"CORRELATION BETWEEN SERUM URIC ACID & DISEASE ACTIVITY IN PATIENTS OF RHEUMATOID ARTHRITIS— A ONE YEAR CROSS SECTIONAL STUDY IN KLE'S DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI"

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LIST OF ABBREVIATIONS

ACR – American College of Rheumatology

EULAR – European Alliance of Associations for Rheumatology

RA – Rheumatoid Arthritis

UA – Uric Acid

DAS – Disease Activity Score

PM – Polymyositis

PsA – Psoriatic Arthritis

SLE – Systemic Lupus Erythematosus

SJ – Sjögren's Sydrome

ACPA – Anticitrullinated Protein Antibodies

DMARDs – Disease Modifying Antirheumatic Medications

NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

GCs – Glucocorticoids

RF – Rheumatoid Factor

HLA – Human Leukocyte Antigen

APCs – Antigen Presenting Cells

PM – Particulate Matter

CRP – C-reactive Protein

NF-KB – Nuclear Factor Kappa B

IL – Interleukin

ROS – Reactive Oxygen Species

VDR – Vitamin D Receptor

UVB – Ultraviolet B

TLR – Toll-like Receptor

NLR – Nod-like Receptor

IFN – Interferon Gamma

TNF – Tumour Necrosis Factor

FLS – Fibroblast-like Synoviocytes

MMS – Matrix Metalloproteinase

VAM – Vascular Adhesion Molecules

VEGF – Vascular Endothelial Growth Factor

RANKL – Receptor Activator of Nuclear Factor-kB Ligand

JAKs – Janus kinases

ESR – Erythrocyte Sedimentation Rate

MCV – Mutant Citrullinated Vimentin

Anti-CarP – Antibodies against carbamylated proteins

TNFSF10 – Tumour Necrosis Factor Ligand superfamily number 10

SAA4 – Serum Amyloid A-4

VDBP – Vitamin D Binding Protein

CT – Computed Tomography

MRI – Magnetic Resonance Imaging

NIR – Near-infrared imaging

PET – Positron-emission Tomography

SPECT – Single-photon Emission Computerized Tomography

EAMs – Extra-articular Manifestations

DHA – Docosahexaenoic Acid

EPA – Eicosapentaenoic Acid

PUFA – Polyunsaturated Fatty Acid

JAKi – Janus Kinase inhibitor

COX – Cyclooxygenase

SSZ – Sulfasalazine

MTX – Methotrexate

LEF – Leflunomide

HCQ – Hydroxychloroquine

FDA – Food and Drug Administration

STAT – Signal Transducers and Activators of Transcription

PMS – Post Marketing Surveillance

MACE – Major Adverse Cardiovascular Events

MSCs – Mesenchymal Stem Cells

ABSTRACT

AIM: To detect the prevalence of hyperuricemia in Indian RA patients and to assess the correlation between serum uric acid levels and disease activity scores.

BACKGROUND: RA is a chronic inflammatory illness with the potential to cause significant disability and death. RA and hyperuricemia were thought to seldom coexist in the past, possibly due to immunosuppressive effect via potent antioxidant properties. A wide range of results have been observed in prior research linking blood uric acid levels to the severity of RA disease, challenging the long-held belief that hyperuricemia and RA are mutually exclusive diseases.

MATERIALS AND METHODS: The present cross-sectional study included 64 RA patients, fulfilling the established inclusion criteria visiting KLEs DR. PRABHAKAR KORE HOSPITAL BELAGAVI between 1st January 2023 to 31st December 2023. Patients were subjected to a questionnaire and clinical examination to assess tender & swollen joint counts, and PGA on a 0-10 scale after obtaining informed consent. General examination ixncluding BMI and waist-hip ratio were recorded. Disease activity was assessed using DAS28-CRP score, CDAI, and SDAI. Investigations including creatinine, and CRP were conducted via venous sampling. Patients' data was collected using proformas and entered in Excel sheet. SPSS Ver. 22 software was used for analysis, with a p-value threshold of 0.05 being considered statistically significant.

RESULT: In a sample size of 64 patients, disease activity measures (VAS, DAS28, CDAI, SDAI) strongly correlated with disease activity levels but not consistently with uric acid levels. Serum creatinine levels showed a significant association with uric

acid levels (P = 0.009), indicating a link with kidney function. Raised uric acid levels were slightly more common in older age groups and exclusively in females. Overall, age, gender, and BMI did not directly predict uric acid levels, but disease activity measures and serum creatinine were significant indicators in understanding uric acid patterns in the study participants.

CONCLUSION: In contrast to earlier beliefs, there was no definitive inverse correlation found between uric acid levels and the severity of RA disease activity, highlighting the necessity for additional research to clarify the role of uric acid in RA severity.

KEYWORDS: Rheumatoid Arthritis, Uric Acid, Disease Activity, DAS28, Hyperuricemia, CDAI, SDAI, CRP, Rheumatoid Factor, Anti-CCP Antibody

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INTRODUCTION

Joint swelling, joint discomfort, and degeneration of synovial joints characterise rheumatoid arthritis, a chronic inflammatory illness that, in accordance with standards of 2010 ACR/EULAR RA Diagnostic criteria,[5] causes significant disability and premature death.

It was previously believed that rheumatoid arthritis and hyperuricemia seldom coexisted. [1,4]

One possible explanation for this reciprocal exclusion is that hyperuricemia has a protective immunosuppressive impact via-

1. Blocking sensitization to antigens which may cause RA
2. Blocking production of immunocompetent lymphocytes
3. Potent antioxidant properties.[1]

For people who run the risk of suffering from Rheumatoid Arthritis, hyperuricemia may be beneficial, or reduce the severity of symptoms in people who already have the disease, which in turn improves their quality of life and the results they report from their treatment.[2]

Another application for hyperuricemia is as a biomarker for RA patients to help find signs of renal impairment and cardiovascular disease risk earlier. [2,3] Other inflammatory markers such C-reactive Protein, ESR and fibrinogen have been studied to determine their prevalence in RA patients and to ascertain their role in disease states and hypercoagulability showing significantly positive results.[6]

The DAS28 is a common tool for measuring patient reported outcomes because it provides a straightforward and objective way to evaluate the severity and course of a patient's condition. The acute phase indicators, like C-reactive protein, may be associated with it. This study intends to demonstrate this link in a subgroup of the Indian population and to analyse its relevance as a preventive factor. Previous studies associating blood uric acid with RA disease severity have shown a range of outcomes.[6-10] Previous studies may have underestimated how frequent hyperuricemia and gout are in patients of RA, and if there is a greater prevalence of raised serum uric acid levels in RA. [8] Hence, our study aims to detect the prevalence of hyperuricemia in this subset of Indian population while assessing its association with RA disease severity and other concomitant factors.

AIMS AND OBJECTIVES

- To detect the prevalence of hyperuricemia in Indian Rheumatoid Arthritis patients.
- To assess correlation between uric acid levels and disease activity scores.

REVIEW OF LITERATURE

The chronic inflammatory process and system-wide autoimmune disease known as rheumatoid arthritis (RA) can cause damage to several organs besides the joints, including heart, the kidneys, the lungs, the digestive system, the eyes, the skin, and the nervous system.[11,12] Though there are many varieties of arthritis, the most prevalent ones are caused by autoimmune processes, infections caused by viruses and bacteria (Neisseria gonorrhoea, Enterovirus, complications from Lyme disease, Staphylococcus aureus, Parvovirus), or crystal deposition secondary to pseudogout, gout, and basic calcium phosphate disease.

Some of these types of arthritis have been studied and commented on in detail. In addition to polymyositis (PM), psoriatic arthritis (PsA), adult-onset scleroderma (ASCD), systemic lupus erythematosus (SLE), and Sjögren's syndrome are all part of the assorted group of autoimmune rheumatic disorders. Differential diagnosis is vital since their symptoms and indications could be identical.[13]

Current thinking is that dysregulation of citrullination causes development of anticitrullinated protein antibodies (ACPAs) [14,15], one of several biomolecular pathways that have been suggested as possible causes of RA. In the absence of effective therapy, rheumatoid arthritis (RA) symptoms deteriorate over time, causing irreparable damage to joints and impacting both physical and mental functioning.[16] RA progression is unpredictable, with episodes of worsening symptoms. Additionally, individuals with RA have a shortened life expectancy due to comorbidities and consequences.[17]

Research on RA has shown that it is both a medical condition and a public health concern, according to statistical analyses and interpretations of quantitative data.

Arthritis is the leading medical cause of functional impairments associated with mobility in people in the United States (US) [18,19].

The expenses of avoiding RA via decreasing risk factors or treating emerging instances are substantially lesser than those produced by hospitalisation and procedures, according to many studies on health and finances that have measured the cost of RA [20,21].

New treatment techniques are now accessible as a result of significant advancements in the pharmaceutical sector. To find a cure, however, is difficult due to our incomplete knowledge of the molecular processes controlling antibody destiny. The best course of therapy involves prompt diagnosis, the use of appropriate pharmaceutical and non-pharmacological interventions, and regular assessments of treatment safety and effectiveness. The goals of treatment include achieving remission while minimising adverse consequences [22]. Pharmacologic medicines that preserve function of joints can be divided into three primary categories: targeted synthetic DMARDs, biologic DMARDs, and traditional synthesized disease-modifying antirheumatic medications (DMARDs). The American College of Rheumatology (ACR) has recently added a new nonbiologic DMARD class [23]. Non-steroidal antiinflammatory medications (NSAIDs) and glucocorticoids (GCs) are used as supplementary treatment to reduce inflammation when RA symptoms are not well controlled [24].

2. Epidemiologic Overview

Over the past 30 years, numerous researchers have conducted extensive research on the prevalence and incidence of RA. All racial, ethnic, national, age, and

gender groups are equally affected by RA, according to this research. The findings of incidence and prevalence studies, however, have evolved across time and are sensitive to demographic factors [15].

2.1. RA Prevalence in Epidemiological Research

Results from epidemiologic studies that assessed the occurrence of RA in a small number of nations across Asia, North America, and South America from 1990 to 2005 were useful and relevant. A greater prevalence ratio was noted in Argentina (1.97%), whereas France (0.31%), China (0.28%), Italy (0.33%), Serbia (0.18%) and the US (0.41%) all had low ratios. In contrast, Japan (1.7%) and Italy (0.33%) had low ratios. Notably, older studies may be vulnerable to methodological biases that result in different estimates of the prevalence of RA due to the significant variations in the study designs (e.g., telephone polling, postal questionnaire, random selection, inception cohort, outpatient, cross-sectional, and hospitalization medical records). There are gender disparities in the prevalence of RA, which has been noted. Females had a 3-to-5-fold greater prevalence in RA compared to males, according to all studies. The Serbian study found the closest numbers (women 0.29%, males 0.09%), whereas the Argentinean study found the most significant difference (3.2% for women and 0.6% for men). [26-30]

From 1990 to the present day, the prevalence of RA has been steadily increasing. The Spanish population grew at a faster rate than any other. Nonetheless, the prevalence rates have been declining in Argentina and Japan.

Approximately 1% of people worldwide currently have RA, with a higher prevalence rate in women.[31]

2.2. Epidemiological Research on the Incidence of RA

Epidemiological studies show that the prevalence of RA varies in various populations and age groups. Over the years, researchers have tried to pin down the prevalence in specific regions and find the factors that would explain why various studies have come to different conclusions. From 1985 to 2002, researchers employed several observational study designs to compile their data. These designs included record review, longitudinal population-based, inception cohort, and prospective case-control studies.[27] The incidence rates are lower in France (8.8 occurrences per 100,000 inhabitants)[32] and Japan (8 incidences per 100,000 inhabitants)[30] With 44.6 instances per 100,000 inhabitants, the United States shows the highest incidence rate.[33] It has also been shown to occur more frequently in women than in males. But new research shows that the incidence has been all over the map for the last 30 years. The United States had an incidence ratio of 40 cases per every 100,000 people in 1994, 43 cases per every 100,000 in 2004, and 41 cases per every 100,000 people today.[34]

Research examining the effect of age on RA incidence reveals that the disease becomes more common as people become older, peaking around the age of 80 before starting to drop. The decline in the incidence rate over the past 60 years has been particularly dramatic among women.[27]

Incidence rates vary by geography even within the same country, according to many research. Environmental contact with climate change, pollutants, infectious illnesses, and diet might have had a role in these variances.[35,36] In addition, there is evidence that those from lower socioeconomic backgrounds who grew up in rural regions had a greater chance of acquiring RA as adults.[37] According to recent

research, the standardised incidence rate is greatest in the UK (27.5 instances per 100,000 people), whereas the incidence rate in Canada has risen the most over the past 30 years.[25,38] Although there is no clear explanation for the rise in the incidence rate, risk factors are likely to have a significant impact.

2.3. Risk Factors for RA

Environmental, genetic, and stochastic variables all play a part in the development of RA.[39] Researchers have calculated a 50% hereditary risk for RA.[40,41] Seropositive and seronegative— presence or lack of anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) can be used to diagnose RA.; also, the risk factors associated with each kind differ.[42,43] Tyrosine phosphatase non-receptor type 22 (PTPN22) risk alleles,[44,45] human leukocyte antigen D-related (HLA-DR) alleles,[42] and tumors necrosis factor-receptor associated factor 1 and complement component 5 (TRAF1/C5) related genes are the main genetic factors associated with an ACPA-positive subtype,[46] while interferon regulatory factor 5 (IRF-5) is confined to the ACPA-negative subtype.[47]

Risk factors in the environment are important for managing RA because of their effect on population health. Cigarette smoking is associated with the onset or worsening of RA, as it is with other illnesses. Serendipitous observation in research with an unrelated aim provided the initial evidence linking smoking to an elevated risk of RA. [48] In the time after, it surpassed all other risk factors for RA in terms of description. After extensive testing, scientists have determined that smoking sends a distinct signal due to the toxic compounds included in tobacco products. There is evidence to suggest that smoking is linked to a genetic history that contributes to the development of a RA subtype.[49] According to some reports, smoking impacts RA

that is positive for RF or ACPA,[50] but has little to no influence on RA that is negative for ACPA.[51] Further, smokers with HLA-DR Beta 1 shared epitope alleles are much more likely to develop ACPA-positive RA.[52] So yet, there is no evidence linking passive smoking to an increased risk of getting RA. The number.[53]

Workplace exposure to silica dust is one factor that increases the risk of RA. There is evidence that silicosis is associated with RA, particularly in individuals who test positive for ACPA-positive RA. [54] An uncommon illness of rheumatoid arthritis patients who have acquired silicosis is rheumatoid pneumoconiosis, often known as Caplan's syndrome.[55]

Consumption patterns and dietary components have also been studied. Dietary factors impact RA, and research suggests that vegetarianism and fasting periods help slow the disease's progression. Additionally, a reduced risk for RA may be linked to a decrease in red meat diet and an increase in fruit and fatty fish consumption. [56, 57] Coffee was not found to have any significant association with RA incidence.[58] Consequently, it is important to think about creating a unique food plan for every individual.

Infections of the skin, joints, and bones are more common in patients of RA than those who have non-inflammatory rheumatic disorders, according to a comparative cohort research.[59] Lyme arthritis, a disease with striking parallels to RA, has also had bacterial triggers identified in its instance.[60] Periodontal disease is caused by the pathogenic bacteria Porphyromonas gingivalis. Reportedly, RA induces citrullination and promotes osteoclast formation, which in turn leads to periodontal disease.[61]

To unravel the mysteries of the intricate biomolecular mechanisms that govern RA, it may be necessary to characterise in detail the interplay between genetics, the environment, and random variables.

3. Pathophysiology of RA

There are a number of ideas on the pathophysiological processes of RA, but no definitive answers. It has been found that immunological processes can take place in the "pre-RA phase", which can last for years before joint inflammatory symptoms are recognized.[62] Immunoglobulin G (IgG), vimentin, and type 2 collagen are examples of modified forms of self-antigens that may arise from the interaction of environmental variables and epigenetic modifications to chromosomal structure. Peptidyl arginine deiminases can carry out a post-translational modification to the arginine-containing proteins called citrullination. [63,64] Additionally, synovial infection & hyperplasia of synovial tissue are two joint diseases that may produce increased cytokine production, inflammation of joints, and changed self-antigens.[65]

Epstein-Barr nuclear antigen 1, α-enolase, vimentin, histones, fibrin, fibronectin, and type II collagen are examples of citrullinated proteins that the immune system is unable to identify as self-structures due to the susceptibility genes, HLA-DR1 and HLA-DR4. Antigen-presenting cells (APCs) are a kind of dendritic cell that takes up antigens and activates the immune system. It is in the lymph node that the whole complex migrates in order to activate CD4+ helper T cells. In addition, costimulation—an immunological process involving the exchange of signals between B cells and T cells—occurs in the germinal centre of lymph nodes.

Between CD28 and CD80/86, for instance, there is costimulation.[66,67,68] Here, B cells proliferate, undergo class-switch recombination or somatic hypermutation, and develop into plasma cells that generate autoantibodies upon exposure to the receptors on their precursor cells.[69] When the immune system stops recognising self-structures as distinct from non-self-structures, it produces autoantibodies, which mistakenly target self-tissues and organs. Most research on RA autoantibodies has focused on RF and ACPA. The constant region, or Fc part, of IgG is the target of RF, an IgM antibody that has an 85% testing specificity in RA patients.[70] In addition, it can travel through synovial fluid as part of an immunological complex that also includes IgG and complement protein. Conversely, ACPA has more selectivity for RA; it attaches itself to citrullinated proteins, and they then collaborate to generate immunological complexes that accumulate inside the synovial fluid.[71] Figure 1 summarizes the response of the immune system during the pre-RA phase.

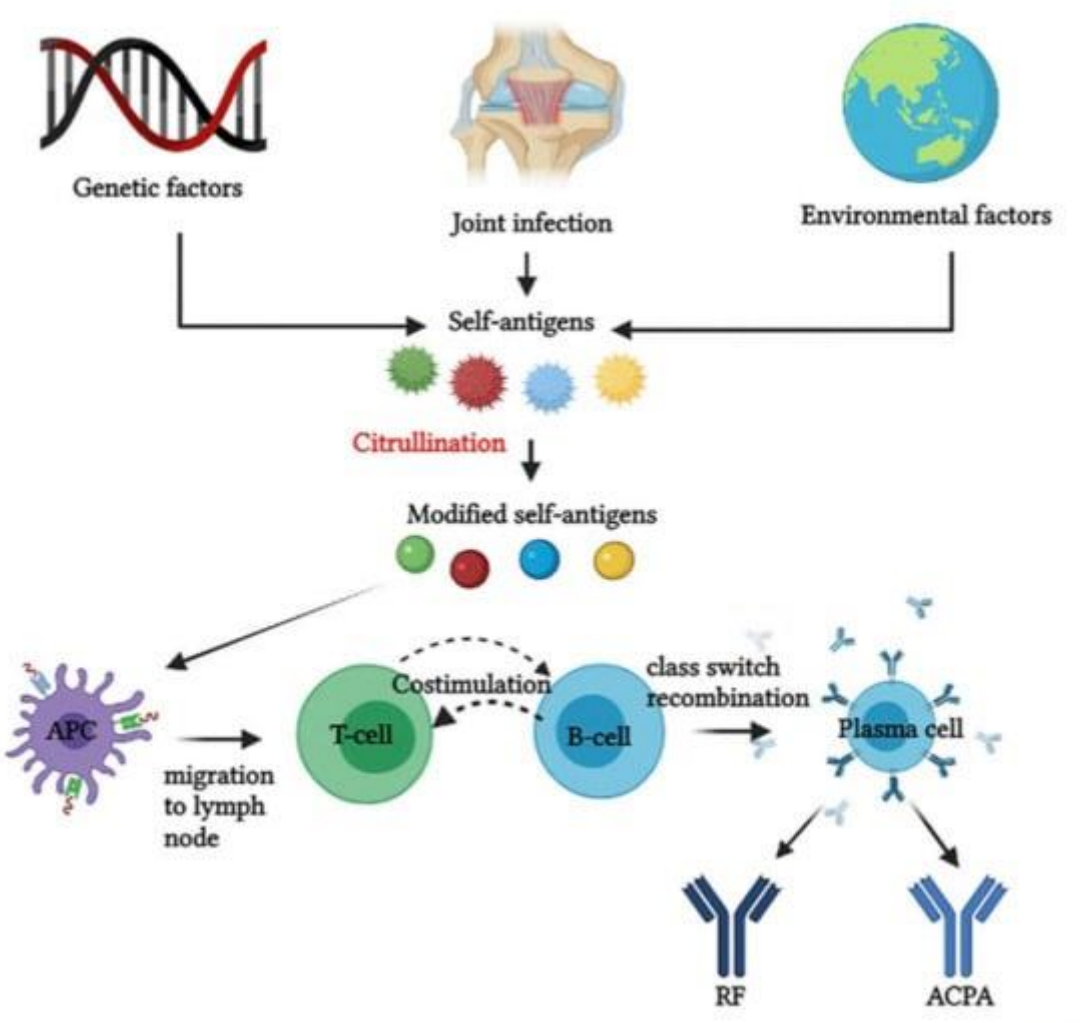

Figure 1. *Immunological mechanisms prior to RA. APC stands for antigen-presenting cells; RF denotes rheumatoid factor; and ACPA stands for anti-citrullinated protein antibodies.*

Air pollution, a combination of gases (nitrates, sulphur dioxide, ozone and carbon monoxide) and suspended particulate particulates (PM) of varying sizes, has lately attracted more attention in the field of RA. Agriculture, burning of fossil fuels, chemical industries, solvent usage, volcanic eruptions, windblown dust, plant emissions, and many other natural and man-made factors contribute to air pollution. Air pollution is typically thought of in terms of respiratory illnesses when it comes to its clinical effects. There have been reports of ozone damaging the alveoli, which are

vital components of the respiratory system responsible for filtering carbon dioxide and oxygen. Secondary damage to lung tissue can occur when pollutants react with certain enzymes, leading to inflammation or infection in the lungs. Air pollution and the aetiology of RA are related, according to three large epidemiological studies carried out in the US, Canada, and Sweden.[72]

Regression models were used in a study by Alsaber et al. (2020) to look into the connections between RA activity and air pollution. Sulfur dioxide and nitrates have been found as significant risk factors in the onset of RA. [73]

Rheumatoid arthritis (RA) severity and reactivations due to non-reaction to biological treatments are associated with higher titers of CRP and air pollution, as per case-crossover research comprising 888 RA patients.[74] There may be a few of mechanisms that explain how air pollution contributes to the development of RA. Inhaled particulate matter (PM) produces free reactive oxygen species (ROS), which may trigger nuclear factor kappa B (NF-KB). NNF-α, interleukin-6 (IL-6), and interleukin-1 (IL-1) are produced by T helper cell type 1. While monocytes are sleeping, these cytokines cause them to develop into dendritic cells. Joint erosion & inflammation are subsequently brought on by auto-antigens that dendritic cells provide to T lymphocytes, which are self-reactive. Reactive oxygen species (ROS) increase systemic inflammation and chronic lung disease and help to citrullinate arginine amino acid residue into citrullinated peptides. Synthesised by metabolic processes, ACPAs cause inflammation in joints and bone erosion by activating complement and attaching to cellular Fc receptors.[72]

The skin's synthesis of 1,25-dihydroxyvitamin D3, an immunomodulator that activates the vitamin D receptor (VDR), drops as exposure to ultraviolet B (UVB)

light drops. Consequently, immunomodulatory capabilities are subpar, which might set up RA. [75]

The gut microbiota, the body's most densely colonised bacterial community, is another critical component that plays a significant role in RA pathogenesis.[76] Toll-like receptor (TLR)-mediated APC stimulation, nod-like receptor (NLR) being activated, molecular mimicry, changes in permeability of the intestine, T cell differentiation progression, as well as enhancement of mucosal surface inflammation through specific pathways are some of the autoimmune pathways and processes associated with dysbiosis of the gut and the RA aetiology.[77]

Microbes in the gut have been shown to impact immunological, metabolic, and neurobehavioral traits. There were notable variations in the gut microbiota composition between healthy controls and RA patients, with some bacterial communities being linked with an increase and others with a reduction.[78]

Through certain sites in the gut known as proximal intestine immunomodulatory cells, the gut flora can influence RA progression. Several case-control studies utilizing 16S rRNA and metagenomic shotgun sequencing have shown detectable alterations in certain bacteria in RA patients. Research shows that the presence of Prevotella copri, Collinsella, & Lactobacillus salivarius stood increased in RA patients and the presence of Bacteroides, Faecalibacterium, Veillonella, & Haemophilus was lower. [76,79] The mechanisms that explain how gut microbiota and air pollutants influence the development of RA are shown in Figure 2. [72, 76, 78]

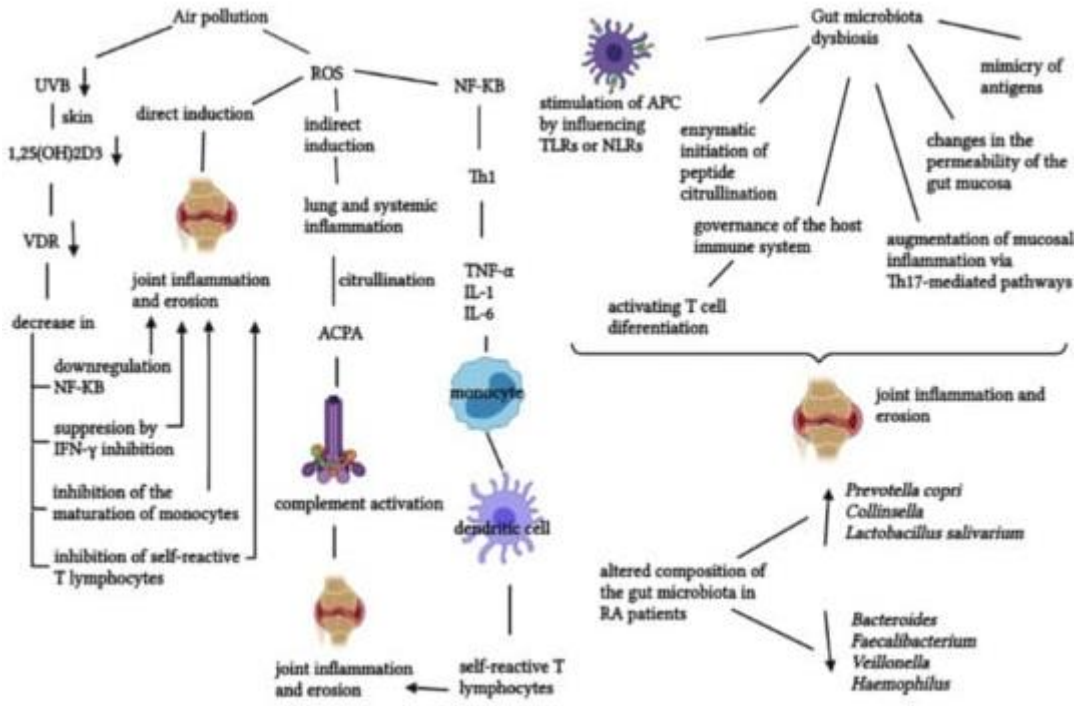

Figure 2. *The evolution of RA and the function of air pollution and microbiota. Nucleus kappa light-chain enhancer of activated B cells, anti-citrullinated protein antibodies, antigen-presenting cells, interferon gamma, interleukin, nuclear factor kappa, toll-like receptor, UVB, tumour necrosis factor alpha, and vitamin D receptor are among the acronyms that are represented by the following: ACPA, APC, IFN, IL, NF-KB, NLR, RA, ROS, TLR, TNF-α, UVB, and VDR.*

In most cases, RA symptoms appear slowly at first, but they increase with time as the illness advances. Although the immunological processes of synovium & synovial fluid are being reported, [80] the underlying etiology of the symptoms of RA is still unknown. Synovial macrophages produce cytokines that are linked to processes of inflammation, activation of fibroblast-like synoviocytes (FLS), and encouragement of activity by osteoclasts. These include tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), & interleukin-6 (IL-6). Erosion of bone occurs as a result of increased activity and maturation of osteoclasts. Matrix metalloproteinase (MMP)

production is a function of active FLS. [81,82] Cartilage can secrete proteases as a feedback mechanism, and matrix metalloproteinase (MMP) can cause cartilage deterioration. [83,84] FLS have the ability to move from one joint to another, resulting in a symmetrical RA pattern.[22] Furthermore, FLS promotes increasing osteoclast activity and thereby contributes to bone degradation by the synthesis of the receptor activator component of RANKL, which permits T cells to attach to osteoclast surface proteins.[85]

CD4+ T cells help encourage inflammation, bone erosion, and cartilage destruction by activating FLS and synovial macrophages, as well as by upregulating RANKL expression and IL-17 production. [86,87] By secreting cytokines and autoantibodies, plasma cells exacerbate inflammation as well.[88]
It has been noted that neutrophils may be found in synovial fluid. These cells release reactive oxygen species (ROS) and proteases, which have the potential to erode bone and cartilage. [89,90]

Another complication of Rheumatoid Arthritis is angiogenesis, the formation of new blood vessels from preexisting ones. While it is beneficial for many physiological functions, it becomes important for RA patients because it increases vascular permeability and stimulates the production of vascular adhesion molecules (VAM 1), that allow immune cells to enter the joints. [91,92,93] Also, proangiogenic VEGF, which stimulates osteoclast production and actively contributes to bone loss, is present in the synovium of RA patients.[92] Figure 3 summarizes the pathophysiological pathways that cause RA symptoms to manifest.

