T.C.
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DEPARTMENT OF CLINICAL PHARMACY

EVALUATION OF MEDICATION ADHERENCE AND DRUG-RELATED PROBLEMS AMONG RHEUMATOID ARTHRITIS PATIENTS IN NORTHERN IRAQ

MASTER THESIS

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APPROVAL

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DECLARATION

I, Karez Omer, solemnly declare that the thesis presented to Yeditepe University for the attainment of the Master of Clinical Pharmacy degree within the School of Pharmacy has not been previously submitted to this university or any other institution. I affirm that this work is the result of my own efforts in both design and execution, and I acknowledge and duly credit all materials incorporated within the document.

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Karez Omer

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LIST OF SYMBOLS AND ABBREVIATIONS

ACR	American College of Rheumatology
CBC	Complete Blood Count
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRP	C- Reactive Protein
CVS	Cardiovascular
DAS-28	Disease Activity Score 28 Joints
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DRP	Drug Related Problem
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
HBA1C	Haemoglobin A1c
HCQ	Hydroxychloroquine
HDL	High Density Lipoprotein
Hgb	Haemoglobin
HTN	Hypertension
LDL	Low Density Lipoprotein
LEF	Leflunomide
MARS-5	Medication Adherence Report Scale 5 Questionnaire
MTX	Methotrexate
OR	Odds Ratio
PAH	Pulmonary Hypertension
PCNE	Pharmaceutical Care Network Europe Association
PT	Patient
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
SBP	Systolic Blood Pressure
SLE	Systemic Lupus Erythematosus
SSZ	Sulfasalazine

TGA	Triglycerides
WBC	White Blood Cell

ABSTRACT

Omer, K. (2023). Evaluation of medication adherence and drug-related problems amoung rheumatoid arthritis patients in northern Iraq. Yeditepe University Institute of Health Sciences, Department of Clinical Pharmacy, MSc Thesis, Istanbul.

Objective: With Rheumatoid Arthritis (RA) being one of the most challenging diseases to manage Drug Related Problems puts further obstacles in the way of reaching the goal of treatment. This study aims to detect and identify DRPs as well evaluate the adherence of patients with rheumatoid arthritis to their medications in Erbil, Iraq.

Materails and Methods: The present study was conducted in two major hospitals in North Iraq. A cross-sectional multicenter design was adopted enrolling 203 RA outpatients from February 15th until June 1st, 2023. Medication adherence and drug-related problems were assessed using the Medication Adherence Report Scale 5 (MARS-5) and relevant RA and medication therapy guidelines. The DRPs were categorized using the PCNE Classification of Drug-Related Problems V9.1. Statistical analysis was carried using SPSS V.26. Binary logistic regression analysis was performed in order to identify variables associated with the disease activity score and *p*-value of < 0.05 was considered to be statistically significant.

Results: Among the 280 visiting outpatients, 203 were eligible and included; 91.1% of the patients were female. The mean (±SD) age of the patients was 51.9 ±12.3 years. Only 36.45% of the patients were found to be adherent to their medications. A total of 423 DRPs with an average of 2.08±1.46 problems per patient were identified. Calculated DAS-28 showed 40.39% of patients were with high disease activity, 35.46% with moderate disease activity, 9.36% with low disease activity, and 14.78% with remission.

Conclusion: medication non-adherence, female gender, and presence of DRPs were found to be strongly associated with the worsening of the disease activity of RA patients. These findings along with a high prevalence of DRPs and nonadherence were found among the RA patients.

Keywords: Rheumatoid arthritis, Adherence, drug-related problems, disease activity score (DAS-28).

ÖZET (Turkish)

Ömer, K. (2023). Kuzey Irak'taki romatoid artrit hastalarında ilaç uyumu ve ilaçla ilgili sorunların değerlendirilmesi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Klinik Eczacılık Anabilim Dalı, Yüksek Lisans Tezi, İstanbul.

Amaç: Romatoid Artrit (RA), yönetimi en zor hastalıklardan biri olarak kabul edildiğinden, İlaçla İlişkili Sorunlar, tedavi hedefine ulaşma yolunda ek engeller oluşturuyor. Bu çalışma, Erbil, Irak'ta romatoid artritli hastaların ilaçlarına bağlı sorunları tespit etmeyi, tanımayı ve aynı zamanda hasta uyumunu değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu çalışma, Kuzey Irak'taki iki büyük hastanede gerçekleştirildi. Kesitsel çok merkezli bir tasarım benimsendi ve 15 Şubat ile 1 Haziran 2023 tarihleri arasında 203 romatoid artrit hastası dahil edildi. İlaç uyumu ve ilaçla ilgili sorunlar, İlaç Uyum Raporu Ölçeği 5 (MARS-5) ve ilgili romatoid artrit ve ilaç tedavisi kılavuzları kullanılarak değerlendirildi. DRP'ler, PCNE İlaçla İlgili Sorunlar Sınıflandırması V9.1 kullanılarak kategorize edildi. İstatistiksel analiz SPSS V.26 kullanılarak gerçekleştirildi. Hastalık aktivite skoru ile ilişkili değişkenleri belirlemek amacıyla ikili lojistik regresyon analizi yapıldı ve $p < 0.05$ p-değeri istatistiksel olarak anlamlı kabul edildi.

Sonuçlar: Ziyaret edilen 280 dış poliklinik hastasından, 203'ü uygun bulundu ve dahil edildi; hastaların %91.1'i kadındı. Hastaların yaş ortalaması (±SD) 51.9 ±12.3 yıldı. Hastaların yalnızca %36.45'inin ilaçlarına uyum gösterdiği belirlendi. Ortalama 2.08±1.46 sorunun her hasta başına geldiği toplam 423 ilaçla ilgili sorun tespit edildi. Hesaplanan DAS-28, hastaların %40.39'unun yüksek hastalık aktivitesine sahip olduğunu, %35.46'sının orta hastalık aktivitesine, %9.36'sının düşük hastalık aktivitesine ve %14.78'inin remisyonda olduğunu gösterdi.

Sonuç: İlaç uyumsuzluğu, kadın cinsiyeti ve ilaçla ilgili sorunların, RA hastalarının hastalık aktivitesinin kötüleşmesi ile güçlü bir şekilde ilişkilendiği bulundu. Bu bulgular, RA hastalarında yüksek ilaçla ilgili sorun ve uyumsuzluk prevalansı ile birlikte değerlendirildi.

Anahtar kelimeler: Romatoid artrit, Uyum, ilaçla ilgili sorunlar, hastalık aktivite skoru (DAS-28).

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, long-term, autoimmune arthritis, often affecting the small and large joints of the body [1], In cases where the illness remains untreated or doesn't respond to treatment, it can lead to problems like joint inflammation, joint damage, and deformities [2]. This can result in reduced mobility, making it difficult to perform everyday tasks, and may even increase the chances of health complications and, in severe cases, death [3]. RA is among the most prevalent autoimmune diseases. According to the Global Burden of Disease Study 2019, between 1990 and 2019, the prevalence of rheumatoid arthritis (RA) rose from 207.46 to 224.25 per 100,000 individuals, showing an annual shift of 0.37%. It's noteworthy that Ireland recorded the highest RA incidence at 30.03 per 100,000, with Finland, Kazakhstan, Mexico, and Honduras following closely [4]. In Babylon, Iraq, the incidence of RA was 1.7 in 2019 with an average age of 43 [5]. Comparing the likelihood of each gender, women had a 3.6% lifetime risk of developing RA compared to men's 1.7% lifetime risk [6]. Rheumatoid arthritis has an elusive etiology. However, researchers have found that Genetics, hormones, and environmental variables may all play a role in its development [7,8]. Joint pain, stiffness, fatigue, fever, and loss of appetite are a few of the signs and symptoms of rheumatoid arthritis, and these presentations and disease severity may differ from one patient to another [9].

