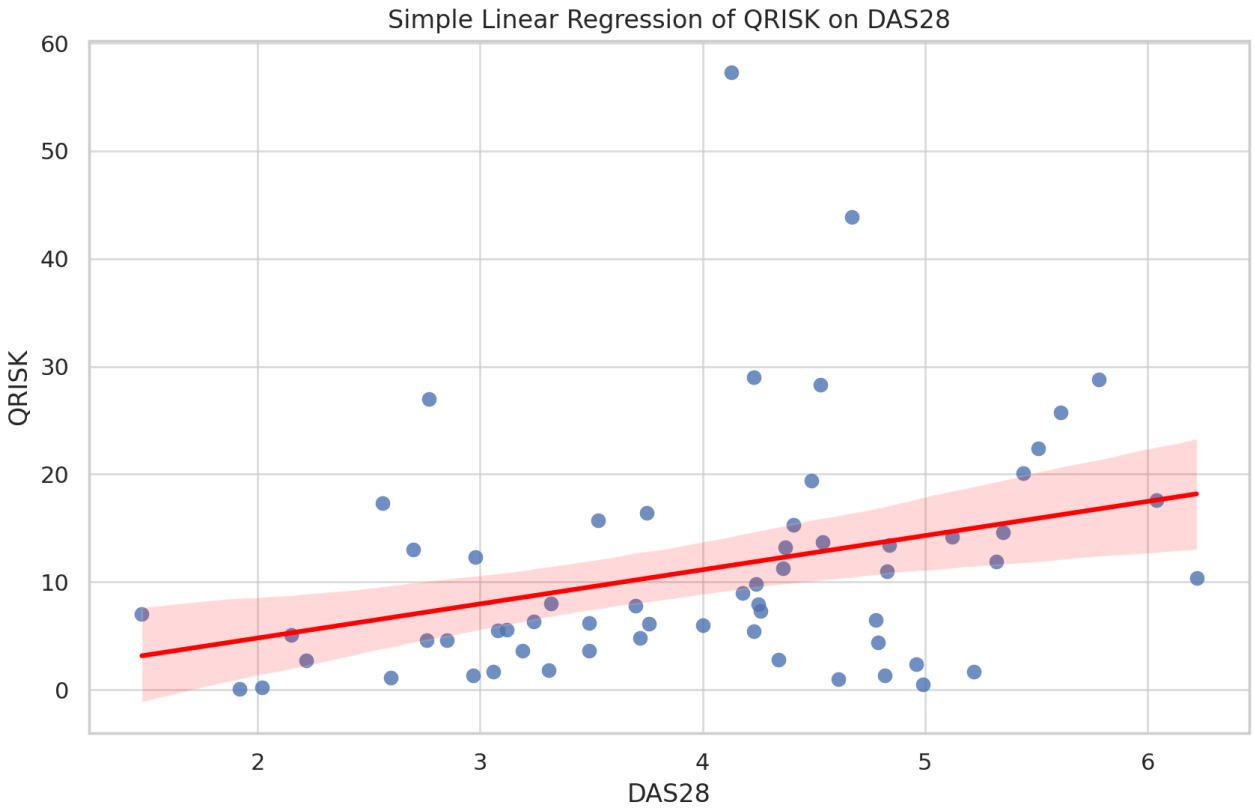


Figure 39. Linear regression of QRISK with DAS28

Multiple regression analysis included the variables "DAS28", "MetS", "UA", "Lp-PLA2", "HYAL", "Crea", "HPSE" and "SYND-1" as predictors for "QRISK". The model explained 64.4% of the variance in "QRISK" as indicated by the R^2 value of 0.644. The adjusted R^2 was 0.664, and the model was statistically significant, ($F(8,47) = 10.62$, $p < .001$). Among the predictor variables, DAS28 and MetS were statistically significant. Specifically, DAS28 had a coefficient of 3.2423 ($t = 3.530$, $p = .001$), and MetS had a coefficient of 6.4282 ($t = 2.167$, $p = .036$). The other variables, UA, Lp-PLA2, HYAL, Crea, HPSE, SYND-1, and IMT, did not reach statistical significance in predicting QRISK in this model.

The results of the regression analysis show that the model is effective and the selected predictors - DAS28, MetS, UA, Lp-PLA2, HYAL, Crea, HPSE, SYND-1 and IMT - together are very powerful in predicting QRISK.

4.5.3. ROC analysis

To establish the predictive accuracy of certain significant markers in detecting increased cardiovascular risk, with the best combination of sensitivity and specificity values, we calculated receiver operating characteristic (ROC). ROC analysis was performed using a dichotomous dependent variable QRISK (> 10 vs ≤ 10) (Figure 40). The model was implemented to differentiate between the presence and absence of increased risk, respectively.

For PECAM, the AUC was 0.636 (95% CI: 0.507 - 0.766), which showed satisfactory predictive value. For DAS28, the calculated AUC was 0.725 (95%[CI]: 0.605 - 0.845), and the model showed good predictive value. The significance achieved allows us to assume a good diagnostic ability of these biochemical assays to discriminate the true positive rate from the false positive rate, given the threshold values obtained (Table 10). The optimal "cut of" value for PECAM was calculated to be 3118 pg/mL and for DAS28 4.37 (Table 11). This represents the point on the ROC curve that maximizes the true positive rate while minimizing the false positive rate, providing the best balance between sensitivity and specificity for this predictor.

The area under the curve for DAS28 is larger compared to that of PECAM, suggesting greater diagnostic accuracy. Table 10 and 11 describe the threshold values, sensitivity and specificity, positive and negative predictive values for DAS28 and PECAM.

Table 10. ROC analysis results:

Variable	AUC	SE	95% CI		p
DAS28	0.725	0.061	0.605	0.845	<0.001
PECAM	0.636	0.066	0.507	0.766	0.03

DAS28, Disease Activity Score in 28 joints; **PECAM**, Platelet Endothelial Cell Adhesion Molecule-1 **AUC**, Area Under the Curve; **SE**, standard error; **CI**, confidence interval; **p** value

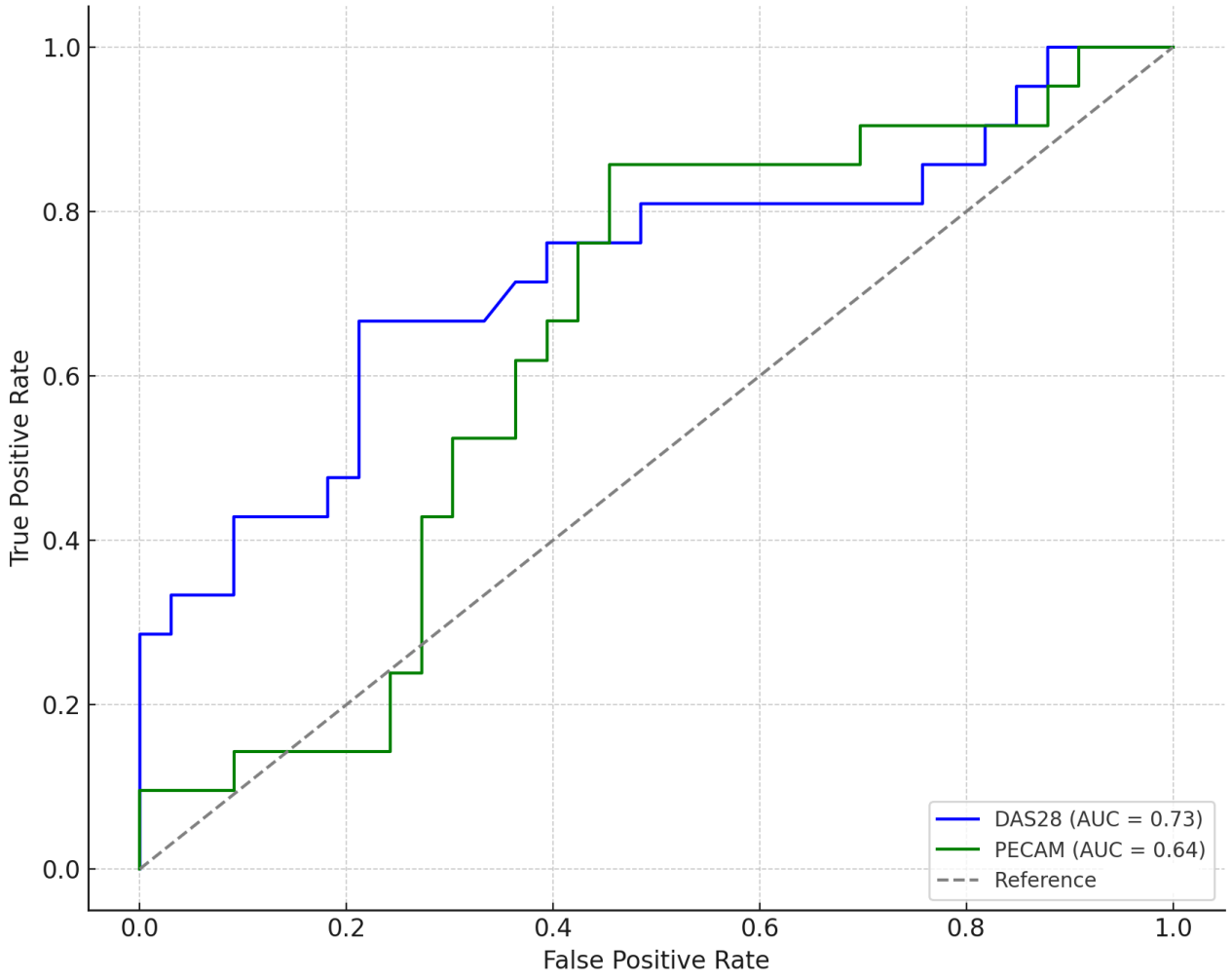


Figure 40. Receiver operating characteristic curves with threshold values of PECAM 3118 pg/mL and DAS28 4.37, for detection of increased cardiovascular risk QRISK >10.

Table 11. ROC analysis results: cut-off, sensitivity, specificity, positive predictive value, negative predictive value

Variable	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
DAS28	4.37	61.9	78.7	65.0	76.4
PECAM	3188	80.9	54.5	53.1	81.8

DAS28, Disease Activity Score in 28 joints; **PECAM**, Platelet Endothelial Cell Adhesion Molecule-1 **Sensitivity**; **Specificity,** specificity; **Cut-off**, cut-off point; **PPV**, positive predictive value; **NPV**, negative predictive value;

4.6 Experimental biomarkers

VCAM-1

For the VCAM1 biomarker, data included 80 observations with a mean of 1.034 (SD = 0.218). Values ranged from a minimum of 0.641 to a maximum of 1.905. The distribution of VCAM1 was assessed for normality using the Shapiro-Wilk test, which yielded a p value less than .001, indicating that the data did not follow a normal distribution. The Mann-Whitney test was then performed to compare VCAM1 levels across groups. The test between PsA and Healthy controls showed a statistically significant difference (U = 416, p = .022). Similarly, the comparison between PsA and RA also showed a significant difference (U = 627, p = .009). However, the Mann-Whitney test showed no statistically significant difference in VCAM1 levels between Healthy Controls and RA (U = 282, p = .729). These results show the variation in VCAM1 levels across groups, especially between PsA and the other two groups, while no statistically significant difference was observed between the Healthy Controls and RA groups.

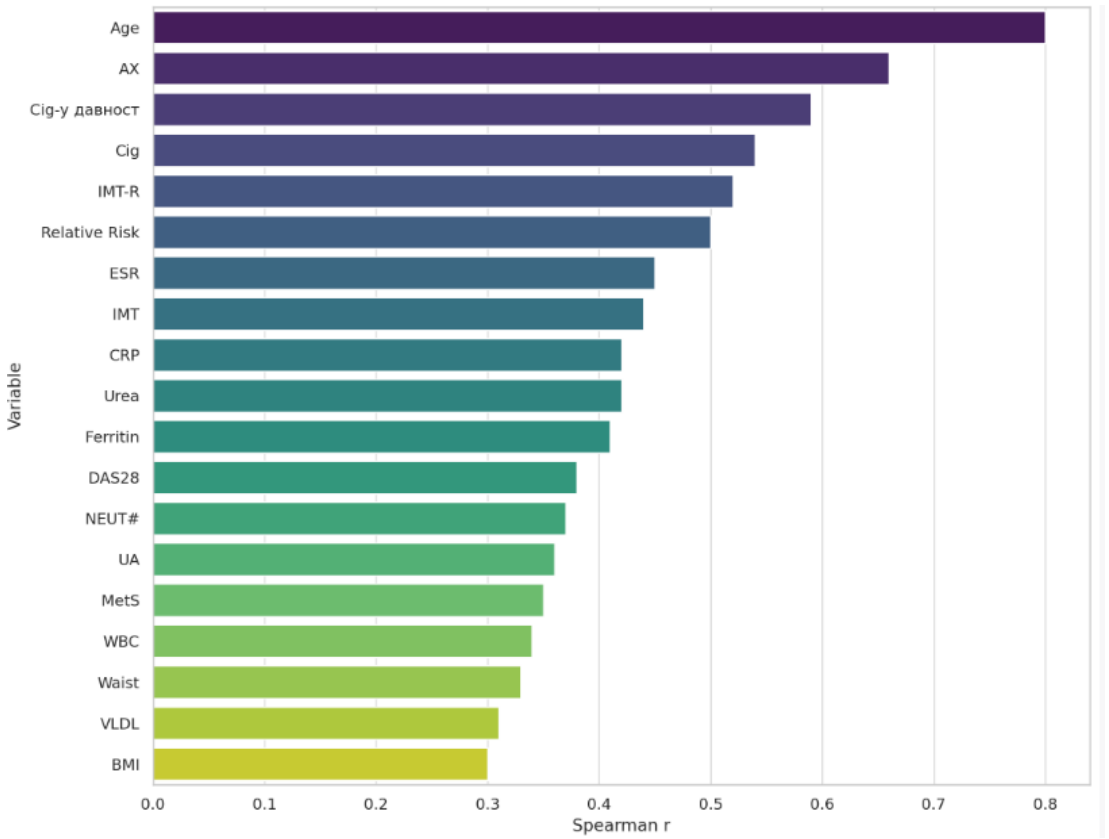


Figure 41. Spearman correlation analysis for VCAM with other variables.