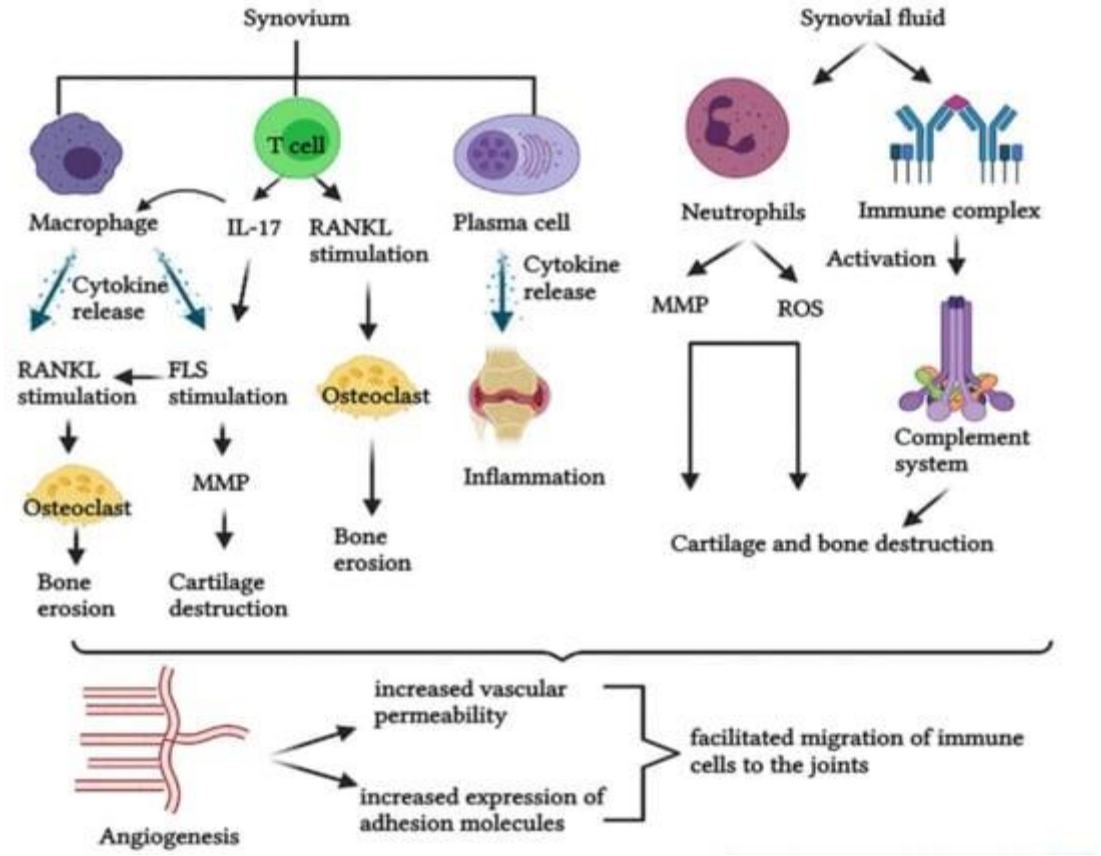

Figure 3. *Interleukin (IL), fibroblast-like synoviocytes (FLS), matrix metalloproteinase (MMP), receptor activator of nuclear factor-kB ligand (RANKL), and reactive oxygen species (ROS) are the components shown in Figure 3 of the RA pathological processes.*

Inflammatory processes rely on a wide variety of signalling molecules, adding another layer of intricacy to this illness. There is pathophysiological significance to Janus kinases (JAKs), which are tiny signalling proteins that can serve as molecular targets for a wide variety of therapeutic treatments.[94] Therefore, in order to optimise future treatments with high safety and effectiveness profiles and to clarify all the pathogenic pathways, more study is required.

4. Clinical Aspects of RA

Important elements of RA therapy include signs and symptoms, biomarkers from predictive tests, differential diagnosis, consequences, extra-articular manifestations, etc. Differentiating between different forms of arthritis and autoimmune diseases, starting the right therapy quickly, and avoiding long-term consequences all depend on an early and precise diagnosis of RA [95]

4.1. RA Diagnosis

The 2010 classification criteria for RA, developed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), refocus attention from managing the disease in its late stages to detecting it early on by evaluating a number of variables, including risk factors, the type and number of joints affected, and the period of symptoms.[96] Over time, we need to reevaluate the following conditions that the classification system reveals are associated with a given score:

- Two to ten big joints correspond to one; one to three tiny joints (±large joints) correspond to two; four to ten small joints (±large joints) correspond to three;
- More than 10 joints, or 5 (minus one small joint plus any additional joints); A local laboratory assay can have two possible outcomes: a low-positive RF and/or ACPA ≤3× the upper limit of normal, which corresponds to 2, or a high-positive RF and/or ACPA >3× upper range of normal, which corresponds to 3. A normal CRP and ESR value of 0; An abnormal erythrocyte sedimentation rate (ESR) and/or abnormal C-reactive protein (CRP) of 1;

- The patient complained of discomfort, edema, and soreness ≥6 weeks, or 1.[97]

If a patient's score is six or higher, RA may be diagnosed.

In order to qualify for a new round of examinations, two stipulations need to be adhered to. According to an expert, one requirement is the existence of edema within one or more joints. This excludes the joints that are frequently impacted by osteoarthritis, including the distal interphalangeal joint, the first carpo-metacarpal joint, and the first metatarsophalangeal joint. The second requirement is that there should not be a competing diagnosis of synovitis. Large joints include ankle, hip, elbow, shoulder, and knee, whereas small joints include the wrists, second through fifth metatarsophalangeal joints, and proximal interphalangeal joints. [98]

Numerous methods have been developed and published for the early detection of RA, having variations in their development based on patient characteristics.[96] Symptoms of rheumatoid arthritis (RA) include swollen, painful, and sensitive joints as well as symmetrical joint degeneration, which manifests gradually over time.[98] Untreated RA, which disproportionately affects the elderly, can cause functional decline, disability, and an increased disease burden. [25,99].

Although it is a difficulty, the best medical strategy is to use differential diagnosis to confirm RA. It is necessary to assess certain characteristics of RA in order to distinguish it from other comparable diseases. In certain cases, a biopsy is necessary to distinguish between illnesses that present similarly. Synovitis is more widely distributed in psoriatic arthropathy (affecting asymmetric joints), ankylosing spondylitis (affecting just small joints), and RA (affecting symmetric joints, great and small joints, including the elbow and wrist). Rheumatoid arthritis causes more severe

inflammation than osteoarthritis.[95] Although RF is most commonly linked to RA, it can also be found in Sjögren's disease and SLE.[100] The prevalence of antinuclear antibodies is higher in SLE compared to RA. On X-rays, RA shows the most severe erosive alterations. Signs on the skin may indicate systemic lupus erythematosus, polysaccharide, [101,102] or systemic sclerosis. PM most commonly manifests as in the hips and shoulders. The majority of SpA inflammatory processes often impact the back and eyes.[95] Lyme arthritis, viral infections (such as Parvovirus or Enterovirus), or both might be suspected in patients whose symptoms have persisted for less than six weeks, making them unable to be categorised using ACR-EULAR criteria.[103] It remains challenging to distinguish osteoarthritis & fibromyalgia, where the only symptom is pain., from polyarthritis, which affects more than four joints. In addition, testing the urine and blood might aid in making a correct diagnosis. There have been further reports of variations related to symptoms that are not located inside the joints themselves.[95]

4.1.1. Biomarkers for diagnosis, prognosis, and prediction in RA

Because of their diagnostic, prognostic, predictive, and therapeutic roles, biomarker panels, once identified and optimised, constitute a potential medical tool. As a biomarker, RF was the only one listed in the 1987 ACR criteria. Four biomarkers—RF, ACPA, ESR, and CRP—make up the most recent accepted categorization; nevertheless, each of these markers has its own set of limitations.[104] More recent studies have identified other diagnostic proteins with roles in early diagnosis of RA: antibodies against mutated citrullinated vimentin (anti-MCV), antibodies against carbamylated proteins (anti-CarP) and 14-3-3 eta protein. A systematic review of studies in which biomarkers were tested for their potential diagnostic role has reported no difference between cyclic ACPA and anti-MCV. Thereby, it can represent a

diagnostic tool when RA and ACPA are negative.[105] Moreover, the diagnostic accuracy of 14-3-3 eta protein has been evaluated in experimental studies and it has been reported that for all RA patients with a negative RF and ACPA, 14-3-3 eta protein was positive.[106,107] Anti-CarP was detected in RA patient serum and several studies have reported that the presence of anti-CarP is associated with pre-symptomatic phases and may also be used as a prognostic tool.[108,109,110]

Recent research has shown that gene profiles are useful diagnostic tools. Studies have compared FLS from healthy subjects to FLS in RA patients to examine genetic variants in members of the heat-shock protein family A, matrix metalloproteinase 1 (MMP1), matrix metalloproteinase 13 (MMP13), and tumour necrosis factor ligand superfamily member 10 (TNFSF10). In addition, proteomics has advanced to the point where it can identify protein panels, which play a crucial role in early diagnosis.[111-114] Proteins having diagnostic potential, particularly for seronegative RA patients, were characterised in experimental research using label-free quantitative proteomics. Tests for diagnostic purposes have demonstrated enough accuracy for the following: retinol-binding protein-4 (RBP4), serum amyloid A-4 protein (SAA4), vitamin D-binding protein (VDBP), and angiotensinogen (AGT).[115] As a diagnostic biomarker, glycoprotein YKL-40 may prove useful.[116] Certain biomarkers, such as anti-MCV, RF, 14-3-3 eta protein, and ACPA, have greater predictive power when they are associated with later stages of RA.[117,118] To find more biomarkers that might be used for prognosis, more study is required.

The therapeutic management of RA relies heavily on predictive indicators to ensure that all patients receive an effective medication. Several studies have found that certain markers may be used to predict how a patient will respond to therapy.

Among these markers are calprotectin, cartilage oligomeric matrix protein (COMP), anti-CCP, anti-MCV, and 14-3-3 eta. [119, 120, 121, 122]

4.1.2. Imaging Diagnosis of RA

Integrating imaging techniques with biomarker identification and quantification allows for more precise diagnosis. The ACR-EULAR 2010 classifies imaging modalities such as CT, MRI, and ultrasonography for early diagnosis because of their advanced accuracy as compared to standard radiography.[97] Joint X-rays can't pick up on erosions and degradations that are already progressing.[123] Despite X-ray's widespread use, cheap cost, and abundance of medical records, the radiations it uses have limitations, such as a lack of sensitivity to early erosion processes and the fact that it only shows 3D anatomical structures in 2D.[124] Yet, X-rays are still employed as a diagnostic technique for joint alterations that occur later in life. Radiology has also revealed a number of characteristic features of RA, including nodules, periarticular osteopenia, joint space constriction, soft tissue edema, symmetrical anomalies, and marginal degeneration. [125, 126]

The diagnostic tool known as ultrasonography creates a picture of a patient's tissues by studying how they interact with sound waves. It has a high degree of sensitivity and can investigate structures to a finer degree than a naked eye can. When it comes to inflammation, Doppler ultrasonography can help distinguish between active and inactive tissues.[127] A case-control study showed that ultrasonography had intrinsic advantages over X-rays, as it found more erosions, particularly in early RA.[128]

CT scans are infrequently utilised because they produce ionising radiation that might harm human cell DNA and because they do not provide enough contrast for

soft tissues. [126,129] Nonetheless, it has a place in medicine for when 3D imaging is necessary. Longitudinal clinical investigations have shown that CT and MRI are quite comparable. [130,131] On the other hand, magnetic resonance imaging (MRI) is the gold standard for detecting early-stage RA. Joint effusion and synovitis can be distinguished with contrast-enhanced magnetic resonance imaging (MRI). In addition to being the most reliable method for detecting bone marrow edema, it can also detect hypertrophies and erosions at an early stage. Despite a high detection accuracy, recent longitudinal research that looked at the use of MRI to predict the course of rheumatoid arthritis in individuals with clinical symptoms found no link between the two.[132]

Depending on the stage of development of RA, different imaging techniques may be more or less useful. When it comes to detecting early changes in RA patients, MRI is the imaging tool of choice. However, when it comes to detecting joint space widening, CT is the better choice. When it comes to alterations that happen later on in the joints, any of the imaging technologies that were stated before can be employed effectively. Among the medical imaging specialties that will deal with issues and optimization strategies in the future are thermal imaging, near-infrared imaging (NIR), positron-emission tomography (PET), and single-photon emission computerized tomography (SPECT).[126]

4.2. RA's Manifestation of Extra-Articular Disease

Rheumatoid arthritis (RA) is a systemic autoimmune disease that primarily affects small joints before progressing to larger ones and can also damage extra-articular tissues. A variety of joints, including those in the upper & lower extremities, as well as the spine and axial joints, can be affected. The high rates of mortality and

morbidity in RA are closely associated with the degree of severity of extra-articular symptoms (EAMs). Proinflammatory cytokines released into the circulation may cause EAMs.[133]

A wide range of organ systems and tissues can be impacted. A retrospective study of 424 cases showed 39.85% of the individuals exhibited severe EAMs, with pleuritis, pericarditis, Felty's syndrome, and vasculitis among the most severe symptoms.[134] Forty percent of RA patients surveyed in a multicenter study with 587 participants had EAMs with extra-articular manifestations.[135]

Symptoms on the skin, in the intestines, heart, and lungs are all possible outcomes of systemic vasculitis. Among seropositive patients with erosive illness, rheumatoid nodules in various locations are the most prevalent cutaneous symptoms. Digital gangrene, ulcerations, and periungual inflammation are further skin symptoms.[12] Ocular symptoms, such as episcleritis, scleritis, keratitis, and kerato-conjunctivitis sicca—the most prevalent of these subsets—are less common than skin symptoms. Oral symptoms may include xerostomia, or enlargement of the salivary glands. On the other hand, Sjögren's syndrome can also present with oral and ocular symptoms.[133]

Common asymptomatic pulmonary issues include arteritis, pulmonary fibrosis, pleural effusions, and interstitial lung disease. Risk of acquiring potentially fatal RA complications is higher among smokers.[12]

The inflammatory processes in RA involve multiple cardiac structures, coronary arteritis, atherosclerosis, valve disease, fibrinous pericarditis, and congestive heart failure, all of which might raise the risk of cardio-vascular death in patients.[136]

Disease prognostic indicators, such as hypertension and dyslipidemia, may be present.[137]

RA patients were at a 48% higher risk of cardiovascular disease as compared to normal population, according to a meta-analysis of 14 randomized controlled studies involving 41,490 participants.[138] Pulmonary hypertension and left ventricular diastolic dysfunction were shown to be rather common in 47 RA patients who did not have any obvious cardiovascular symptoms in a study that used the Doppler echocardiography approach.[139]

Peripheral neuropathy as well as cervical myelopathy can result from neurological consequences.[140] On the other hand, renal symptoms such as vasculitis, glomerulonephritis, and interstitial renal disease are rare.

Anemia is the most prevalent hematological anomaly in those with RA, which is brought on by hepcidin activation, that prevents iron migration. Furthermore, data[141] suggest that hepcidin could be a good predictive biomarker for RA. Thrombocytopenia, eosinophilia, neutropenia, and malignancies are among other EAMs.[2] Felty's syndrome, a severe EAM, is more likely to occur in seropositive individuals with splenomegaly and low white blood cell count. They are thus at a higher risk of contracting opportunistic infections.[142]

These factors will greatly affect the worldwide care of RA because of the strong correlation between ageing and new comorbidities such cancer, infections, interstitial lung disease, and cardiovascular disease (CVD). In addition, forming a multidisciplinary team of medical experts and being aware of the present state of RA-associated comorbidity management are crucial components in the effort to reduce mortality and morbidity rates.[143]

By closely monitoring 225 RA patients, the RBSMR research was able to establish the comorbidity profile. Heart disease was prevalent in 23.1% of cases, whereas lung disease was seen in 5.77 %.[144]

It is important to regularly test for and evaluate comorbidities and risk factors, and to manage these illnesses as they arise. As part of the care plan, the patient should get recommendations for healthy lifestyle choices, such as getting enough exercise, eating well, not smoking, and getting the most recent vaccines.

There is evidence that reducing inflammation with DMARDs, particularly targeted treatment, can reduce the risk of cardiovascular disease. [145,146] According to a recent cross-sectional real-life research, rheumatologists are now more aware of the possible impact of RA medications on comorbidities, as seen by the increased use of bDMARDs and decreased use of glucocorticoids in patients with cardiovascular comorbidities.[147]

Modern approaches to cardiovascular risk management focus on managing inflammatory states in addition to assessing traditional risk factors such as diabetes, obesity, dyslipidemia, and hypertension utilising HeartScore®. When it comes to assessing risk factors and providing management for RA patients, the rheumatologist is most suited, according to EULAR guidelines.[148] A cardiologist's opinion is required in order to determine the LDL-cholesterol level, testing frequency, and outcomes of the cardiovascular risk assessment. Moreover, carotid artery plaque indicates a significant level of cardiovascular risk, according to EULAR. Carotid artery plaque affects almost 60% of RA patients.[149] But research shows that statins not only lower cholesterol and RA linked cardio-vascular risk, but also offer a number of other benefits, including angioprotection, anti-inflammatory, and antioxidant

protection. For this reason and due to the fact that statins have a generally positive safety profile, they may be useful in the management of vascular comorbidities associated with RA. [150]

One part of managing and screening for comorbidities is determining the patient's cardiovascular risk. Infections, respiratory diseases, and cancers are among of the hazards linked to RA, and RA itself or its therapies can make these problems worse.[151] Both pathology and immunosuppressive medications increase the risk of infection, making immunisation a crucial consideration. The vaccination schedule for people with RA should be the same as it is for the general population: yearly flu vaccinations, polio, tetanus, and diphtheria vaccines every ten years, and pneumococcal vaccines every five years.[152]

A foremost cause of non-articular complications & deaths in RA patients is lung illness. The 6-minute walk test along with the 5-point Medical Research Council dyspnea scale must be used in medical assessments to gauge exercise tolerance.[153] Because there is little information, no global guidelines for the management of interstitial lung disease, a frequent co-morbidity of rheumatoid arthritis, exist. While treating those suffering from RA with moderate or severe pulmonary disease, collaboration with a respiratory specialist is crucial due to the evidence of significant pulmonary complications while using RA medications.[154] Tests for cancer that are utilized on the general population may be beneficial especially for patients with RA as early screening and detection contribute to decreased morbidity and mortality.[155]

Current medical data suggests that comorbidity management is insufficient and calls for more investigation. Including screening tests in RA patient diagnostic procedures and integrating comorbidities into RA management on a daily basis would

allow a more thorough standard of care. The Canadian Dermatology-Rheumatology Comorbidity Initiative issued 19 guidelines on managing comorbidities of RA patients.[156] These guidelines emphasized the importance of differentiating comorbidities caused by RA and those caused by treatment medicines.

Several cohort studies have described a decrease in EAMs in RA in the past few decades. [134,157,158] As a result of improvements in technology and medicine, the mechanism underlying the effects has become more understood, improving the therapy of EAMs in RA.

5. Therapeutic Approaches in RA

Over the years, many therapeutic strategies have been used to improve patient outcomes, reduce adverse medication events (EAMs), and determine the safety & efficacy profile of new active ingredients. The American Cancer Society's guiding concept is "Treat to target," which means selecting an effective treatment with the goal of achieving remission or, failing that, a decrease in disease activity. Because preexisting erosions cannot be reversed, therapeutic action must be swift and forceful.[97] A precise diagnosis is the first step in a comprehensive treatment plan that also incorporates preventative measures, treatments that do not use pharmaceuticals, and therapies that do contain pharmaceuticals. The 2021 ACR guidelines regarding treatment of RA amended the pharmaceutical management of RA and included 37 conditional recommendations in addition to seven strong ones.[159]

5.1. Approaches Other Than Medication for RA

Methods for avoiding RA can be derived from the identification and description of risk factors. An integral aspect of RA care may involve a focus on prevention. It has been shown that there are primary, secondary, tertiary, as well as clinical preventive levels. Primary prevention seeks to stop pathological processes before they start, secondary prevention targets risk factors to identify and reduce them, and tertiary prevention concentrates on mechanisms that mitigate harm. It is important to reduce complications and stop relapses as part of clinical prophylaxis.[160]. One possible way to reduce RA incidence and prevalence rates is to implement screening measures for individuals at risk of getting the disease. Individuals who fall into the risk category—such as blood relatives, twins of RA patients, and seropositive patients—should be closely observed.[161]

Nonpharmacological methods can help with discomfort, anxiety, depression, and limited mobility. Recently, there has been increased focus on polyunsaturated fatty acids (PUFAs), which are connected to numerous brain diseases, including depression and anxiety. Within this class of polyunsaturated fatty acids (PUFAs) include the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).[162] The usefulness of polyunsaturated fatty acids (PUFAs), namely EPA and DHA, in reducing depression was investigated using a meta-analysis of 26 randomized, placebo-controlled trials. This demonstrated that PUFAs from omega-3 greatly alleviated depression. Most studies have shown that EPA to DHA ratios of 2:1 or 3:1 have antidepressant effects.[163] Furthermore, formulations with 60% or more EPA were shown to be the most beneficial in two meta-analyses. [164,165] The possibility that PUFAs might alleviate symptoms of anxiety was also evaluated in

another meta-analysis of nineteen clinical studies. According to the available medical research, polyunsaturated fatty acids (PUFAs) may affect many brain mechanisms that contribute to anxiety. The most significant discovery, in spite of the range of diagnoses, was that, in comparison to controls, omega-3 PUFAs were linked to a significant reduction in anxiety symptoms.[166] Furthermore, by inversely linking patients' pain scores with DHA blood levels, PUFA supplementation might improve pain relief, according to a recent prospective study including 36 JAKi patients. Large prospective studies are necessary to validate the idea[167] because the study only covered a limited number of participants.

Pain, despair, and anxiety are symptoms of rheumatoid arthritis (RA) that are linked to the disease's progression and a lack of mobility. Medical research suggests that polyunsaturated fatty acids (PUFAs) have potential as symptom controllers; however, further research is required to confirm this.

Surgery, physical therapy, exercise, occupational therapy, and rest can all help. Along with rest, physical exercise and psychosocial therapies for rheumatoid arthritis (RA) fatigue patients have shown promise in reducing disease progression and stress on inflamed tissues. [168,169] Improved joint function was one finding of a meta-analysis of 42 studies examining the benefits of occupational therapy for rheumatoid arthritis patients.[170]

Joint surgery is reserved for patients with advanced RA. Nevertheless, for RA patients younger than 60 years of age, the rates of surgery are rather low. Joint function and pain alleviation are both achieved through surgical techniques. Numerous techniques have become accessible as a result of recent advancements in the surgical profession. These consist of tens-synovectomy, metatarsal head excision

arthroplasties, joint fusion, arthroscopy, and osteotomy.[171] Complementary treatments that may be helpful in nonpharmacological pain management include positioning, massage, transcutaneous electrical nerve stimulation, acupuncture, hot and cold therapy, and progressive muscle relaxation, according to scientific data.[172] To enhance the efficacy of pharmaceutical therapies, nonpharmacological techniques should be used in conjunction with them.