The diagnosis of RA is done based on the 2010 ACR/EULAR criteria, which were released by the European Alliance of Associations for Rheumatology and the American College of Rheumatology in 2010. Classification as definite RA is based upon the presence of synovitis in at least one joint, the absence of a different diagnosis that more adequately explains the synovitis, and a minimum score of at least 6 out of a total of 10 points [10,11]. The scores are based upon four main domains, which include the number and type of joints involved, low and high positive serology tests (Rheumatoid Factor RF or anti-citrullinated protein autoantibodies ACPA), elevated acute phase reactants (Erythrocyte sedimentation rate ESR and C-reactive protein CRP), and lastly, the duration of the symptoms ($\geq$ 6 weeks). Each of them receives a specified number of points, for a total of 10 points [11].

Management of Rheumatoid Arthritis is directed towards the goal of attaining remission or low disease activity, which is achieved with the help of Disease-modifying antirheumatic drugs DMARDs, which are classified into conventional DMARDs like

methotrexate (MTX) and hydroxychloroquine (HCQ), biological DMARDs like infliximab, and rituximab, and targeted synthetic DMARDs like baricitinib and tofacitinib. Other medications that are used alongside DMARDs are anti-inflammatory medications like NSAIDs and glucocorticoids, which are used as bridging therapies to quickly suppress inflammation and minimize and prevent long-term joint damage. The initial pharmacological strategy for managing active rheumatoid arthritis (RA) involves initiating treatment with MTX as the preferred DMARD therapy. However, because it takes a considerable amount of time, often weeks or months, for MTX to achieve its maximum effectiveness, anti-inflammatory NSAIDs or glucocorticoids are introduced alongside it to help mitigate the disease's activity. Hydroxychloroquine (HCQ), Sulfasalazine (SSZ), or Leflunomide (LEF) may be substituted for MTX in patients who are unable to take it. The 2021 American College of Rheumatology (ACR) recommendations advocate adding a biologic or targeted synthetic DMARD if a patient is resistant to DMARD therapy, which is commonly done by using a combination of DMARDs [12]. An alternate biologic or synthetic DMARD, in addition to anti-inflammatory medications, may be used if a patient is resistant to a combination therapy or treatment that includes a biologic or targeted synthetic DMARD [12,13].

Drug-related problems (DRP) refer to circumstances where the patient encounters any unfavorable event that involves or is considered to involve drug therapy, which may potentially worsen optimal clinical outcomes [14]. While medication adherence is the extent to which a patient's actions and behaviors match the agreed-upon advice from a healthcare professional [15]. In patients with chronic diseases like rheumatoid arthritis, having good medication adherence is a key component for the management of the disease. Because it not only impacts health outcomes but also affects overall healthcare expenses and the quality and length of life. However, only 50% of patients with chronic conditions take their medications as prescribed, making achieving the goal of treatment a greater challenge [16]. According to present studies, elderly RA patients are likely to have a greater prevalence of DRPs due to multiple co-morbidities and drug regimens [9].

Different studies have been done regarding the prevalence and type of drug-related problems and adherence for various diseases, but when it comes to rheumatoid arthritis, there is a dearth of studies involving detecting such findings, particularly in Middle Eastern nations like Iraq. To determine whether patients require additional support, information describing the frequency and type of DRPs that patients encounter

is required. For this reason, this study is essential to providing additional information on the types and factors associated with DRPs as well as the level of adherence in RA patients.

Aim of The Study:

This study aims to identify and categorize the types of drug-related problems among rheumatoid arthritis outpatients visiting and receiving treatment at both public hospital clinics and private clinics in Erbil, Iraq, as well as measure the degree and extent of the patient's adherence to their medications. This will enable us to comprehend some of the obstacles that may prevent RA patients from achieving their therapy goals and eventually figure out how to overcome them. This study is limited to emphasizing the significance and function of clinical pharmacists in the identification of medication issues and poor adherence in RA patients. It does not involve any kind of pharmaceutical intervention being applied by a clinical pharmacist but rather only observing these findings. By bringing these findings to light, future efforts can be directed toward finding solutions to these problems.

2. LITERATURE REVIEW

2.1 Rheumatoid Arthritis:

Rheumatoid Arthritis is classified as a systemic autoimmune rheumatic disorder (SARD), which is a variety of illnesses collectively defined by an immune reaction to self-antigens that are brought on by a confluence of environmental factors, immune system dysfunction, and genetic predisposition. Other disease examples that also fall into this category are systemic lupus erythematosus (SLE), systemic sclerosis, and systemic vasculitis [17,18].

The prevalence of RA changes according to the race and geographic location studied, with some variances in race and geographic location having a nearly 1% prevalence. Between 2014 and 2019, a cross sectional study conducted in Iraq's Babylon Province identified 1814 new cases of rheumatoid arthritis, observing a rise in its incidence from 1.1 to 1.7 [5]. In 2012, For every 100,000 individuals per year, 40 were newly diagnosed with RA [19]. However, according to data provided by the WHO, in 2019, it was estimated that 18 million individuals globally were suffering from rheumatoid arthritis, with 70% of them being females, and 55% of those females were above the age of 55 [20]. Native American and Indian populations have the highest prevalence (approximately 5%–6%) compared to Southern European, Eastern Asian, and African countries, which have a lower prevalence [21,22]. In a study published in 2020, Luca Silva-Fernández and her colleagues estimated the prevalence of rheumatoid arthritis (RA) in individuals in Spain aged 20 and older to be 0.82% [23]. Another study comparing the prevalence rates of France, Serbia, Turkey, and Lithuania—four distinct European nations—found that the prevalence rate of rheumatoid arthritis varied among these four nations. France had the lowest prevalence (0.29%), while Turkey had the highest prevalence (0.57%) [24].

Rheumatoid arthritis (RA) is a complicated disorder affected by genetic and nongenetic factors, with the HLA-DRB1 gene being the most frequently linked genetic element [25]. Hormonal changes, like reduced estrogen after menopause or oophorectomy, are linked to increased RA risk [26]. Testosterone and other sex hormones have protective effects, with men diagnosed with RA having lower testosterone levels [27,28]. Oral contraceptives in females may help prevent RA [29].

External factors such as smoking, obesity, alcohol, and infections also contribute

to RA. Smoking causes immunological reactivity to citrullinated proteins, increasing RA risk [30]. Genetic predisposition to smoking initiation is linked to RA risk [31]. Obesity, especially higher BMI, raises RA susceptibility [32,33]. Alcohol, containing ethanol, impacts immune function and T cell differentiation [34].

Infections may trigger RA through neo-autoantigens and molecular mimicry [35]. In summary, hormonal, lifestyle, and infectious factors collectively contribute to RA development.