Spearman correlation analysis between VCAM1 and different variables showed different degrees of relationships (Figure 41). "Age" demonstrated a very strong positive correlation with VCAM1 ($r = .80$, $p < .001$). Arterial hypertension also showed a strong positive correlation ($r = .66$, $p < .001$). Years of smoking ($r = .59$, $p = .004$) and active smoking ($r = .54$, $p < .001$) also showed strong positive correlations with VCAM1. IMT of d. carotid IMT-R exhibited a strong correlation ($r = .52$, $p < .001$), as did relative CV risk calculated from QRISK ($r = .50$, $p < .001$). "ESR" ($r = .45$, $p < .001$), "IMT" ($r = .44$, $p < .001$), "Urea" ($r = .42$, $p < .001$), "CRP" ($r = .42$, $p < .001$), and "Ferritin" ($r = .41$, $p = .0045$). Other variables such as "DAS28" ($r = .38$, $p = .0027$), "NEUT#" ($r = .37$, $p < .001$), "UA" ($r = .36$, $p = .0011$), "MetS" ($r = .35$, $p = .0017$), "WBC" ($r = .34$, $p = .0044$), Waist Circumference ($r = .33$, $p = .0065$) and "VLDL" ($r = .31$, $p = .006$) "BMI" ($r = .30$, $p = .009$) showed moderately strong correlations.

4.6.2. PECAM

For PsA, the mean PECAM level was 3812.1 (SD = 799.8), with a range from 2366.3 to 5421.6. For the healthy control, the mean PECAM level was 3393.1 (SD = 696.8), with a range of 2318.9 to 4811.1. In the RA group, the mean PECAM level was 3260.5 (SD = 948.8), and its range was 1458.6 to 4877.9 (Figure 42).

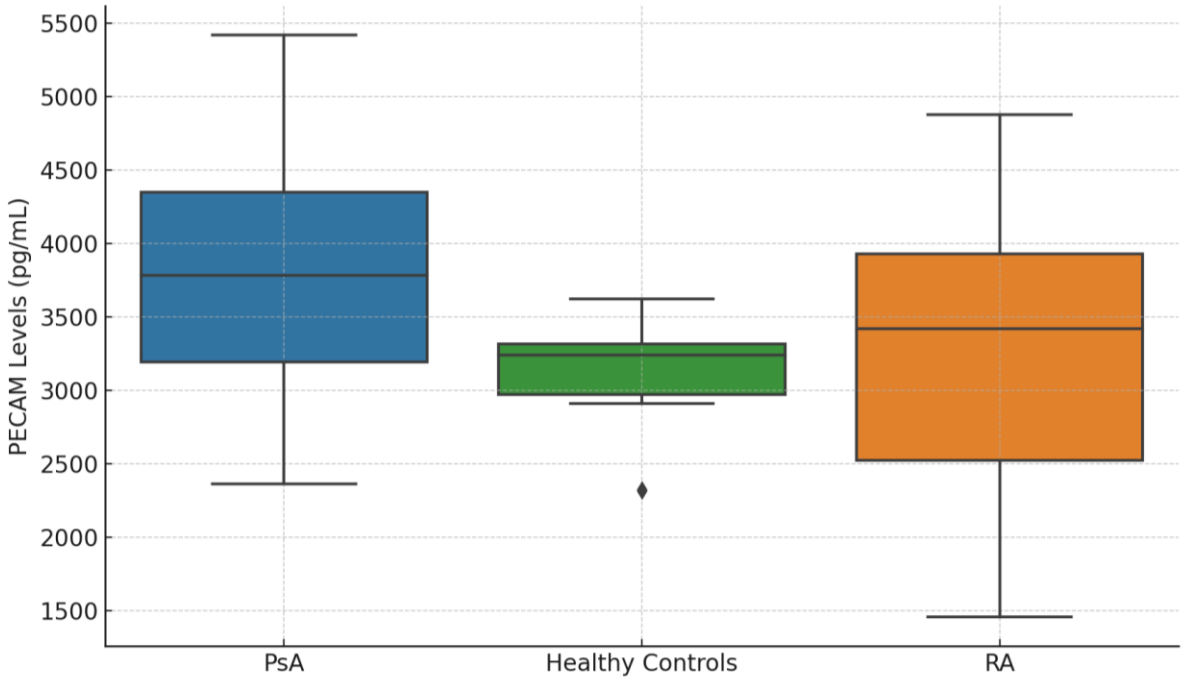


Figure 42. Box-plot showing the distribution of PECAM between groups

Normality was assessed using the Shapiro-Wilk test. PECAM values for Groups 1 and 3 were normally distributed ($p = 1.00$ for both groups), whereas the distribution for Group 2 violated the assumption of normality ($p = .010$).

A significant difference in PECAM levels was found between PsA and healthy controls ($p = .044$), and between PsA and RA ($p = .032$). However, no significant difference was found between healthy controls and RA ($p = .737$). Therefore, the analysis indicates that PECAM levels differ significantly between psoriatic arthritis patients and the other two groups, but not between healthy controls and rheumatoid arthritis patients. These findings may indicate a potential role for PECAM as a discriminative biomarker in psoriatic arthritis.

Pearson correlation analysis showed specific relationships between PECAM and various other variables (Figure 43). YKL-40 showed a moderate positive correlation with PECAM ($r = .46$, $p < .001$), indicating a statistically significant relationship. MDA had a moderate negative correlation with PECAM ($r = -.40$, $p = .030$), while BSAPs exhibited a moderate positive correlation ($r = .40$, $p = .030$), both of which were statistically significant. Similarly, PASI also showed a moderate positive correlation with PECAM ($r = .38$, $p = .037$). In the category of weak correlations, IL17 had a positive correlation with PECAM ($r = .32$, $p = .005$), which was statistically significant. RDW and HYAL showed similar positive correlations ($r = .28$, $p = .016$ for RDW and $r = .28$, $p = .015$ for HYAL), both of which were statistically significant. DPAS had a weak negative correlation with PECAM and was statistically significant ($r = -.27$, $p = .031$). HPSE showed a negative correlation ($r = -.25$, $p = .031$). QRISK and Crea both showed very weak positive correlations, with respective p values of .050 and .043 that made them statistically significant.

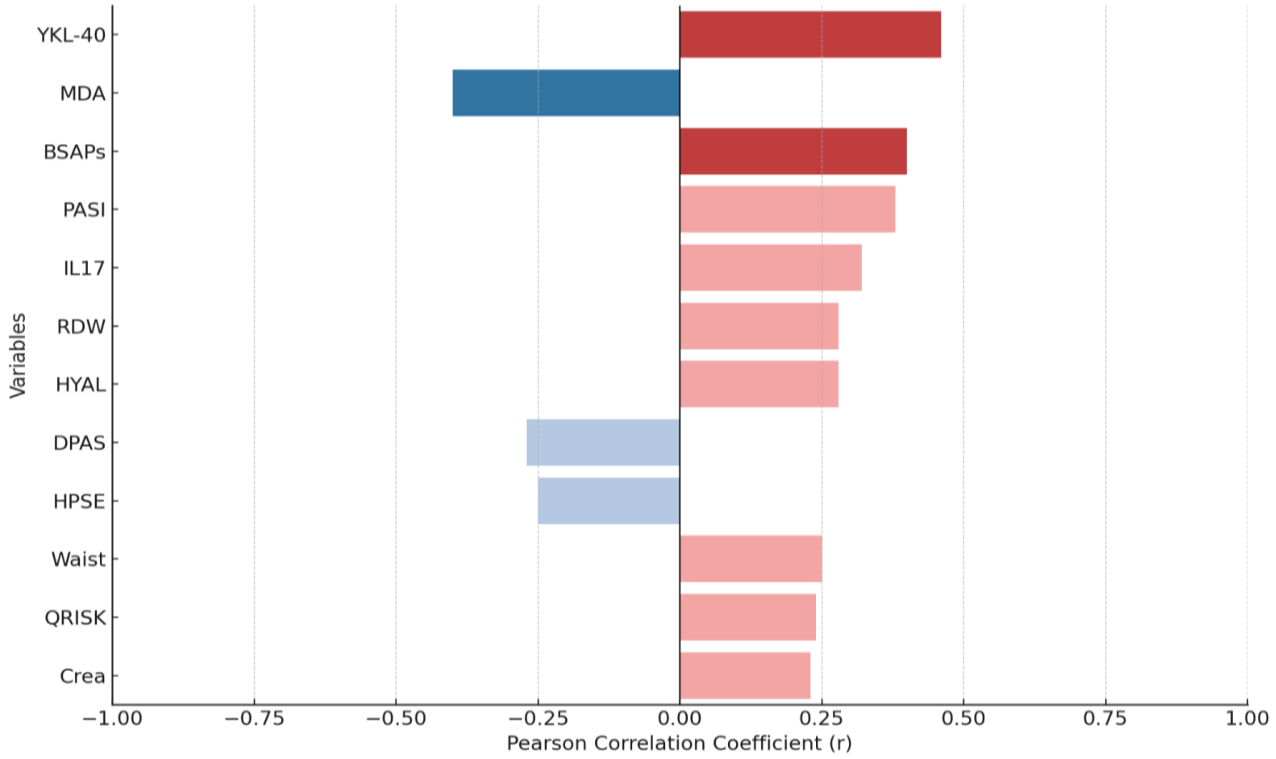


Figure 43. Bar plot visualizing PECAM correlations with key markers.

4.6.3. YKL-40

For patients with PsA, the mean YKL-40 level was 6443.52 pg/mL (SD = 1636.02). Values ranged from 2212.32 to 9452.92 pg/mL. The Shapiro-Wilk test for normality gave a value of p = .347, indicating that the data were normally distributed. In the group of healthy controls, the mean YKL-40 level was 5609.81 (SD = 1446.00). The range for this group was 2187.28 to 8079.71. Normality for this group was confirmed by a Shapiro-Wilk value of p = .372. For RA patients, the mean YKL-40 level was 4343.70 (SD = 2369.53). Values in this group ranged from 924.73 ng/mL to 8285.88 ng/mL (Figure 44). The Shapiro-Wilk test yielded a value of p = .061, indicating a marginal violation of the normality assumption. Regarding the comparison between groups, the Mann-Whitney test showed statistically significant differences in YKL-40 levels between PsA and healthy controls (U = 409, p = .032), and between PsA and RA (U = 647, p = .001). However, the difference between healthy controls and RA was not statistically significant (U = 379, p = .072).

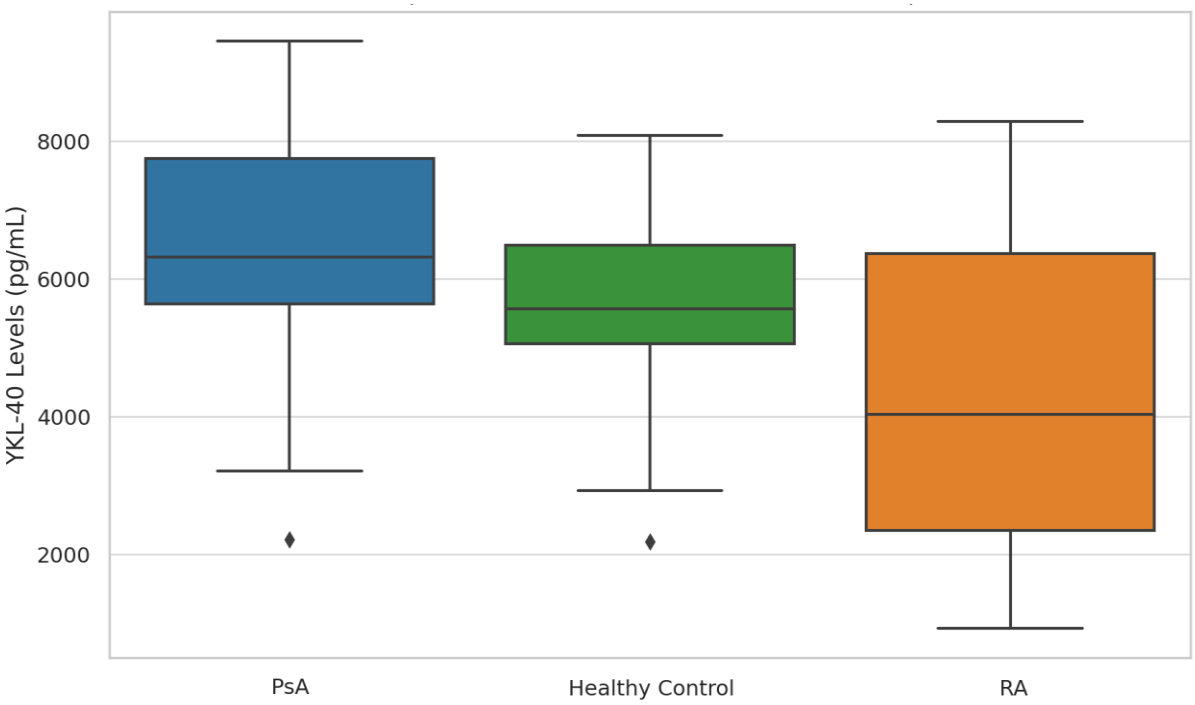


Figure 44. Box-plot showing the distribution of YKL-40 between groups

Correlation analysis between the YKL-40 variable and other biomarkers and clinical indicators in the dataset revealed different relationships (Figure 45). Specifically, RF showed a strong negative correlation with YKL-40 ($r = -.6$, $p < .001$). That is, as RF levels increased, YKL-40 levels tended to decrease, and this relationship was statistically significant. Furthermore, years of psoriasis duration showed a moderate negative correlation with YKL-40 ($r = -.47$, $p = .008$), indicating that greater psoriasis was associated with lower YKL-40 levels. HPSE also exhibited a moderate negative correlation with YKL-40 ($r = -.44$, $p < .001$). Conversely, PECAM showed a moderate positive correlation with YKL-40 ($r = .42$, $p < .001$), suggesting that higher levels of PECAM are associated with higher levels of YKL-40. Additionally, anti-CCP ($r = -.33$, $p = .004$) and QUICKI ($r = .32$, $p = .004$). ptPAIN also exhibited a weak negative correlation with YKL-40 ($r = -.32$, $p = .013$). DAS28 ($r = -.28$, $p = .029$) and HYAL ($r = .23$, $p = .040$) also showed weak correlations.