5.2. Pharmaceutical Approaches to RA

Significant strides have been made in pharmacological methods to discovering a treatment for RA because to the continuous advancement of drug design strategies' procedures and methodologies. The symptoms have been alleviated, the progression has been slowed, and consequences have been avoided thanks to the new treatment alternatives. The current therapy choices for RA, as recommended by the ACR and EULAR, address the illness from two angles: first, by alleviating symptoms (with NSAIDs and GCs), and second, by changing the disease (with DMARDs). [159,173] While NSAIDs and glucocorticoids are the mainstays of RA symptom therapy, a careful evaluation of the benefits and risks may lead to the use of mild opioid analgesics for the temporary relief of pain.[24]

In the acute phase response, nonsteroidal anti-inflammatory drugs (NSAIDs) such naproxen, ibuprofen, and coxibs are used to decrease inflammation and lessen discomfort. Nonsteroidal anti-inflammatory drugs (NSAIDs) work by blocking the enzyme cyclooxygenase (COX), particularly COX-2, which is upregulated in inflammatory conditions. On the other hand, it's important to think about the potential risks, as blocking prostaglandins can cause major adverse effects such gastrointestinal ulcers, bleeding, disorientation, seizures, kidney failure, heart failure, rashes, and

renal failure. In response, Eleven evidence-based guidelines were created for the pharmacological treatment of pain in IA. [174] Cholecoxib, rofecoxib, and valdecoxib are nonsteroidal anti-inflammatory drugs (NSAIDs) that selectively target COX-2.[14,175] Randomised controlled studies that included individuals who did not get GC therapy showed that NSAIDs were efficacious in RA. [176]

Since GCs (prednisone, hydrocortisone, prednisolone, and dexamethasone) have complex anti-inflammatory and immunosuppressive effects, they are more potent and effective than NSAIDs, despite the fact that NSAIDs have a somewhat better safety profile.[177] Gaining weight, retaining water, weakening muscles, diabetes, deteriorating bones, etc. are all long-term negative consequences of GCs. Oral, intravenous, intramuscular, and intra-articular administration are all viable options for their short-term usage.[178] When treating rheumatoid arthritis (RA), GCs serve a dual purpose: first, as a bridge therapy between the beginning of DMARD effects and the end of treatment, and second, as an adjuvant therapy for active RA that does not respond to DMARDs.

DMARDs are pharmaceuticals that slow or stop joint deterioration and autoimmune activity, two factors that contribute to remission. Because they act slowly with an onset that is anywhere from six weeks to six months delayed, it is imperative that therapy start as quickly as possible for the best potential outcomes. Commonly used DMARDs include csDMARDs, bDMARDs, and tsDMARDs, which stand for targeted synthetic DMARDs.[179] Patients newly diagnosed with RA usually begin treatment with csDMARDs. When first-line therapy fails or is poorly tolerated, bDMARDs or tsDMARDs are suggested. The oral administration of tsDMARDs, such as Janus kinase inhibitors (JAKi), is a benefit.[180]

Sulfasalazine (SSZ), methotrexate (MTX), leflunomide (LEF), and hydroxychloroquine (HCQ) are among the several drugs known as csDMARDs. Having lesser efficacy and better safety profile, these medications are used more frequently than others in the class, such as azathioprine, d-penicillamine, cyclosporine, minocycline, and cyclophosphamide. Through their action mechanisms, they cause the hyperactive immune system to be suppressed in a non-specific manner.[22,177]

The 2021 ACR guideline for RA therapy lists MTX as a first-line treatment due to its low cost, ease of administration, efficacy, and safety profile. It may be taken alone alone or in conjunction with other medications. In addition, for patients without prior experience with DMARDs for RA who have moderate to high inflammatory activity, the recommendation suggests MTX monotherapy instead of hydroxychloroquine, sulfasalazine, bDMARDs, or tsDMARDs. It also includes conditional recommendations such treating RA patients who have not had DMARD medication with MTX rather than LEF, or using MTX alone rather than dual or triple csDMARD therapy, or using MTX in combination with bDMARDs or tsDMARDs. In order to achieve its anti-inflammatory effects, MTX activates adenosine receptors, inhibits purine biosynthesis and cytokine production. If a patient has never taken a DMARD before, the doctor may advise them to take MTX orally instead of through another method of administration.[159] In a recent meta-analysis of 73 RA clinical studies, MTX was found to have the best safety profile and highest effectiveness rates among csDMARDs.[181,182] Irregular bowel movements, nausea, liver damage (rarely cirrhosis), thrombocytopenia, leukopenia, pulmonary fibrosis, and pneumonitis are some of the infrequent toxic consequences that have been documented throughout time.[183]

A meta-analysis comparing the safety and effectiveness of LEF and MTX found that the two had comparable safety profiles, with LEF having a somewhat inferior safety profile owing to a larger rise in liver enzymes.[182] So, for patients who have a hard time tolerating MTX, LEF can be a way to start treatment instead.[184] The immunomodulatory properties of HCQ, including a decrease in release of cytokines, make it a viable choice for the treatment of RA. In a multicenter, randomised, double-blind, placebo-controlled clinical trial, RA patients discovered that HCQ was well-tolerated and effective.[185] The lack of myelosuppressive, renal, or hepatic adverse effects is HCQ's main advantage. On the other hand, pre-retinopathy can develop in the eye at greater doses. [177,186]

The two-metabolite prodrug SSZ has immunosuppressive and anti-inflammatory properties. Despite being equally as effective as LEF, according to a multicentric, randomised, double-blind, placebo-controlled clinical study, SSZ is difficult to utilize due to its side effects, which include urticaria, nausea, diarrhea, rash, and serum sickness. It is possible to lessen the likelihood of adverse effects by controlling potential alterations and doing certain laboratory tests serially.[22]

For patients who are DMARD-naive and have modest disease activity, HCQ is conditionally recommended as a substitute to other csDMARDs in the 2021 ACR guidelines for the management of RA. Instead of MTX, SSZ is recommended, and MTX is preferred over LEF, but only under certain conditions. As shown in Figure 4.[187] the chemical structures of the csDMARDs that are most often given are displayed.

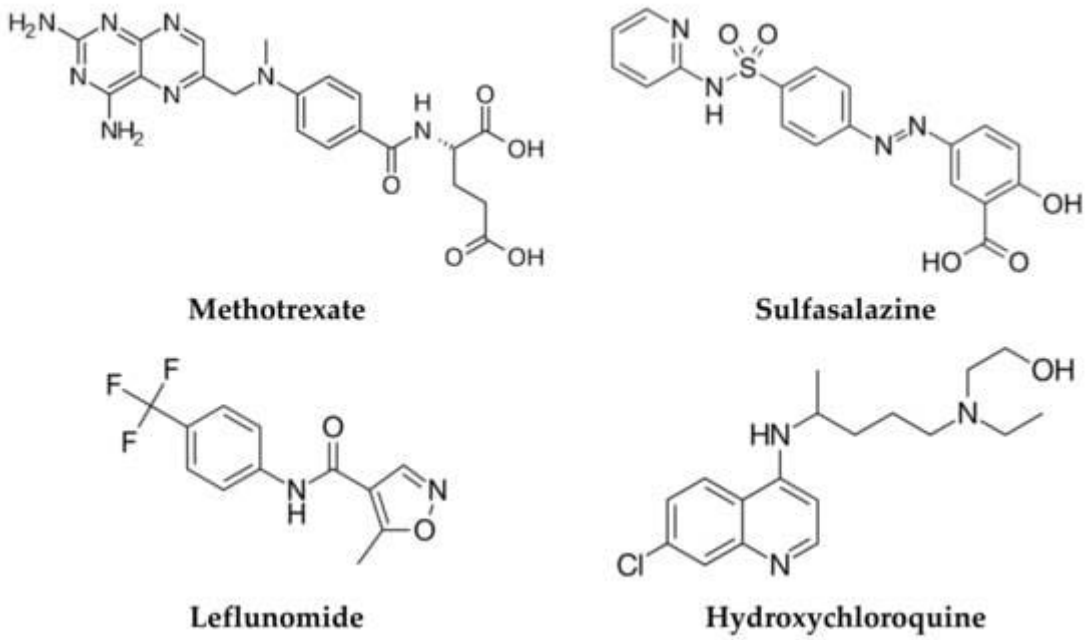

Figure 4. *The molecular makeup of the most popular csDMARDs.*

Biosimilars, bDMARDs, tsDMARDs, combination treatments, and other therapeutic options are available in case of csDMARDs being unsuccessful or poorly tolerated. A more recent method for treating RA, bDMARDs offer focused therapy on immune system components.[22] bDMARDs are genetically engineered protein molecules that are categorized into many types based on their method of action:

- TNF-α inhibitors, such as certolizumab pegol, etanercept, infliximab, golimumab, and adalimumab;
- B-cell depleters (ofatumumab, rituximab);B-cell receptor inhibitors (belimumab, atacicept, tabalumab);
- CD28 antagonists on T-cells (belatacept, abatacept);IL-1 inhibitors (anakinra, canakinumab, rilonacept);

- Inhibitors of IL-6 (clazakizumab, sarilumab, tocilizumab, sirukumab, olokizumab);IL 12/23 inhibitor (ustekinumab);
- IL-17 inhibitors, such as brodalumab, secukinumab, and ixekizumab;
- the inhibitor of granulocyte-macrophage colony-stimulating factor (mavrilimumab, otilimab);
- inhibitor of RANKL (denosumab) [22,159,188,189]

The usage of bDMARDs has increased since they were discovered. Research that used annual cross-sectional studies to examine prescription trends of csDMARDs and bDMARDs spanning 2004 and 2011 lends credence to this assertion. [189,190] Compared to bDMARDs, csDMARDs are still used far more often. The usage of csDMARDs increased steadily throughout the course of the seven-year research, rising between 6.53% in 2004 to 8.93% in 2011. The yearly prevalence of bDMARD use increased significantly between 2004 (0.35%) to 2011 (1.54%), according to the research. Adalimumab (in the range of 0.07–0.35%), etanercept (between 0.16–0.46%), and rituximab (between 0.03–0.21%) were the most often administered bDMARDs. Furthermore, the percentage of prescriptions has gone up over time, with the exception of anakinra, whose percentage has stayed steady at 0.01%.[189]

A phase III clinical study evaluated the safety and efficacy of adalimumab as a monotherapy, and was conducted on people with RA who had not responded to csDMARDs.[191] The results showed a statistically significant reduction in disease activity together with a favorable safety profile.

Nevertheless, bDMARDs affect an individual's vulnerability to infections since they weaken the immune system, and this should be closely watched. A meta-analysis spanning 9 clinical trials on adalimumab used to treat RA has found that the medicine

is related with a dose-dependent increased risk of severe infections.[192] Usage of bDMARDs, particularly TNF-α inhibitors, predisposes to development of tuberculosis (TB). In a population-based cohort analysis of RA patients from an area with high TB incidence, TNF-α inhibitor usage was associated with an eighteen-fold increase in the frequency of the illness. Adalimumab was linked with a greater and more rapid diagnosis of tuberculosis as compared to etanercept.[193] Other reviews found a similar safety and efficacy profile for biosimilars comparable to that of Adalimumab in the treatment of those with RA. [194]

The FDA initially authorized etanercept as an anticytokine drug for the treatment of RA. [195] It constitutes the solitary TNF-α inhibitor that functions as a dimeric fusion protein rather than an antibody. A long-term safety and efficaciousness profile of etanercept was evaluated in 549 RA patients in an open-label experiment. The results indicated that etanercept exhibited both a positive safety profile and long-term efficacy after 36 months of therapy.[196] It exhibits a toxicity profile similar to infliximab and is injected subcutaneously twice a week. Additionally, it has shown promise in slowing the advancement of radiography in RA patients. The percentage of patients who used etanercept to achieve clinical remission ranged from 50% to 75%, per the medical literature. Tetanercept-szzs and Tetanercept-ykro, two biosimilars, have been approved by the FDA to treat RA. Etanercept demonstrated the greatest drug survival among all TNFi, [198] despite a comprehensive analysis of all Cochrane papers on bDMARDs for RA indicating that adalimumab, etanercept, and infliximab had equivalent efficacy profiles.[197]

The importance of long-term safety and effectiveness studies of bDMARDs is growing as they are used more often and for longer durations of time. In one such experiment, the safety and efficaciousness profile of etanercept after 10 years of

therapy was assessed in 1272 patients with RA across North America who received 25 mg of the medication every two weeks. The study reported five opportunistic infections, 29 sepsis episodes, 14 lymphomas, and 61 deaths; nevertheless, individuals with long-term RA had a higher incidence of major adverse events than patients with early-stage RA. However, because of its excellent safety record and efficacy, etanercept has been demonstrated to have a reasonable risk against benefit ratio, making it a feasible option for long-term therapy.[199]

Infliximab is a chimeric monoclonal antibody with a human antibody backbone that binds to all forms of TNF-α to oppose its biological action. Intravenous infusion is the method of delivery. IL-1, IL-6, IL-8, and adhesion molecules were reduced in RA patients after starting infliximab.[22]

Based on scientific data, individuals treated with infliximab respond quickly and the medication effectively prevents joint degradation. In spite of using biologic disease-modifying antirheumatic drugs (bDMARDs) as tocilizumab, adalimumab, golimumab, etanercept, or abatacept, a cohort study examined 24 cases of patients with RA having moderate to severe disease activity. The pharmacological intervention was switching to infliximab, and the results showed a significant efficacy profile, as seen by the 70.8% individuals who had a moderate or high EULAR response and the 37.5% of patients who got low disease activity.[200] Because there was just one major adverse event (an infection that required hospitalization), the overall safety profile was similarly excellent.

For the treatment of RA, the biosimilars infliximab-dyyb, infliximab-abda, infliximab-qbtx, and infliximab-axxq have been approved by the FDA. In terms of

safety and efficacy, infliximab biosimilars and bio-originals do not differ statistically significantly.

Golimumab is a human monoclonal antibody that is injected subcutaneously once per month. In patients who have not responded to many biological therapies, golimumab is less successful than other TNFi, while having a comparable safety and effectiveness profile to other TNFi. But because of its bulk, it may serve as a useful therapeutic choice when nursing. Golimumab biosimilars are now in the preclinical stage of development.[202]

A human monoclonal antibody named certolizumab is injected subcutaneously every two weeks. This is a biological molecule which has been authorized to treat cases of RA in pregnant women and may be administered safely during pregnancy since it does not pass to the fetus.[203] Certolizumab biosimilars are now in the preclinical stage of development.[202]

A fusion protein called abatacept prevents the activation of T cells by obstructing its interaction with CD28. It should be given intravenously every four weeks following the initial infusion and then every two and four weeks after that. Many trials in phase 3 have looked into abatacept's safety and effectiveness characteristics. Patients with RA who did not react favourably to MTX therapy participated in a double-blind trial comparing the safety and efficacy of abatacept or infliximab with placebo. The results of the trial show that while the efficacy profiles of abatacept and infliximab are similar, abatacept has a more favourable safety profile and fewer adverse effects.[204] That being said, in order to compare the cancer incidence among RA patients on abatacept to those on other bDMARDs, a comparative observational post-marketing analysis looked at specific case safety

records from VigiBase. Only a melanoma risk increase among RA patients was substantially related with abatacept when compared to other bDMARDs.[205]

A monoclonal antibody that inhibits IL-6 is called tocilizumab. It is offered as an infusion in the pharmaceutical market and can be injected or subcutaneously applied. Regardless of the mode of administration, findings from 14 phase 3 clinical trials revealed that tocilizumab had a low immunogenicity risk.[206] It has been demonstrated that tocilizumab therapy is superior to adalimumab monotherapy in reducing signs and symptoms in individuals with RA who did not react well than MTX treatment.[207] The most common adverse events reported in clinical research include cellulitis, nasopharyngitis, upper respiratory tract infections, and increased blood pressure.[202]

Rituximab acts as a well-tolerated medication that doesn't raise the chance of infection. Using a fixed-effect meta-analysis, the infection rates between rituximab and placebo were assessed. The results of the trial demonstrated that even at greater dosages, there is little chance of a major infection whenever rituximab is used.[208] Furthermore, a prospective, noninterventional research showed that rituximab, a monoclonal antibody, is effective in treating RA. As such, patients who do not respond well to MTX or TNF-α inhibitors may consider rituximab as an option.[209]

A network meta-analysis comprising the best Cochrane papers on bDMARDs for RA assessed the safety and efficacy of six different bDMARDs: etanercept, abatacept, adalimumab, anakinra, infliximab, and rituximab. The findings indicated that etanercept and adalimumab outperformed anakinra in terms of effectiveness, whereas etanercept is safer than anakinra, infliximab, and adalimumab [197]

Scientific advances known as bDMARDs have completely changed how RA is treated. Many advantages have been documented in those with RA who did not respond well to csDMARDs. The goal of therapeutic treatment is to intervene quickly and forcefully with the best medications. One of the main obstacles preventing patients from receiving bDMARDs is the costly nature of biologics. Nonetheless, over time, patient profiles have evolved to reflect decreased disease activity and quicker disease progression. Patients with comorbidities who have RA are increasingly being prescribed bDMARDs as their first line of therapy.[210]

The administration of JAKi is the most recent RA treatment strategy that has been authorized by the FDA & EMA. These substances are divided into two groups according to how selective they are: low-selectivity inhibitors that stop the signaling process of a broad range of cytokines make up the first group, while inhibitors that may block certain signaling pathways make up the second. JAKs are cytoplasmic proteins that connect signal transducers and activators of transcription (STAT) transcription factors to membrane receptor-derived cytokine signaling. In addition to providing the greatest control over the inflammatory response, this can be a crucial treatment strategy for autoimmune diseases.[211] Additionally, JAKi can target four members of the JAKs family in addition to seven distinct kinds of STATs.[212] Along with their good efficacy and safety profiles, JAKi provide noteworthy advantages over bDMARDs, such as their oral administration and lower production costs.[213,214,215]

The guidelines for utilizing JAKi in cases when csDMARDs are not working for treating RA have been modified in the 2021 ACR guideline. Additionally, patients who get JAKi monotherapy may adhere to it more closely than those who receive several csDMARD medications, even if the safety profile in this instance is

poorer.[159,216] Immunization is advised prior to starting therapy since immune system suppression might increase the risk for infections, particularly pulmonary ones.[217,218] A dose-dependent change in lipid metabolism has also been shown, although it hasn't been linked to a higher risk of heart disease.[212] An overview of JAKi is given in Table 2, which also highlights its molecular targets as well as safety profiles.[212,219] This highlights their originality in RA therapy.

Comprehensive data regarding the safety and effective profile of JAKi have been obtained from clinical studies, [220-223] and it is predicted that their usage will increase as the pharmacological properties of therapeutic agents and the pathophysiological causes of RA become more known. Post-marketing surveillance (PMS) results are increasingly being used in this context to identify areas for improvement and to confirm that therapeutic techniques remain safe and effective.[224]

A thorough meta-analysis was conducted using tofacitinib PMS records obtained from Pfizer safety databases, covering the period from November 2012 to November 2015. Additionally, a twice-daily dose of 5 mg of tofacitinib was used to estimate worldwide sales in order to quantify patient exposure. After approval, 34,223 patient-years were expected to be exposed to tofacitinib globally during a three-year period. 102 fatal cases were documented among the 9291 case reports which were reviewed in total. (82.9% of which were not severe). The estimated relative risks (RRs) for infections were 2.57, neoplasms were 0.45, and heart diseases were 0.43. Among the 25,417 adverse events that were recorded, medication ineffectiveness accounted for 13.2%, headaches for 9.0%, and pain for 6.4% of all complaints.[225]

An analysis of recent observational studies was conducted to compare the risk of malignancy in patients with RA getting tofacitinib therapy vs non-TNFi treatment,

in contrast to those receiving csDMARDs or TNFi. Among the 2819 discovered publications, ten studies total were included, comprising 40,587 patients treated with non-TNFi along with 2221 patients treated with tofacitinib. Tofacitinib, rituximab, and tocilizumab had no connection to an increased risk of cancer, whereas exposure to abatacept was linked to a little increased risk of cancer development.[226] A recent phase 4 study that assessed major adverse cardiovascular events (MACE) and malignancies, with the exclusion of non-melanoma skin cancers, found that tofacitinib was safer than adalimumab and etanercept. The research was conducted from 2014 to 2020. The purpose of this study was to show that tofacitinib, as opposed to TNFi, is not less effective in treating these disorders. The established non-inferiority criterion was not satisfied, according to the results.[227] Moreover, JAKi, in particular tofacitinib, have been associated with a higher incidence of venous thromboembolisms in PMS trials.[228] Tofacitinib was found to raise risk only when administered at a dosage of 10 milligrams twice per day, which is more than the amount that most nations suggest for RA. [229]

Currently, tofacitinib is used more often than baricitinib. Baricitinib's safety and effectiveness profile in Japanese patients having RA were examined in an all-case PMS research conducted from September 2017 till June 2020. Baricitinib ought to be used in compliance with recommendations, as evidenced by the data gathered, which showed no extra safety concerns.[230]

The majority of phase 4 research are still in progress since JAKi offer novel treatment possibilities. There are presently two large phase 4 trials underway to examine the safety of TNFi against baricitinib in relation to venous thromboembolic events. [231,232] Additionally, two trials on the utilization of upadacitinib are now underway. The first one began in October 2020 and evaluated how adult Canadian

participants having moderate-to-severe RA were doing in terms of their illness symptoms (CLOSEUP). An estimated 390 participants are expected to be enrolled across many sites in Canada, and the research is expected to be completed in September 2024.[233] The subsequent phase 4 research comprises 3000 individuals and was conducted in January 2021, making it more current. Upadacitinib's effectiveness and safety profile are being assessed in Korean adult RA participants as part of a PMS.[234] Furthermore, PMS are crucial, particularly for novel treatments, and the information they provide will help to refine JAKi therapy.

Because of the current epidemiological conditions, investigations have been conducted to determine whether coronavirus disease 2019 (COVID-19) and RA are associated in any way. The assessment of the cytokine storm and additional data have been examined, which indicate a rise in serum ACPA levels subsequent to SARS-CoV-2 infection. [235,236] Though individuals with RA seemed to be more susceptible due to their autoimmune disorder, the epidemiological features and development of SARS-CoV-2 infection have not differed from those observed in the general public, based on the findings from cross-sectional and cohort research published thus far. Immunosuppressive medications also don't seem to be associated with the development of COVID-19, therefore non-infected individuals can safely continue receiving therapy. Since the effect of RA medications on patients with SARS-CoV-2 is yet unknown and requires more research, it becomes critical to monitor each stage of therapy.[237]

6. Novel Approaches and Upcoming Paths in the Management of RA

Over the past few decades, there has been a substantial shift in the care of RA, which has improved patient outcomes and quality of life. The effective identification

of many pathways implicated in the pathophysiology of RA has made this possible. Despite this, there are still some unfulfilled needs regarding management of RA since the processes behind the inflammatory mechanisms and the pharmacological effects of therapeutic agents remain partly understood. These include improving our understanding of the mechanisms underlying the similar efficacies of various treatments, figuring out why some patients gradually lose responsiveness, spotting pre-RA and starting an intensive early treatment regimen, and improving the safety and efficacy profiles of novel drugs, especially JAKis.[31,238] Currently, a variety of experimental animal studies are being used to study a multitude of techniques to improve RA therapy. To achieve a full remission of RA, a plethora of new therapeutic areas are being investigated, and prospective treatment drugs are undergoing varying levels of testing. Figure 5 provides an overview of targeted treatments' past, present, and future. [22,219]

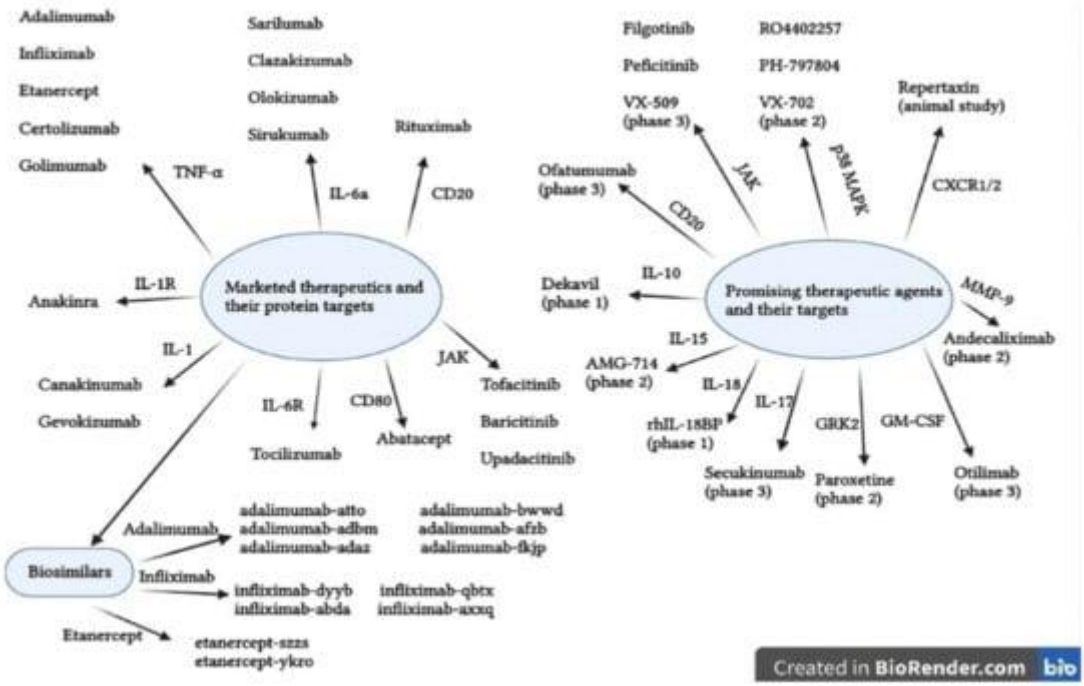

Figure 5: *Status and future targeted therapies in RA: AMG stands for human monoclonal antibody; CD20 for membrane-embedded surface molecule; CXCR for α-chemokine receptor; IL for interleukin; CD80 for CD28 protein ligand; JAK for Janus kinase; MAPK for mitogen-activated protein kinases; MMP for matrix metallopeptidase; and TNF-α for tumor necrosis factor alpha.*

Huang et al. (2021) updated and considered complex data about potential therapeutic agents, complex information regarding small molecular metabolite targets and epigenetic targets along with protein targets (p38 mitogen-activated protein kinase, complex G protein-coupled receptor kinase 2, granulocyte-macrophage colony-stimulating factor) alongside additional targets (DNA methylation, RNA methylation, etc.) [219]

Mesenchymal stem cells (MSCs) are a potential therapeutic approach because they have the ability to differentiate into new tissues such as bone and cartilage and because they have demonstrated immunosuppressive properties in vitro by preventing T cell activation. Furthermore, by lowering blood concentrations of IL-1, IL-6, IL-8, and TNF-α, therapy with MSCs has been found to ameliorate RA symptoms and diminish the proinflammatory response both in animal model studies as well as clinical trials involving RA patients.[239]

The toll-like receptor 4 is shown to play a part in the pathophysiology of RA by inducing joint inflammation. Consequently, therapeutic medicines targeting this specific receptor or its ligands, such heat-shock protein crystalline or tenascin C, can be optimized.[239] The range of available therapy choices for RA is growing, and a number of ongoing research may find novel therapeutic agents, molecular targets, and ways to mitigate adverse effects, all of which might significantly improve the condition of RA patients. Future medical research might be revolutionized by a customized strategy that doubles down on evidence-based medicine and genetic studies to successfully treat incurable diseases.[240]

The role of uric acid as a biomarker for disease severity in RA has been previously studied, with results ranging from protective effect of hyperuricemia in RA disease severity, while other studies postulated that joint inflammation severity directly correlated with higher UA levels in rheumatoid arthritis patients. The above demonstrates that serum UA levels and RA disease activity share a complex relationship.