2.1.1 Pathophysiology, Clinical Manifestation and Assessment

Rheumatoid arthritis (RA) is a complex autoimmune disorder characterized by a breakdown in immune tolerance, resulting in inflammatory processes, tissue destruction, and uncontrolled cell proliferation. This pathology encompasses a dysregulation of both inflammatory and immunological pathways, an overactivation of innate immune mechanisms, elevated proinflammatory cytokine levels, and an increase in anti-citrullinated protein antibodies (ACPA) [36–38].

RA's ramifications extend beyond the confines of synovial joints, impacting various organ systems and rendering individuals susceptible to a range of systemic complications [39]. This clinical landscape is often accompanied by constitutional symptoms such as myalgias, asthenia, fatigue, and weight loss. A prominent feature is morning stiffness, a distinct manifestation characterized by limited joint mobility following periods of rest.

The diagnostic framework for RA necessitates a comprehensive evaluation, encompassing clinical presentation, serological investigations, and radiological assessments, including the evaluation of specific autoantibodies like rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA). RF, while non-specific and found in various conditions, exhibits variable diagnostic sensitivity, ranging from 26% to 90%, with an average of 69%, and specificity, typically around 85% [40,41]. It serves as an imperfect measure for monitoring disease activity but may provide insights into therapeutic responsiveness. For instance, RF-positive RA patients often demonstrate more favourable responses to rituximab, while higher baseline RF levels may predict suboptimal outcomes with TNF-alpha inhibitors [42,43].

In contrast, ACPA, particularly anti-cyclic citrullinated peptide antibodies (anti-CCP), demonstrate heightened specificity in RA diagnosis [44]. The ACPA immune response is dichotomized into distinct phases—the initial hit, influenced by environmental or genetic factors, and the subsequent hit, characterized by enhanced antibody diversity and maturation [45]. Notably, HLA-DRB1 genes play a contributory role in the development of ACPA-positive RA [44]. Seropositivity, ascertained by the presence of RF or ACPA, discriminates RA from seronegative conditions, though RA can still be diagnosed in the absence of both antibodies based on complementary clinical findings [46].

For monitoring disease progression, conventional radiography remains the cornerstone, albeit with limitations in early detection and the assessment of inflammatory activity. In this regard, ultrasound and magnetic resonance imaging (MRI) offer valuable alternatives for assessing soft tissue and bone involvement, with MRI demonstrating the ability to detect early erosions up to three years in advance of conventional radiography [47].

The American College of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR) introduced innovative classification criteria for RA, designed to identify high-risk individuals with early erosive or chronic arthritis. This facilitates the expeditious initiation of disease-modifying antirheumatic drug (DMARD) therapy and augments diagnostic accuracy, particularly in the early stages of RA [10]. The classification was updated in 2010. Table 2.1 illustrates the 2010 RA classification criteria.

Table 2.1. The 2010 RA Classification Criteria: Domains, Categories and Point Scores [10]

	Domain A	**Domain B**	**Domain C**	**Domain D**
Points	**Joint involvement**	**Serology (RF and/or anti-CCP)**	**Acute phase reactants (ESR &/or CRP)**	**Symptom duration**
0	1 large joint	Negative RF and Negative anti-CCP	Normal ESR &/ or Normal CRP	< 6 weeks
1	2- 10 large joints (from among shoulders, elbows, hips, knees, & ankles)		Elevated ESR &/ or CRP	≥ 6 weeks
2	1-3 small joints ±large joints	Low positive (above the upper limit of normal)		
3	4-10 small joints ±large joints	High positive (greater than three times the upper limit of normal		
4				
5	>10 joints (at least 1 small joint)			

To be classified with definite RA, a patient should exhibit swelling in at least one joint that cannot be attributed to another medical condition and score 6 or more points on a specific assessment system [10].

2.1.2 Disease Management

Effective management of rheumatoid arthritis (RA) encompasses various strategies and interventions, as supported by relevant research findings. Swift intervention by a rheumatologist is crucial, as early diagnosis and treatment with disease-modifying antirheumatic drugs (DMARDs) are associated with reduced joint damage and functional disability [48]. A comprehensive approach, including frequent disease activity assessment and tailored exercise regimens, leads to better radiographic and functional results [49].

Physical activity plays a significant role in managing RA, especially for older individuals or those with inflammation and reduced physical fitness [50]. Tailored

exercise programs improve pain, function, fatigue, and overall quality of life [51]. Low-impact exercises and home-based interventions are recommended alternatives, as demonstrated in studies [52–54].

Psychological issues like anxiety and depression are common in RA. Management often involves education and self-management programs, including online options, to alleviate pain and fatigue and improve well-being, as suggested by various studies [55–57].

Dietary modifications and supplements are explored as potential treatment options. Mediterranean diets, vitamin D supplementation, and probiotics have shown promise, as indicated by available clinical evidence [58–61]. Balneotherapy, laser acupuncture, and other non-pharmacological treatments can also alleviate pain and disease activity, as supported by studies [62–65].

These multifaceted approaches offer individuals with RA the potential for improved quality of life and overall well-being, emphasizing the importance of a holistic approach to treatment.

Drug Modifying Anti-Rheumatoid Drugs (DMARDs)

DMARDs are a family of medications that are intended for treating rheumatoid arthritis as well as other inflammatory arthritis and some cancers. They are immunosuppressive and immunomodulatory drugs that can be categorized as conventional DMARDS, biological DMARDs, or synesthetic/targeted DMARDs as shown in Table 2.2. [66].

Table 2.2. Classification of DMARDs used in RA [66]

	Conventional DMARDS	**Biological DMARDS**	**Synthetic/Targeted DMARDS**
	Methotrexate Leflunomide Hydroxychloroquine Sulfasalazine		
TNF-α Inhibitors		Etanercept Infliximab Adalimumab Golimumab, Certolizumab Pegol	
Il-6 Inhibitors		Tocilizumab Sarilumab	
T-Cell Co-stimulation Blocker		Abatacept	
Anti-CD20 B-Cell Depleting Monoclonal Antibody		Rituximab	
JAK Inhibitors			Tofacitinib Baricitinib Upadacitinib Filgotinib Peficitinib

Rheumatoid arthritis (RA) management involves a nuanced understanding of the disease's severity, patient characteristics, and preferences, leading to individualized therapeutic choices. The selection of therapy often considers the disease severity, the presence of comorbidities, patient preferences, and financial aspects [67].

Disease-Modifying Antirheumatic Drugs (DMARDs): DMARDs, the cornerstone of RA treatment, exhibit diverse mechanisms targeting inflammatory pathways. Methotrexate, a folate antagonist, suppresses T cells, macrophages, endothelial cells, and fibroblast-like synoviocytes involved in RA development [68]. Leflunomide inhibits lymphocyte proliferation by suppressing dihydroorotate dehydrogenase, a critical enzyme in pyrimidine synthesis [69]. Biologics, such as tofacitinib, act selectively by modulating cytokine signalling and immune responses [70].

Methotrexate **(**MTX), the initial choice for managing active RA, is frequently used as the anchor medication in DMARD combinations [71]. Dosage, usually between 7.5 and 15 mg weekly, is tailored based on disease activity, patient size, age, comorbidities, and desired dose. Subcutaneous administration offers an alternative for patients with gastrointestinal symptoms [72]. Leflunomide (LEF), effective in RA, can be used alone or with other DMARDs. A loading dose of 100 mg/day for three days achieves a quicker steady state, followed by a maintenance dose of 20 mg/day, potentially reduced to 10 mg/day for gastrointestinal intolerance. It should be avoided in pregnancy, breastfeeding, and liver or lung diseases [73,74]. Sulfasalazine (SSZ), preventing oxidative damage, starts at a daily dose of 500 mg, escalating to 2 g daily, with concurrent folic acid supplementation. It can be used but with caution during pregnancy or breastfeeding [75,76]. Hydroxychloroquine (HCQ), an antimalarial and anti-inflammatory DMARD, affects antigen processing. It is typically dosed at 400 mg daily, presenting gastrointestinal and ocular adverse effects, especially at higher doses [77,78].