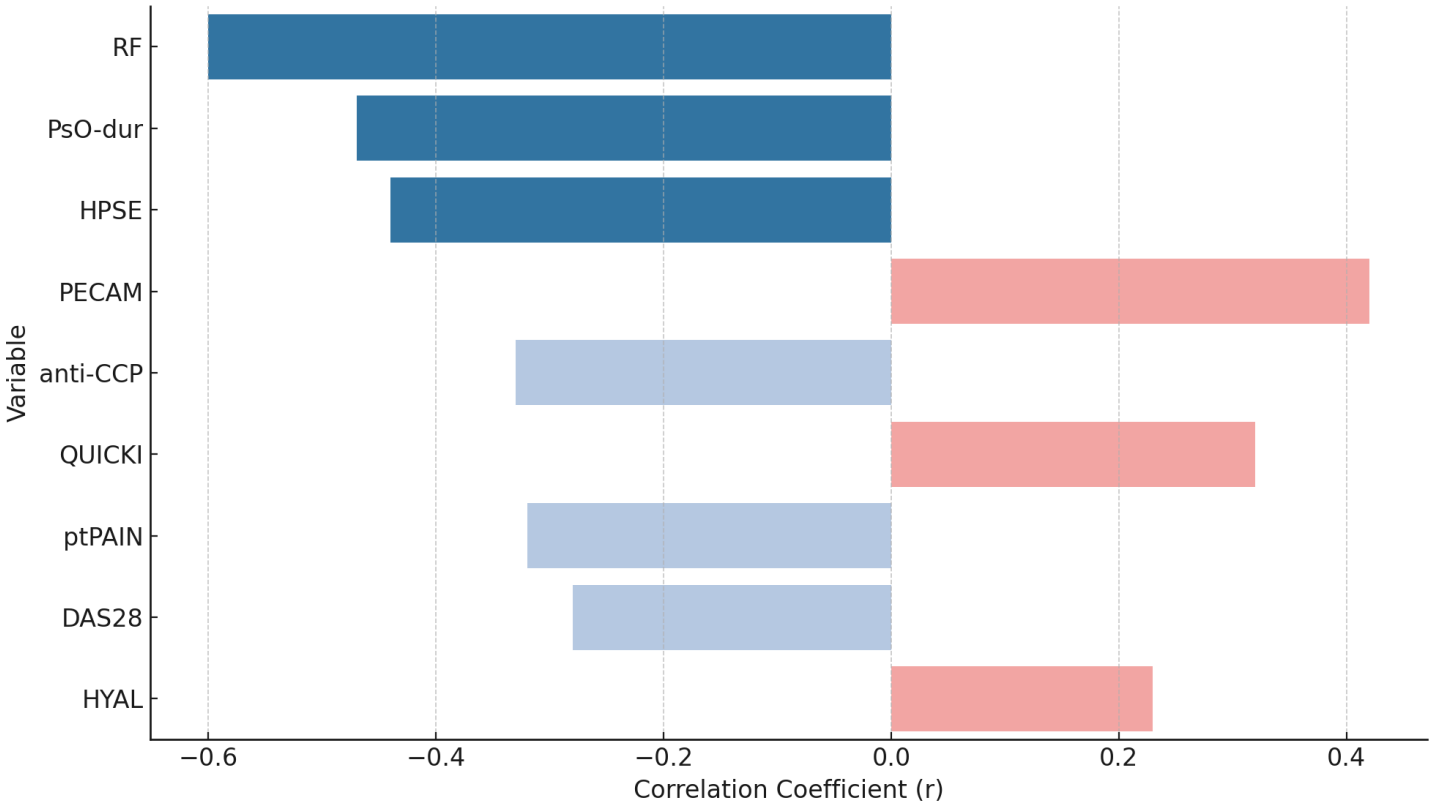


Figure 45. Bar-plot visualizing statistically significant correlations of YKL-40 with other markers.

4.6.4. Heparanase

First, descriptive statistics for HPSE in each group were calculated. For PsA, the mean HPSE was 3.62 pg/mL (SD=19.79) (Figure 46); for Healthy Controls, the values were consistent, with a mean of 0.012, and virtually zero standard deviation (SD ≈0); and for RA, the mean HPSE was 70.40 (SD=156.86). It is important to note that the standard deviations show significant variance in Groups 1 and 3, whereas Group 2 presents almost no variability. The Shapiro-Wilk test was then performed to assess the normality of HPSE levels in each group. P-values from this test indicated that the distribution of HPSE levels significantly deviated from normal in all groups ($p < 0.001$). Comparisons performed using the Mann-Whitney test showed a significant difference in HPSE levels between PsA and RA ($p = .002$), and between Healthy Controls and RA ($p = .003$). However, comparison between PsA and healthy controls did not yield a significant result ($p = .438$).

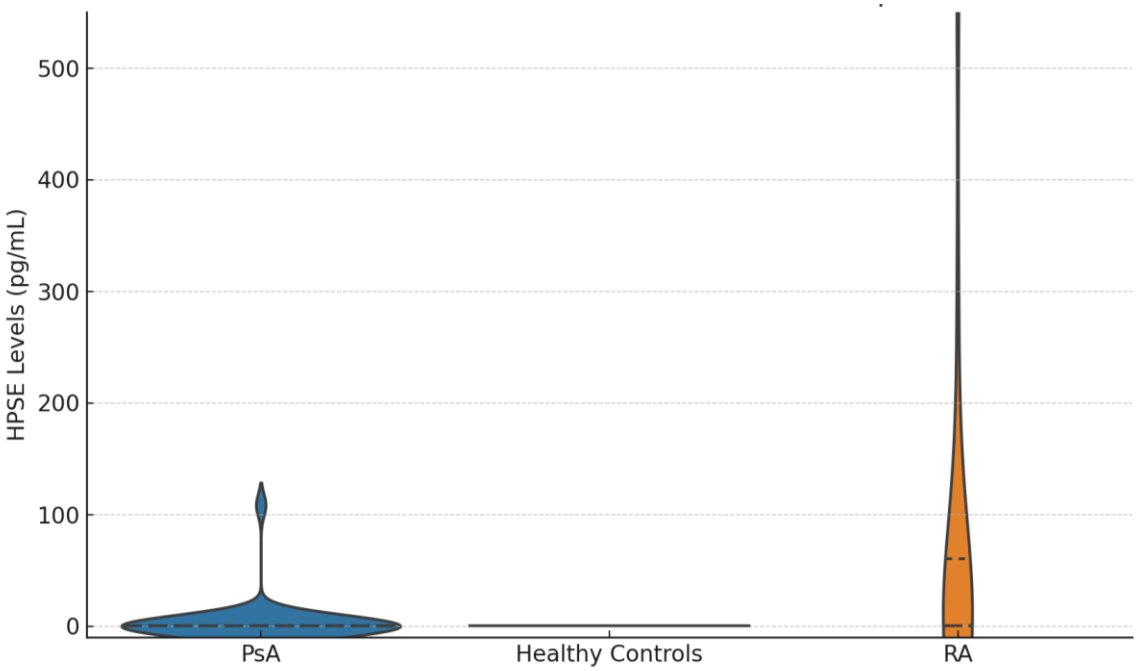


Figure 46. The vial diagram provides a more detailed visualization of HPSE levels in the three groups. This type of plot combines the features of a box plot plot with kernel density estimation, providing a more detailed view of the data distribution.

"RF" ($r = .66$, $p < .001$) and "Cig-y age" ($r = .63$, $p = .002$) showed a strong positive correlation with HPSE, which may highlight the importance of these variables in the context of the biomarkers studied. "YKL-40" ($r = -.55$, $p < .001$), on the other hand, showed a strong negative correlation, which may be an indicator of an inverse relationship with HPSE. The variables "anti-CCP" ($r = .46$, $p < .001$), "SYND-1" ($r = .44$, $p < .001$), and "ESR" ($r = .42$, $p < .001$) showed moderate correlation, suggesting that they also have relevance, albeit to a more moderate degree. Variables such as "QUICKI" ($r = -.38$, $p < .001$), "Insulin" ($r = .38$, $p < .001$) and "HOMA-IR" ($r = .38$, $p < .001$), "RAQoL" ($r = .37$, $p = .05$), "CRP" ($r = .33$, $p = .002$), and "relative risk" /calculated by QRISK/ ($r = .31$, $p = .018$) showed moderate to weak but statistically significant correlation. Finally, variables such as "NLM" ($r = .28$, $p = .014$), "nsaid" ($r = .27$, $p = .034$), and "HYAL" ($r = -.25$, $p = .026$) showed weak but statistically significant correlations, which may warrant future research. Analysis revealed a complex web of factors that were associated with HPSE, with the strength of these associations ranging from strong to weak (Figure 47).

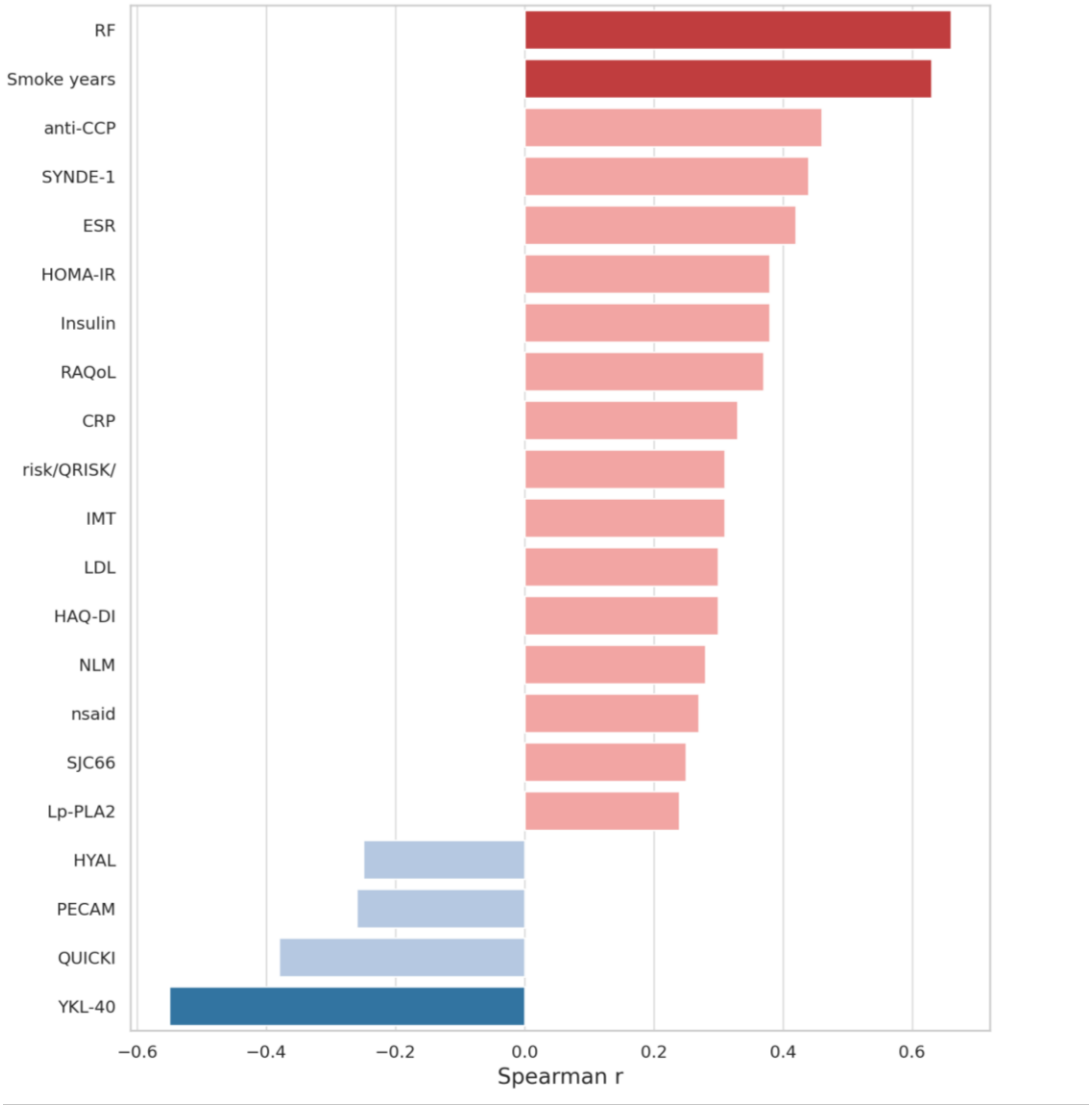


Figure 47. Spearman correlations with HPSE and other markers

To establish the predictive accuracy of certain significant markers in detecting elevated HPSE with the best combination of sensitivity and specificity values, we calculated the receiver operating characteristic (ROC) curve. ROC analysis was performed using a dichotomous dependent variable HPSE (> 0.012 vs ≤ 0.012 pg/mL) (Figure 48).

The significance achieved allows us to assume a good diagnostic ability of these tests to distinguish the true positive rate from the false positive rate, at the threshold values obtained (Table 12). The optimal "cut of" values are presented in Table 13. This represents the point on the ROC curve that maximizes the true positive rate while minimizing the false positive rate, providing the best balance between sensitivity and specificity for this predictor.

The area under the curve for RF is greater than that of anti-CCP, suggesting greater diagnostic accuracy, although the threshold value is significantly greater. Table 12 and 13 describe the threshold values, sensitivity and specificity, positive and negative predictive values for RF, anti-CCP, CRP and IMT.