A study conducted by Agudelo C, Turner R, Panetti M, Pisko, E. showed improvement or decreased rheumatoid activity in periods of hyperuricemia, and exacerbations occurred when serum uric acid levels normalised.[241]

A study by Chiou A, England B, Sayles H, Thiele G, Duryee M, Baker J, et al. showed no significant associations of enrolment serum Uric Acid or gout with RA disease activity or treatment. Strong associations were found between hyperuricemia and CVD mortality in RA population.[242]

A study by Nada D, Gaber R, Mahmoud A, Elkhouly R, Alashkar, D. showed significant correlation between serum uric acid and disease activity by DAS28. Acute phase reactants and inflammatory markers were also significantly elevated in RA patients with low and high S. UA compared to those with normal S.UA.[243]

Serum uric acid levels were found to be substantially greater in males than in females in a research study by Yanti A, Faridin H.P, Bakri S, Kasim H, Rasyid H, Tandean P, et al., although there was no significant link between serum uric acid and RA disease activity.[244]

A study by Yildirim K, Karatay S, Melikoglu MA, Gureser G, Ugur M, Senel K showed strongly positive correlation between DAS28 score and serum CRP score in RA patients. There were also significantly high correlations between DAS28 scores and other Acute phase reactant levels.[245]

A study by Ghosh B, Baidya D, Halder P, Mandal S. showed higher disease activity, hs-CRP and serum uric acid levels in higher age groups. It also showed a decrease in all three parameters in RA patients after 3 months of DMARD therapy.[246]

A study conducted by Jebakumar A, Udayakumar P, Crowson C, and Matteson E. found that among RA patients, the cumulative 25-year prevalence of gout, as determined by clinical criteria, was 5.3%. It was discovered that although gout does develop in RA patients, it does so less frequently than in people without RA. [247]

MATERIALS AND METHODS

Source of Data:

Patients with an established diagnosis of Rheumatoid Arthritis seen at Dr. Prabhakar Kore Hospital and Research Centre, Belagavi during the study period of January 2023 to December 2023, fitting the inclusion criteria, were included.

Study Design:

This study was a cross-sectional study.

Study Period:

The study was conducted from 1st January 2023 to 31st December 2023.

Sample Size:

The sample size was calculated to be **64**. The minimum sample size formula based on prevalence rate was used, where P is the prevalence rate of hyperuricemia in Rheumatoid Arthritis patients, and d is the percentage likely difference in the prevalence.

Reference: Nada D, Gaber R, Mahmoud A, Elkhouly R, Alashkar D, 2021. Hyperuricemia Among Egyptian Rheumatoid Arthritis Patients. Is It an Association or an Inflammatory Marker? A Cross-Sectional Observational Study. Open Access Rheumatology: Research and Reviews, Volume 13, pp.305-314.

For a 5% level of significance, zα is 1.96. The parameter considered in the calculation is the proportion of hyperuricemia in rheumatoid arthritis.

With P = 60% and d = 20% of P = 12%, the sample size is **64** using the formula—

$$n = \frac{z_\alpha{}^2 P(1-P)}{d^2}$$

where P is the prevalence rate of hyperuricemia in Rheumatoid Arthritis patients and d is the percentage likely difference in the prevalence.

Sampling Technique:

A cross-sectional study was conducted where all consecutive patients fulfilling the inclusion criteria were included in the study. Statistical analysis was performed using SPSS with descriptive analysis and Chi-Square test.

Inclusion Criteria:

1. Patients meeting the 2010 American College of Rheumatology/EULAR Classification criteria for Rheumatoid Arthritis diagnosed by a licensed medical professional.
2. Patients who consented to participate in the study.
3. Patients aged 18 years and older.

Exclusion Criteria:

1. Patients with a history of end-stage renal disease requiring dialysis.
2. Individuals already on urate-lowering medications (allopurinol, febuxostat, Rasburicase).
3. Organ transplant recipients requiring immunosuppressive therapy (Cyclosporine).
4. Patients having history of cerebrovascular accident or ischemic heart disease on low-dose aspirin.
5. Patients with myeloproliferative or lymphoproliferative malignancies or those on chemotherapy.
6. Patients with known cases of hemolytic anemia.
7. Patients on hormone replacement therapy with estrogen and pregnant females.

Study Protocol:

1. Informed consent was obtained before enrolling patients in the study.
2. Patients fulfilling the inclusion criteria were explained the protocol and instructed on how to fill the self-assessment questionnaires.
3. Patients were subjected to a questionnaire and thorough clinical examination to assess swollen and tender joint counts, and the Patient Global Disease Activity (PGA) on a 0-10 scale.
4. General examination including BMI, waist-hip ratio, and blood pressure was recorded.
5. Disease activity was assessed using DAS28-CRP score, CDAI, and SDAI.
6. Laboratory tests including fasting blood sugar, lipid profile, creatinine, and CRP were conducted via venous sampling.

Data Collection Procedure:

1. Patients were subjected to a questionnaire and thorough clinical examination to assess tender and swollen joint counts, and PGA on a 0-10 scale.
2. General examination including BMI, waist-hip ratio, and blood pressure was recorded.
3. Disease activity was assessed using DAS28-CRP score, CDAI, and SDAI.
4. Laboratory tests including fasting blood sugar, lipid profile, creatinine, and CRP were conducted via venous sampling.
5. Collected data was tabulated in percentages in an Excel sheet.

Statistical Analysis:

1. Collected data was tabulated in percentages in an Excel sheet.
2. SPSS ver. 22 was used to perform statistical analysis with descriptive analysis and Chi-Square test. Categorical data was depicted using frequency counts and percentage distributions. The chi-square test served as the significance test for categorical variables. Continuous data was summarized using the mean and standard deviation. statistical P value less than 0.05 is deemed indicative of statistical significance.

RESULTS

Table 1: Age group amongst study population

Age group	Frequency (n=64)	Percent (%)
21 to 30 years	10	15.6%
31 to 40 years	13	20.3%
41 to 50 years	14	21.9%
more than 50 years	27	42.2%
Total	64	100.0%

The majority of participants were over 50 years old, making up 42.2% of the sample. The age group 41 to 50 years follows with 21.9%, while the age groups 31 to 40 years and 21 to 30 years constitute 20.3% and 15.6%, respectively.

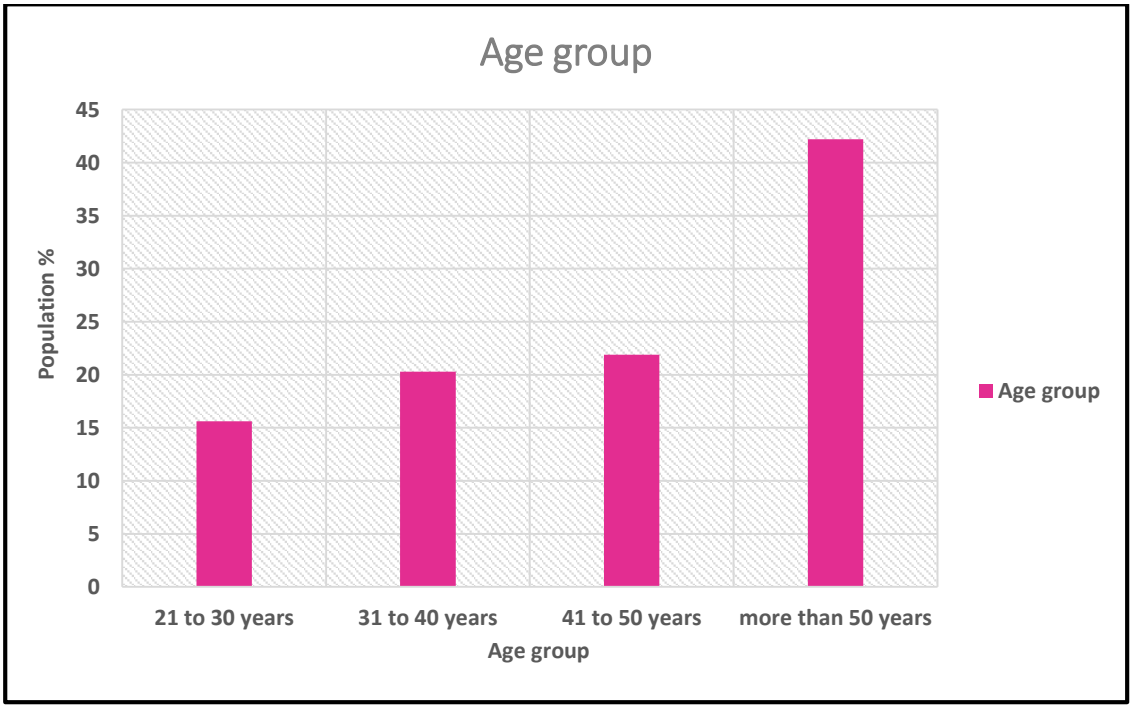

Fig. 6: *Distribution of age groups amongst study population*

Table 2: Gender distribution of study population

Gender	Frequency (n=64)	Percent (%)
Female	55	85.9%
Male	9	14.1%
Total	64	100%

The majority of participants were female, making up 85.9% of the sample. Males were a minority comprising of 14.1% of the study population.

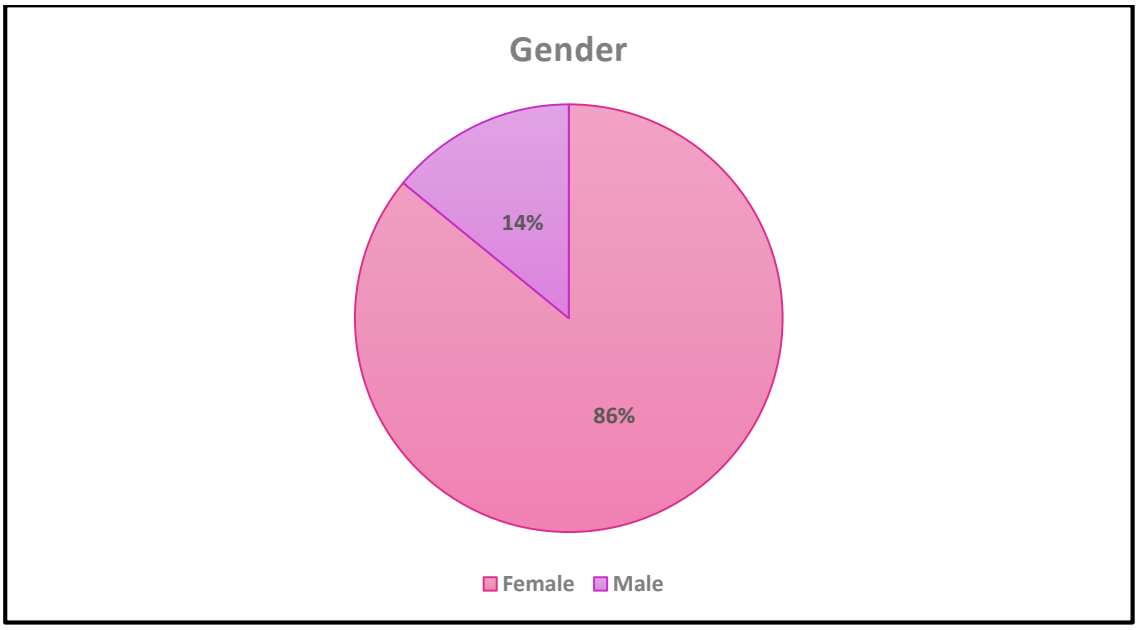

Fig. 7: *Distribution of gender amongst study population*

Table 3: Body Mass Index amongst study population

BMI	Frequency (n=64)	Percent (%)
Overweight (>23 kg/m2)	12	18.8%
Normal (18.5 -22.9 kg/m2)	48	75%
Underweight (<18.5 kg/m2)	4	6.3%
Total	64	100%

A significant majority of participants had a normal BMI, comprising 75% of the sample. Overweight individuals account for 18.8%, while 6.3% are underweight.

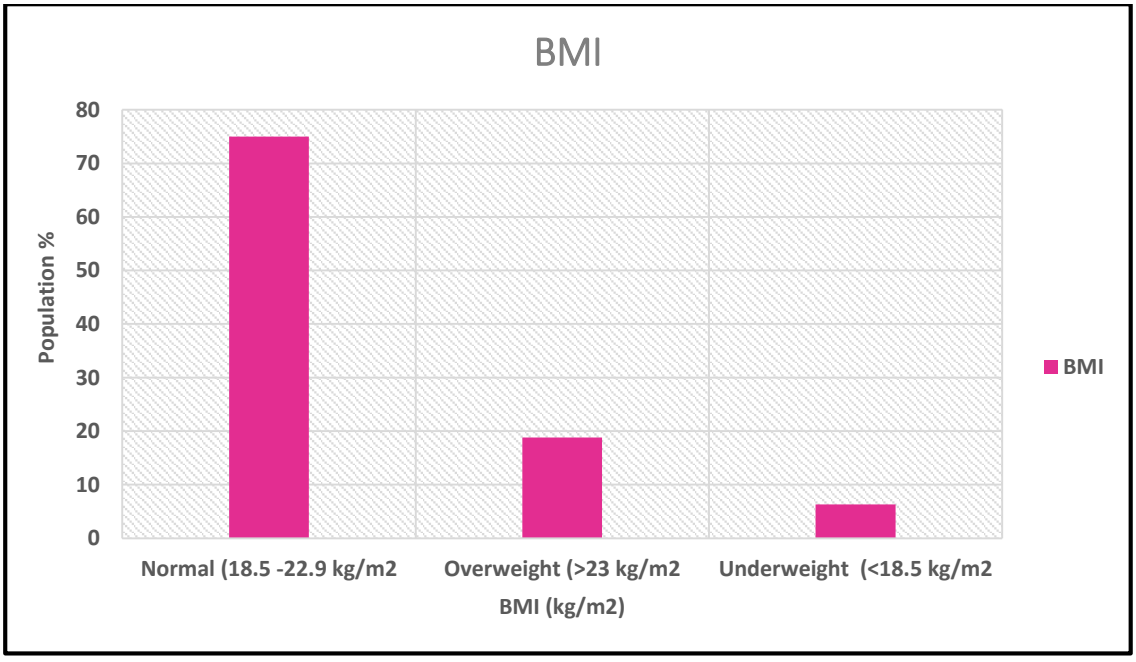

Fig. 8: *Distribution of BMI classes amongst study population*

Table 4: Visual Analogue Scale Score distribution of study population

VAS	Frequency (n=64)	Percent (%)
0-2 (mild)	31	48.4%
3-6 (moderate)	23	35.9%
more than 6 (severe)	10	15.6%
Total	64	100%

Nearly half of the participants (48.4%) reported low pain levels (0-2 on the VAS scale). Those reporting moderate pain (3-6) make up 35.9%, and 15.6% experience high pain levels (more than 6).

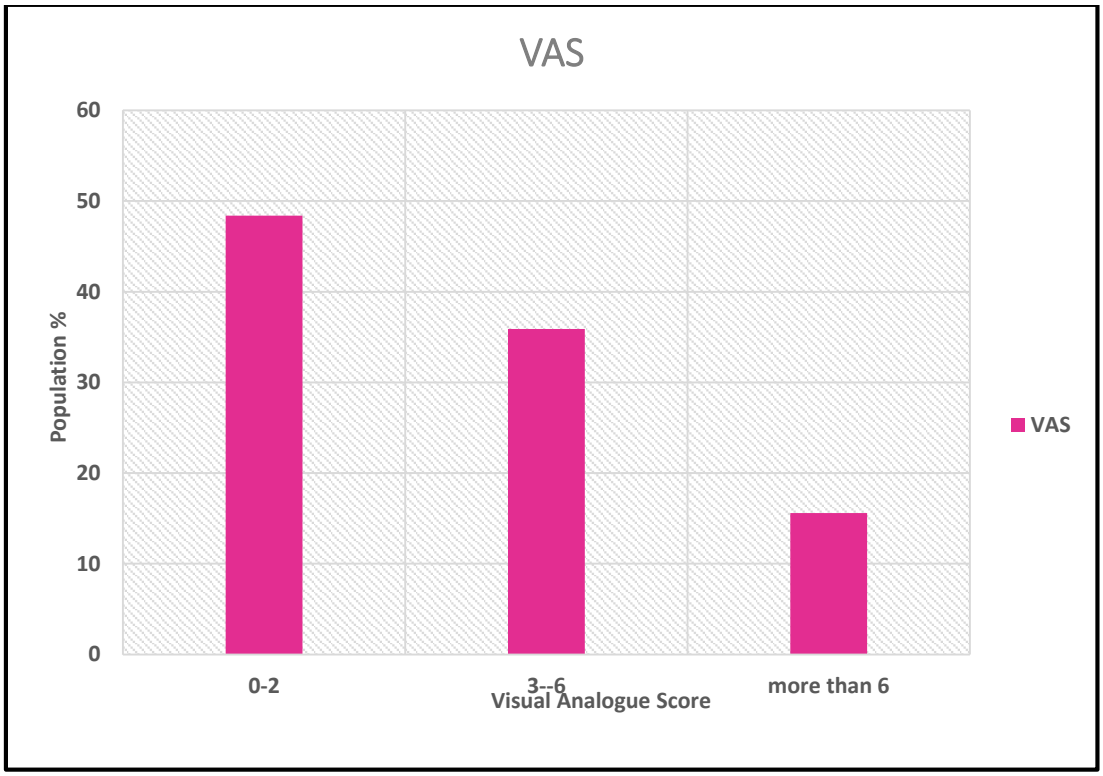

Fig. 9: *Distribution of Visual Analogue Scores in study population*

Table 5: Serum Creatinine Levels amongst study population

Serum Creatinine	Frequency (n=64)	Percent (%)
Normal (0.5-1.1mg/dl)	56	87.5%
Raised (>1.1mg/dl)	8	12.5%
Total	64	100%

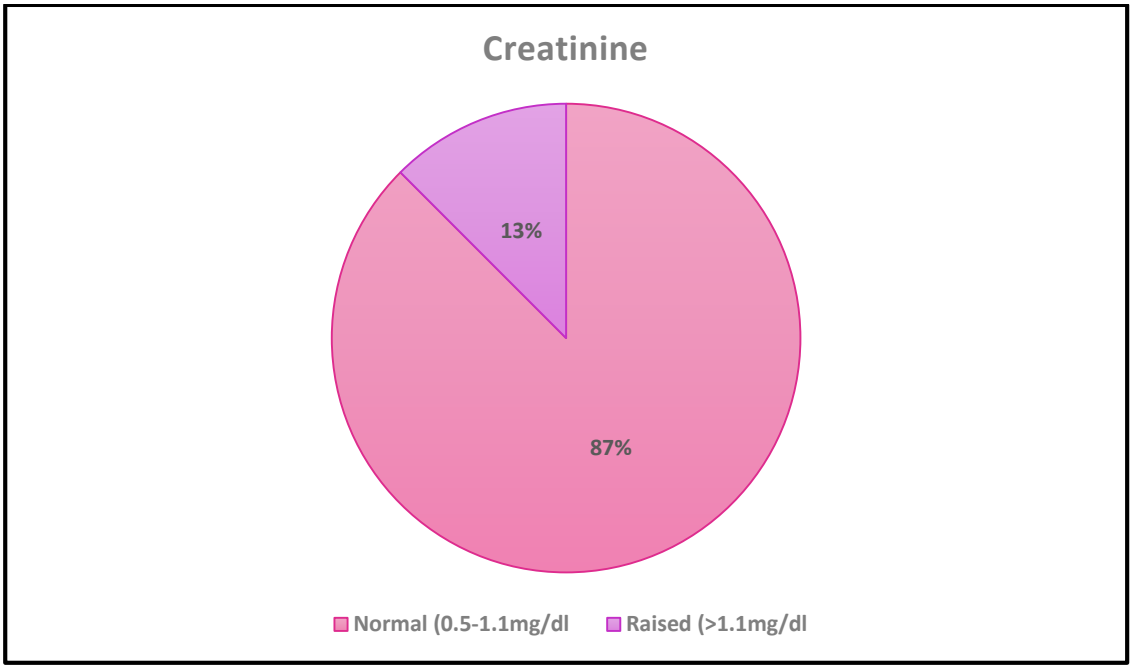

Fig. 10: *Serum Creatinine levels amongst study population*

Most participants had normal creatinine levels, with 87.5% falling within this range. Raised creatinine levels were seen in 12.5% of the participants.

Table 6: Serum Uric Acid Levels amongst study population

Serum Uric Acid	Frequency (n=64)	Percent (%)
Normal (2.4 -5.7 mg/dl)	53	82.8%
Raised (> 5.7 mg/dl)	11	17.2%
Total	64	100%

The majority of participants (82.8%) had normal uric acid levels, while 17.2% have raised levels.

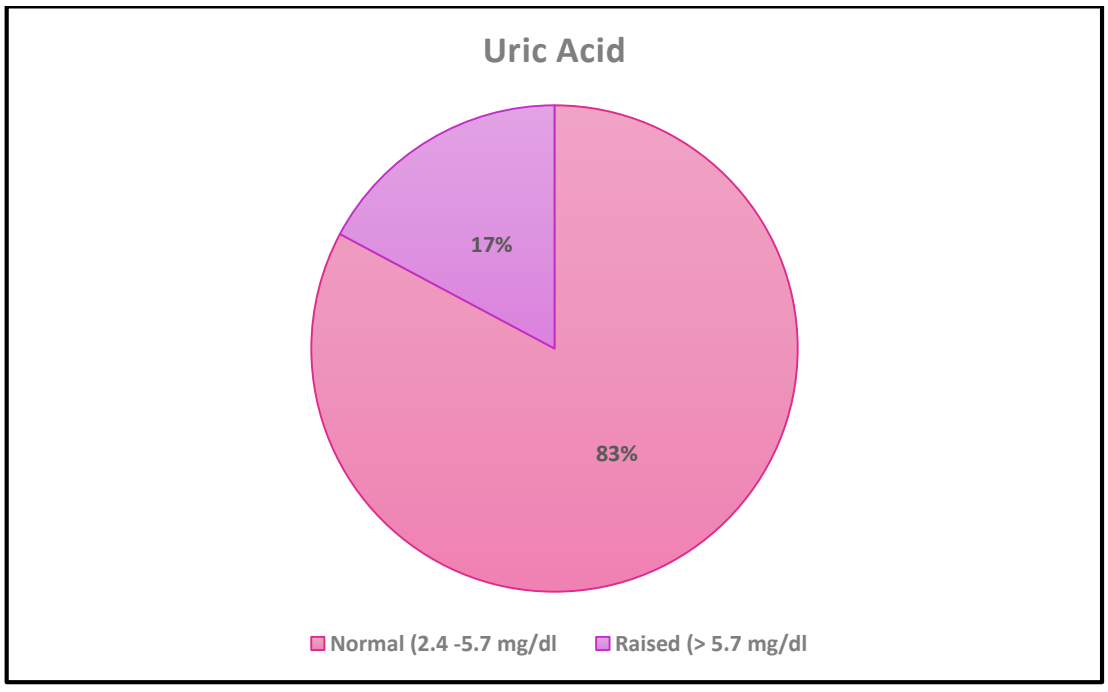

Fig. 11: *Serum Uric Acid levels amongst study population*

Table 7: Disease Activity using DAS28 score for Rheumatoid Arthritis amongst study population

DAS28	Frequency (n=64)	Percent (%)
High disease activity (>5.1)	13	20.3%
Moderate disease activity (>3.2- <5.1)	32	50.0%
Low disease activity (2.6 -< 3.2)	10	15.6%
Remission (<2.6)	9	14.1%
Total	64	100.0%

A significant portion of participants (70.3%) had Moderate DAS28 scores. Those with high and low DAS28 scores were 20.3% and 15.6%, respectively.