Biologic DMARDs**,** like TNF antagonists (Infliximab, Etanercept, etc) are employed for RA treatment, blocking TNF to alleviate inflammation [79]. Infliximab, approved in 1999, offers flexible dosing, with initial infusions at 3 mg/kg every 0, 2, and 6 weeks [80]. Etanercept, the first FDA-approved TNF inhibitor for RA, is administered subcutaneously at 25 mg twice a week or 50 mg once a week [80,81]. Adverse effects include infusion/injection site reactions, increased infection risk (particularly tuberculosis and fungal infections), and potential long-term complications [82].

Rituximab (RTX): RTX, a B-cell inhibitor, is administered in cycles, targeting CD20 on B cells. Infusion-related reactions occur in about 30% of patients. Caution with active infections and Hepatitis B status is imperative [83]. Adverse effects include reduced immunoglobulin levels, progressive multifocal leukoencephalopathy, and tuberculosis reactivation [84].

Interleukin-6 (IL-6) Inhibitors: Tocilizumab, an IL-6 inhibitor, can be used alone or with other DMARDs. Adverse effects include upper respiratory tract infections, headaches, elevated transaminases, abdominal pain, increased cholesterol levels, and infusion reactions [85].

IL-17 Inhibitors: Secukinumab, targeting IL-17, poses infection risks, necessitating tuberculosis evaluation before treatment [86].

T-Cell Costimulation Blockers: Abatacept, a T-cell costimulation blocker, treats RA and juvenile idiopathic arthritis. Adverse effects include infusion reactions, infections, and headaches [87].

Janus Kinase (JAK) Inhibitors: JAK inhibitors (Tofacitinib, Baricitinib, Upadacitinib, Filgotinib, and Peficitinib) reduce cytokine production. They can be used alone or with conventional DMARDs, but not combined with biological or other JAK-inhibitor DMARDs [88,89]. Adverse effects encompass cancer risk, heart disease, gastrointestinal problems, severe infections, and respiratory issues, necessitating regular monitoring [90,91].

In RA management, understanding the diverse mechanisms and potential adverse effects of these treatments allows for tailored therapeutic approaches, enhancing patient outcomes and quality of life.

Drugs for Flares

Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are used to manage inflammation, but they rarely help most patients prevent joint injuries or maintain long-term disease control. Serious infections are more likely with chronic usage, especially at moderate to high doses. In patients beginning treatment with disease-modifying antirheumatic drugs (DMARDs), these medications are used either as an additional therapy or as a short-term means of controlling the disease activity. NSAIDs shouldn't be viewed as an alternative to effective DMARD treatment [92]. A systemic review of prior studies revealed that gastrointestinal problems like abdominal pain, diarrhoea, dyspepsia, nausea, hypertension, and headaches were the most often reported adverse effects by individuals taking NSAIDs, with diclofenac and naproxen having the highest prevalence [93].

The treatment strategy for active rheumatoid arthritis (RA) is based on the widely accepted notion that all patients should be given disease-modifying antirheumatic medications (DMARDs), typically methotrexate (MTX), in order to avoid, stop, or delay disease-related damage. The basic strategy is in line with the

recommendations made by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) in 2021. Methotrexate is recommended as the first line of treatment, followed by leflunomide, sulfasalazine, hydroxychloroquine, or a tumour necrosis factor inhibitor in patients who are unable or unwilling to take MTX. For the initial symptomatic treatment of inflammation while awaiting DMARDs response, nonsteroidal anti-inflammatory medications (NSAIDs) and/or glucocorticoids are used.

Combination therapy is preferred in patients who, after three to six months of receiving the recommended doses of MTX monotherapy, have not achieved remission or have only mild disease activity [94,95].

2.1.3 Monitoring and Outcomes

Until the condition is stable and under control, regular monitoring and reevaluating of the disease's activity and the treatment's effectiveness for all patients is required every three to five weeks. A minimum of every three months should be the minimum assessment frequency. Patients with well-controlled arthritis may need laboratory testing in between regularly planned appointments and should get in touch with their treating clinician if their symptoms worsen. Depending on the medicine, the dosage being increased, the comorbidity, the flare-up, or the change in therapy, more regular laboratory monitoring may be necessary [96].

Disease Activity Score (DAS-28)

The Disease Activity Score 28 is a rheumatoid arthritis evaluation tool that assesses the disease activity and treatment response. There are two versions of DAS28: DAS28-ESR, which uses ESR, and DAS28-CRP, which uses CRP. Joint counts, test findings, and patient self-evaluation are used to calculate both scores [97]. Higher scores on the DAS28-ESR and DAS28-CRP scale indicate more active disease. Scores on the scale range from 0 to 10. inside Das28-ESR A decrease of 0.6 denotes a moderating improvement while a decrease of more than 1.2 denotes a considerable improvement. It helps medical personnel monitor the progression of RA patients' illnesses and the effectiveness of their treatments [98]. A different set of cutoffs is used by DAS28-ESR to identify high disease activity and remission. In some instances, DAS28-CRP may understate disease activity [97].

2.2 Target Achievement and Barriers of Disease Control

In rheumatoid arthritis, the goal is to attain clinical remission, characterized by the absence of inflammatory disease signs and symptoms, to enhance the patient's long-term quality of life, function, and social participation [99]. The treat-to-target (T2T) strategy, which sets specific treatment goals, has proven effective in improving outcomes. Research indicates that achieving a major response within 3 months significantly boosts the chances of remission at 6 months [100]. However, real-life data shows that around 43% of patients don't reach treatment targets, with only about 20% achieving remission within a year, suggesting that while the T2T approach works, it may not always be feasible in practice [101].

Treating RA can be quite challenging due to the different barriers there, these barriers can be late diagnosis of the disease, high cost of treatment and patient's low financial status, drug-related problems, medication non-adherence, presence of co-morbidities, lack of patient-physician communication and patient awareness [102–104].

Drug-Related Problem (DRP)

A drug-related problem is a set of circumstances involving drug therapy that interferes with or may interfere with planned or anticipated health outcomes. A classification system for DRPs, known as PCNE V9.01, was developed to categorize these problems based on their causes, prevalence, and incidence. This system is intended to help healthcare practitioners and researchers document information related to DRPs and their effects on pharmaceutical care services. Unlike other systems, PCNE V9.01 consistently uses the term "drug" and distinguishes between the causes and effects of these problems [105].

PCNE V9.01 includes several sections:

1. P-Code: Describes expected or unexpected events or situations related to drug therapy.
2. C-Code: Identifies the causes of DRPs, which often lead to planned interventions.
3. I-Code: Specifies the interventions proposed to address the root of the problem.
4. A-Code: Indicates the level of acceptance of the proposed interventions.