Table 12. Results of ROC analysis of heparanase:

Variable	AUC	SE	95% CI		p
anti-CCP	0.756	0.090	0.578	0.933	0.005
RF	0.947	0.048	0.853	1.000	<0.001
IMT	0.726	0.093	0.543	0.909	0.015
CRP	0.756	0.090	0.578	0.933	0.005

anti-CCP- Anti-cyclic citrullinated peptide; **RF-** Rheumatoid factor; **IMT** - Intima-Media Thickness; **CRP** - C-reactive protein; **AUC** - Area Under the Curve; **SE** - standard error; **CI** - confidence interval; **p-value**

Figure 48 Receiver operating characteristic curves with threshold values of anti-CCP 41.9, RF 256 U/mL, IMT 617.5 μm and CRP 5.7 mg/L for detection of elevated heparanase (HPSE > 0.011 pg/mL)

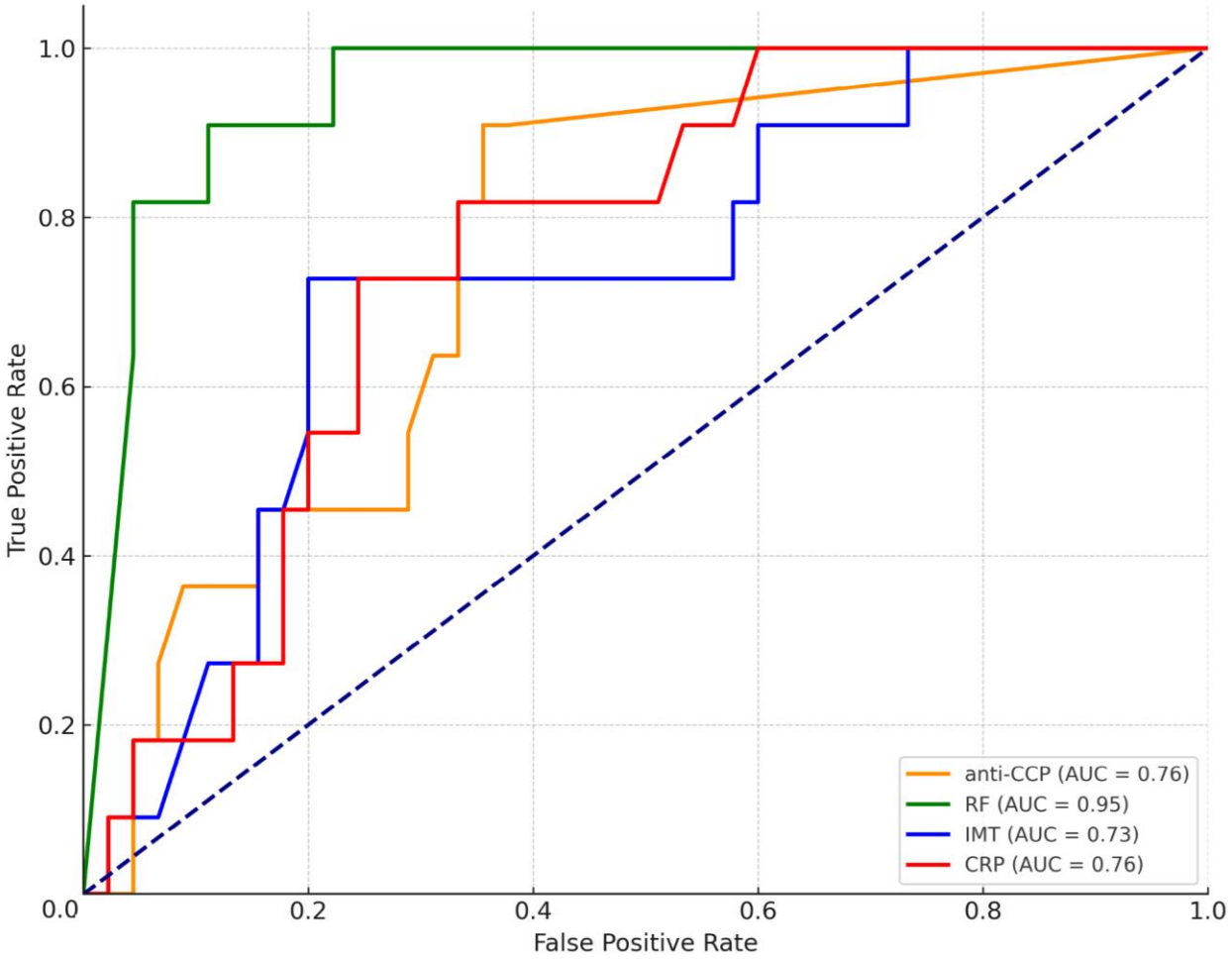


Table 13. Results of ROC analysis of heparanase: cut-off, sensitivity, specificity, positive predictive value, negative predictive value:

Variable	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
anti-CCP	41.9	81.82	64.44	36.00	93.55
RF	256.0	81.82	88.89	64.29	95.24
IMT	617.5	63.64	80.00	43.75	90.00
CRP	5.7	72.73	75.56	42.11	91.89

anti-CCP- Anti-cyclic citrullinated peptide; **RF-** Rheumatoid factor; IMT- Intima-Media Thickness; CRP- C-reactive protein; **Sensitivity-** sensitivity; **Specificity-** specificity; **Cut-off-** cut-off point; PPV- positive predictive value; NPV- negative predictive value;

4.6.5. Hyaluronidase

Descriptive statistics showed that the PsA group had a mean HYAL level of 55.69 ng/mL (SD = 8.72). This was noticeably higher compared to the control group, which showed a mean SD level of 40.45 (SD = 9.75). The RA group also showed a relatively high mean HYAL level , which was (SD = 10.81) (Figure 49). The normality of HYAL levels was assessed for each group with the Shapiro-Wilk test. The resulting p-values were 0.955 for the healthy control group, 0.714 for PsA, and 0.478 for RA, indicating that the data for each group did not deviate significantly from a normal distribution. Subsequent Mann-Whitney tests revealed significant differences in HYAL levels between certain groups. A noticeably significant difference was observed between HYAL levels in the PsA and healthy control groups ($p < .001$) and between healthy controls and RA ($p < .001$). However, no significant difference in HYAL levels was observed between the PsA and RA groups ($p = .818$).

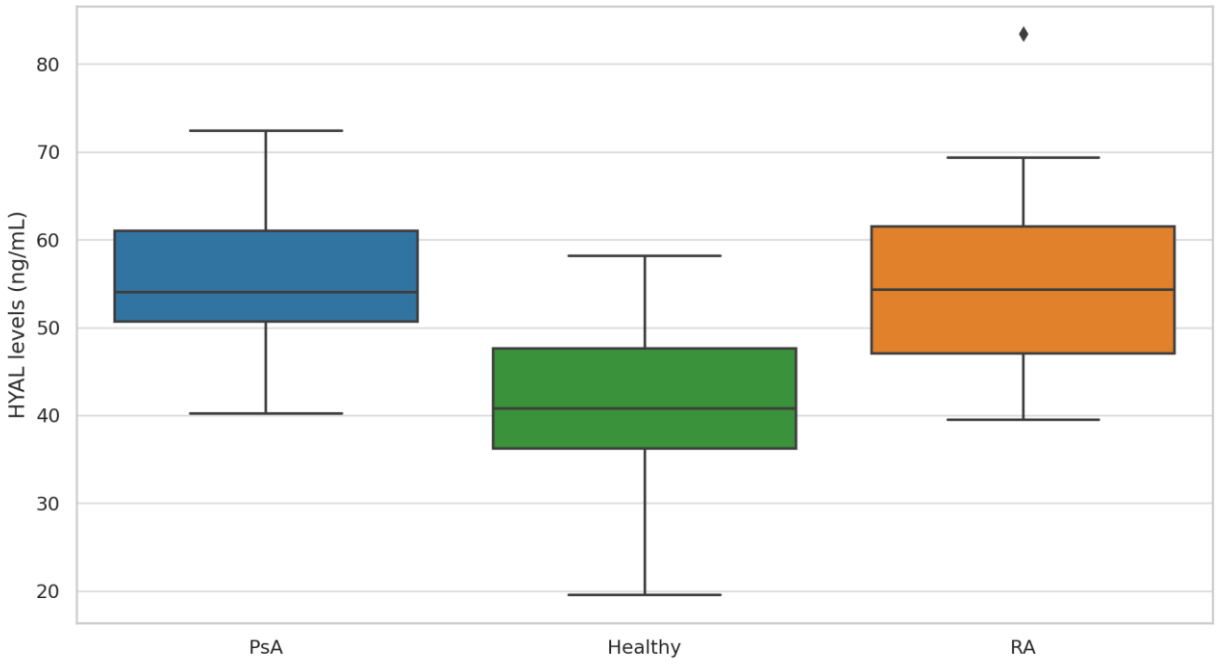


Figure 49. Box-plot depicting the distribution of hyaluronidase (HYAL) between groups.

HYAL showed varying degrees of correlation with multiple data variables (Figure 50). In particular, Lp-PLA2 ($r = .57$, $p < .001$), QRISK ($r = .56$, $p < .001$), GLS ($r = .54$, $p < .001$), CVE ($r = .43$,

p < .001), and Insulin (r = .42, p < .001) demonstrated moderate to strong positive correlations. In addition, PECAM (r = .26, p = .02) and YKL-40 (r = .23, p = .04) showed weak positive correlations. This implies that there is a slight tendency for "HYAL" levels to increase as PECAM and YKL-40 levels increase, although the strength of this relationship is not as pronounced as for the previously mentioned variables. Interestingly, TNF (r = .2, p = .073) and anti-CCP (r = .2, p = .087) showed a weak negative correlation, although this was not statistically significant at the usual p > .05 level.

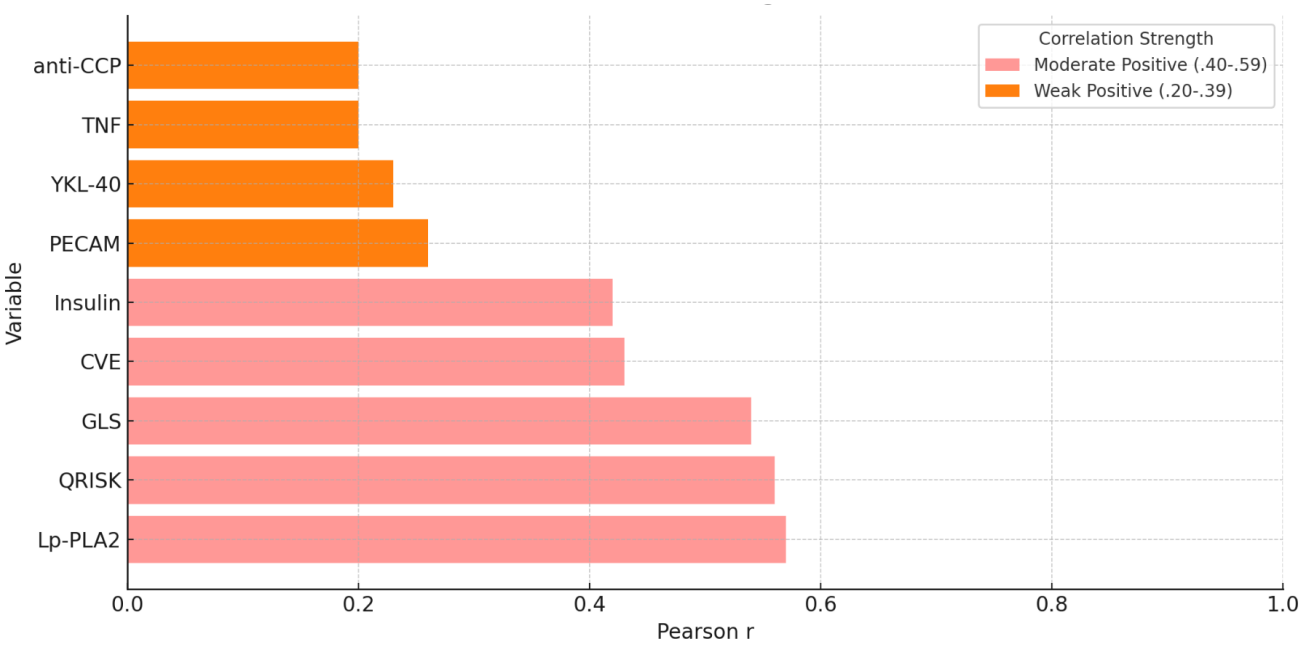


Figure 50. Correlation analysis with hyaluronidase (HYAL). **anti-CCP**: Antibodies to Citrullinated Peptide; **TNF**: Tumor Necrosis Factor Alpha; **YKL-40**: Chitinase-3-like protein 1; **PECAM**: Platelet Endothelial Cell Adhesion Molecule-1; **GLS** global longitudinal strain; **Lp-PLA2**: Lipoprotein-associated Phospholipase A2

4.6.6. Syndecan-1

For the SYND-1 biomarker, the following descriptive statistics were observed for each group: In the PsA group, the mean SYND-1 level was 64.57 ng/mL (SD = 84.21), ranging from a minimum of 6.02 to a maximum of 450.34. In Healthy Controls, the mean SYND-1 level was 59.83 (SD = 80.41), with a minimum of 6.02 and a maximum of 350.89. In RA, the mean SYND-1 level was 72.25 (SD = 55.32), with values ranging from 6.02 to 240.01. To assess the normality of SYND-1 distribution in each group, the Shapiro-Wilk test was performed. The results showed that the distribution was not normal for any of the groups, with p-values less than 0.05 for all three groups: p < 0.001 for PsA, p < 0.001 for Healthy Controls, and p = 0.017 for RA (Figure 51). In view of the non-normal distribution, the Mann-Whitney test was used

to assess differences in SYND-1 levels between groups. The results were as follows: No significant difference was observed between RA and Healthy controls (p = 0.617). No significant difference was observed between PsA and RA (p = 0.190). There was also no significant difference between Healthy Controls and RA (p = 0.129). Therefore, SYND-1 may not serve as a distinguishing biomarker between these groups based on the current data.

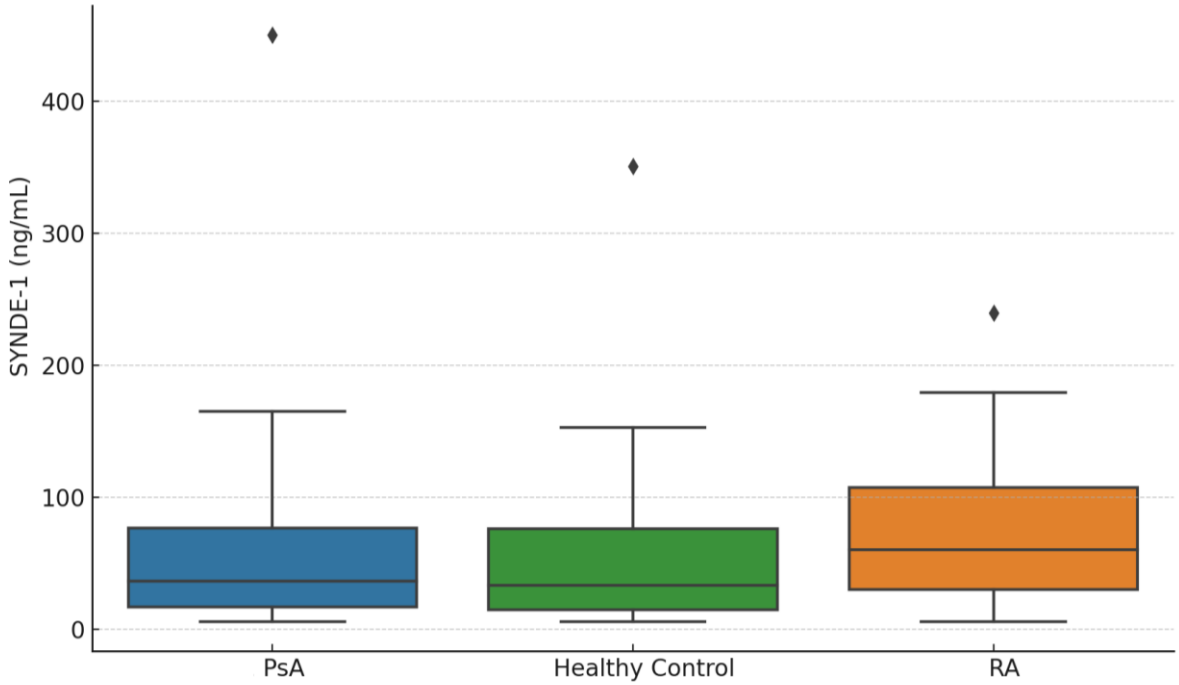


Figure 51. Box-plot showing the distribution of SYND-1 in the groups

Spearman correlation analysis revealed varying degrees of association between "SYND-1" and other variables in the dataset (Figure 52). The strongest correlation was observed with "HPSE" (r = .44, p < .001), falling into the moderate strength category. The variable "RAQoL" also showed a moderate correlation with SYND-1 (r = .40, p = .033). Physician assessment of skin involvement by psoriasis "PhysSk" (r = .36, p = .044), "RF" (r = .34, p = .002), and "BSAPs" (r = .34, p = .059) showed weak to moderate correlations. Although the strength of these correlations is not as reliable as the first two, they are still remarkable, especially "RF," which is statistically significant at p = .002. "PhysSk" also yielded a significant result (p = .044), while "BSAPs" was borderline significant (p = .059). Variables such as "PhysGA" (r = .30, p = .023), "HAQ-DI" (r = .28, p = .02), "Lp-PLA2" (r = .28, p = .012) and "ESR" (r = .25, p = .031) followed, showing weak but statistically significant correlations with "SYND-1". Use of the NSAIDs "nsaid" (r = .23, p = .08), "DPAS" (r = -.23, p = .064), "Insulin" (r = .23, p = .041), and "YKL-40"

(r = -.23, p = .049) also showed weak correlations. Among them, "Insulin" and "YKL-40" were statistically significant or borderline significant, while "nsaid" and "DPAS" were not.