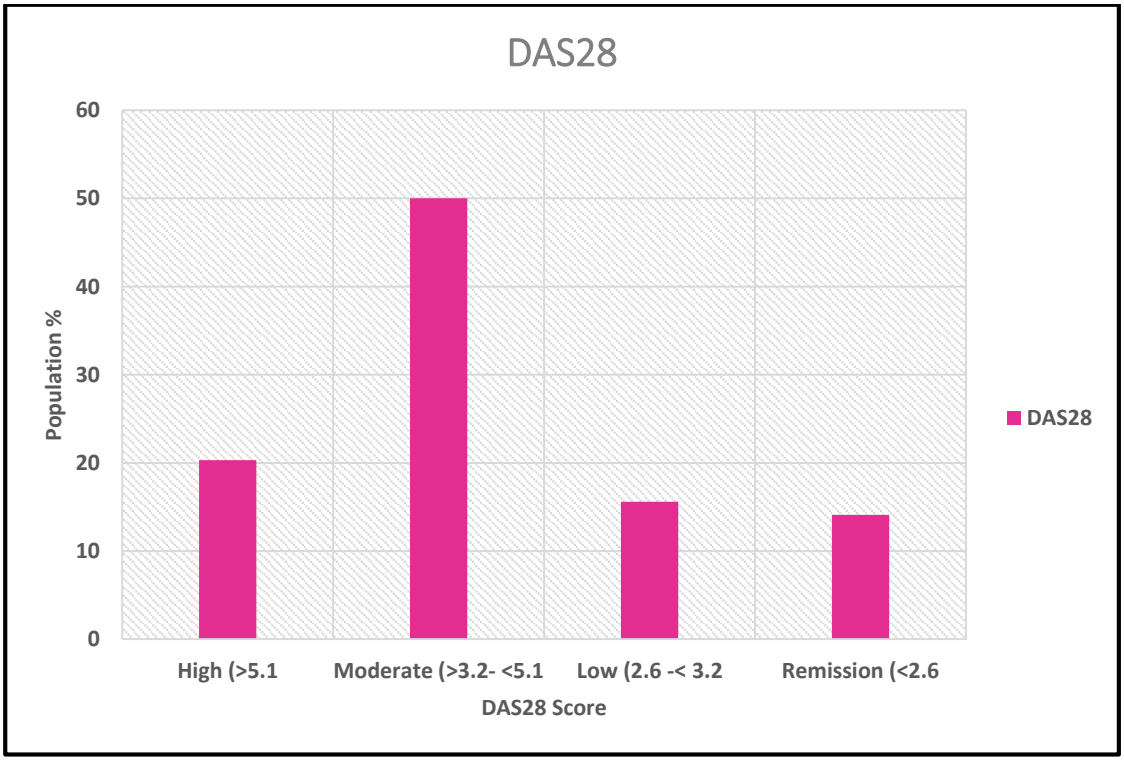

Fig. 12: *Distribution of DAS28 scores amongst study population*

Table 8: Disease Activity using CDAI score for Rheumatoid Arthritis amongst study population

CDAI	Frequency (n=64)	Percent (%)
High disease activity (>22)	13	20.3%
Moderate disease activity (10-22)	21	32.8%
Low disease activity (>2.8-10)	18	28.1%
Remission (<2.8)	12	18.8%
Total	64	100%

Most participants fall within the moderate category (32.8%) for CDAI scores, with a notable 18.8% in remission. High and low CDAI scores were observed in 20.3% and 28.1% of participants, respectively.

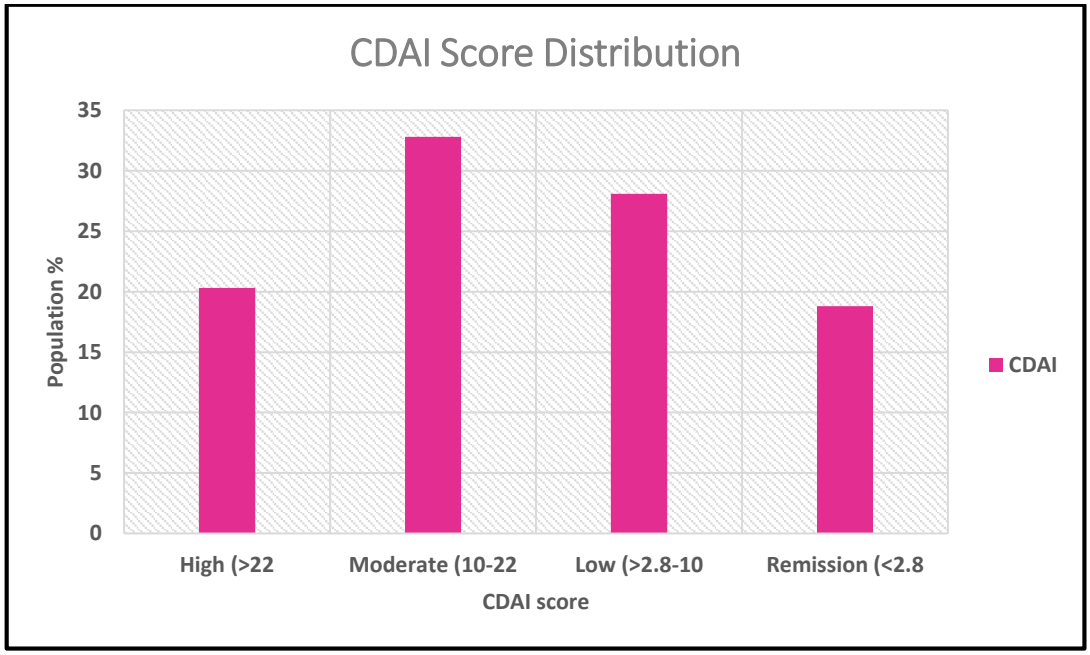

Fig. 13: *Distribution of CDAI scores amongst study population*

Table 9: Disease Activity using SDAI score for Rheumatoid Arthritis amongst study population

SDAI	Frequency (n=64)	Percent (%)
High disease activity (>26)	14	21.9%
Moderate disease activity (11-26)	28	43.8%
Low disease activity (3.3-11)	19	29.7%
Remission (<3.3)	3	4.7%
Total	64	100%

A large portion of participants (43.8%) had moderate SDAI scores, while 29.7% had low scores. High SDAI scores and remission were observed in 21.9% and 4.7% of participants, respectively.

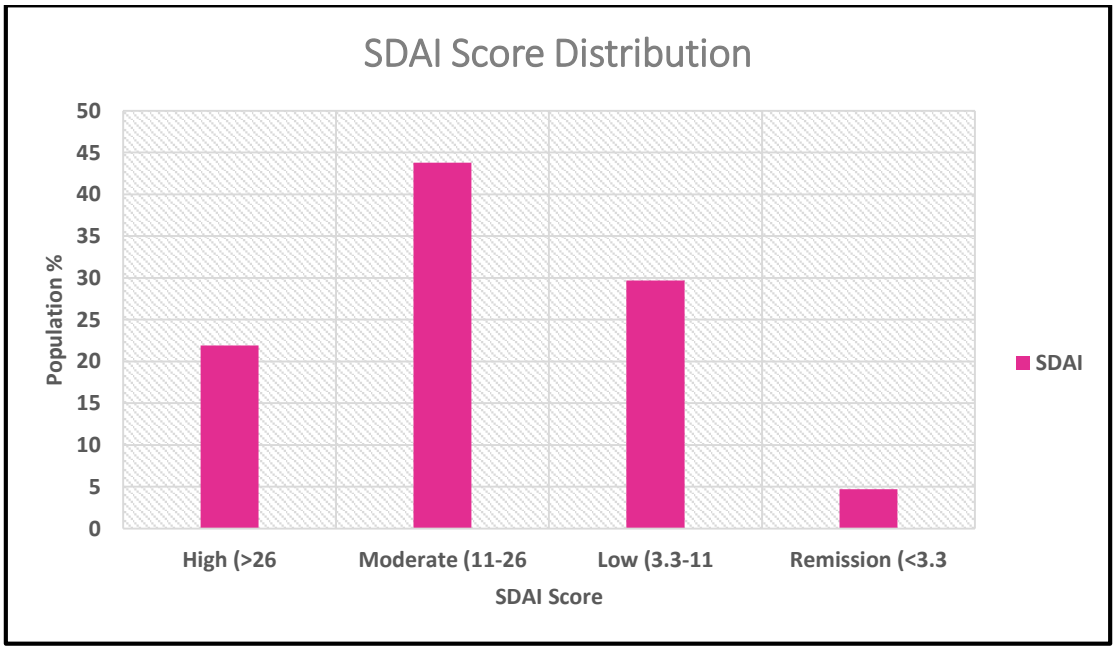

Fig. 14: *Distribution of SDAI scores amongst study population*

Table 10: Overall Disease activity amongst study population

Disease activity	Frequency (n=64)	Percent (%)
High disease activity	13	20.3%
Moderate disease activity	31	48.4%
Low disease activity	12	18.8%
Remission	8	12.5%
Total	64	100%

Nearly half of the participants (48.4%) have moderate **disease activity**. High and low severity were seen in 20.3% and 18.8% of participants, respectively. Remission was reported in 12.5% of the sample.

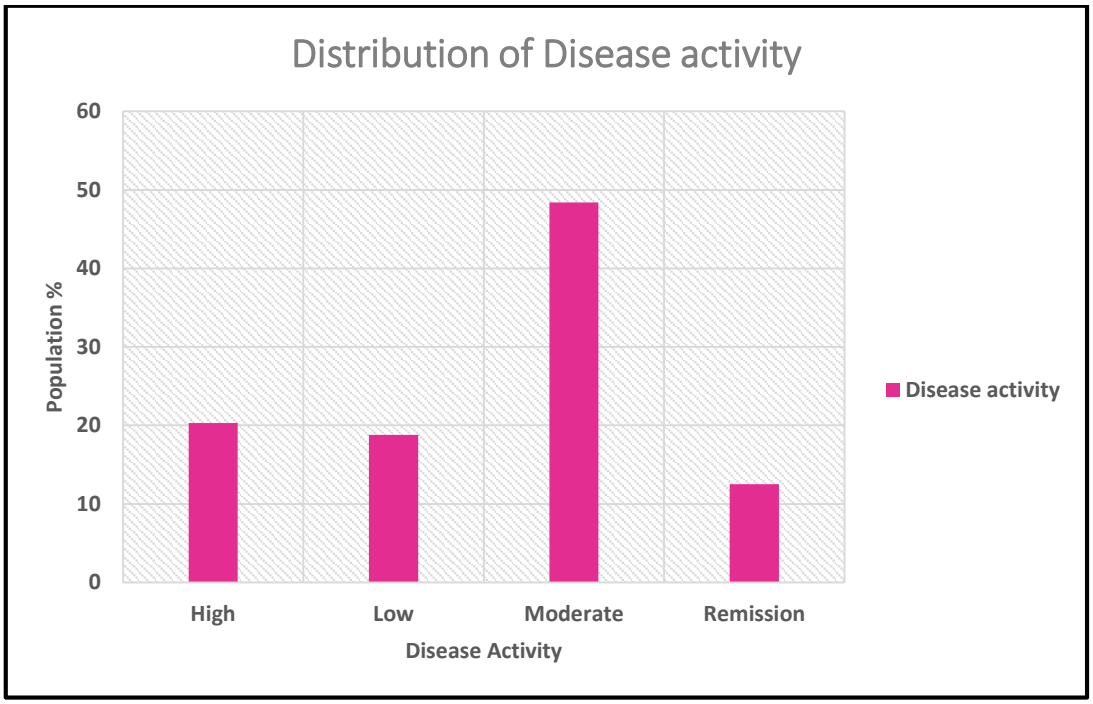

Fig. 15: *Overall disease severity distribution in study population*

Table 11: Rheumatoid Factor status amongst study population

Rheumatoid Factor	Frequency (n=64)	Percent (%)
Negative	15	23.4%
Positive	49	76.6%
Total	64	100.0%

A majority of participants (76.6%) tested positive for Rheumatoid Factor, while 23.4% tested negative.

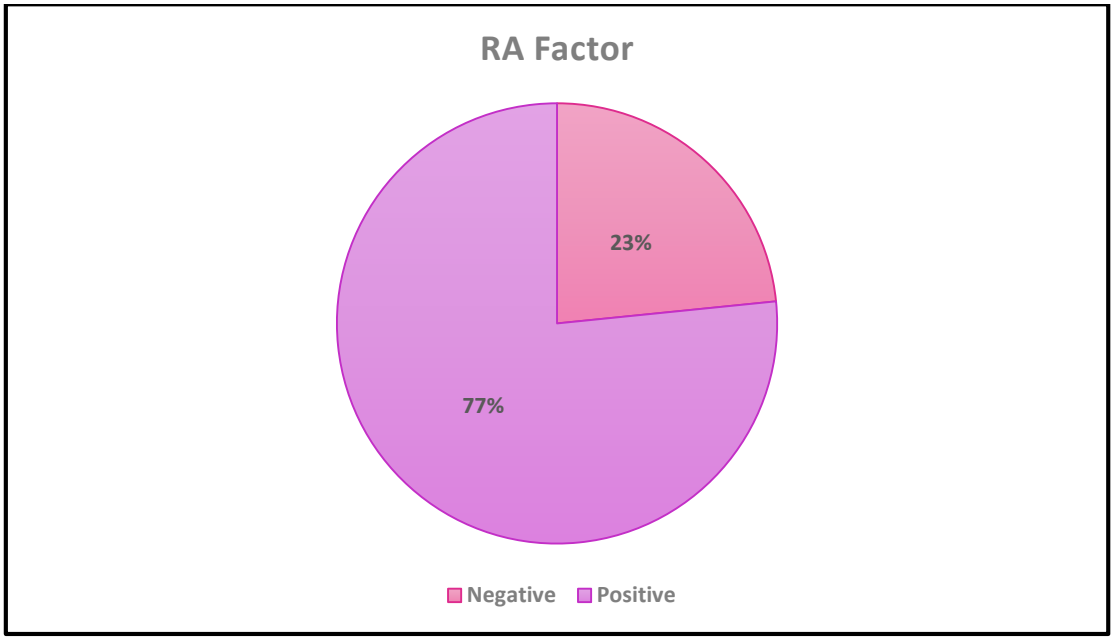

Fig. 16: *Rheumatoid Factor status distribution amongst study population*

Table 12: ACCP Antibody status amongst study population

ACCP Antibody	Frequency (n=64)	Percent (%)
Negative	20	31.3%
Positive	44	68.8%
Total	64	100.0%

A majority of participants (68.8%) tested positive for ACCP antibodies, while 31.3% tested negative.

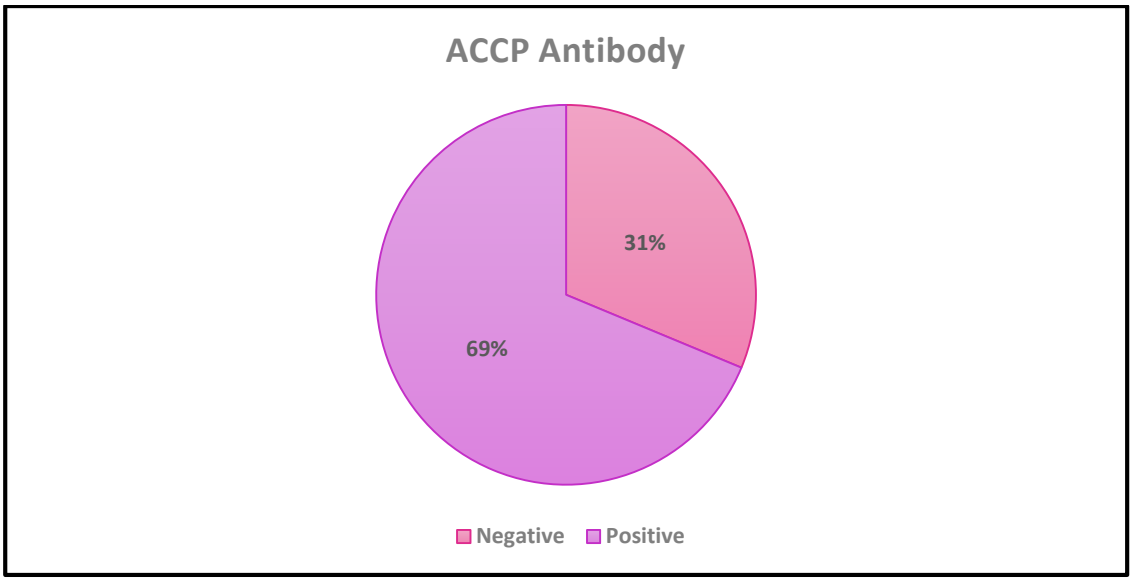

***Fig. 17**: ACCP Antibody status distribution amongst study population*

Table 13: Usage of Disease Modifying antirheumatic drugs (DMARDs) amongst study population

Treatment	Frequency	Percent (%)
Methotrexate	47	73.4%
Hydroxychloroquine	36	56.3%
Leflunomide	15	23.4%
Steroids	22	34.4%
Sulfasalazine	2	3.1%
Tofacitinib	8	12.5%

Methotrexate was the most commonly used treatment, with 73.4% of participants taking this medication. Hydroxychloroquine was used by 56.3% of the sample, followed by steroids at 34.4%. Leflunomide and tofacitinib were taken by 23.4% and 12.5% of participants, respectively, while sulfasalazine was the least used at 3.1%.

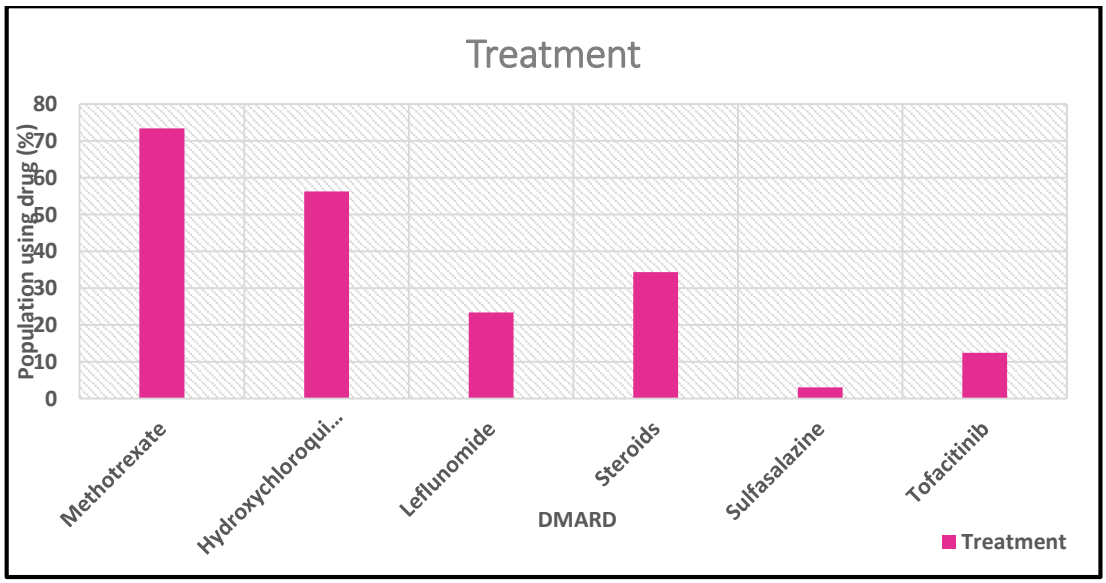

Fig. 18: *Usage of DMARDs amongst study population*

Table 14: Correlation of Age Groups with Serum Uric Acid levels

Age Group	Normal SUA N (%)	Raised SUA N (%)	Total N (%)
21 to 30 years	8 (15.10%)	2 (18.20%)	10 (15.60%)
31 to 40 years	11 (20.80%)	2 (18.20%)	13 (20.30%)
41 to 50 years	11 (20.80%)	3 (27.30%)	14 (21.90%)
More than 50 years	23 (43.40%)	4 (36.40%)	27 (42.20%)
Total	**53 (100.00%)**	**11 (100.00%)**	**64 (100.00%)**

Chi square test, P value- 0.947

Most patients fall in the age group of more than 50 years, with 43.40% having normal uric acid levels and 36.40% raised. Age groups 21 to 30, 31 to 40, and 41 to 50 years are fairly evenly distributed between normal and raised uric acid levels. The chi-square test P-value of 0.947 indicates no significant association between age group and **Uric acid level**.

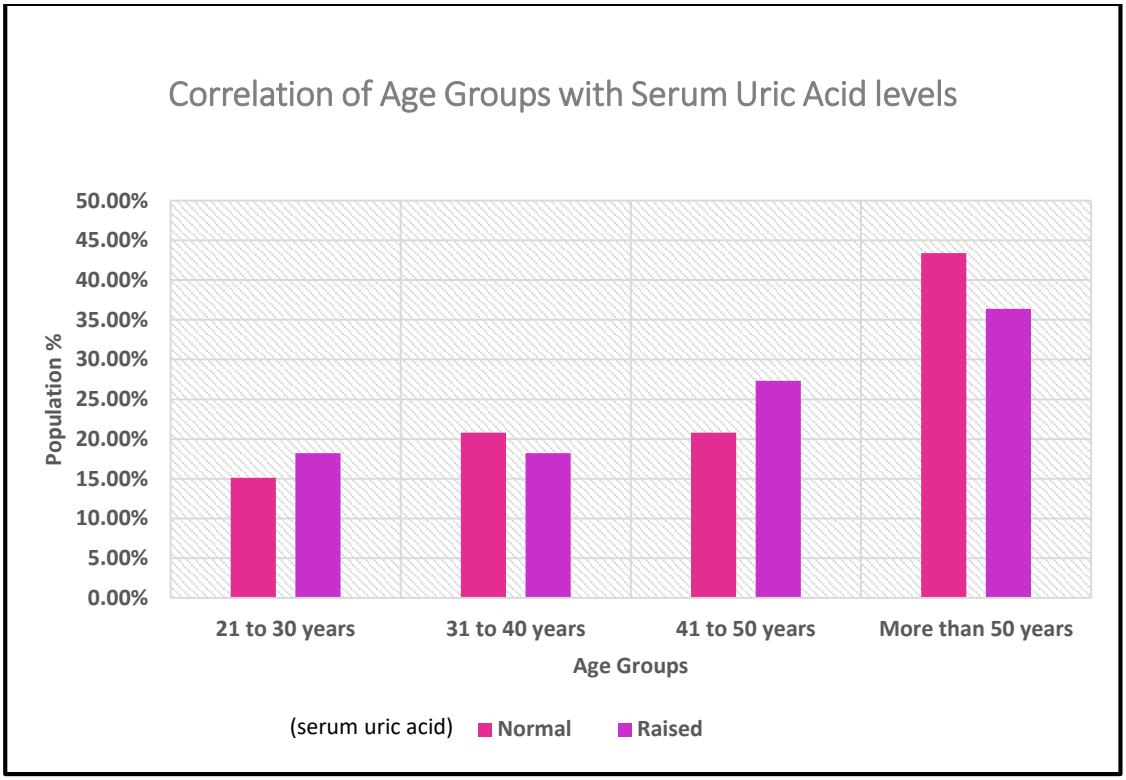

***Fig. 19**: Correlation of Age Groups with Serum Uric Acid levels*

Table 15: Correlation of Gender with Serum Uric Acid Levels

Gender	Normal SUA (2.4 – 5.7 mg/dl) N (%)	Raised SUA (>5.7 mg/dl) N (%)	Total N (%)
Female	44 (80.00%)	11 (20.00%)	55 (100.0%)
Male	9 (100.00%)	0 (0.00%)	9 (100.0%)
Total	**53 (100.00%)**	**11 (100.00%)**	**64 (100.00%)**

Chi square test, P value- 0.14

80.00% of females had normal uric acid levels and 20.00% raised, while males had 16.98% of normal and none of the raised uric acid cases. The chi-square test P-value of 0.14 indicates no significant association between sex and **Uric acid level**.

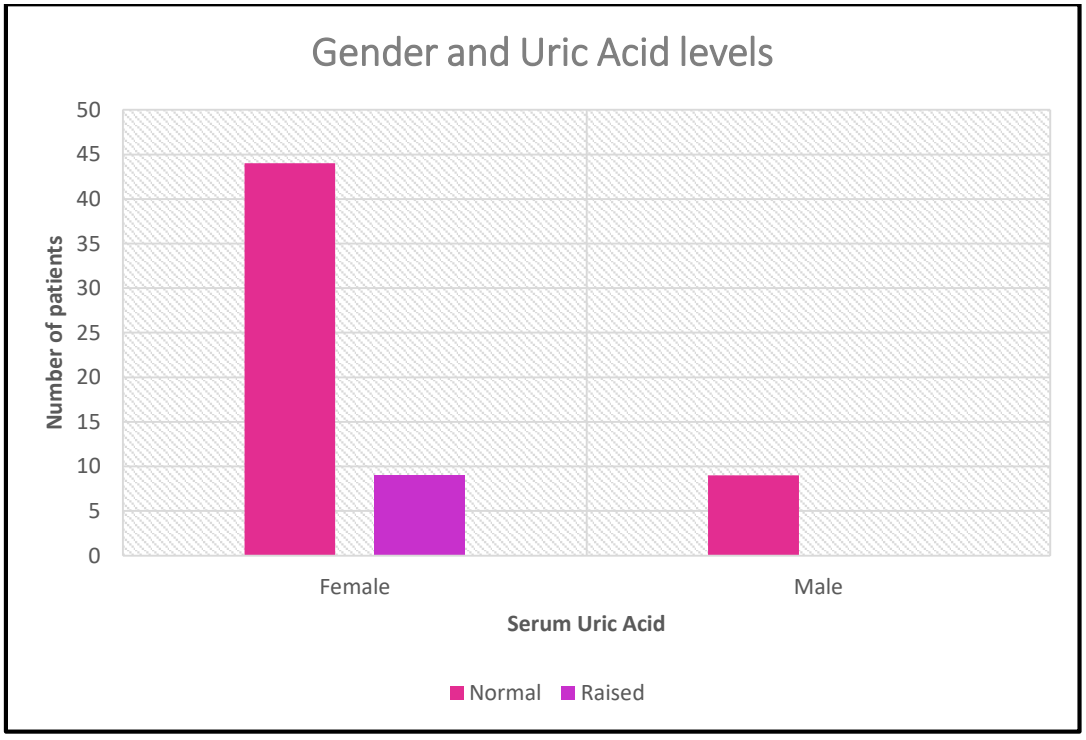

Fig. 20: *Correlation of Gender with Serum Uric Acid Levels*

Table 16: Correlation of Body Mass Index with Serum Uric Acid levels

BMI	Normal SUA N (%)	Raised SUA N (%)	Total N (%)
Normal (>23 kg/m2)	39 (73.60%)	9 (81.80%)	48 (75.00%)
Overweight (18.5-22.9 kg/m2)	10 (18.90%)	2 (18.20%)	12 (18.80%)
Underweight (<18.5 kg/m2)	4 (7.50%)	0 (0.00%)	4 (6.30%)
Total	**53 (100.00%)**	**11 (100.00%)**	**64 (100.00%)**

Chi square test, P value- 0.633

The majority of patients with normal BMI have normal (73.60%) uric acid levels. 81.8% of patients with raised uric acid levels had normal BMI. Overweight patients are 18.90% of normal and 18.20% of raised uric acid levels, while underweight patients are 7.50% of normal uric acid cases and none with raised levels. The chi-square test P-value of 0.633 indicates no significant association between BMI and **Uric acid level**.