5. O-Code: Identifies whether the problem has been resolved or not.

The number of studies on drug-related problems in RA is unfortunately quite small. One study by Lex L. Haegen and her colleagues involved samples from 52 pharmacy outpatients with rheumatic diseases (65% of patients were RA) in the Netherlands, where the patients were subjected to a structured interview guide by telephone four times within a 2-month period to detect DRPs. The most frequently observed DRP was adverse drug effects. The small sample size studied was the major weak point of this study [106].

Another prospective observational study in Iowa, USA, with a larger sample size of 461 patients from 12 different pharmacies, examined the effects of different DRPs on quality of life using different surveys, including the main Short Form-36 (SF-36) general health survey and Health-related quality of life (HRQOL). The inability to identify patient-level determinants, and the inability to analyze changes in HRQoL as a function of DRP resolution are some of the drawbacks of this study [107].

Sujit Kumar Sah and his colleagues conducted two different studies in regards to DRP: an interventional prospective study including 860 patients with systemic autoimmune diseases [108], and a cohort study measuring the frequency of DRP in 320 hospitalized RA patients [109]. Both studies were done in India, and the same tools, PCNE V8.02, were used for recording the DRPs. In both studies, treatment safety was the most recorded DRP, with 96.4% resolution of those DRPs by the interventions proposed by the pharmacist in the interventional study.

Another cohort study by Machado J. and his colleagues that focused on recording the incidence of adverse drug reactions in RA patients in Colombia showed a total of 949 ADR reports from 419 patients, with an incidence of 32.8 ADRs per 100 patient-years. With the highest incidence rates for ADRs reported for tocilizumab, rituximab, and infliximab [110]. In a different city in Colombia, González J. and his colleagues studied only 78 patients on biological DMARDs using the DADER methodology and measured the DRP and negative clinical outcomes according to the Necessity, Effectiveness, and Safety of pharmacological therapy in patients with RA. 96 Negative clinical outcomes were identified in 49 patients, of which 11 were problems of need, 28 were effectiveness problems, and 57 were safety problems [111].

One retrospective study by Shu Ning Ma and her colleagues in Malaysia used the PCNE V5.01 tool and recorded a total of 289 DRPs with an average of 1.5±1.0 problems per patient, with adverse drug reactions or treatment safety being the most commonly encountered DRP [103].

And lastly, a randomized clinical trial by Hagar Omer and his colleagues in Cairo, Egypt, involved measuring the impact of pharmaceutical care services provided by pharmacists over a 6-month period on 60 RA patients and resulted in improved disease activity, quality of life, and acute reactants. Although of great value, the study had several limitations: a small sample size, the majority of patients being female, an open-label nature, and the use of subjective self-reporting questionnaires. These were the weak points or gaps In this study [112].

Overall, these studies highlight the importance of addressing DRPs in RA management, but further research is needed to fully understand and optimize pharmaceutical care for RA patients.

Medication Adherence

Medication Adherence signifies that the patient and doctor working together to promote the patient's health by integrating the physician's medical opinion and the patient's lifestyle, values, and preferences for care [113]. Despite that adherence and compliance are sometimes used interchangeably, they differ from one another. Compliance emphasizes patient obedience and submission to the doctor's authority [114].

Nonadherence to medication can take various forms, intentional nonadherence is when patients consciously choose not to follow their prescribed medication regimen, often due to personal beliefs and experiences. Unintentional nonadherence results from forgetfulness or misunderstanding dosing instructions and is less influenced by beliefs [115]. Non-conforming nonadherence, when patients deviate from the prescribed regimen, taking the wrong dose or adhering to an improper schedule [15]. Primary nonadherence occurs when patients don't obtain a newly prescribed medication within an acceptable timeframe. Finally secondary nonadherence happens when patients initially filled their prescriptions but later fail to refill them as directed [116].

Understanding these types helps healthcare providers tailor interventions to improve adherence and enhance treatment outcomes. According to studies only around 50% of those with chronic illnesses are adherent to their medications [117,118]. Lack of compliance with recommended regimens can result in pharmaceutical waste, the advancement of an illness, a decline in functional abilities, and a lower quality of life [15].

There are various tools and methods employed to assess medication adherence among patients. Questionnaires are conducted through direct interviews that involve face-to-face discussions with patients about their medication usage. Adherence is often quantified based on the omission of a specified number of doses over a set period, with an 80% or greater adherence rate considered satisfactory. Questionnaires like the (Compliance Questionnaire for Rheumatology) CQR and (Medication Adherence Report Scale) MARS evaluate adherence and patient beliefs and behaviours related to medications. Objective data can be gathered using the (Medication Event Monitoring System) MEMS, which electronically records medication container openings. Pharmacy records and tablet counting offer additional insights into adherence. Some methods involve analyzing blood samples, which may contain markers indicating medication use. Self-questionnaires and specific tests help assess medication adherence, often with predefined cutoff points. Examples include the Morisky test [116–118].

These diverse tools aid healthcare providers in comprehensively evaluating and addressing patients' adherence to prescribed medications. It is important to note that the choice of the most suitable adherence tool depends on the setting, the population, and the validity of the adherence tool. Therefore, the use of a combination of tools might offer the best solution.

Several studies shed light on the complex landscape of medication adherence among rheumatoid arthritis (RA) patients. In a Korean study, approximately 91.3% of patients exhibited good adherence to their prescribed methotrexate (MTX) regimen, with adherence measured using the Medication Possession Ratio (MPR). Notably, the non-adherent group used less MTX, but the study's limitations included reliance on MPR and a single-center design [119].

An Italian cohort study focused on anti-TNFα therapy revealed that adherence in RA patients is influenced by various factors, including age, disease activity, and discomfort associated with injections. Non-adherence was notably linked to higher disease activity and injection-related issues, emphasizing the importance of addressing these factors to enhance adherence [120].

In a Spanish study examining subcutaneous biological therapy, patients expressed high satisfaction with treatment tolerability, although this did not consistently correlate with adherence. Interestingly, individuals receiving monthly therapy tended to have their tolerability expectations better met, potentially enhancing adherence. Nevertheless, this study had limitations, such as a small sample size and a narrow focus on specific subcutaneous medications [121].

Another Spanish study found that approximately 59.1% of RA patients were adherent to their treatment. Factors influencing adherence included the type of treatment, patient trust, agreement on treatment, and the provision of information about treatment adaptation. However, limitations included potential external validity issues and questionnaire variations [122].

A U.S. study involving RA patients highlighted the significance of patient beliefs. It revealed that stronger beliefs in the necessity of medication improved adherence to oral DMARDs or prednisone. Conversely, higher self-efficacy was associated with poorer adherence. This study, however, relied on self-reported data and had a cross-sectional design [123].

A Pakistani study uncovered that about 36% of RA patients were non-adherent, with factors like unemployment, lower education, stress, disease activity, and comorbidity influencing non-adherence. Although gender, age, marital status, and rural living showed no significant associations, the study underscored the need to consider these factors in RA treatment plans [124].

Furthermore, a review study emphasized that factors such as depression and high treatment costs act as potential barriers to adherence in RA patients. It stressed the importance of addressing these barriers for more effective RA treatment outcomes [125].

Lastly, an international study found that only 60% of visits adhered to the recommended treat to target (T2T) treatment strategy among RA patients, with adherence fluctuating over time. Female patients and smokers faced potential gaps in their care. Rheumatologists leaned toward clinical biomarkers for treatment decisions but were cautious about escalation without clear physical signs of synovitis [126].