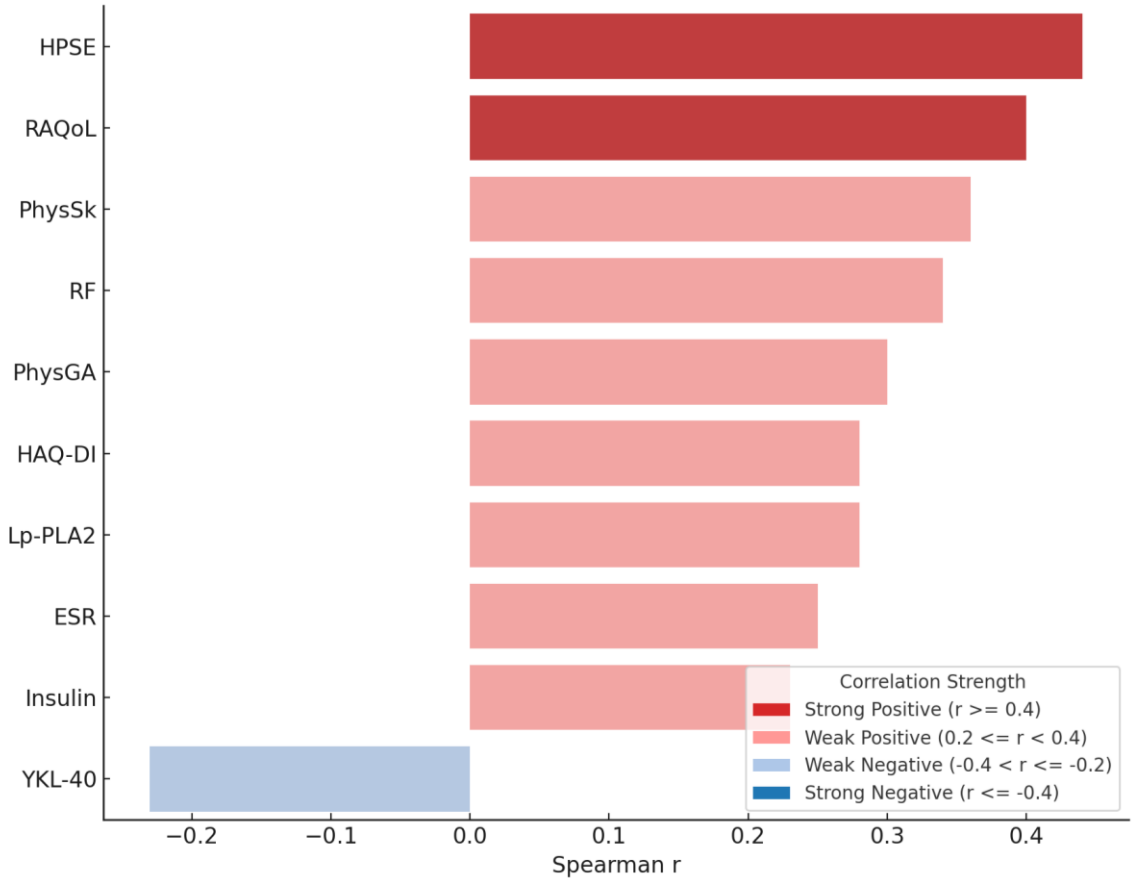


Figure 52. Significant correlations with SYND-1

4.6.7. Lp-PLA2

In the analysis of Lp-PLA2 levels among the three groups, the following results were observed. For the PsA patients, the mean Lp-PLA2 level was 207.70 ng/mL (SD = 890.60), with a variation from 32.53 to 5084.60. In healthy controls, the mean was 413.46 (SD = 1575.97), with a range of 34.45 to 7106.21. For RA patients, the mean Lp-PLA2 level was 43.40 (SD = 15.19), with a range of 31.45 to 101.53. The Shapiro-Wilk test showed that Lp-PLA2 levels were not normally distributed in any of the groups ($p < .001$ for all groups). Therefore, nonparametric tests were used for subsequent analyses. The Mann-Whitney test showed no statistically significant differences between psoriatic arthritis and healthy controls ($p = .167$), between psoriatic arthritis and rheumatoid arthritis ($p = .463$), or between healthy controls and rheumatoid arthritis ($p = .056$). Results should be interpreted with caution because of the wide

range and high standard deviations observed in Lp-PLA2 levels, particularly in PsA and healthy controls. Future studies with larger samples are needed to further investigate these observations.

Spearman correlation analysis revealed the following relationships between Lp-PLA2 and other variables (Figure 53). Notably, LEI showed a moderate negative correlation with Lp-PLA2 (r = -.44, p = .011), indicating that as LEI score increased, Lp-PLA2 levels tended to decrease. This result may warrant further investigation, especially given the statistical significance of the correlation ($p < .05$). Similarly, YKL-40 also showed a weak negative correlation with Lp-PLA2 (r = -.36, p = .001). This negative relationship was statistically significant and suggests that higher levels of YKL-40 are associated with lower levels of Lp-PLA2. On the other hand, left carotid IMT value IMT-L (r = .25, p = .056), RF (r = .25, p = .03), HPSE (r = .24, p = .038), and HDL (r = .24, p = .034) all showed weak positive correlations with Lp-PLA2. Among them, RF, HPSE, and HDL had statistically significant p-values ($p < .05$). However, the correlation with IMT-L was not statistically significant (p = .056), warranting caution in interpreting this particular relationship. Summarizing, the correlation coefficients mostly fell in the range indicating weak to moderate strength, suggesting that while Lp-PLA2 is associated with these variables, it is not the only factor influencing them.

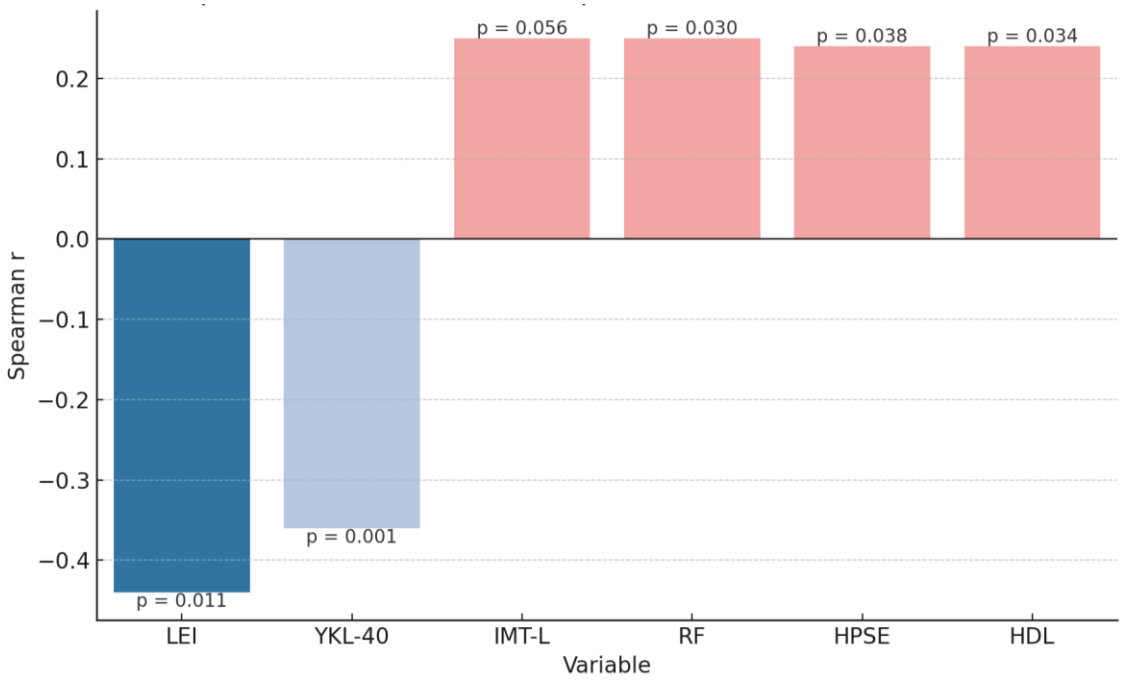


Figure 53. Bar-plot depicting significant correlations with Lp-PLA2

V. DISCUSS

In the present study, extensive statistical methods were applied to ensure the most accurate and objective assessment of the data collected to elucidate the cardiovascular risks associated with psoriatic arthritis (PsA). The understanding of PsA as a systemic disease with significant cardiovascular involvement is highlighted in the study results, supporting the need for an integrated approach in understanding the links between inflammatory arthritis, skin manifestations and cardiovascular disease (CVD). Using a multidisciplinary approach, the study incorporated various indices of disease activity, metabolic profiles, innovative serum biomarkers, and imaging techniques, including echocardiography and carotid ultrasonography, to build a comprehensive picture of cardiovascular outcomes in patients with PsA. Comparison of patients with PsA, rheumatoid arthritis (RA), and healthy controls provides a unique opportunity to evaluate different cardiovascular risk profiles and their potential differentiation based on synovial and enthesopathic inflammation characteristics.

5.1. Disease activity

When examining C-reactive protein (CRP) levels, the PsA group showed the highest mean CRP level of 9.47 (SD = 20.36), and the RA group 8.18 (SD = 9.20). The control group had a CRP level of 2.07 (SD = 2.13). The elevated CRP levels observed in the groups not only indicate an increased inflammatory response consistent with the pathophysiological processes involved in these conditions, but also suggest that CRP is an important biomarker of cardiovascular risk. This is supported by literature evidence suggesting that elevated CRP levels are predictive of cardiovascular events (32). Other large cohort studies have found that systemic inflammation is more pronounced in RA compared with PsA and psoriasis (PsO), which is in contrast to our results (33,34). CRP was found to be significantly elevated six months before myocardial infarction (MI) in RA patients, with a strong association between higher CRP levels and the occurrence of MI (35).

We found high levels of reported pain and global disease activity scores in RA and PsA, highlighting the significant burden these diseases impose on patients. Although the number of painful joints was comparable between the two diseases, the number of swollen joints was slightly more pronounced in RA. Our analysis also looked at disease activity, as indicated by the DAS28 score, and found that while the correlation between arthritis duration and disease activity was not statistically significant, the relationship between psoriasis duration and DAS28 was moderate and significant. This indicates that it is possible that the duration of psoriasis influences arthritis activity. This highlights the importance of early and proactive therapeutic interventions in the treatment of PsA. We also found that prolonged duration of arthritis correlated with a significant negative impact on quality of life as measured by the SF-36. This is consistent

with previous research in this area. A systematic review of depression and anxiety in PsA was conducted in a study by Kamalaraj et al. They found that there was a moderate prevalence of depression and anxiety, which was similar or slightly higher than the general population and comparable to that seen in other rheumatic diseases. This suggests that the negative impact on quality of life in PsA may be influenced by the presence of comorbid psychiatric conditions (36). Another study examined the relationship between depression, anxiety, and remission in RA and PsA. They found that depression and anxiety may reduce the likelihood of joint remission based on composite scores in both conditions. This suggests that the presence of depression and anxiety may contribute to poorer quality of life in individuals with PsA (37). A post hoc analysis of two randomized controlled trials and found that optimal improvement in patients' health-related quality of life depends on successful treatment of both joint and skin symptoms (38).

5.1.1. IL-17 and TNF levels

In spite of the manifestation of similar clinical symptoms on the peripheral joints and the sometimes difficult differentiation between them, psoriatic and rheumatoid arthritis are distinct disease entities with their own unique features, including in pathophysiological aspects. Enthesitis, as a focal inflammation of the insertions of the ligaments, tendons or joint capsule to the bone, is the primary focus and main feature of spondyloarthritis, to which PsA belongs. Later changes associated with enthesitis include periostitis and osteitis, formation of new bone (ossifying enthesitis) and enthesial erosions, inflammation of the synovial membrane and adjacent soft tissues (39). McGonagle et al. maintain that synovitis in spondyloarthritis is secondary, resulting from release of proinflammatory mediators from the entheses, in contrast to synovitis in rheumatoid arthritis, which is primary (40). Appel and Braun also point out that synovitis in SpA is of secondary importance, especially when compared with other inflammatory joint diseases such as rheumatoid arthritis (41). It has been firmly established that in RA, the synovium is the primary and main localization of the inflammatory process and left untreated, synovitis leads to irreversible bone-cartilage erosions and destruction and progressive joint deformities, subluxations and ankyloses (42).

Cytokines produced in response to immune activation play a key role in the immunopathogenesis of chronic inflammatory arthritis. Excessive, decreased, or abnormal cytokine responses contribute significantly to immune-mediated inflammation. In this regard, the aim of our study was to analyze the serum levels of two key proinflammatory cytokines, TNF-α and IL-17, in two inflammatory arthropathies peculiar in nature.