Table 17: Correlation of Waist-Hip Ratio with Serum Uric Acid levels

Uric Acid	Normal		Raised		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
WH Ratio	0.6715	0.12	0.6718	0.12	0.994

Chi square test, P value- 0.994

The t test P-value of 0.994 indicates no significant association between Waist-Hip Ratio and **Uric acid level**.

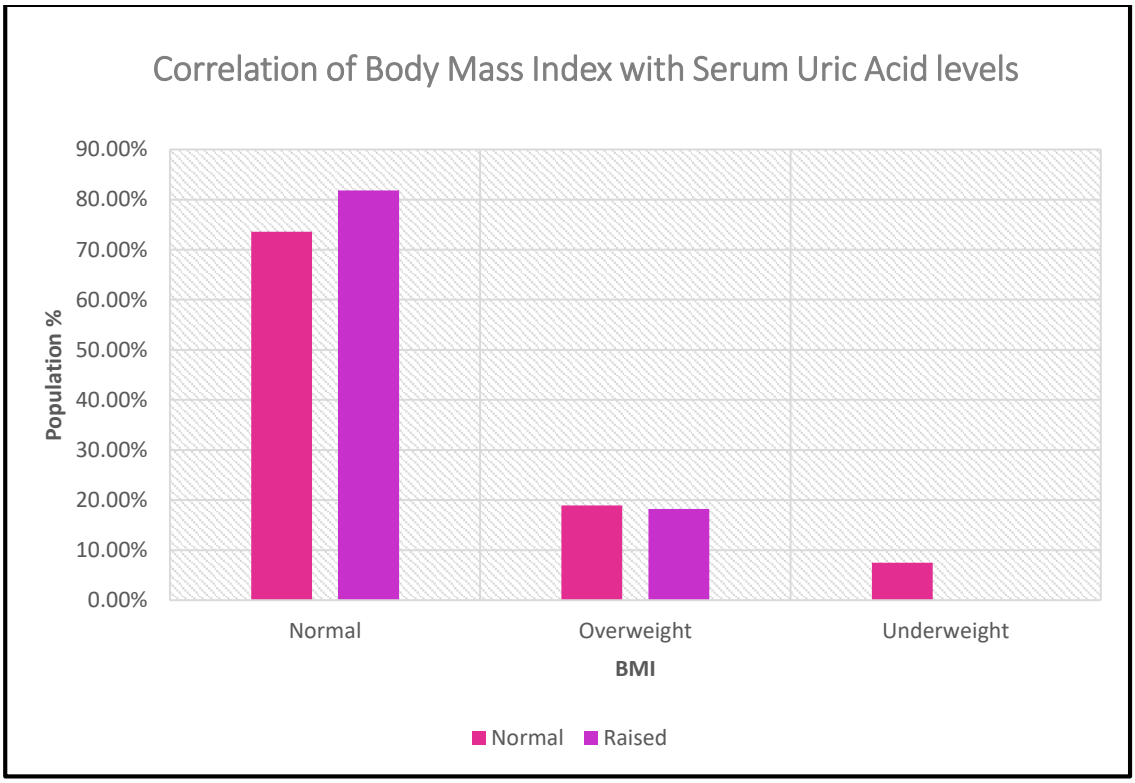

Fig. 21: *Correlation of Body Mass Index with Serum Uric Acid levels*

Table 18: Correlation of Serum Creatinine with Serum Uric Acid levels

Creatinine	Normal Serum Creatinine (0.5-1.1mg/dl) N (%)	Raised Serum Creatinine (>1.1 mg/dl) N (%)	Total N (%)
Normal S. UA	49 (92.50%)	7 (63.60%)	56 (87.50%)
Raised S. UA	4 (7.50%)	4 (36.40%)	8 (12.50%)
Total	**53 (100.00%)**	**11 (100.00%)**	**64 (100.00%)**

Chi square test, P value- 0.009

Most patients with normal creatinine levels have normal (92.50%) uric acid levels. Raised creatinine levels are seen in 7.50% of normal uric acid and 36.40% of raised uric acid cases. The chi-square test P-value of **0.009** indicates a significant association between creatinine and **Uric acid level**.

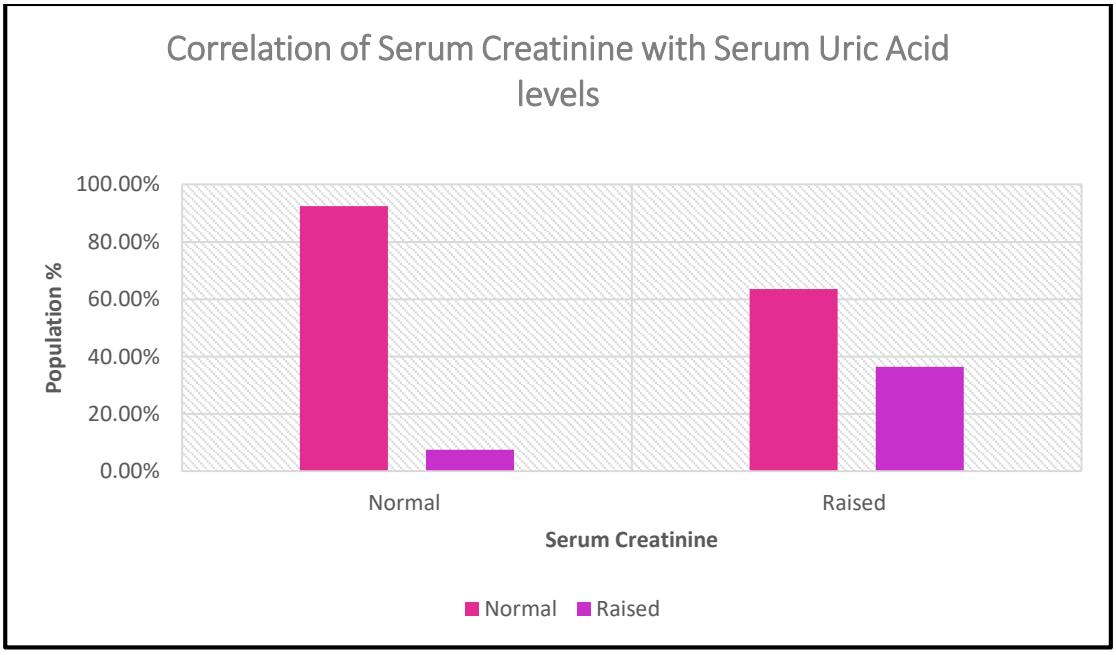

Fig. 22: *Correlation of Serum Creatinine with Serum Uric Acid levels*

Table 19: Correlation of VAS scores with Uric Acid Levels

VAS	Uric Acid Normal N (%)	Uric Acid Raised N (%)	Total N (%)
0-2	25 (53.20%)	4 (40.00%)	29 (50.90%)
3-6	18 (38.30%)	4 (40.00%)	22 (38.60%)
more than 6	4 (8.50%)	2 (20.00%)	6 (10.50%)
Total	47 (100.00%)	10 (100.00%)	57 (100.00%)

Chi square test, P value- 0.516

As seen in the above table, 53.2% of individuals with normal uric acid levels have a VAS score between 0-2, compared to 40.0% of those with raised uric acid levels. For VAS scores between 3-6, 38.3% of individuals with normal uric acid levels fall into this range, while 40.0% of individuals with raised uric acid levels do. For VAS scores greater than 6, 8.5% of individuals with normal uric acid levels fall into this category compared to 20.0% of those with raised uric acid levels. The chi-square test yields a P value of 0.516, indicating no significant association between VAS scores and uric acid levels.

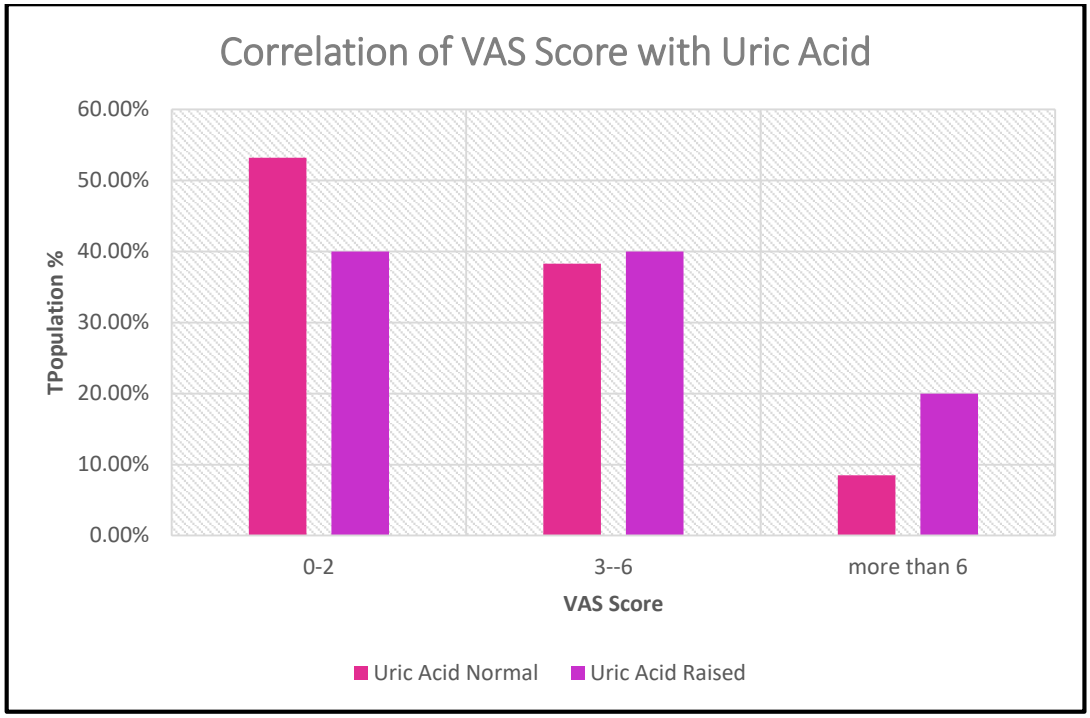

Fig. 23: *Double bar graph representing correlation of VAS Scores with Uric Acid Levels*

Table 20: Correlation of CDAI score for Rheumatoid Arthritis with Serum Uric Acid levels

CDAI	Normal SUA N (%)	Raised SUA N (%)	Total N (%)
High (>22.0)	8 (15.10%)	5 (45.50%)	13 (20.30%)
Moderate (10.0-22.0)	18 (34.00%)	3 (27.30%)	21 (32.80%)
Low (2.8-10.0)	16 (30.20%)	2 (18.20%)	18 (28.10%)
Remission (<2.8)	11 (20.80%)	1 (9.10%)	12 (18.80%)
Total	**53 (100.00%)**	**11 (100.00%)**	**64 (100.00%)**

Chi square test, P value- 0.146

Patients with high CDAI scores are more likely to have raised uric acid levels (45.50%), while those with normal uric acid levels are mostly in the moderate CDAI category (34.00%). Low CDAI scores are seen in 30.20% of normal and 18.20% of raised uric

acid cases. Remission is observed in 20.80% of normal and 9.10% of raised uric acid levels. The chi-square test P-value of 0.146 indicates no significant association between CDAI and **Uric acid level**.

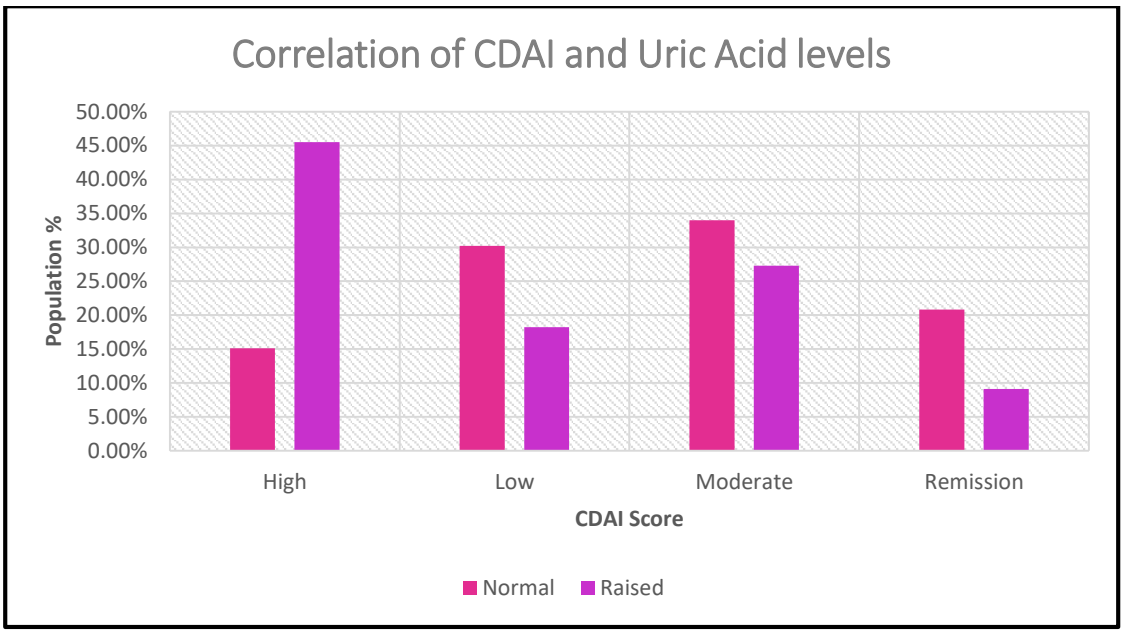

Fig. 24: *Double bar graph depicting correlation of CDAI score for Rheumatoid Arthritis with Serum Uric Acid level*

Table 21: Correlation of SDAI scores for Rheumatoid Arthritis with Serum Uric Acid levels

SDAI	Normal SUA N (%)	Raised SUA N (%)	Total N (%)
High (>26)	10 (18.90%)	4 (36.40%)	14 (21.90%)
Moderate (11-26)	22 (41.50%)	6 (54.50%)	28 (43.80%)
Low (3.3-11)	19 (35.80%)	0 (0.00%)	19 (29.70%)
Remission (<3.3)	2 (3.80%)	1 (9.10%)	3 (4.70%)
Total	**53 (100.00%)**	**11 (100.00%)**	**64 (100.00%)**

Chi square test, P value- 0.104

Moderate SDAI scores are the most common, with 41.50% of patients having normal and 54.50% having raised uric acid levels. High SDAI scores are more prevalent in raised uric acid cases (36.40%), whereas low SDAI scores are seen only in normal uric acid levels (35.80%). Remission is rare, with 3.80% in normal and 9.10% in raised uric acid levels. The chi-square test P-value of 0.104 indicates no significant association between **SDAI** and **Uric acid level**.

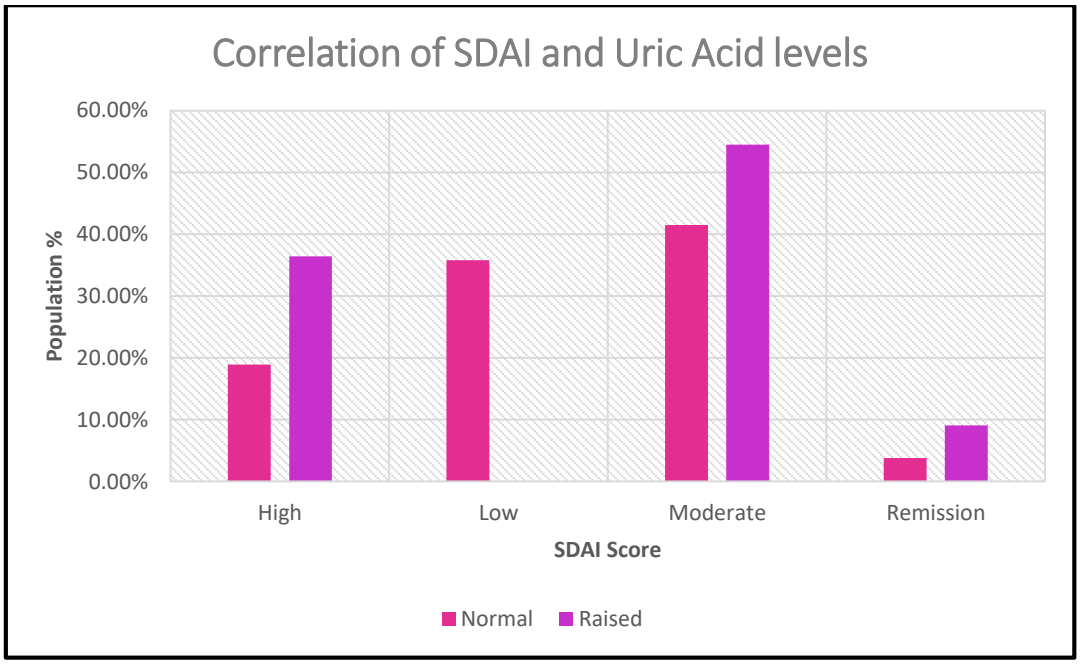

Fig. 25: *Double bar graph depicting SDAI scores for Rheumatoid Arthritis with Serum Uric Acid levels*

Table 22: Correlation of DAS28 scores for Rheumatoid Arthritis with Serum Uric Acid levels

DAS28	Normal N (%)	Raised N (%)	Total N (%)
High (>5.1)	9 (17.00%)	4 (36.40%)	13 (20.30%)
Moderate (3.2-5.1)	26 (49.10%)	6 (54.50%)	32 (50.00%)
Low (2.6-3.2)	10 (18.90%)	0 (0.00%)	10 (15.60%)
Remission (<2.6)	8 (15.10%)	1 (9.10%)	9 (14.10%)
Total	**53 (100.00%)**	**11 (100.00%)**	**64 (100.00%)**

Chi square test, P value- 0.256

The distribution shows that 49.10% of patients with normal uric acid levels and 54.50% with raised uric acid levels have moderate DAS28 scores. High DAS28 scores are seen in 17.00% of patients with normal uric acid levels and 36.40% with raised levels. Low DAS28 scores are present in 18.90% of normal uric acid cases and none with raised levels, while remission is observed in 15.10% and 9.10% respectively. The chi-square test P-value of 0.256 indicates no significant association between **DAS28** and **Uric acid level**.

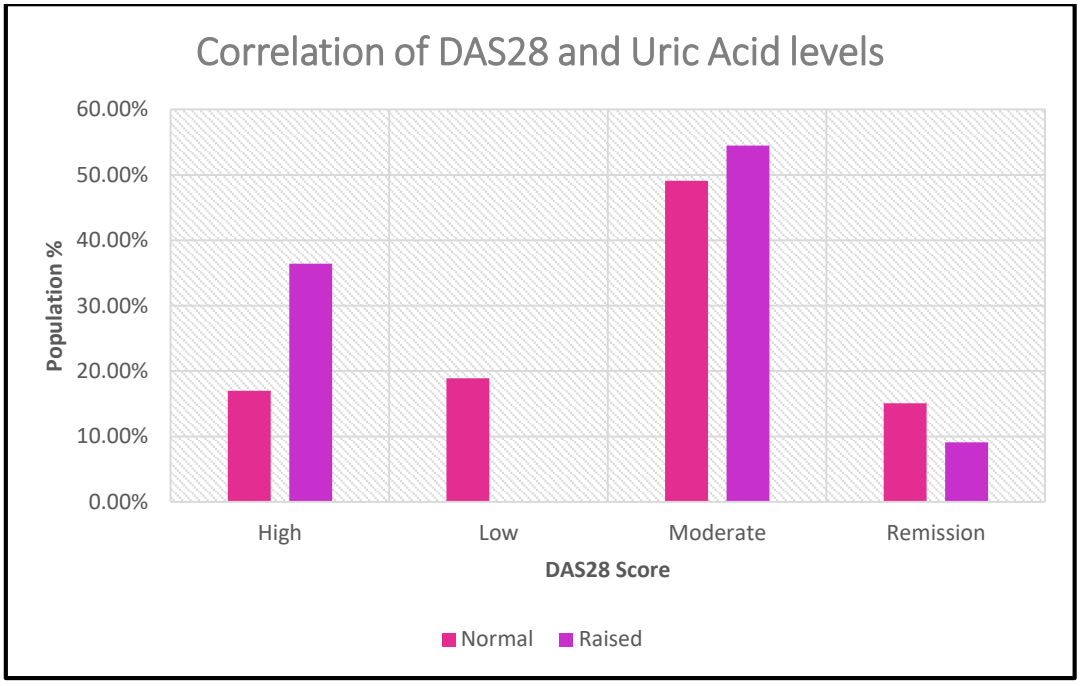

Fig. 26: *Double bar graph depicting correlation of DAS28 scores for Rheumatoid Arthritis with Serum Uric Acid levels*

Table 23: Correlation of Overall Disease Activity with Uric Acid Levels

Disease Severity	Uric Acid Normal N (%)	Uric Acid Raised N (%)	Total N (%)
High	7 (14.90%)	3 (30.00%)	10 (17.50%)
Low	11 (23.40%)	0 (0.00%)	11 (19.30%)
Moderate	23 (48.90%)	6 (60.00%)	29 (50.90%)
Remission	6 (12.80%)	1 (10.00%)	7 (12.30%)

Chi square test, P value- 0.311

As seen in the above table, disease severity and uric acid levels, it is observed that the majority of patients with moderate disease severity have normal uric acid levels (48.90%) and raised uric acid levels (60.00%), indicating a higher prevalence of moderate disease severity among both uric acid groups. Patients with high disease severity exhibit a notable proportion of raised uric acid levels (30.00%) compared to

normal levels (14.90%). Conversely, patients with low disease severity are more likely to have normal uric acid levels (23.40%) with none exhibiting raised levels (0.00%). Among patients in remission, a majority have normal uric acid levels (12.80%) compared to those with raised levels (10.00%). The chi-square test indicates that there is no statistically significant association between disease severity and uric acid levels (P value = 0.311).

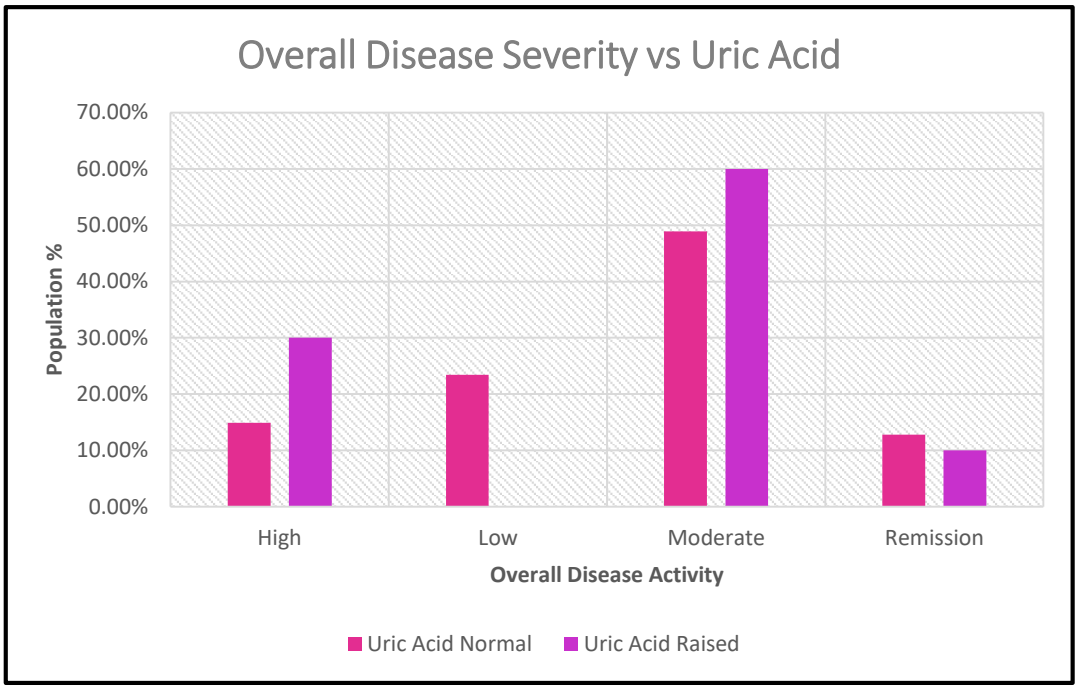

Fig. 27: *Double bar graph representing overall disease severity correlation with Uric Acid levels*

Table 24: Correlation of Rheumatoid Factor and Uric Acid Levels

Rheumatoid Factor	Uric Acid Normal N (%)	Uric Acid Raised N (%)	Total N (%)
Negative	13 (27.70%)	1 (10.00%)	14 (24.60%)
Positive	34 (72.30%)	9 (90.00%)	43 (75.40%)
Total	47 (100.00%)	10 (100.00%)	57 (100.00%)

Chi square test, P value- 0.239

As seen in the above table, 27.7% of individuals with normal uric acid levels are negative for rheumatoid factor, compared to 10.0% of those with raised uric acid levels. Among those who tested positive for rheumatoid factor, 72.3% have normal uric acid levels, while 90.0% have raised uric acid levels. The chi-square test yields a P value of 0.239, indicating no significant association between rheumatoid factor status and uric acid levels.