In summary, these studies collectively underscore the multifaceted nature of RA medication adherence, influenced by factors ranging from patient beliefs and disease activity to injection-related discomfort and treatment costs. Addressing these factors is crucial to enhancing adherence and improving the overall quality of RA care.

2.3 Role of Pharmacist in RA

Pharmacists serve indispensable roles in various healthcare settings, making substantial contributions to patient care and overall healthcare outcomes [127]. In hospital settings, pharmacists serve as integral members of the healthcare team, ensuring patients receive appropriate medications and furnishing guidance on the safe and effective use of medicines [128]. They provide essential drug-related information to both patients and other healthcare providers, thus supporting the management of chronic diseases [129].

Community pharmacists offer not only general healthcare counsel but also engage in the dispensing of both prescription and over-the-counter medications [130]. Their pivotal role lies in educating patients regarding potential side effects, drug interactions, and the significance of adhering to prescribed treatment regimens [129,131].

Within primary care units, pharmacists collaborate closely with physicians and other healthcare providers to optimize medication therapy and enhance patient outcomes. Some states grant pharmacists varying degrees of prescriptive authority, empowering them to provide medication therapy management services [128].

Independent prescriber pharmacies grant pharmacists the autonomy to independently prescribe medications, thereby enabling them to provide holistic care, including prescribing, monitoring drug therapy, and offering patient education [132].

Telepharmacy services, encompassing medication review, dispensing, patient counseling, and monitoring, prove particularly valuable in regions with limited access to healthcare services [129]. Pharmacists also assist patients in selecting appropriate digital health products and furnish education on usage, self-management, result interpretation, and data submission into electronic health records (EHRs) [131].

Ambulatory pharmacists, who are experts in managing medication therapy, operate within outpatient clinics. Their responsibilities encompass maintaining records of patient medication histories, ensuring compliance, and overseeing medication reconciliation and drug interaction management. They collaborate closely with pharmacy managers and contribute to the education of pharmacy students. Their approach is centered on individualized patient care, tailoring treatment plans, and giving importance to cautious discontinuation of medications when required [133].

Clinical pharmacists play an active role in identifying, preventing, and resolving drug-related issues, assuming a pivotal function in the context of rheumatoid arthritis (RA) therapy. They impart critical information to patients, underlining the importance of comprehending potential adverse events (AEs), grasping the dynamics of drug interactions, and ensuring adherence to prescribed treatment regimens. Clinical pharmacists guide prescribers in selecting medications, taking into account factors like intolerance, interactions, and cost-effectiveness [134].

Clinical pharmacists engage in comprehensive medication management, encompassing the formulation of policies governing medication use, the establishment of patient-centered care services, and the provision of vital drug-related information. They develop clinical care plans, manage disease states, and meticulously monitor and promptly report adverse drug reactions. Their patient-centered approach includes the cultivation of empathetic patient relationships, encompassing thorough drug history collection, addressing patient queries regarding medications, preparing infusion medications, rigorously scrutinizing potential drug interactions, and, when necessary, offering informed guidance on appropriate dosages [135].

Clinical pharmacists, recognizing that patients with inflammatory arthritis often seek guidance from pharmacies prior to consulting physicians, play a pivotal role in mitigating any delays in patients seeking essential care. This assumes particular

significance in the context of rheumatoid arthritis, where symptoms may act as a deterrent to timely medical attention [136].

The incorporation of a clinical pharmacist into a rheumatology practice, whether through on-site presence or consultation, yields a multitude of advantages. Their inclusion promotes patient adherence to prescribed treatment plans, streamlines disease monitoring endeavours, and effectively addresses medication-related issues and side effects. This collective effort contributes to a holistic and empathetic approach to patient care.

The multidimensional role of clinical pharmacists in managing RA includes medication counselling, informed drug selection, thorough medication management, patient relationship-building, a decrease in patient delay, and overall improved treatment delivery. Their professional advice promotes patient wellbeing while reducing the dangers related to drug-related problems and providing the highest level of care [137,138].

3. MATERIALS AND METHODS

3.1. Study Deign, Participants and Setting:

The study participants were previously diagnosed RA patients recruited from two major hospitals in Erbil city, through outpatient clinics or routine biological DMARD visits from February 15th to June 1st, 2023. With 500 inpatient beds, Rizgari Teaching Hospital, offers complex procedures and outpatient services from 8 a.m. to 1 p.m. Meanwhile Consultant Medical City (CMC) Private Hospital in Erbil, Situated on Koye Street, adheres to global healthcare standards, boasting over 100 specialists, advanced technology, and specialized units such as ICU, IVF, and cardiac care—all geared towards prioritizing patient-centered healthcare [139 ,140].

3.1.2 Study Participants

Inclusion Criteria:

All rheumatoid arthritis patients on medications, who were diagnosed with RA at least 3 months ago, aged 18 or older, and who gave informed consent, were included in this study.

Exclusion Criteria:

Patients with missing files information, and patients with active infections, cancers or other inflammatory diseases were excluded.

3.1.3 Sampling and Sample Size:

Patients visiting the clinic during the study period and matching inclusion criteria were invited to participate. The minimum sample size was calculated using the Raosoft Sample Size Calculator, and the confidence level was set at 95% with a 5% margin of error, with the population of Erbil city being 897,000 in 2023 [141].. The recommended minimum sample size was 257 patients. Totally 280 patients were randomly approached, but due to lack of complete patient information (33) and the inability to provide informed consent from them (15), along other reasons (29), 203 patients were included finally in the assessment.

3.2 TOOLS AND MATERIALS:

3.2.1 Instruments

Three types of Biozek tubes were used in the present study. Biozek is a Dutch biotech company that manufactures a wide range of medical diagnostics and advanced tools, and their test tubes were chosen for this study due to the high quality of their products [142).

- **The purple EDTA K3 BIOZEK tube:** The ethylene diamine tetra-acetic acid tri-potassium, or EDTA K3, tube was used for the complete blood cell (CBC) test.
- **The yellow gel and clot activator BIOZEK tube:** The Gel and Clot Activator tube was used for C-reactive protein (CRP); the lipid profile (T. cholesterol, triglycerides, LDL, and HDL); and the HbA1c test.
- **The black sodium citrate 3.8% ESR tube from BIOZEK:** The ESR tube was used to carry out the estimated sedimentation rate (ESR) test.

Six different kits were used in the study, including the following:

- **CRP4** Tina-quant C-reactive protein IV (REF 07876033190) (System ID 07 7607 6), Roche Diagnostics, Indianapolis, made in Germany
- **HDLC4** HDL-Cholesterol Gen.4 (REF 07528566190), (System ID 07 7589 4) ROCHE Diagnostics, Indianapolis, made in Germany
- **CHOL2** Cholesterol Gen.2 (REF 03039773190), (System ID 07 6726 3), Roche Diagnostics, Indianapolis, made in Germany
- **A1C-3** Tina-quant hemoglobin A1c Gen.3 (REF 05336163 190), (System ID 07 7455 3), Roche Diagnostics, Indianapolis, made in Germany
- **TRIGL** Triglycerides (REF 20767107322) (System ID 07 6710 7), Roche Diagnostics, Indianapolis, made in Germany
- **LDLC3** (REF 07005717 190) (System ID 07 7565 7) Roche Diagnostics, Indianapolis, made in Germany

Three main measuring devices was also used, these include

- **The COBAS Integra 6000** is a software-controlled potent instrument for full diagnostic laboratory automation, was used for qualitative and quantitative in

vitro determinations of a variety of tests like CRP, Lipid Profile, and HbA1c.