We found significantly elevated circulating levels of TNF-α in RA, regardless of disease activity status, compared with healthy subjects (2.7-fold), and also compared with PsA patients, as 1/3 of RA patients had TNF-α levels higher than the 95th percentile of mean cytokine levels in healthy controls. In

psoriatic patients, although nonsignificant, TNF-α was 2.1-fold higher in serum relative to healthy controls and did not differ according to clinical disease activity. Our results are consistent with other studies. High levels of TNF-α have been detected in both serum and synovial fluid and membrane of patients with PsA (43,44) and RA (45), suggesting that this cytokine plays an important role in the pathogenesis of these diseases through its proinflammatory effect.

TNF-α is one of the most extensively studied cytokines due to its key role in a number of human diseases. It has been found in elevated amounts in a number of autoimmune lesions and its dysregulation characterizes many autoimmune diseases. TNF-α is known to be present in higher serum concentrations in patients with RA and PsA. The important role of TNF in these diseases is confirmed by their successful treatment with TNF antagonists (46). In cultures of synovial cells from RA patients, where TNF-α has been shown to play a dominant role, blocking it with antibodies significantly reduced the production of IL-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (47). Therefore, blockade of TNF-α in disease may have a more global effect on inflammation than blockade of other cytokines present in high concentrations in synovial fluid, such as IL-1. The concept of a central role for TNF-α in multiple immune-mediated diseases is firmly accepted. In autoimmunity, it is an autocrine stimulator and strong paracrine inducer of the expression of other proinflammatory cytokines and chemokines, IL-1, IL-6, IL-8 and GMCSF, and induces or enhances the expression of adhesion molecules by binding to tumor necrosis factor receptor (TNFR), which is present on almost all nuclear cells. It also promotes angiogenesis and plays a major role in the protection of synovial fibroblasts and suppression of regulatory T cells, as well as in pain induction (48-50). Although most studies have found that the levels of these cytokines in PsA are somewhat lower than those found in the joints of RA patients, as is our finding regarding serum levels, the general pattern of cytokine expression is similar; there is some similarity in cytokine status, suggesting that it is a common mediator of joint inflammation and destruction (43,51).

Regarding IL-17, we found a significant increase in systemic cytokine levels compared to healthy controls in both PsA (1.7-fold) and RA (2.1-fold), with a skew towards the higher values in nearly 1/4 of RA patients, at the expense of only 1/8 of those affected by PsA. In the two inflammatory arthropathies, we found no difference in serum IL-17 profiles according to disease activity.

Th17 are a stimulator of the inflammatory pathological process in autoimmune diseases. Many, if not most, autoimmune diseases are related in some way to IL-17 or to Th17. IL-17 has been shown to enhance T cell priming, stimulating various cell types including fibroblasts, endothelial cells, macrophages, and epithelial cells to produce proinflammatory mediators (IL-1, IL-6, TNF-α, IL-8, inducible NO synthetase, matrix metalloproteinases, and chemokines) (52,53).

There is strong evidence for a role of IL-17 in triggering human RA, although not all studies fully share this view. High levels of IL-17 and its receptor have been found in synovial fluid and tissue explants in the disease (54,55). In support of the above, there is some evidence of improvement in symptoms and therapeutic response scores in RA from treatment with monoclonal anti-interleukin-17A antibodies, but the primary efficacy endpoint was not met in some of the clinical trials, justifying the need for further studies in this regard (56). It should be kept in mind that studies suggesting a greater importance of Th1 cells than Th17 cells for inflammation in RA have been reported (57).

In a study by Benham et al, the concentration of IL-17 secreted by stimulated peripheral blood mononuclear cells in the supernatants of patients with PsA and psoriasis was significantly higher than that of healthy controls (58). IL-17 inhibitors have been shown to be efficacious against key clinical domains in psoriatic arthritis (59). Our present findings of increased circulating levels of IL-17 are consistent with earlier publications. These data confirm the potential functional importance of this cytokine in the disease and that IL-17 mediates effector biological actions associated with the pathology of inflammatory injury.

Although IL-17 alone has the ability to induce proinflammatory factors, its activity is significantly increased when combined with other cytokines, especially TNF-α. IL-17 synergizes with TNF-α to stimulate induction of almost all of its target genes, and in many cases synergy with interferon-gamma (IFN-γ) and IL-1β is also observed (60). Thus, the TNF-α and IL-17 pathways remain cardinal and occupy an important place in the hierarchical structure of cytokines in many rheumatic diseases. Our correlation analyses and stratification subanalyses showed no association of the two proinflammatory cytokines with clinical and laboratory activity parameters in either disease. This supports the contention that TNF-α and IL-17 do not accurately reflect disease activity in the Bulgarian population with PsA and RA and are not useful markers for its assessment. It is important to note that in our study cytokines and disease activity status were assessed at a fixed point in time. Prospective tracking of variations in serum cytokine concentrations over the course of disease could reveal more valuable data. On the other hand, patients were treated with various pharmacological agents during the study, including anti-TNF therapy as well as IL-17 inhibitors for those with PsA.

5.1.2. YKL-40

A systematic review shows that YKL-40 has significant potential as a biomarker for RA, with promising applications in both diagnosis and treatment. Further research is needed to fully understand the clinical relevance and practical use of YKL-40, particularly with respect to autoimmune diseases such as psoriasis, systemic lupus erythematosus (SLE), Behcet's disease, inflammatory bowel disease, and other conditions determined by immune mechanisms (61,62).

Our study revealed interesting and contradictory data to the literature. Analysis of the dataset revealed various relationships between YKL-40 and other biomarkers and clinical parameters. Our PsA group had the highest mean values relative to RA and healthy controls. RF and anti-CCP showed a negative correlation with YKL-40, meaning that as RF and anti-CCP levels increased, YKL-40 levels tended to decrease significantly. Furthermore, the duration of psoriasis had a moderate negative correlation with YKL-40, meaning that individuals with longer-standing psoriasis had lower levels of YKL-40. A positive correlation with PECAM, HYAL, and HPSE may reflect the relationship between YKL-40 and extracellular matrix turnover or cell migration. We also found a weak correlation with DAS28.

5.1.3. Cell ratios

There is a growing interest in investigating the use of haematological cell ratios as potential biomarkers for autoimmune diseases such as PsA and RA. The importance of these ratios in diagnosing, monitoring and understanding the pathophysiology of these conditions is supported by various studies.

Our results show significant differences in the neutrophil:lymphocyte ratio (NLR) and platelet:lymphocyte ratio (PLR) between groups. NLR was significantly higher in RA compared with PsA and healthy controls, whereas PLR differed significantly between PsA and the other groups. These differences could reflect the different inflammatory profiles characteristic of PsA and RA. NLR showed moderate positive correlations with key markers such as anti-CCP, CRP and SUE. These correlations reinforce the notion of NLR as a reflection of the inflammatory state. in RA. Red cell Distribution Width to Platelet Ratio (RPR) showed a moderate positive correlation with GLS, suggesting a potential association between this hematological parameter and cardiac function. Furthermore, the study revealed moderate positive correlations of PMR with the number of edematous joints (SJC66), suggesting its utility in assessing the severity of joint inflammation. Furthermore, the lymphocyte to monocyte ratio (LMR) demonstrated strong negative correlations with the Leeds Dactylitis Index (LDI), BASDAI and psoriasis duration.

PLR is increasingly recognized as an important marker in inflammatory rheumatic diseases, reflecting acute inflammatory and prothrombotic conditions. It is particularly valuable when considered alongside NLR, which provides insight into disease activity, neutrophilic inflammation and potential complications such as infection and organ damage in conditions such as systemic lupus erythematosus. High PLR values are also indicative in the diagnosis of systemic vasculitis such as giant cell arteritis. Although studies have shown that PLR can decrease in response to anti-inflammatory treatment, challenges in its implementation include preanalytical issues, lack of standardization in laboratory measurements, and subject selection. Despite these limitations, PLR, especially when interpreted with other hematologic

indices, is a useful tool for the diagnosis and treatment of inflammatory rheumatic diseases and their comorbidities (63). Increases in NLR and PLR have been observed in RA patients, consistent with their role as markers of systemic inflammation. Previous studies found a positive correlation of NLR with CRP, SUE and DAS28. Regarding PLR, correlations with CRP and DAS28 were found, but no correlation with SUE was found, suggesting different underlying inflammatory mechanisms or disease processes These results reinforce the well-established notion that PLR and NLR serve as critical biomarkers for the assessment of systemic inflammation, disease activity, and response to anti-inflammatory treatment (64-66). A study involving 2002 RA patients found that higher NLR was a significant predictor of increased long-term mortality, including cardiovascular mortality. Participants with a higher NLR (≥3.28) had twice the risk compared with those with a lower NLR (<3.28), even after adjusting for various factors. Kaplan-Meier analysis confirmed the lower survival in the higher NLR group. The study concluded that NLR may be an effective, inexpensive prognostic marker in RA (67). In patients with cutaneous psoriasis alone who had comorbidities, a study by Bakic et al found lower platelet and PLR levels. As well as higher levels of RPR and MPR compared to patients without comorbidities. This suggests that changes in these haematological parameters may be related to the presence of comorbidities in patients with PsA (68). A study of 963 patients with non-ST elevation myocardial infarction (NSTEMI) showed that MLR was associated with the severity of coronary lesions. It also outperformed NLR in reflecting the severity of these lesions. Furthermore, MLR serves as an independent prognostic factor for both in-hospital and long-term major adverse cardiac events (MACE) in patients with NSTEMI. This suggests that MLR, as a readily available and cost-effective inflammatory biomarker, may be a valuable tool for early risk stratification in patients with NSTEMI, helping to identify those who may benefit from more aggressive treatment and closer monitoring (69).

The overall insights from these studies highlight the potential of hematological cell ratios as accessible, noninvasive biomarkers in autoimmune diseases. They offer a window into the systemic inflammatory state and disease activity in PsAi RA, which may be critical for early diagnosis, monitoring disease progression, and tailoring treatment strategies. However, as with any emerging area of research, these findings should be interpreted with caution given their inherent variability and the need for further validation. Incorporation of these biomarkers into routine clinical practice requires more extensive studies to not only confirm these associations but also to establish standardized thresholds and protocols for their use. The potential for these simple blood count ratios to have a significant impact on the treatment of

PsAand RA is considerable, promising a more nuanced and personalized approach to these complex autoimmune diseases.

5.2. Cardiovascular risk

5.2.1. Lipid profile

Our study revealed a statistically significant correlation between arthritis duration and serum triglyceride (TG) levels as well as global longitudinal strain (GLS) measured by speckle-tracking echocardiography. However, the duration of psoriasis did not reach statistical significance in this regard. These findings are consistent with those reported by Dattilo et al. who also revealed a significant correlation between disease duration and GLS, suggesting an interaction between PsA disease activity and cardiovascular risk factors (70). In a study including 31 patients with PsA, subclinical changes in myocardial deformation were observed in multidimensional planes including GLS while maintaining normal left ventricular ejection fraction despite the absence of clinically manifest CVD. The investigators reported no correlation between strain measurements and risk factors. Therefore, the use of this innovative imaging modality may offer additional advantages for early detection of cardiovascular complications and risk stratification among individuals with PsA (71).

Our results show that although total cholesterol and LDL are comparable between PsA and RA, there are significant differences in HDL levels and Chol/HDL ratio, potentially reflecting differences in cardiovascular risk and systemic inflammation. Also, patients with PsA are significantly more likely to have an existing metabolic syndrome compared with RA. We found a correlation between LDL levels and vascular disease activity measured by DAS28. Although there was no statistically significant difference in mean TG levels between RA and PsA, a wider interquartile range and bias was observed in PsA patients. This suggests that metabolic and lipid profiles in PsA may be characterized by greater heterogeneity, which may have implications for cardiovascular risk stratification and highlights the need for further investigation of the underlying mechanisms contributing to these variations. This is consistent with the literature where increased clustering of abnormal lipids, metabolic syndrome, and diabetes was also observed in patients with PsA compared with RA (72). Another study highlights the association between higher activity in PsA and changes in lipid profile, such as an increase in total cholesterol, TG levels and a decrease in high-density lipoprotein (HDL). This study highlights a potential link between PsA, lipid metabolism and broader cardiovascular risks, including obesity (73).

5.2.2. QRISK3

QRISK® is a predictive algorithm for assessing the risk of developing CVD over the next 10 years. The QRISK® model incorporates a variety of risk factors to provide a more individualized assessment than traditional risk models. These factors include age, gender, ethnicity, systolic blood pressure, cholesterol levels, smoking, diabetes, BMI, family history of CVD, and use of certain medications that may affect CVD risk, such as antihypertensives and statins. QRISK® has gone through several iterations, with QRISK3 being the most recent version to date. QRISK3 includes additional factors such as chronic kidney disease, migraine, corticosteroid use, systemic lupus erythematosus, use of atypical antipsychotics, severe mental illness, and erectile dysfunction (11,74). In the United Kingdom, current recommendations from the National Institute for Health and Care Excellence (NICE) recommend the use of QRISK instead of the Framingham Risk Score (FRS).

QRISK® assessments are considered significant for clinical decision making, public health strategies, and individual patient health planning, contributing to personalized medicine approaches to cardiovascular disease prevention. Although not validated specifically for PsA it is superior to FRS and SCORE in the assessment of patients with SLE, RA, and other diseases (75-79). It is possible that the FRS index as well as the Reynolds Risk Scale underestimate CVD risk in patients with RA. Whereas in contrast, QRISK3 tends to overestimate CVD risk, especially in individuals classified as high-risk. This discrepancy in risk prediction highlights the need for improved risk assessment tools that can more accurately determine CVD risk in patients with arthritis (80).

Our study found a strong correlation between IMT and QRISK. Regression analysis showed that DAS28 was a significant independent predictor of QRISK. Multiple regression analysis including a broader set of variables explained a significant 64.4% of the variance of QRISK, with DAS28 and metabolic syndrome emerging as significant factors. ROC highlighted the accuracy of DAS28, CRP, and SUE in predicting risk. Furthermore, the analysis provided insight into the prognostic capabilities of PECAM.

According to a study using QRISK2, patients with PsA who have symmetric polyarthritis may have a reduced risk of developing CVD compared with other subtypes. Furthermore, this particular subtype is associated with a significantly lower incidence of comorbid diabetes mellitus. In contrast, individuals with a predominant distal interphalangeal PsA subtype tend to have a higher QRISK2 score. This suggests that patients with this subtype may require closer monitoring and management of CVD risk factors to reduce potential cardiovascular complications (81). Using SCORE and QRISK2, Degboe et al. found that patients with PsA had a higher risk relative to healthy controls (82).

5.2.3. Ultrasonography

Supporting the application of ultrasound as a valuable tool in the clinical setting, a study of patients with PsO found a moderate to strong positive association between FRS values and IMT measurements (83). A high mean IMT value in the common carotid artery was associated with an increased risk of CVD (84,85).