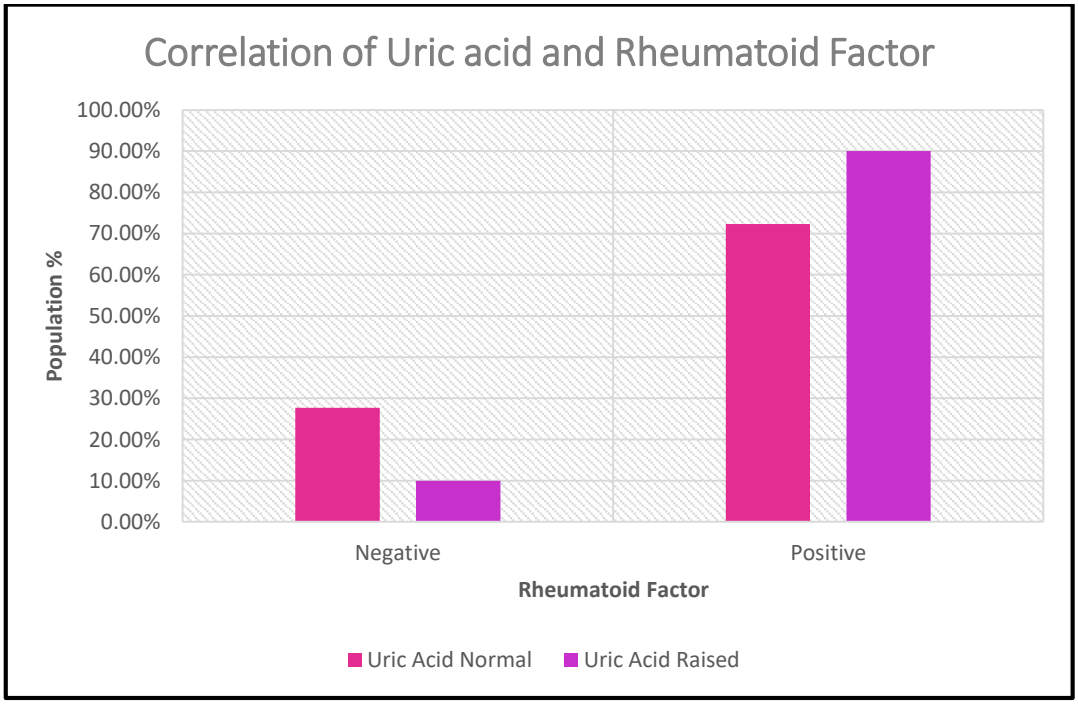

Fig. 28: *Double bar graph representing correlation of Rheumatoid Factor and Uric Acid*

Table 25: Correlation of ACCP Antibody and Uric Acid Levels

ACCP Antibody	Uric Acid Normal N (%)	Uric Acid Raised N (%)	Total N (%)
Negative	15 (31.90%)	5 (50.00%)	20 (35.10%)
Positive	32 (68.10%)	5 (50.00%)	37 (64.90%)
Total	47 (100.00%)	10 (100.00%)	57 (100.00%)

Chi square test, P value- 0.277

As seen in the above table, 31.9% of individuals with normal uric acid levels are negative for ACCP antibody, compared to 50.0% of those with raised uric acid levels. Among those who tested positive for ACCP antibody, 68.1% have normal uric acid levels, while 50.0% have raised uric acid levels. The chi-square test yields a P value of 0.277, indicating no significant association between ACCP antibody status and uric acid levels.

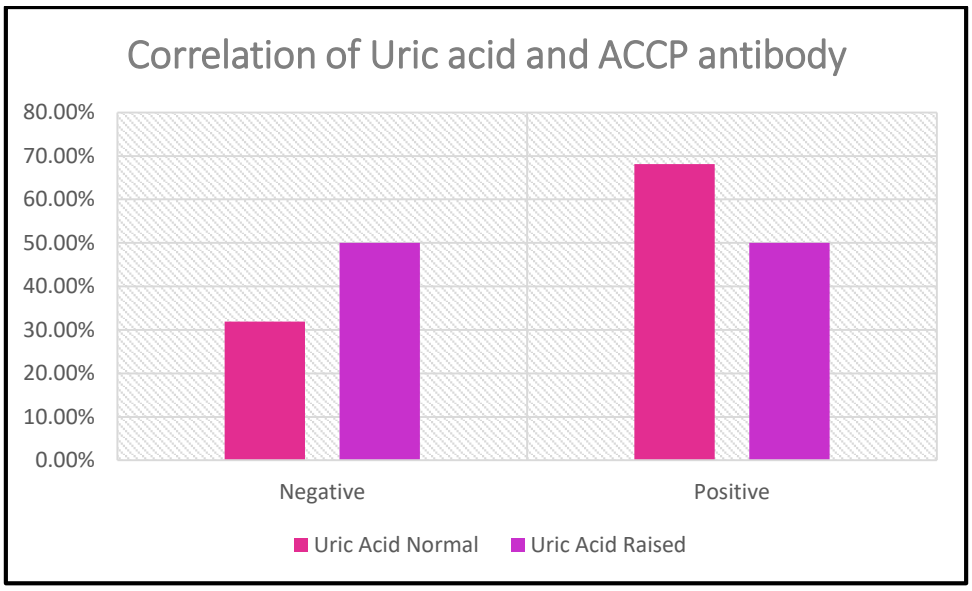

Fig. 29: *Double bar graph representing correlation of ACCP Antibody and Uric Acid*

Table 26: Multivariate analysis of variables with Serum Uric Acid amongst study population

Variable	Category	Normal Uric Acid N (%)	Raised Uric Acid N (%)	p-value
Age group	21 to 30	8 (15.10%)	2 (18.20%)	0.947
	31 to 40	11 (20.80%)	2 (18.20%)	
	41 to 50	11 (20.80%)	3 (27.30%)	
	> 50	23 (43.40%)	4 (36.40%)	
Gender	Female	44 (83.00%)	11 (100.00%)	0.14
	Male	9 (17.00%)	0 (0.00%)	
BMI	Normal	39 (73.60%)	9 (81.80%)	0.633
	Overweight	10 (18.90%)	2 (18.20%)	
	Underweight	4 (7.50%)	0 (0.00%)	
Creatinine	Normal	49 (92.50%)	7 (63.60%)	**0.009****
	Raised	4 (7.50%)	4 (36.40%)	
CDAI	High	8 (15.10%)	5 (45.50%)	0.146
	Low	16 (30.20%)	2 (18.20%)	
	Moderate	18 (34.00%)	3 (27.30%)	
	Remission	11 (20.80%)	1 (9.10%)	
SDAI	High	10 (18.90%)	4 (36.40%)	0.106
	Low	19 (35.80%)	0 (0.00%)	
	Moderate	22 (41.50%)	6 (54.50%)	
	Remission	2 (3.80%)	1 (9.10%)	
DAS28	High	9 (17.00%)	4 (36.40%)	0.256
	Low	10 (18.90%)	0 (0.00%)	
	Moderate	26 (49.10%)	6 (54.50%)	
	Remission	8 (15.10%)	1 (9.10%)	

The table compares the distribution of normal and raised uric acid levels across different categories (age group, sex, BMI, creatinine, CDAI, SDAI, DAS28) and their respective p-values to assess statistical significance. It shows that raised uric acid levels are slightly more common in older age groups (>50 years: 36.40%) and exclusively in females (100%). Normal BMI patients predominantly have normal uric acid levels (73.60%), with overweight and underweight categories showing less variation. Elevated creatinine levels are significantly associated with raised uric acid (**p = 0.009**), indicating a link between kidney function and uric acid levels. However, no significant associations are found between uric acid levels and age group, gender, BMI, CDAI, SDAI, and DAS28 categories ($p > 0.05$).

DISCUSSION

The degenerative condition known as rheumatoid arthritis (RA) affects the joints over time. In RA patients, disease activity serves as the gold standard for guiding different therapy approaches. Other objectives include improving quality of life, as measured by HAQ, and reducing radiographic erosions. Previous research has looked into how different variables affect the course of disease. The combination of hyperuricemia with RA has long been believed to be exceedingly uncommon, but several investigations have revealed that it can occur in as many as 5% of RA patients, challenging the notion that the two are mutually incompatible.[2] Furthermore, in relation to the general population, hyperuricemia has been linked to a roughly two-fold higher risk of cardiovascular disease and mortality,[137,138] indicating that serum urate concentrations may have predictive significance for individuals with RA. Serum uric acid (UA) concentrations have a substantial correlation with renal failure in individuals with RA,[250] which emphasizes the usefulness of serum UA as a biomarker for early renal impairment diagnosis. It is uncertain, therefore, how gout and/or hyperuricemia may affect the course of the RA illness, the choice of medications, and the long-term results. Therefore, the purpose of our research is to determine the frequency of hyperuricemia in Indian patients with RA and evaluate its correlation with the degree of disease activity.

The present cross-sectional study was conducted to evaluate the prevalence of hyperuricemia in a subset of Indian Rheumatoid arthritis patients while assessing correlation of their uric acid levels and other baseline characteristics with disease activity scores.

The study included 64 participants diagnosed with RA using the 2010 American College of Rheumatology/EULAR Classification for Rheumatoid Arthritis. This study was comparable to a study done by Karthiga Murugan et al.[9] in terms of number of patients in a single center study, in which serum uric acid levels of recently diagnosed RA patients were correlated with disease activity.

Female predominance was present among the 64 participants, comprising 85.9% of the total population. Males made up 14.1% of the total population. The age distribution showed that majority of the patients were over 50 years old, representing 42.2% of the sample. This was followed by 21.9% of participants in the age group of 41 to 50 years, while age groups of 31 to 40 and 21 to 30 constituted 20.3% and 15.6% respectively.

The present study compared the distribution of normal and raised uric acid levels across different categories (age group, sex, BMI, creatinine, CDAI, SDAI, DAS28) and their respective p-values to assess statistical significance. It showed that raised uric acid levels are slightly more common in older age groups (>50 years: 36.40%) and exclusively in females (100%). Normal BMI patients predominantly had normal uric acid levels (73.60%), with overweight and underweight categories showing less variation. Elevated creatinine levels were significantly associated with raised uric acid ($p = 0.009$), indicating a potential link between kidney function and uric acid levels. However, no significant

associations are found between uric acid levels and age group, gender, BMI, CDAI, SDAI, and DAS28 categories ($p > 0.05$).

Uric Acid Levels and Disease Activity

The majority of participants (82.8%) had normal uric acid levels, and 17.2% had raised levels. High disease activity was more common in individuals with normal uric acid levels (69.2%), and there was no significant association between uric acid levels and disease activity (P-value = 0.221). This is consistent with research by Chiou et al. (2020),[2] which found that while hyperuricemia may exist alongside RA, it does not significantly correlate with RA disease activity. Nonetheless, studies like that of Nada et al. (2021) [3] have highlighted that elevated uric acid levels could be a marker of inflammation and may contribute to comorbidities in RA patients.

DAS28 Scores and Disease Activity

A significant portion of participants (70.3%) had moderate DAS28 scores, with significant associations found between DAS28 scores and disease activity (P-value = 0.001). High DAS28 scores were exclusively associated with high disease severity (100%), while moderate DAS28 scores correlated strongly with moderate disease activity (93.5%). These findings are in line with studies by Aletaha et al. (2005), which emphasize the DAS28 score as a robust measure for assessing RA disease activity and predicting treatment outcomes. Additionally, Smolen et al. (2016) [242] demonstrated that DAS28 is a reliable indicator for categorizing disease activity levels, guiding therapeutic decisions, and monitoring disease progression.

CDAI Scores and Disease Activity

CDAI scores showed significant associations with disease activity (P-value = 0.001). High disease activity was predominantly seen in the high CDAI group (92.3%). This is consistent with Aletaha and Smolen (2005) [243] who highlighted CDAI as a practical and effective measure for assessing RA disease activity.

SDAI Scores and Disease Activity

SDAI scores were also significantly associated with disease activity (P-value = 0.001). High disease activity was exclusively seen in the high SDAI group (100%). Aletaha and Smolen (2005) [243] confirmed that SDAI is a robust tool for evaluating disease activity in RA, providing a comprehensive assessment by incorporating clinical and laboratory data.

RA Factor and ACCP Antibody Levels and Disease Activity

Neither RA Factor nor ACCP antibody levels were significantly associated with disease activity (chi-square P-value of 0.135). Most cases were positive for RA Factor/ACCP antibodies (76.6%). Other studies, such as Serdaroğlu et al. (2010) [244] have shown that while RA Factor and ACCP antibodies are useful for diagnosis, their presence does not necessarily correlate with disease severity.

Age Groups and Uric Acid

Most patients fell in the age group of more than 50 years, with 43.40% having normal uric acid levels and 36.40% raised. Age groups 21 to 30, 31 to 40, and 41 to 50 years were fairly evenly distributed between normal and raised uric acid levels. The chi-square test P-value

of 0.947 indicates no significant association between age group and Uric acid level. This echoes the findings of a study by Nilsson et al. (2021) [245] which suggested that although hyperuricemia occurring in advanced age, especially for women, should be considered a risk factor for worse disease outcome— there is no significant correlation between serum uric acid levels and age groups. Estrogen in pre-menopausal women also contributes to increased uric clearance, which may act as a confounding factor.

Gender and Uric Acid

A study by Kundu et al. (2023) [10] studying the prevalence of hyperuricemia in RA patients and associated factors showed no significant association between gender and uric acid levels. However, most of the hyperuricemic patients were women. This can be explained by the fact that RA shows a significant preponderance towards the female gender. In our study, 80.00% of females had normal uric acid levels and 20.00% raised, while males had 16.98% of normal and none of the raised uric acid cases. The chi-square test P-value of 0.14 indicates no significant association between gender and Uric acid level. Of the 11 participants with raised serum uric acid levels, all members were female. All 9 males included in the study had normal uric acid levels. Traditionally studies show that males have higher serum uric acid levels. However, peri and post-menopausal women, which was the bulk of our sample size may have increased uric acid levels due to estrogen-mediated excretion of uric acid via urine. [10]

BMI and Uric Acid

A study by Bilecik et al. (2014) [247] investigating metabolic syndrome and insulin resistance in RA patients as compared to a control group found no significant differences with regard to age group, BMI and waist hip ratio in cases and controls. There was also no significant difference between serum uric acid levels in the two groups. With reference to the present study, 81.8% of patients having raised uric levels had normal BMI while overweight patients represented 18.90% of normal and 18.20% of raised uric acid levels respectively. None of the underweight patients had raised uric acid levels. The chi-square test P-value of 0.633 showed no significant association between BMI and uric acid levels. Similar to the abovementioned study, no significant association was found between Waist-Hip ratio and uric acid levels with a P-value of 0.994.

VAS and Uric Acid

In the present study, 53.2% of individuals with normal uric acid levels had a VAS score indicating mild levels of pain, compared to 40.0% of those with raised uric acid levels. For VAS scores indicating moderate pain levels, 38.3% of individuals with normal uric acid levels fell into this range, while 40.0% of individuals with raised uric acid levels had moderate pain levels. For VAS scores indicative of severe pain, 8.5% of individuals with normal uric acid levels fell into this category compared to 20.0% of those with raised uric acid levels. The P value of 0.516 indicated that there was no significant association between VAS Scores and uric acid levels. Similarly, a study by Alkhudir et al. (2023) [248] explored the association between serum uric acid levels and disease activity levels in RA patients. This study also found no significant relationship between uric acid levels and VAS scores

(P= 0.184). This may be explained by differences in treatment regimens and the subjective nature of the VAS Score.

RF and Uric Acid

This study showed that compared to 10.0% of people with elevated uric acid levels, 27.7% of those with normal uric acid levels tested negative for rheumatoid factor. Ninety-one percent of the individuals who tested positive for rheumatoid factor had elevated uric acid levels, whereas 72.3% of them had normal levels. The results of the chi-square test showed that there is no significant correlation between uric acid levels and rheumatoid factor status (P = 0.239). Kundu et al. (2023) [10] also found that serological status of RA patients did not have a significant association with UA levels. On the contrary, Nada et al. [3] found a significant correlation between patients with hyperuricemia and RF positivity. Since levels of RF fluctuate slowly, it has been considered difficult to track disease progression using RF, hence UA levels have been studied as a potential substitute biomarker. However, the present study showed no significant correlation between UA levels and RF positivity.

Overall, in the present study significant associations are noted for VAS, DAS28, CDAI, and SDAI (P < 0.001), indicating these factors are strongly linked to disease activity levels. Females constitute the majority with 80.00% having normal uric acid levels and 20.00% raised, while males represent 16.98% of normal and none of the raised uric acid cases. The chi-square test P-value of 0.14 indicates no significant association between gender and Uric acid level. Most patients with normal BMI have normal (73.60%) and raised (81.80%) uric acid levels. Overweight patients are 18.90% of normal and 18.20% of raised uric acid levels, while underweight patients are 7.50% of normal uric acid cases and

none with raised levels. The chi-square test P-value of 0.633 indicates no significant association between BMI and Uric acid level. Most patients with normal creatinine levels have normal (92.50%) and raised (63.60%) uric acid levels. Raised creatinine levels are seen in 7.50% of normal and 36.40% of raised uric acid cases. The chi-square test P-value of 0.009 indicates a significant association between creatinine and Uric acid level.

Clinical Disease Activity Index (CDAI) and Uric Acid Levels

In this study, patients with high CDAI scores were more likely to have raised uric acid levels (45.50%), whereas those with normal uric acid levels were mostly in the moderate CDAI category (34.00%). Low CDAI scores were seen in 30.20% of normal and 18.20% of raised uric acid cases. Remission was observed in 20.80% of normal and 9.10% of raised uric acid levels. The chi-square test P-value of 0.146 indicates no significant association between CDAI and uric acid levels.

These findings are consistent with previous research which suggests a potential but non-significant association between hyperuricemia and increased disease activity in rheumatoid arthritis (RA) patients (Choe et al., 2014; Lee et al., 2016). Choe et al. (2014) [251] found that elevated serum uric acid was associated with higher CDAI scores, but the association did not reach statistical significance. Similarly, Lee et al. (2016) [252] reported a trend towards higher disease activity in RA patients with hyperuricemia, although the relationship was not statistically significant.

Simplified Disease Activity Index (SDAI) and Uric Acid Levels

Moderate SDAI scores were the most common, with 41.50% of patients having normal and 54.50% having raised uric acid levels. High SDAI scores were more prevalent in raised uric acid cases (36.40%), whereas low SDAI scores were seen only in normal uric acid levels (35.80%). Remission was rare, with 3.80% in normal and 9.10% in raised uric acid levels. The chi-square test P-value of 0.104 indicates no significant association between SDAI and uric acid levels.

These results align with the work of Tsuruta et al. (2017), [254] who observed a trend where higher uric acid levels were associated with increased disease activity as measured by SDAI, but without a significant correlation. Another study by Karadag et al. (2018) [255] reported similar findings, suggesting that although there appears to be a relationship between uric acid levels and SDAI, the association is not statistically significant.

Disease Activity Score-28 (DAS28) and Uric Acid Levels

The distribution showed that 49.10% of patients with normal uric acid levels and 54.50% with raised uric acid levels had moderate DAS28 scores. High DAS28 scores were seen in 17.00% of patients with normal uric acid levels and 36.40% with raised levels. Low DAS28 scores were present in 18.90% of normal uric acid cases and none with raised levels, while remission was observed in 15.10% and 9.10% respectively. The chi-square test P-value of 0.256 indicates no significant association between DAS28 and uric acid levels.

This observation concurs with the findings of Choe et al. (2014), [251] who noted that reduction in uric acid levels did not translate to lower disease activity scores, signifying

that uric acid may not be a reliable marker in systemic inflammatory responses of RA. Furthermore, studies by Lee et al. (2016) [252] and Jin et al. (2018) [253] corroborate the lack of a significant relationship between DAS28 scores and serum uric acid levels in RA patients.

Overall Disease Activity and Uric Acid

The correlation between uric acid levels and disease activity in RA is a scarcely studied area in the disease progression and outcomes of RA. Previous studies have attempted to explain the relationship between the two, with a wide range of findings. A study by Alkhudir et al. (2023) [248] found that higher UA levels were associated with overall lower disease activity. This was attributed to difference in steroid usage in low and high disease activity groups as prednisolone causes increased clearance of UA. Additionally, patients with high disease activity would have active inflammatory changes in the synovium. Changes in the properties of synovial fluid may result in increased solubility of uric acid leading to its depletion.

Conversely, a study in Egypt by Nada et al. [3] demonstrated hyperuricemia in RA patients with active disease, suggesting that UA levels may indicate severity of joint inflammation. It was also found that steroid usage was positively associated with hyperuricemia in the study population. Frequent use of NSAIDs and GCs in RA patients may mask the clinical manifestations of hyperuricemia in these patients, indicating that RA and gout may overlap more often than previously reported.

A study by Garg et al. (2019) [249] compared uric acid levels in RA patients with healthy controls and found no significant difference in UA levels between the two groups. The results were explained by the enhanced use of uric acid to capture the free radicals generated in rheumatoid arthritis.

Overall, in the present study there was a larger frequency of moderate disease severity across both uric acid groups, as evidenced by the majority of patients with moderate disease severity having normal uric acid levels (48.90%) and elevated uric acid levels (60.00%). When compared to normal levels (14.90%), patients with high disease severity had a significant percentage of elevated uric acid levels (30.00%). On the other hand, individuals with mild illness severity were more likely to have normal uric acid levels (23.40%), with no patient showing elevated levels (0.00%). Compared to patients with elevated levels (10.00%), the majority of patients in remission (12.80%) had normal levels of uric acid. According to the chi-square test, there was no statistically significant correlation (P value = 0.311) between the severity of the disease and uric acid levels, although a general positive trend was seen for the same.

The inclusion of the patients' RF and Anti-CCP status in addition to disease activity ratings for comparison with SUA was one of our study's strongest points. Comprehensive analysis was done using various disease activity scales like CDAI, SDAI and DAS28. The study draws comparisons with previous research highlighting differences and similarities in associations between several factors RA and serum UA levels. This contextualizes the findings and underscores their significance.

The study's sample size is small and not representative of the broader population; hence the findings may not be generalizable. Specific demographic or regional biases could affect the applicability of the result**s.** The lower frequency of hyperuricaemia in our group is predicted, though, given that SUA levels are lower in women and in those under 50 years of age, while RA is known to be more common in women.

Although our study did not find a statistically significant association between hyperuricemia and disease activity in RA, the generally positive trend in correlation suggests that further research is needed to ascertain the role of UA as an inflammatory biomarker to predict and monitor RA disease activity. Further research is required to definitively determine whether uric acid is merely a biomarker or if it actually plays a pathophysiological role in systemic inflammation. Should the latter be the case, uric acid could become one of the primary indicators of the severity of the disease in RA, which could help guide therapeutic decision making and disease activity monitoring by physicians.

SUMMARY

- **Age**: Patients over 50 years old had higher disease activity. Most patients fell in this age group, with 43.40% having normal uric acid levels and 36.40% having raised levels. Age groups 21 to 50 years were fairly evenly distributed between normal and raised serum uric acid levels, and there was no significant association between age group and uric acid level (P = 0.947).
- **Gender**: Females were predominant across all disease activity categories. Among females, 80.00% had normal uric acid levels and 20.00% had raised levels, while males represented 16.98% of normal and none of the raised uric acid cases. There was no significant association between gender and uric acid level (P = 0.14).
- **BMI**: Patients with normal BMI mostly fell into the moderate disease activity category. The majority of patients with normal BMI had normal (73.60%) uric acid while 81.8% of those with raised uric acid were of normal BMI. Overweight patients were 18.90% of normal and 18.20% of raised serum uric acid levels, while underweight patients were 7.50% of normal uric acid cases and none had raised levels. There was no significant association between BMI and serum uric acid level (P = 0.633). Additionally, the t test P-value of 0.994 indicated no significant association between Waist-Hip Ratio and serum uric acid levels.
- **RF/ACCP Antibodies**: The majority of participants tested positive for both RF and ACCP antibodies. Nearly one-third of individuals with normal uric acid levels are negative for rheumatoid factor, compared to one-tenth of those with raised uric acid levels. The chi-square test yields a P value of 0.239, indicating no significant association between rheumatoid factor status and uric acid levels.

- **VAS, DAS28, CDAI, SDAI**: These factors were strongly linked to disease activity levels, with significant associations ($P < 0.001$). However, no significant associations were found between elevated serum uric acid levels and higher disease activity levels.
- **Serum Creatinine**: Out of the 64 included participants, raised creatinine levels are seen in 7.50% of normal uric acid and 36.40% of raised uric acid cases. Most patients with normal creatinine levels have normal (92.50%) uric acid levels. There is a significant association between creatinine and uric acid level ($P = 0.009$).
- Overall, raised uric acid levels are slightly more common in older age groups and exclusively in females. Normal BMI patients predominantly have normal uric acid levels. Elevated creatinine levels are significantly associated with raised uric acid ($P = 0.009$), indicating a potential link between kidney function and uric acid levels. No significant associations are found between uric acid levels and age group, gender, BMI, CDAI, SDAI, and DAS28 categories ($P > 0.05$).

CONCLUSION

1. There was no significant association between age, gender, BMI and serum uric acid levels.
2. Elevated creatinine levels were significantly associated with raised uric acid levels, indicating a link between kidney function and uric acid levels.
3. Overall uric acid levels were not significantly associated with disease activity measures such as CDAI, SDAI, or DAS28, contradicting previous research indicating that hyperuricemia may have significant long-term effects on disease activity.
4. Further, an inverse relationship of serum uric acid and disease activity was not observed, challenging the notion that uric acid may play a protective role in severity of disease activity in RA as observed in earlier studies.
5. As such, further research beyond the scope of this study needs to be undertaken to establish the exact mechanisms and effects of uric acid in Rheumatoid Arthritis severity as its role is still uncertain.

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ANNEXURES

ANNEXURE I: CONSENT FORM

KAHERs JNMC BELAGAVI

INFORMED CONSENT FORM

You have been requested to participate in this study as you fit into the laid-out criteria for a study 'subject'/ participant.

Your participation in study is voluntary. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge. Your decision whether or not to participate in the study will not affect your treatment in any form. If you decide to participate you are free to withdraw at any time.

TITLE OF THE STUDY:

"CORRELATION BETWEEN SERUM URIC ACID & DISEASE ACTIVITY IN PATIENTS OF RHEUMATOID ARTHRITIS"

Name of the Student/Principal Investigator: _____

Name of the Guide/Co-investigator: _____

PURPOSE OF THE STUDY: To detect the prevalence of hyperuricemia in Indian Rheumatoid Arthritis patients and assess correlation between uric acid levels and disease activity scores.

PROCEDURES INVOLVED: If you agree to enroll yourself in my study, you will be asked to fill a set of self-assessment questionnaires, following which a relevant general examination will be done including recording of vitals and body measurements.

Examination of your joints will be done to check for pain and swelling.

Then you will be subjected to a few blood investigations, namely Liver function tests, Serum Uric Acid, serum creatinine, lipid profile, fasting blood sugar, complete hemogram, hsCRP.

RISKS AND BENEFITS: There are no potential risks involved in this study.