- **ESR analyzer JOKOH** was used for easy and rapid measurement of ESR with low biological risk.
- **The CBC EDEN H30 was** used for the measurement of CBC, is a completely automatic homological analyzer. It has better stability and lower maintenance costs, making it suitable for people looking for low-cost, high-quality solutions.

3.2.2 Disease Activity Score (DAS-28):

The disease activity score (DAS) was developed to measure the disease activity of individuals with RA using 28 joint counts (DAS28) in clinical research and the evaluation of patients in clinics. The disease activity score is a worldwide summative and continuous score for disease activity assessment. The four components of the DAS28 are tender joint count, swollen joint count, visual analogue scale (VAS) score, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). It has cut-off points of 2.6, 3.2, and 5.1 for remission, low disease activity, and high disease activity, respectively, and is frequently used [144). However, due to DAS28-ESR's reliance on ESR, disease activity may occasionally be exaggerated, leading to the possibility of unnecessary therapy. CRP-based DAS28-CRP provides a more accurate representation of transient fluctuations. Both methods give joint and health evaluations similar weight, with ESR and CRP differences principally accounting for score differences [97). In this study the DAS cumulative score was obtained from both DAS-28 ESR and DAS-28 CRP.

3.2.3 Pharmaceutical Care Network Europe Volume 9.01 (PCNE V9.01):

A classification system for drug-related problems (DRPs) was developed during the Pharmaceutical Care Network Europe working session in January 1999. The most recent version, V9.01, was created following a validation round and expert workshop in February 2020. This classification is intended to assist healthcare practitioners and investigators in documenting DRP information in terms of the cause, prevalence, and incidence of the DRPs, as well as studies on the effect of pharmaceutical care services on them. In contrast to other classifications that might use the phrase "medicine," this one uses the word "drug" throughout, and it differs from other systems because it distinguishes between the causes and effects of problems. Quality professionals are

aware that the majority of the causes are frequently referred to as "medication errors" by others.

The first section of PCNE V9.1 is the P-code, or problem, which is divided into 3 main domains and 7 subdomains, essentially describing the expected or unexpected events or situations that are wrong or might be wrong in drug therapy. The action (or lack of action) that causes the occurrence of a potential or actual problem is the cause, or the C-code, with 9 domains and 43 subdomains. Typically, this results in one or more planned interventions to address the root of the problem. The I-Code has 5 domains and 17 subdomains. Then the A-Code, with 3 domains and 10 subdomains, mentions the level of acceptance of the inventions proposed. And lastly, the O-Code, namely the outcome, identifies whether the problem has been resolved or not with four primary domains and seven subdomains [105].

3.2.4 Medication Adherence Report Scale 5 (MARS-5):

MARS-5 is a self-report questionnaire used to measure the level of medication adherence in patients. It has been used in a variety of chronic conditions like hypertension, IBD, stroke, type 2 DM, and COPD. MARS-5 has been recommended for use in a therapeutic context because of its simplicity, low cost, and validity [145].

The MARS-5 uses a 5-level response structure (1—always, 2—often, 3—sometimes, 4—rarely, and 5—never) to evaluate a patient's normal medication adherence through 5 questions (e.g., "I forget to take my medication"; "I alter the dose of my medication"). Higher scores indicate greater levels of adherence, with total scores ranging from 5 to 25 after adding together responses. In the past, the MARS-5 cutoffs for adherence in an IBD population were 20 or below, while other chronic diseases defined adherence at a cutoff as high as 25. Another study considered a MARS-5 score of 5–22 non-adherents and a score of 23–25 adherents [146]. A validated Kurdish version of MARS-5 was utilized for the purpose of this study

3.2.5 Cardiovascular (CVS) Risk Score

This score is intended to target individuals between the ages of 40 and 79. It aids in predicting your risk of having a heart attack, stroke, or dying from cardiovascular

illness over the next ten years. Update's cardiovascular risk assessment in adults (10-year, ACC/AHA 2013) online score calculator was the tool used in this study [147].

3.3 Data Collection and Blood Sample Collection:

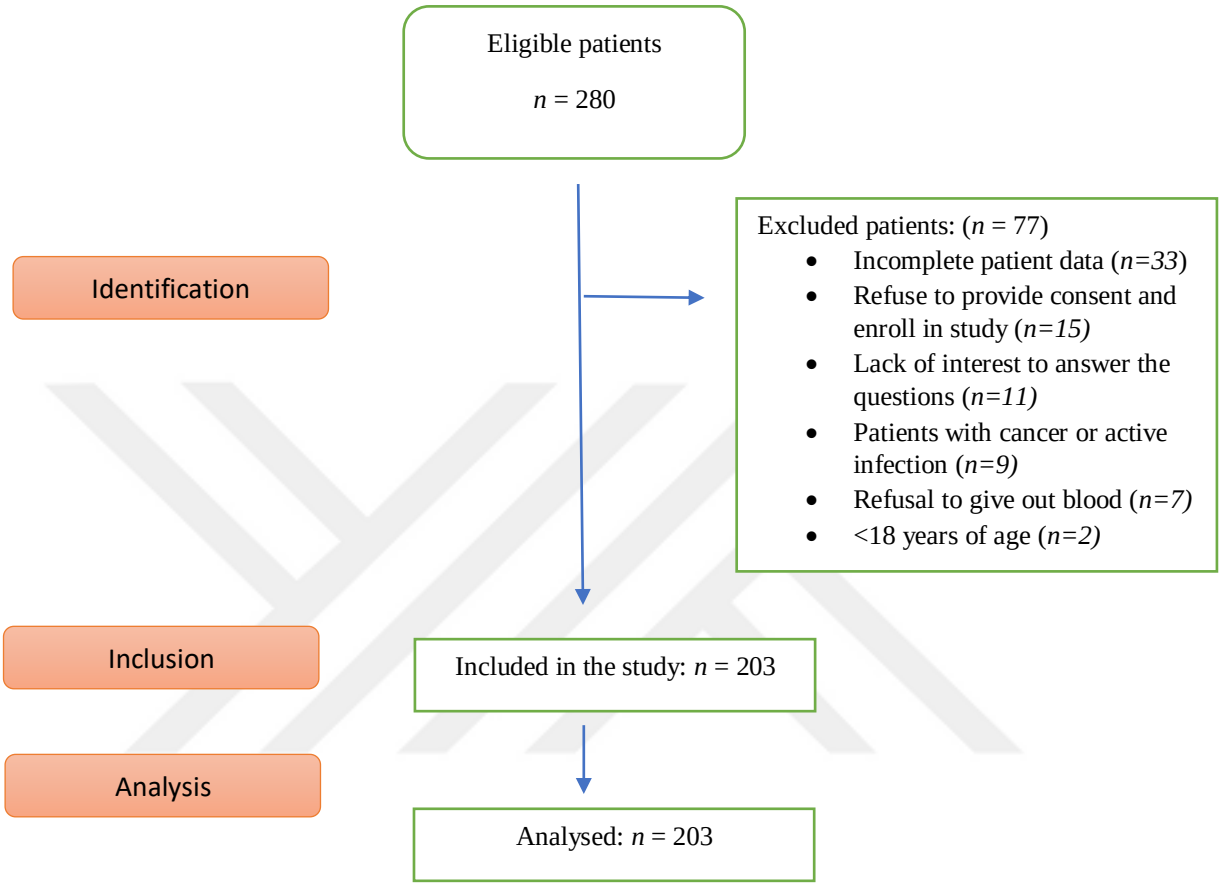


Figure 3.1. Study Flow Chart

A Questionnaire form was employed by the researcher to gather patient information. Independent variables gathered included age, gender, current medication history, educational level, social habits, family medical history, height, weight, duration of rheumatoid arthritis (RA), co-morbidities, and employment status.