Our study highlights the important role that various clinical and laboratory parameters play in the assessment of atherosclerotic risk as measured by IMT. We found that factors such as smoking duration, serum glucose levels, SUE, HPSE, AH, metabolic syndrome, serum urea, and BMI were associated with an increase in IMT. These results support the idea that chronic inflammatory processes and metabolic disturbances are closely associated with the development of atherosclerosis. The weak correlations found between IMT and parameters such as PASI, age, GGT, LDL, uric acid, HbA1C, and Chol/HDL, as well as MDS, may suggest that these factors have less direct influence on structural changes in the vasculature, or that their role may be more complex and mediated by other mechanisms. It is interesting to note that the positive correlations with GLS, especially for metabolic syndrome, Chol/HDL, QRISK, triglycerides, and VLDL, suggest a link between patients' metabolic profile and their cardiac function. The observed negative but not statistically significant correlation with HDL suggests that high HDL levels may have a protective effect, although statistical significance was not reached in our study.

Findings from multiple linear regression highlight the importance of metabolic syndrome, age, glucocorticoid treatment, and serum glucose as predictors of IMT. This suggests that a comprehensive approach to the treatment and management of patients at increased cardiovascular risk should incorporate multiple aspects of health, including metabolic status and inflammatory profile. Finally, the logistic regression model highlights the importance of DMARDS, HbA1C and MDS treatment as significant factors in predicting pathological IMT. The use of DMARDS and higher MDS values, which implies adherence to a Mediterranean diet, were associated with reduced risk, whereas elevated HbA1C levels were associated with increased risk. These results may lead to considerations about potential therapeutic interventions that may reduce cardiovascular risk in patients, as well as the importance of nutrition and medication management in the management of patients at increased risk.

There are numerous studies in the literature that link arthritis treatment with DMARDS to a reduction in IMT (86-88). Because HbA1C and metabolic syndrome is associated with increased CVD risk and increased IMT, the results add another layer of complexity (89-91). Our findings regarding associations with lipid profile are consistent with other studies in the literature (92,93).

Our data show that increased levels of red blood cell distribution width (RDW) and ratio of RDW to platelet count (RPR) are positively associated with increased prevalence of CVD. Intriguingly, the relationship between RPR levels and CVD prevalence was non-linear, suggesting that the interaction between these haematological parameters and CVD risk is complex. the study highlights that elevated RDW levels are particularly associated with higher CVD prevalence in women and smokers, whereas elevated RPR levels are more indicative of increased CVD prevalence in individuals under 60 years of age. Despite these correlations, the underlying biological mechanisms linking RDW and RPR to cardiovascular health remain unclear, signaling the need for further research to understand the causes of these associations and potentially uncover new targets for intervention (94). RPR serves as an independent predictor of mortality during hospitalization in patients suffering from acute MI who are critically ill (95). RPR has the potential to be an independent predictor of adverse outcomes in breast cancer and mortality in pancreatitis, suggesting its utility as a novel biomarker for prognostic assessment (96,97). Our results showed that RPR demonstrated a moderate positive correlation with GLS. General population analysis indicated that GLS served as an independent predictor of CVD and mortality. GLS improves prognostic estimates beyond what current risk stratification models offer by contributing additional prognostic information for both composite cardiovascular outcomes and heart failure. The prognostic power of GLS for these cardiovascular events appears to be more pronounced in men than in women, suggesting that sex differences may influence the prognostic significance of GLS. This highlights the importance of incorporating GLS into risk assessment models to improve prediction of cardiovascular outcomes (93).

5.2.4. Lp-PLA2

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is increasingly recognized as an important biomarker for the prediction of atherosclerotic diseases. It is detected in atherosclerotic plaques and new data suggest its proatherogenic role, possibly mediated by its metabolic by-products. Lp-PLA2, a member of the phospholipase A2 enzyme family, is associated with macrophage activity in atherosclerotic vessels. It is strongly associated with the risks of coronary heart disease and stroke, potentially offering prognostic value for recurrent stroke. The association of inflammatory markers such as Lp-PLA2 with stroke prognosis remains an area of ongoing research (98). Lp-PLA2 activity has a positive correlation with the severity of coronary artery disease. This suggests that higher levels of Lp-PLA2 activity may be associated with more severe forms of atherosclerosis (99).

Our analysis of Lp-PLA2 levels in the different groups showed no significant differences between PsA patients, healthy controls and RA patients. The wide range and high standard deviations, especially in PsA and healthy controls, suggest caution in interpreting these results and indicate the need for further studies with larger samples. Correlation analysis showed moderate negative correlations of Lp-PLA2 with

LEI and YKL-40, indicating a decrease in Lp-PLA2 levels with increasing levels of these markers. Weak positive correlations were found with RF, HPSE and HDL, although the correlation with IMT-L was not statistically significant. These findings suggest an association between Lp-PLA2 and these variables, but also suggest that Lp-PLA2 is not the only influencing factor.

In a study by Kiluk et al, serum levels of Lp-PLA2 were investigated in patients with psoriasis, and its association with disease severity, metabolic/inflammatory parameters, and systemic effects of treatment was examined. It included 33 patients with active plaque-type psoriasis and 11 healthy controls, with blood samples taken before and after 3 months of treatment with acitretin or methotrexate. The main finding was that patients with severe psoriasis had significantly higher levels of Lp-PLA2 than controls, both before and after treatment. However, systemic treatment had no significant effect on Lp-PLA2 levels despite clinical improvement. This suggests that Lp-PLA2 may be a useful marker for assessing the risk of cardiometabolic comorbidities in severe psoriasis, particularly in obese patients (100).

In a prospective study, they examined levels of lipoprotein-associated Lp-PLA2 and subclinical atherosclerosis in patients with early RA. Patients from northern Sweden were included, and the association of Lp-PLA2 with IMT, FMD, and other cardiovascular risk factors was assessed. Results showed that Lp-PLA2 concentration was associated with both subclinical atherosclerosis and disease severity, although no significant difference in Lp-PLA2 levels was found between RA patients and controls (101).

5.3 Quality of life, diet and physical activity

Lower health-related quality of life (HRQoL), particularly in its physical aspects, has been identified as a predictor of higher rates of re-hospitalisation and mortality in patients with CVD. It has been suggested that physical HRQoL, in combination with clinical data, may be essential to identify individuals at increased risk of developing CVD. This highlights the importance of incorporating HRQoL assessments into routine clinical assessments to better predict and manage CVD risks (102).

The relationship between CVD and depression is complex and bidirectional. Patients with CVD tend to have higher rates of depression compared to the general population and conversely, those with depression are at greater risk of developing CVD and have higher mortality rates. Depression severity correlates with increased risk of mortality and cardiovascular events in patients with CVD. Although depression may be a marker for more severe CVD, it is also considered a significant contributor to reduced quality of life. Management of depression in cardiac patients is critical, involving strategies such as cardiac rehabilitation, cognitive behavioural therapy, antidepressants and support programmes, regardless of the causal relationship between depression and CVD (103).

Our study revealed several key associations between quality of life, diet and physical activity among patients with PsA and RA. We observed a positive association between SF-36 and Mediterranean

diet score (MDS), indicating that greater adherence to the Mediterranean diet was associated with improved quality of life. Our study found a moderate negative correlation between DAS28 and the Dijon physical activity score (DPAS), indicating that higher disease activity was associated with lower levels of daily physical activity. Although DAS28 did not correlate significantly with other variables such as body mass index (BMI), body surface area (BSA) or MDS. However, there was a notable negative correlation between patient global assessment (ptGA) and DPAS, suggesting that higher DPAS scores are associated with lower patient-perceived disease impact. There was a positive correlation between DPAS and SF-36, suggesting that increased physical activity corresponds to improved quality of life. We found a negative correlation between Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL) scores and MDS, and between smoking duration and DPAS, indicating that longer smoking history is associated with lower levels of physical activity. We observed a positive correlation between MDA and DPAS, implying that higher levels of physical activity were associated with better disease control. In regression analysis, DPAS emerged as a significant predictor of MDA in PsA patients. Together, these results underscore the importance of integrating lifestyle and dietary considerations into the clinical management of PsA and RA, highlighting the potential of physical activity and diet to improve patient outcomes.

Our study has a limitation in interpreting the observed correlations: the challenge of determining causality. Specifically, it is unclear whether high disease activity leads to reduced physical activity or whether patients with an inherently lower level of physical activity have a more aggressive form of the disease. Although the data suggest an association between disease activity and physical activity levels, they do not provide conclusive evidence to indicate whether reduced physical activity is a consequence of high disease activity or contributes to disease severity. Further studies, possibly including longitudinal data tracking changes in physical activity over time and their subsequent impact on disease progression, or intervention studies assessing the impact of increasing physical activity on disease activity, would be needed to establish causality. Without such targeted studies, the exact nature of the relationship between disease activity and physical activity remains speculative.

Individuals who eat a healthy diet and engage in regular physical activity have the lowest risk of death from all causes, and in particular from cardiovascular problems. Interestingly, the reduction in cardiovascular mortality was seen in individuals who were physically active, regardless of the quality of their diet, but not in those who followed a healthy diet without physical activity. In non-obese individuals, practicing one of two health behaviours - physical activity or healthy eating - was associated with a reduced risk of all-cause mortality. However, for reducing the risk of death from cardiovascular disease, adherence to a healthy diet alone without accompanying physical activity did not confer a significant benefit compared with individuals with an unhealthy diet and an inactive lifestyle (104).

In a study of patients with PsA using a dietary questionnaire and Dual-energy X-ray Absorptiometry (DXA) scanning, they found a possible deleterious association between fat-including body adiposity, saturated fat intake, and serum LDL levels-and the severity of joint and skin involvement. Consequently, individuals with active PsA tend to exhibit a higher incidence of obesity and excessive body and abdominal fat. In addition, metabolic syndrome, insulin resistance, and suboptimal dietary fat consumption are frequently observed in these patients. These observations suggest a negative association between lipid and glucose metabolic processes and joint and skin disease activity in PsA (105). New research in the literature suggests that a personalized anti-inflammatory diet and increased physical activity, in line with WHO recommendations, are beneficial for people with PsA. Despite the potential health benefits, people with PsA tend to be less active and less likely to engage in regular, vigorous exercise. Advances in the field of nutrigenomics are providing the basis for new nutritional guidelines that could significantly improve the quality of life for people with psoriasis. In addition, regular to vigorous exercise has been shown to have benefits for both mental and physical health, including potentially reducing the severity of PsO. However, patients with psoriasis often fail to achieve these levels of physical activity. Further research is needed to confirm the most effective types and timing of exercise for managing and preventing psoriasis. This information is critical for health professionals, including dietitians and physical therapists, to develop comprehensive educational programs that incorporate diet and exercise as nonpharmacologic interventions for psoriasis management and prevention (106).

Although the landscape of PsA treatment has changed with the advent of new biologic drugs and small molecules that allow many patients to achieve remission or maintain low disease activity, the needs of patients with ongoing active disease, functional impairment, impaired quality of life, or additional comorbidities remain unmet. The benefits of a comprehensive non-pharmacological holistic approach through lifestyle adjustments in people with PsA is needed. These interventions promise to improve quality of life by complementing traditional pharmacological treatments and addressing aspects of the disease that cannot be fully addressed with medication alone (107).

5.4. Endothelial glycocalyx degradation markers

Heparanase (HPSE) is an enzyme that cleaves heparan sulfate in the extracellular matrix, playing a role in its degradation and remodeling. It is frequently overexpressed in inflammatory conditions and tumors, promoting invasiveness and angiogenesis. HPSE also influences various cell signaling pathways, contributing to its proangiogenic activity. The enzyme is synthesized as an inactive precursor that becomes active after proteolytic cleavage. Studies have shown that certain modified heparins can effectively inhibit

heparanase, reducing tumor metastasis, angiogenesis, and inflammation in experimental models. This makes heparanase a potential target for anticancer and anti-inflammatory drugs (108).

Our analysis of HPSE showed considerable variability in levels across groups. We found positive correlations of HPSE with factors such as RF, anti-CCP, SYND-1, SUE, smoking duration and a negative correlation with YKL-40. There is a pathophysiological rationale for increased HPSE activity to increase serum SYND-1 concentration. Recent studies have identified a novel role for heparanase in promoting tumor metastasis and angiogenesis by inducing SYND-1 release. This process facilitates the binding of VEGFR2 and VLA-4 to the cell surface, enhancing metastatic and angiogenic capabilities. Furthermore, heparanase influences gene expression by affecting factors such as HGF, MMP-9 and VEGF. The ongoing development of specific inhibitors of heparanase, including monoclonal antibodies and small molecule inhibitors, remains a challenge for the effective treatment of cancer and inflammatory diseases (109).

A study of the role of HPSE in synovial fluid and tissue from patients with RA, osteoarthritis, and asymptomatic donors found significantly higher HPSE activity in patients with RA compared with patients with OA and donors. In addition, the study found an association between HPSE activity and the expression of angiogenesis-related genes in RA synovium. These findings suggest that HPSE is a potential prognostic factor in RA progression and a target for treatment (110). In collagen-induced arthritis in transgenic mice overexpressing human HPSE, mice exhibit earlier and more severe symptoms. An increased ratio of immune cells, including macrophages and T cells, was observed in the mice, indicating an enhanced immune response. This suggests that increased HPSE expression may enhance both innate and adaptive immune responses in this model of arthritis (111).

In our study, hyaluronidase (HYAL) levels in PsA were significantly higher than controls, but there was no significant difference between PsA and RA groups. Correlation analysis showed moderate to strong positive correlations of HYAL with variables such as Lp-PLA2 and QRISK. In addition, weak positive correlations were noted with PECAM and YKL-40, as well as weak negative correlations with TNF and anti-CCP, although these were not statistically significant. Literature data regarding serum HYAL levels in inflammatory joint diseases are scarce. A study aiming to assess serum hyaluronidase activity in patients with spondyloarthropathies, particularly psoriatic arthritis, to aid differential diagnosis. The results showed significantly higher serum hyaluronidase activity in patients with spondyloarthropathy than in controls, especially in psoriatic arthritis. The method had high diagnostic sensitivity (92%) and specificity (86%) for differentiating psoriatic arthritis from other spondyloarthropathies (112).

In our study of syndecan-1 (SYND-1) as a biomarker, descriptive statistics revealed no significant differences in its levels in the PsA, RA and healthy control groups. Shapiro-Wilk tests showed an abnormal distribution in all groups. Spearman correlation analysis showed moderate correlations of SYND-1 with HPSE and RAQoL and weaker correlations with other variables such as RF and PhysSk. These findings

suggest that SYND-1 may not serve as a distinct biomarker to differentiate these groups based on the current data. Studies examining serum SYND-1 concentrations in patients with PsA are lacking in the literature.