BENEFITS OF TAKING PART IN THIS RESEARCH: By taking part in this study, the disease activity correlation with your serum uric acid level can be assessed. Additionally, hyperuricemia can be used as a biomarker for early detection of renal impairment and risk of cardiovascular disease.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM THE STUDY: Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

ALTERNATIVES: Your decision regarding participation in study will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You would simply be excluded from the study if you wish to, and all your details shall be kept confidential and you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY: All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If, however

during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent. The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

- In emergency to protect your rights AND welfare.
- If required by law.

AUTHORIZATION TO PUBLISH RESULT: The results of the study may be used to publish an article. When the results of research published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION: No additional costs shall be incurred upon you for the purpose of this study. It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

COMPENSATION: In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, or you will be given information about where to receive medical care. However, no reimbursement, compensation or free medical care will be given.

QUESTIONS/CONTACT DETAILS: You shall be free to contact the principal investigator on the given mobile number/email ID anytime during the study period for any clarification or help as you may desire for.

CONSENT FORM

I, voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me, this consent form and have had all the questions answered.

……..……..	…..……
Name of the Participant	Signature of the participant or Left-Hand Thumb impression
……	……
Name of Investigator	Signature of investigator
…….	……..
Name of Witness	Signature of Witness or Left-Hand Thumb impression

Date:

Place:

ANNEXURE II

PROFORMA

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION:

ON WHICH TREATMENT FOR RA:

GENERAL PHYSICAL EXAMINATION:

Vitals-

Pulse Rate:

Blood Pressure:

Anthropometry-

Waist-Hip Ratio:

BMI:

Specific Testing for DAS28/CDAI/SDAI:

1. **Tender Joint Count:**
2. **Swollen Joint Count:**
3. **Patient Global disease Activity**
4. **Visual Analogue Score**

INVESTIGATIONS

- **Complete hemogram**
- **Liver function tests**
- **RFT including Serum Uric Acid**
- **Serum hs C-reactive Protein**
- **Lipid Profile**
- **Fasting Blood Sugar**

Composite Scores:

1. **DAS28-**
2. **CDAI-**
3. **SDAI-**

Disease Activity Score-28 for Rheumatoid Arthritis with CRP (DAS28-CRP)

1. Tender joint count

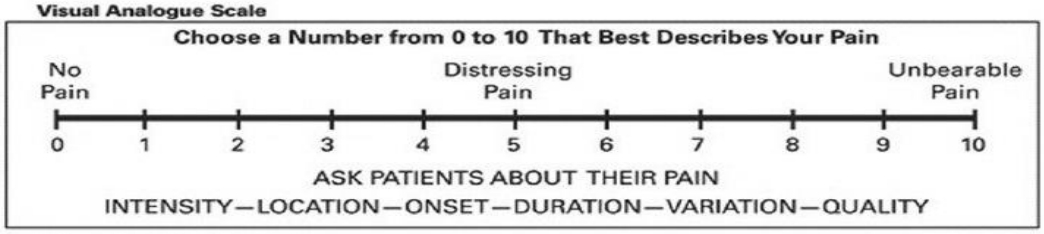
2. Swollen joint count

3. C-reactive protein (CRP)

4. Global health

As reported in cm on visual analogue scale –

0.0 - Very Well
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0 - Very Poor



Clinical Disease Activity Index (CDAI) for Rheumatoid Arthritis

1. Tender joint count
2. Swollen joint count

Ask the patient: Considering all the ways arthritis affects you, how well are you doing?

0.0 - Very well
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0 - Very poor

Per medical opinion: Considering all the ways arthritis affects the patient, how well are they doing?

0.0 - Very well
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0 - Very poor

Simplified Disease Activity Index (SDAI) for Rheumatoid Arthritis

1. **Tender joint count**
2. **Swollen joint count**
3. **C-reactive protein (CRP)**

Ask the patient: Considering all the ways arthritis affects you, how well are you doing?

0.0 - Very well

0.5

1.0

1.5

2.0

2.5

3.0

3.5

4.0

4.5

5.0

5.5

6.0

6.5

7.0

7.5

8.0

8.5

9.0

9.5

10.0 - Very poor

Per medical opinion: Considering all the ways arthritis affects the patient, how well are they doing?

0.0 - Very well

0.5

1.0

1.5

2.0

2.5

3.0

3.5

4.0

4.5

5.0

5.5

6.0

6.5

7.0

7.5

8.0

8.5

9.0

9.5

10.0 - Very poor

ANNEXURE: III

MASTER CHART KEY

RF – Rheumatoid Factor

ACCPA – Anti-cyclic Citrullinated Peptide Antibody

MTX – Methotrexate

HCQ – Hydroxychloroquine

LEF – Leflunomide

GC – Glucocorticoids

SSZ – Sulfasalazine

TOF – Tofacitinib

PR – Pulse Rate

BP – Blood Pressure

WHR – Waist-hip Ratio

BMI – Body Mass Index

TJC – Tender Joint Score

SJC – Swollen Joint Score

PaGDS – Patient Global Disease Score

PhGDS – Physician Global Disease Score

VAS – Visual Analogue Score

Hb – Haemoglobin

TC – Total Counts

AST – Aspartate Transaminase

ALT – Alanine Transaminase

SC – Serum Creatinine

SUA – Serum Uric Acid

T. Chol. – Total Cholesterol

TG – Triglycerides

LDL – Low Density Lipoprotein

HDL – High Density Lipoprotein

FBS – Fasting Blood Sugar

DAS28 – Disease Activity Score

CDAI – Clinical Disease Activity Index

SDAI – Simplified Disease Activity Index

ANNEXURE IV: MASTER CHART

Name	Case No.	Age	Sex	IP/OP	Address	Occupation	RF	ACCPA	Treatment	MTX	HCQ	LEF	GC	SSZ	TOF	PR	BP	WHR	BMI	TJC	SJC	PaGDS	PhGDS	VAS	Hb	TC	Platelet	AST	ALT	SC	SUA	hsCRP	T. Chol	TG	LDL
Saraswati Nezarekar	1	51	F	6595796	Chikkodi	Farmer	Positive	Negative	SC MTX 7.5/week	1	0	0	0	0	0	94	130/70	0.73	22.5	8	10	4	6	4	11.9	22	363	19	20	0.59	3.7	6.7+	164	161	73
Megha Kadam	2	42	F	10009187	Belagavi	Housewife	Positive	Positive	NSAIDs	0	0	0	0	0	0	84	130/100	0.92	25.2	12	16	8	7	8	10	23	469	407	78	0.83	5.8	80.3+	392	184	160
Nazreen Jahangirdar	3	38	F	6866827	Belagavi	Housewife	Positive	Positive	T. HCQ 300 OD	1	1	0	0	0	0	106	150/100	0.63	21.4	4	10	3	5	4	11.7	29	413	18	15	1.4	2.9	1.6-	152	104	76
Nanda Ashok	4	44	F	1098533	Kagal	Tailor	Positive	Positive	SC MTX 15/week, HCQ 200 BD	1	1	0	0	0	0	88	110/70	0.67	20.6	2	4	2	2	2	9.1	14	560	13	16	0.75	3.6	2.37-	126	56	67
Supriya Tadakod	5	35	F	7066044	Belagavi	Housewife	Positive	Negative	T. MTX 5 2-0-0	1	0	0	0	0	0	92	120/80	0.78	22.8	5	3	1	3	1	12.7	6.5	225	31	16	0.6	8.6	2.2-	120	46	86
Vanita Vernekar	6	53	F	7010053	Belagavi	Farmer	Negative	Positive	NSAIDs	0	0	0	0	0	0	76	140/90	0.69	23.9	8	10	7	7	6	11.2	18	453	22	25	1.05	6	352.7+	184	101	68
Savitri Badiger	7	53	F	7147622	Bijapur	Housewife	Positive	Negative	T. SULFASALAZINE ER 500 OD	0	0	0	0	1	0	86	130/80	0.63	20.7	4	6	3	3	5	12.6	9.3	292	37	52	0.56	3.6	4.9-	162	110	86
Shahbanu Sayyed	8	52	F	7194467	Mumbai	Business	Negative	Positive	T. MTX 10 OD, T. HCQ 300 OD	1	1	0	0	0	0	82	160/80	0.88	25.6	9	4	3.5	6	5	11.7	4.4	160	21	20	0.72	10.6	4.8-	104	86	44
Ujwala Kamble	9	23	F	1167516	Belagavi	Housewife	Positive	Negative	SC MTX 15/week, HCQ 200 BD	1	1	0	0	0	0	92	126/80	0.7	21.6	0	2	1	0	2	11.8	11	325	50	28	0.37	1.6	85+	326	168	186
Parvati Avubayagol	10	50	F	933828	Gokak	Teacher	Positive	Negative	T. MTX 10 OD	1	0	0	0	0	0	70	100/80	0.58	19.6	2	1	3	1	0	7.3	12	548	10	23	0.6	3.2	2.62-	282	121	84
Usha Kolkar	11	62	F	10004695	Belagavi	Housewife	Positive	Positive	NSAIDs	1	0	0	0	0	0	126	100/70	0.91	28.3	14	12	9	8	10	9	13	160	18	12	3.19	16.8	139+	66	88	24
Shafiya Mohammed	12	40	F	6529481	Belagavi	Teacher	Positive	Negative	SC MTX 15/week, HCQ 300 OD	1	1	0	0	0	0	76	110/80	0.77	22.4	5	4	3	5	2	11.1	5	227	49	22	0.65	6.8	1.82-	96	77	42
Neelamma Baddi	13	38	F	6990483	Raibag	Farmer	Negative	Positive	NSAIDs	1	1	0	0	0	0	106	130/90	0.68	20.8	8	4	6	4	8	11	14	373	13	10	0.55	6.6	24+	98	64	42
Aditi Lodh	14	43	F	3608004	Belagavi	Business	Positive	Positive	NSAIDs	0	0	0	0	0	0	82	140/70	0.58	19.7	4	6	2	2	2	11.8	6.4	292	21	24	0.63	3.8	6.8+	108	66	84
Usha Murugmath	15	56	F	6659171	Hukkeri	Housewife	Positive	Negative	NSAIDs	0	0	0	0	0	0	76	110/80	0.76	23.2	6	6	3	5	5	9.6	15	118	68	46	1.1	16.2	7.4+	126	88	40
Shridevi Sharamannavar	16	29	F	4104276	Belagavi	Student	Positive	Negative	T MTX 5 OD, T HCQ 200 OD	1	1	0	0	0	0	86	120/90	0.65	21.9	15	6	8	5	10	7.6	21	89	126	110	3.9	18.1	10.5+	365	121	112
Ashwini Kumar	17	46	M	6185923	Belagavi	Security	Negative	Positive	NSAIDs	0	0	0	0	0	0	104	150/100	0.89	27.6	18	20	8	8	10	17.6	5.6	230	16	18	0.9	2.8	3.86-	98	64	60
Padmavati Halingal	18	32	F	3484781	Belagavi	Housewife	Positive	Positive	T MTX 5 OD, T HCQ 200 BD	1	1	0	0	0	0	86	140/80	0.63	20.3	3	7	2	4	2	12.4	4.8	121	62	50	1.2	12.2	3.4-	226	184	108
Savitri Badskannavar	19	23	F	6449047	Raibag	Student	Negative	Positive	NSAIDs	0	0	0	0	0	0	93	100/70	0.6	15.6	4	8	6	4	7	10.2	8.5	211	24	26	0.53	2.6	3.64-	106	53	36
Sabeeya Shaikh	20	39	F	6993971	Belagavi	Tailor	Negative	Positive	T. LEFUMIDE 10 OD, T HCQ 200 OD	0	1	1	0	0	0	68	106/80	0.71	20.7	20	12	6	8	4	9.8	14	184	62	48	1	4.8	268.4+	384	220	126
Asra Herekar	21	44	F	7109835	Belagavi	Housewife	Positive	Negative	SC MTX 7.5/WEEK	1	0	0	0	0	0	94	130/70	0.74	22.2	4	2	2	2	2	12	6.2	206	14	11	0.63	23	1.24-	106	98	62
Nilamma Bidam	22	48	F	1699099	Gokak	Housewife	Positive	Positive	NSAIDs	0	0	0	0	0	0	74	160/80	0.57	18.9	7	9	3	7	5	11	4.4	122	92	88	2.2	14.6	36.5+	121	48	106
Shrinath Dhede	23	21	M	7159841	Belagavi	Student	Positive	Positive	NSAIDs	0	0	0	0	0	0	84	110/80	0.6	17.6	2	7	3	6	2	15.4	3.8	372	22	28	1.16	1.6	5.74-	128	82	66
Uzma Murshal	24	24	F	6265336	Belagavi	Student	Positive	Negative	SC MTX 7.5/WEEK, T HCQ 300 OD	1	1	0	0	0	0	98	100/70	0.66	21.5	18	6	7	4	8	8.8	10	121	66	70	0.93	9.2	4.81-	136	60	56
Balamma Bhuvi	25	72	F	174	Bailhongal	Housewife	Positive	Positive	MTX 17.5 per weel/ Lefno 20 mg OD/ Omnacortil 2.5 OD	1	0	1	1	0	0	86	120/90	0.57	20	1	1	2	2	2	11.3	13	278	23.15	28.7	0.99	7.03	12.59+	120	46	86
Anand Ekkal	26	54	M	2504	Kolhapur	Farmer	Negative	Positive	MTX 7.5 twice a week/Prednisolone 40D/Leflunomide 20OD	1	0	1	1	0	0	68	140/100	0.69	20.6	18	12	5	8	5	13.9	7.5	277	33.68	28.7	0.95	6.73	0.61 -	184	101	68
Mahadev Patil	27	61	M	2503	Pirarwadi	Farmer	Negative	Positive	MTX 10 per week/ HCQ 300 OD/ Omnacortil 5 OD	1	1	0	1	0	0	90	140/100	0.75	23.3	16	16	8	8	10	14.4	9.7	379	33.15	29.9	0.96	5.93	30.76+	162	110	86
Ashwini Damannavar	28	28	F	2209	Gokak	Teacher	Positive	Positive	MTX 15 per week/ HCQ 300 OD/ Omnacortil 2.5 OD	1	1	0	1	0	0	70	120/70	0.56	19.6	1	1	3	3	4	10	8.1	340	28.64	22.1	0.82	3.84	1.8 -	104	86	44
Nanda Dhamnekar	29	64	F	229	Belagavi	Housewife	Positive	Positive	MTX 25mg per week/ HCQ 200 OD/ Tofacitinib 11 OD/ Ivepred 2 OD	1	1	0	1	0	1	82	140/90	0.74	21.7	14	4	5	7	4	11.2	8.2	284	34.49	29.5	1.03	5.14	5.97 -	326	168	186
Savitri Samal	30	36	F	16	Sankeshwar	Housewife	Positive	Negative	MTX 15 per week/ HCQ 200 OD/ Tofacitinib 11 OD/ Omnacortil 5 OD	1	1	0	1	0	1	76	146/100	0.62	18.8	0	0	0	0	0	10.5	8	275	24.54	30.2	0.94	4.87	18.46+	282	121	84
Krutika Kamat	31	36	F	1005	Belagavi	Housewife	Positive	Positive	HCQ 300 OD/ MTX 20 OD	1	1	0	0	0	0	90	130/80	0.7	20.4	3	0	1	1	1	13.2	7.4	280	29.55	23.1	0.94	5.74	2.02 -	166	88	24
Anuradha Shinde	32	42	F	1050	Chandgad	Housewife	Positive	Positive	MTX 25mg per Week/ HCQ 200 OD/ Leflunomide20OD/Tofacitinib 11 OD	1	1	0	0	0	1	80	120/80	0.76	22.9	8	8	5	4	5	12.2	11	311	32.45	27.2	0.96	9.21	18.46+	96	77	42
Sonali Devidas	33	36	F	133	Goa	Housewife	Positive	Positive	MTX 15/ Tofacitinib 5/ HCQ 300	1	1	0	0	0	1	80	120/80	0.94	28.2	0	0	0	0	0	11.4	9.6	316	30.18	24.5	0.92	4.98	7.58 +	98	64	42
Raieshree Kulkarni	34	55	F	949	Belagavi	Housewife	Negative	Positive	MTX 17.5 per week/ HCQ 200 OD/ Tofacitinib 5 OD	1	1	0	0	0	1	76	160/100	0.9	26.9	0	0	0	0	0	10.7	10	432	26.78	31.5	0.95	6.91	4.73 -	108	66	84
Valutai Gijavane	35	52	F	111	Nipanni	Housewife	Positive	Positive	Leflunomide 20 OD/ Tofacitinib 11 OD/ Omnacortil 2.5 OD	0	0	1	1	0	1	92	150/90	0.76	21.1	4	2	4	4	3	11.4	8	250	20.27	26.2	0.93	6.51	8.96 +	116	74	68
Manjula Mane	36	38	F	2181	Raibag	Labour	Positive	Positive	HCQ 300 OD/ MTX 15 per week/ Omnacortil 2.5 OD/ Leflunomide 20 OD	1	1	1	1	0	0	86	110/80	0.84	25.3	6	3	4	4	3	11.2	12	362	24.76	30.5	0.89	4.09	21.19+	136	48	56
Krishna Inchal	37	59	M	153	Belagavi	Labour	Positive	Positive	HCQ 200 OD/ MTX 15 OD/ Leflunomide 10 OD, Ivepred 2mg OD	1	1	1	1	0	0	76	140/90	0.77	21.3	5	1	9	6	9	12.5	4.2	220	31.77	25.9	0.95	5.68	0.86 -	90	42	36
Yallubai Shahapurkar	38	65	F	87	Malagaw	Housewife	Positive	Negative	HCQ 200 OD/ MTX 17.5 per week	1	1	0	0	0	0	90	120/70	0.96	28	0	0	2	1	2	11.8	5.7	272	33.17	25.9	0.89	5.73	3.85 -	106	60	48
Sheetal Yenechavandikar	39	33	F	736	Gadhinglaj	Housewife	Positive	Positive	MTX 7.5 per week/ HCQ 200 OD/ Leflunomide 10 OD/ Omnacortil 2.5 OD	1	1	1	1	0	0	72	140/80	0.65	19.4	0	0	0	0	0	11.8	10	399	24.59	27.4	0.91	4.73	1.46 -	88	34	48
Vidya Sawant	40	38	F	2509	Aira	Farmer	Negative	Positive	MTX 15mg per week/ Leflunomide 10 OD/ Omnacortil 5 OD	1	0	1	1	0	0	90	130/70	0.88	27.1	18	5	6	6	4	8	8.1	476	14	18	0.94	7	8.36 +	142	74	66
Laxmibai Dhondiba Pol	41	70	F	30	Chikkodi	Housewife	Positive	Positive	MTX 7.5 per week/ HCQ 200 OD/ Leflunomide 20 OD/ Omnacortil 2.5 BD	1	1	1	1	0	0	100	150/100	0.83	25.2	0	3	1	2	1	11.6	15	275	25.03	29.8	0.93	6.64	5.27 -	190	86	76
Parvati Chincholi	42	64	F	195	Malinepur	Housewife	Positive	Positive	Sulfasalazine 1gm OD/ Omnacortil 2.5mg BD/ Tofacitinib 5 OD	0	0	0	1	1	1	110	100/80	0.78	23.2	1	1	3	3	4	13.7	4	235	32.51	27.5	0.96	5.83	12.4 +	144	84	68
Nandkumar Zende	43	61	M	51	Chandgad	Farmer	Positive	Negative	HCQ 200 OD/ Leflunomide 20 OD/ MTX 20 mg per week	1	1	1	0	0	0	92	120/70	0.58	24.4	4	4	4	2	2	11.3	9.4	266	22.47	29.7	1.13	6.09	2.39 -	205	96	80
Sukumula Patil	44	57	F	171	Sankeshwar	Housewife	Positive	Positive	MTX 10 per week/ Leflunomide 10 OD/ Omnacortil 2.5 OD	1	0	1	1	0	0	80	140/90	0.64	20.6	0	0	0	0	0	11.5	5.3	243	29.46	23.9	0.94	7.26	0.5 -	118	45	62
Renuka Chandargi	45	30	F	412	Mudgol	Farmer	Positive	Negative	MTX 15/wk / Omnacortil 2.5 OD	1	0	0	1	0	0	88	130/80	0.76	23.9	7	2	6	4	4	11.7	7.9	358	32	27	0.92	4.86	5.34 -	120	56	70
Sonali Patil	46	30	F	2237	Chandgad	Farmer	Positive	Positive	MTX 17.5/wk / HCQ 200 OD/ Omnacortil 5 OD	1	1	0	1	0	0	78	110/80	0.65	22.5	2	0	3	2	2	12.5	8.2	306	25	20.5	0.88	5.61	0.92 -	86	40	36
Prakash Jaganur	47	51	M	1129	Belagavi	Business	Positive	Negative	MTX 15 per week/ Leflunomide 10 OD/ Omnacortil 2.5 OD	1	0	1	1	0	0	86	130/90	0.55	19	0	0	0	0	0	12.6	8.4	285	31.54	28.6	0.98	5.99	4.73 -	102	60	48
Shobha Vandre	48	55	F	182	Chandgad	Housewife	Negative	Positive	MTX 20 per week/ Leflunomide 10 OD/ HCQ 200 OD	1	1	1	0	0	0	80	120/80	0.69	20.4	0	0	1	1	1	12.1	7.2	291	30.18	26.6	0.91	4.17	1.43 -	98	40	56
Shobha Yatale	49	50	F	46	Kadalgi	Farmer	Negative	Positive	MTX 25 per week/ HCQ 200 OD/ Omnacortil 2.5 OD/ Tofacitinib 5 OD	1	1	0	1	0	1	70	120/60	0.6	19.8	0	0	1	1	0	12.6	14	473	26.2	29.5	0.92	6.38	7.49 +	126	64	60
Vandana Kesarkar	50	45	F	851	Sankeshwar	Housewife	Positive	Positive	MTX 25 per week/ HCQ 200 OD/ Omnacortil 2.5 OD	1	1	0	1	0	0	92	110/70	0.66	21.1	0	0	5	3	3	11.1	8.2	170	29.46	34.6	0.93	5.14	1.43 -	110	46	54
Renuka Usalkar	51	45	F	1269	Kolhapur	Housewife	Positive	Positive	MTX 10 per week/ HCQ 300 OD/ Omnacortil 5 OD	1	1	0	1	0	0	86	120/80	0.7	23.8	4	2	5	4	4	10.2	12	188	26.45	21.9	0.83	4.65	0.5 -	92	36	48
Shobha Rathod	52	20	F	7429828	Belagavi	Student	Negative	Positive	NSAIDs	0	0	0	0	0	0	90	90/60	0.54	18.8	3	3	4	5	4	11	11	406	12	10	0.62	3.7	4.5 -	152	74	94
Anjuya Devannavar	53	41	F	4498320	Belagavi	Business	Positive	Positive	MTX 15mg /week	1	0	0	0	0	0	88	110/70	0.63	21.6	2	2	2	1	2	13	14	540	19	15	0.61	1.8	12.1 +	164	91	110
Lata Veerapoudar	54	67	F	5298841	Belagavi	Housewife	Negative	Positive	MTX 7.5/week / HCQ 200 OD	1	1	0	0	0	0	98	130/90	0.96	28.5	14	8	8	7	9	9	7.3	317	17	20	1.37	3.6	5.9 -	126	48	42
Rupa Banakar	55	38	F	7441261	Honga	Housewife	Positive	Negative	MTX 15mg /week / HCQ 300 OD	1	1	0	0	0	0	72	120/70	0.58	22.5	10	4	6	2	6	10.4	4.5	400	18	17	0.66	2.2	28+	171	178	119
Mahadevi Kalagar	56	53	F	10059011	Belagavi	Housewife	Negative	Positive	NSAIDs	0	0	0	0	0	0	96	150/100	0.72	23.4	7	4	3	3	6	12.1	4	169	29	14	1.02	2.6	23.6+	170	76	118
Prasanna Gumati	57	23	M	10064115	Belagavi	Student	Positive	Positive	MTX 7.5/week / HCQ 200 OD	1	1	0	0	0	0	106	100/70	0.52	16.8	0	0	1	0	1	12	4.1	212	99	72	0.79	6.5	93.9+	88	64	36
Jotiba Gavade	58	42	M	7481823	Chandgad	Farmer	Positive	Positive	NSAIDs	0	0	0	0	0	0	68	120/80	0.74	20	0	0	0	0	0	14	10	196	22	7	0.58	4.1	9.7+	171	96	122
Suvarna Sangoli	59	72	F	10065712	Belagavi	Housewife	Positive	Negative	MTX 15 per week/ Leflunomide 10 OD/ HCQ 200 OD	1	1	1	0	0	0	90	114/70	0.68	20.2	2	2	1	1	1	10.7	7	114	49	20	0.62	1.9	0.8 -	110	54	66
Satavva Chougala	60	32	F	5814269	Belagavi	Farmer	Positive	Positive	MTX 17.5 /week / HCQ 300 OD	1	1	0	0	0	0	88	130/90	0.7	22.4	4	4	3	3	2	10.7	10	460	23	12	0.76	3.5	5.8-	188	62	136
Surekha Benake	61	55	F	7392789	Madgaon	Business	Positive	Positive	MTX 5 per week/ Omnacortil 2.5 OD/ HCQ 200 OD	1	1	0	1	0	0	102	100/80	0.56	21.5	2	0	0	0	0	9.1	5.5	206	24	20	0.98	2.4	3.8 -	110	67	45
Mahananda Patil	62	41	F	7473958	Belagavi	Housewife	Positive	Negative	NSAIDs	0	0	0	0	0	0	68	130/90	0.72	17.6	3	3	2	2	2	10.9	6.2	233	26	18	0.58	2.9	0.8 -	114	61	66
Kashavva Karigar	63	60	F	10067635	Belagavi	Housewife	Positive	Positive	MTX 20 per weel/ HCQ 200 OD/ Lefno 20 OD/ Omnacortil 2.5 OD	1	1	1	1	0	0	86	160/90	0.9	27.9	0	0	0	0	0	12.9	9.1	327	28	24	0.57	4.4	1.2 -	134	66	100
Gangavva Naik	64	70	F	10067872	Belagavi	Housewife	Positive	Positive	NSAIDs	0	0	0	0	0	0	88	140/90	0.64	19.2	6	4	6	6	4	12.3	10	310	19	11	0.88	4	19.5+	146	141	96