In a study of 39 RA patients, the effects of DMARDs on SYND-1 and MMP-9 were investigated. Of these, 19 started monotherapy with MTX and 20, a combination of TNFi and MTX. The study found a significant reduction in serum SYND-1, after six weeks of treatment, independent of change in systemic inflammation, suggesting a role for DMARDs in preserving endothelial glycocalyx, which may contribute to their cardioprotective effects (113). SYND-1 modified null mice exhibit more severe RA symptoms, including significant atrophy and loss of articular cartilage, increased macrophage infiltration, changes in the trabecular meshwork, and bone erosions. These findings highlight the critical role of Sdc-1 in RA pathophysiology and the potential protective effects of intact SYND-1 on EG (114).

5.5. Adhesion molecules

5.5.1 VCAM-1

Vascular Cell Adhesion Molecule 1 (VCAM1) is a protein that is expressed on the surface of endothelial cells. Its main function is to mediate leukocyte adhesion and migration. It plays a key role in immune response and inflammation, particularly in the context of CVD and immune diseases in which endothelial dysfunction is a factor. When an inflammatory response is initiated, cytokines such as TNF-α and interleukins are released that can stimulate VCAM1 expression on endothelial cells. In the early stages of atherosclerosis, VCAM1 expression increases at sites of potential plaque formation. This allows leukocytes to adhere to the endothelium and move into the intimal layer of the blood vessel, contributing to the development of atherosclerotic plaques.Elevated levels of soluble VCAM1 in the blood are often indicative of systemic inflammation and are associated with a variety of diseases, including cardiovascular, autoimmune, and cancer (115,116).

In the context of our discussion, the strong positive correlations between VCAM1 and variables such as age, arterial hypertension, smoking, and IMT highlight the potential of VCAM1 as a biomarker for vascular inflammation and endothelial dysfunction. The particularly strong correlation with age may reflect the cumulative effect of vascular stress over time (117). Similarly, the positive correlation with arterial hypertension is consistent with the understanding that high blood pressure is a chronic stressor for the vascular endothelium, potentially leading to increased expression of adhesion molecules such as VCAM1 (118).

The association of smoking, both in terms of duration and active status, with elevated VCAM1 levels highlights the detrimental effects of tobacco on vascular health, possibly through oxidative stress and

inflammation. Evidence from the literature confirms increased VCAM1 expression by smoking in a time- and dose-dependent manner through influencing cytokine expression in endothelial cells, increasing adhesion migration of monocytes (119-121). The association between VCAM1 with IMT and QRISK strengthens the link between structural changes in the arterial wall, molecular markers of endothelial activation, and cardiovascular risk. A study by Edwards et al in patients with systemic lupus found increased VCAM expression and pulse wave velocity (PWV) in high-risk patients according to QRISK3 (79).

Furthermore, the positive correlations of VCAM1 with ESR, CRP, and ferritin suggest that systemic inflammation, regardless of its etiology, may have a significant impact on vascular health. The moderate correlations with metabolic factors, such as NEUT#, UA, MetS, waist circumference, VLDL, and BMI, support the notion that metabolic abnormalities contribute to the inflammatory milieu that may manifest in the vasculature.

These findings suggest that VCAM1 may serve not only as a marker of cardiovascular risk but also reflect broader systemic inflammatory and metabolic disorders. This information is valuable for clinicians considering a comprehensive approach to patient care in which addressing underlying metabolic and inflammatory conditions may be as important as managing overt cardiovascular risk factors. The multifaceted associations of VCAM1 with a number of clinical variables provide a rich area for further study to understand the complexities of CVD and their interactions with other systemic conditions. These results suggest that VCAM1 has varying degrees of association with different physiological and biochemical parameters. These correlations may offer valuable clues to the potential role of VCAM1 as a biomarker in PsA.

5.5.2. PECAM-1

Platelet Endothelial Cell Adhesion Molecule-1 (PECAM), or known as CD31, is a cell adhesion molecule found on the surface of endothelial cells that line blood vessels, and is also present on platelets, monocytes, neutrophils, and some T cells. As part of the immunoglobulin superfamily, PECAM-1 is integral to a variety of biological functions, including angiogenesis, transendothelial migration, and maintenance of endothelial barrier integrity. It also plays a role in cell signaling pathways that govern immune responses of the vasculature, as well as in modulating platelet functions such as activation and aggregation. Given its role in these critical processes, PECAM-1 is not only a valuable biomarker for a number of diseases, particularly those related to cardiovascular health and systemic inflammation, but is also considered a potential target for therapeutic interventions (122).

The finding of significant differences in PECAM levels in PsA patients compared to healthy controls and RA places PECAM as a potential biomarker specific for PsA. The lack of differences between RA patients and healthy controls further isolates the association of this marker with PsA. The established correlations between PECAM levels and various clinical parameters enrich its role. The moderate positive correlation with YKL-40, a marker associated with inflammation and tissue remodeling, suggests an association between PECAM levels and inflammatory activity in PsA. A negative correlation between MDA and PECAM suggests that as lower disease activity is achieved, PECAM levels decrease, indicating its potential use as a marker of disease activity. A study by Magkham et al found a significant reduction in serum PECAM, PASI, ASDAS, and inflammatory infiltrate scoring levels by immunohistochemistry of PsO with infliximab treatment, suggesting endothelial deactivation (123).

The positive correlations we found with BSAPs and PASI highlight the association between PECAM and psoriasis severity. The significant but weaker correlations with IL17, as well as HYAL, suggest that PECAM may reflect a broader spectrum of pathophysiological changes in PsA. PECAM as a predictor of MDA attainment in PsA highlights its potential utility in clinical practice. An identified cutoff point for PECAM may be essential in clinical decision making, indicating a threshold that can distinguish active from controlled disease states.

In the context of the pathogenesis of psoriasis characterized by increased dermal vascular activity, in a recent study researchers examined serum PECAM levels among individuals with various forms of psoriasis and healthy controls. They found that PECAM levels were significantly lower in patients with PsA compared with PsA. After systemic therapy, PECAM levels in PsA patients dropped to those of healthy controls, indicating the molecule's potential as a biomarker of disease activity and therapeutic efficacy. This study highlights the importance of PECAM-1 in the pathophysiological development of psoriasis and its systemic inflammatory profile (124).

An innovative way of drug delivery using specially designed nanoparticles has been developed. To these particles are attached antibodies that specifically target PECAM, which is expressed on cells in inflamed tissues. The method aims to precisely deliver inhibitors of the NF-κB signaling pathway to the sites where they are most needed. This approach could potentially help treat severe inflammation, such as in the serious cases of COVID-19 and rheumatic diseases (125).

5.6. Outlook for future work

Future work in this area could focus on:

1. Further detailed research: further investigation of the molecular and cellular mechanisms linking PsA and CVD, with particular focus on the role of specific cytokines, glycocalyx and immune cells.

2. Clinical trials: conduct extensive clinical trials to evaluate the effectiveness of targeted therapies in reducing cardiovascular risks in patients with PsA.

3. Longitudinal studies: conduct long-term observational studies to better understand the progression of CVD in patients with PsA and the impact of different treatment strategies.

4. Interdisciplinary approaches: developing collaborative approaches between rheumatologists, cardiologists and other healthcare professionals to optimise patient care.

5. Patient education and lifestyle interventions: Exploring the role of patient education, lifestyle changes and preventive strategies in the management of both PsA and associated cardiovascular risks.

These perspectives aim to improve understanding and management of the complex interaction between PsA and GCC.

VI. CONCLUSIONS

1. Chronic systemic inflammation is associated with increased cardiovascular involvement measurable by serum biomarkers, clinical indices and ultrasonography.
2. Arterial hypertension and metabolic syndrome are the most common comorbidities associated with PsA, presenting with a higher frequency compared to RA.
3. Cardiovascular risk as measured by QRISK was significantly increased in patients with psoriatic arthritis compared with healthy controls and similar to that of RA sufferers, although PsA patients exhibited greater heterogeneity in risk levels.
4. DAS28-CRP is a significant predictor of CVD, demonstrating that high disease activity may increase the risk of cardiovascular events.
5. Higher serum HYAL and PECAM concentrations in patients with PsA compared with RA and controls were associated with increased cardiovascular risk, disease activity, and area of cutaneous psoriasis.
6. Patients with PsA and RA have comparable levels of quality of life, impaired function, diet and physical activity.
7. Patients with PsA and RA had comparable IMT values and similar pathology rates.
8. IMT values were correlated with QRISK, smoking, dietary scor, CRP, HPSE, metabolic syndrome.
9. Serum glucose, uric acid, and GLS levels have predictive value for pathological IMT.
10. Impaired GLS was associated with high Tg, Chol/HDL levels, metabolic syndrome, RPR and relative CV risk calculated by QRISK.
11. The role of the proinflammatory milieu and cytokine profile reveal potential new treatment strategies and targets.

VII. CONTRIBUTIONS

Scientific - theoretical

1. A large panel of biomarkers has been studied to determine the role of chronic inflammation, adhesion molecules, and endothelial glycocalyx degradation in the development of cardiovascular complications. Analyzing a set of different biomarkers offers significantly greater informative value for assessing the complex interrelationship.

2. Differences in serum levels of biomarkers and ultrasonographic data in PsA patients with RA and control group were investigated.

3. Potential predictors influencing the likelihood of developing cardiovascular complications in patients with inflammatory joint disease have been identified.

Methodological

For the first time in rheumatology practice in our country, a comprehensive assessment of cardiovascular involvement in patients with PsA was performed and compared with RA and healthy controls using serum markers and ultrasonographic tests.

Scientific - Applied

1. The role of sociodemographic, anamnestic, and clinical characteristics of patients with PsA and RA in real-world clinical practice is evaluated, offering a new perspective on the relationship between chronic inflammatory joint disease and cardiovascular health.

2. The utility of investigating serum biomarkers of cardiovascular involvement in patients with PsA and RA in the context of clinical practice was determined.

3. The specificity, sensitivity, positive and negative predictive value of key biomarkers as a diagnostic test for the detection of cardiovascular risk was determined.

4. The study contributes new data on subclinical cardiovascular changes in patients with PsA and RA through ultrasound studies of IMT and GLS

5. Changes in myocardial function assessed by GLS were evaluated, and a relationship between activity and potential subclinical cardiovascular changes was found.

6. Cell ratios have been evaluated as potential markers of systemic inflammation and cardiovascular inflammation, respectively, as a cheap and readily available method for additional informativeness.

7. The change in systemic levels of biomarkers with increased disease activity was found.

Contributions of a confirmatory nature

1. The important role of chronic inflammation and metabolic disturbances in PsA in the development of cardiovascular disease is confirmed, emphasizing the utility of controlling disease activity and the use of potential prognostic markers.

2. The role of physical activity, quality of life and diet in cardiovascular disease risk has been confirmed.

VIII. SCIENTIFIC PRODUCTION RELATED TO THE DISSERTATION

Publications:

- Angelov AK**,** Markov M, Ivanova, M, Georgiev T. The genesis of cardiovascular risk in inflammatory arthritis: insights into glycocalyx shedding, endothelial dysfunction, and atherosclerosis initiation. Clinical rheumatology. 2023. 42(10), 2541-2555. DOI: 10.1007/s10067-023-06738-x IF 3.65

- Angelov AK, Vasilev G, Yordanova A, Ivanova-Todorova E, Kyurkchiev D, Ivanova M. Elevated serum levels of TNF-α and IL-17 in psoriatic and rheumatoid arthritis. Revmatologiia (Bulgaria). 2023. 1:23-36. DOI: 10.35465/31.1.2023.pp23-36.

- Angelov AK, Kopchev A, Georgiev T and Ivanova M. Cardiovascular disease in patients with psoriatic arthritis: correlation or causation? Revmatologiia (Bulgaria). 2019. 1:30-43. DOI: 10.35465/27.1.2019.pp30-43

Conference participation:

- Angelov AK, Gospodinova MV, Yordanova A, Vasilev G, Velikov T, Ivanova M. Biomarkers for cardiovascular damage and glycocalyx shedding in psoriatic and rheumatoid arthritis. National Rheumatology Conference. Pravets. 29.09-01.10.2023. pg 18.

- Angelov AK, Velikov T, Kopchev A, Vassilev G, Ivanova M. Risk factors for cardiovascular involvement in inflammatory joint diseases. The role of intima-media thickness and speckle-tracking echocardiography. National Rheumatology Conference. St. Vlas. 16-19.09. 2021. pp 12.

- Angelov AK, Velikov T, Vasilev G, Ivanova M. Cardiovascular risk and endothelial dysfunction induced by systemic inflammation in psoriatic arthritis. National Rheumatology Conference. Pravets. 15-18.10.2020. p. 36.

Research projects:

- "Young Researcher -2020" D-83/24.06.2020, entry No. 8429/21.11.2019 to MU-Sofia
  - Excellent evaluation for the research activity performed
  - Appreciation for the contribution of the results obtained to shape the dissertation
  - High evaluation of the contribution of the realized work on the process of doctoral preparation

- National Scientific Programme "Young Scientists and Postdoctoral Fellows" - 2021, Module "Young Scientists". № 111/26.02.2021.

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ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisor, Prof. Dr. Mariana Ivanova, for her invaluable scientific input, guidance and support throughout the process of my research and writing of this thesis. Her expertise, in-depth knowledge and true scientific dedication provided me with a foundation on which to develop my research style.

I would like to express my gratitude to the team of the Clinic of Rheumatology at the University Hospital "St. Ivan Rilski" - Sofia, Dr. Alexander Kopchev and Assoc. Prof. Dr. Tsvetoslav Georgiev, for their unreserved help, professionalism and valuable guidance, which were crucial for the success of my research and the development of this dissertation.

My heartfelt thanks to Assoc. Prof. Dr. Mariana Gospodinova and Dr. Tony Velikov for their collaboration and specialized contribution with the specific cardiological examinations, which is an important part of this thesis.

I express my gratitude to the team of the Laboratory of Clinical Immunology at the University Hospital "St. Ivan Rilski" - Sofia, Dr. Adelina Yordanova, as well as to Dr. Georgi Vasilev, for their extremely professional attitude and cooperation.

I express my deepest and sincere thanks to my family: my wife Victoria and my daughter Debora, as well as to my parents for their immeasurable and long-standing support. They have been my support and inspiration all these years, helping me to cope with the challenges and to move forward despite the difficulties. Without their love, understanding and encouragement I could not have achieved all that I have today!