Furthermore, dependable variables were gathered. A joint assessment for tenderness and swelling was conducted with the collaboration of the treating rheumatologist. Subsequently, patients were requested to assess their pain level using a Visual Analog Scale (VAS), where zero denoted the absence of pain and 100 signified the utmost discomfort.

An average systolic and diastolic blood pressures of the patients were recorded following a 5–10-minute relaxation period, utilizing a digital sphygmomanometer. Weight measurements were conducted on patients who lacked knowledge of their current weight, and body mass index (BMI) calculations were subsequently performed.

Additionally, cardiovascular risk scores were computed using the Update's cardiovascular risk assessment tool for adults (10-year, ACC/AHA 2013) online score calculator.

Patients were also queried about their medication adherence and behaviours, with adherence recorded and assessed using the Medication Adherence Report Scale (MARS-5). Following this, patients were guided to a dedicated blood withdrawal room, where nurse assistants obtained blood samples and promptly placed them in appropriate containers, ensuring their preservation.

The cooled containers containing patient blood samples were then transported to King's lab, where immediate testing was carried out to yield precise results. Based on the information gathered from the patients and the results of laboratory tests, potential drug-related issues were evaluated utilizing the Pharmaceutical Care Network Europe (PCNE) V9.01 criteria.

Patients who were unable to recall medication names or other vital information were contacted through text messages and phone calls to acquire the necessary details. Those who did not respond or were unable to provide specific information were excluded from the study, and their data was not included in the final analysis.

3.4 Statistical Analysis

The collected data was entered in Microsoft Office Excel 2016 and Statistical Package for the Social Sciences (SPSS) software (version 26.0). Descriptive statistics were employed to present categorical data as frequencies or percentages and continuous variables as Mean ± SD. Regarding the association between categorical and continuous variables, the student t-test and ANOVA test were used as relevant. A chi-square test was used to evaluate the association between categorical variables. A binary logistic regression analysis was performed in order to identify variables associated with the

disease activity score (DAS-28 ESR) and the disease activity score (DAS-28 CRP) of the RA patients. A *p* value of < 0.05 was considered statistically significant.

3.5 Ethical Consideration

An oral informed consent form was obtained from all the patients after they were informed about the study's objectives. Also, they were informed that all the data provided would be treated in a completely confidential manner. Ethical approval of this study was obtained from the Research Ethics Committee of the Ministry of Higher Education and Scientific Research.

The reference number is **Hmu-Ec-Ph 0704-2022-442.**

4. RESULTS

4.1. Socio-demographic Characetistics of Patients

Out of 280 patients visiting the study setting 203 RA patients accepted and participated in the study (72.5%). Majority of the patients being female (*n* = 185 patients, 91.9%). The greatest proportion were aged within the 46–55 years (*n* = 62 patients, 30.5%). More than three quarters of the patients were having a BMI score of more than 25 (overweight or obese). Only 20.2% (*n* = 41) were found having obtained 12 years or more of education. 94.1% (*n* = 191) were married, and more than half of the patients had a positive family history of autoimmune disease (*n* = 109, 53.7%). Table 4.3 summarizes the characteristics of the patients.

Table 4.3. Socio-demographic Characetistics of Patients

		Frequency (%)	**Mean ± SD**
Age	16-25 years old 26-35 years old 36-45 years old 46-55 years old 56- 65 years old 66-75 years old 76- 85 years old	5 (2.5) 13 (6.4) 46 (22.7) 62 (30.5) 44 (21.7) 30 (14.8) 3 (1.5)	51.9 ±12.3
Geriatric	Yes (≥ 65) No (<65)	37 (18.2) 166 (81.8)	
Gender	Male Female	18 (8.9%) 185 (91.1%)	
BMI	Underweight Normal weight Overweight Obese Type 1 Obese Type 2 Obese Type 3	1 (0.5%) 42 (20.7%) 53 (26.1%) 72 (35.5%) 24 (11.8%) 11 (5.4%)	30.29±5.7
Overweight	Yes No	160 (78.8) 43 (21.2)	
Occupation	Employed Unemployed	31 (15.3%) 172(84.7%)	
Educational Level	< 12 years of formal education ≥ 12 years of formal education	162(79.8%) 41(20.2%)	
Marital Status	Single Married	12 (5.9%) 191(94.1%)	
Family History	Yes No	109 (53.7%) 94 (46.3%)	
Smoking	Yes No	14 (6.9%) 189(93.1%)	
Alcohol	Yes No	0 (0%) 203 (100%)	

4.2. Clinical Characteristics of Patients

The Clinical characteristics of study samples included the presence or absence of diagnosed comorbidities alongside rheumatoid arthritis (RA). Among the 203 patients, a total of 202 comorbidities were identified. The majority of patients had at least one comorbid disease (*n* =120, 59.1%). While the remaining 40.9% of the patients (*n* = 83) had no comorbid disease other than RA. Table 4.4 and Figure 4.2 shows patient medical history and percentage of comorbidities.

Table 4.4. Frequency of Comorbidities in the Study Population

No. of Comorbidities	Frequency	Percentage %
0	83	40.9%
1	67	33.0%
2	32	15.8%
3	13	6.4%
4	8	3.9%

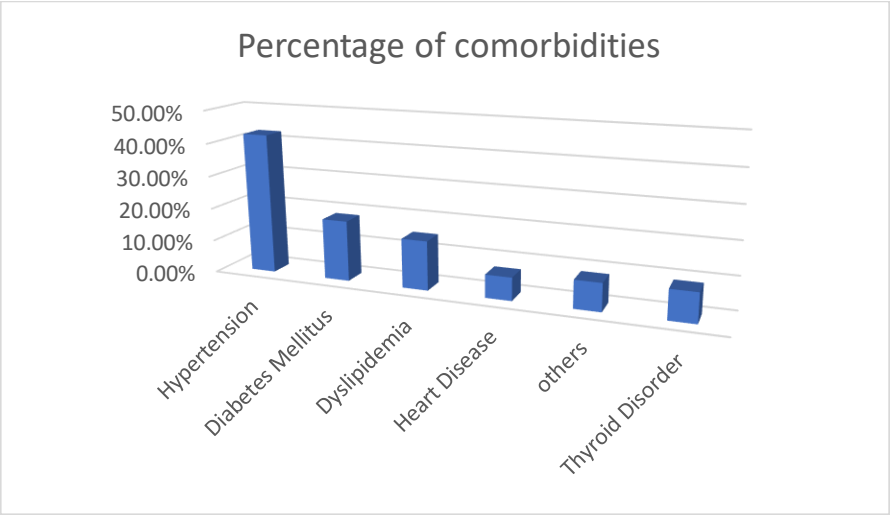


Figure 4.2. Percentage of Comorbidities in the Study Population

The use of DAS-28 ESR for disease activity assessment in the study indicated comparable scores to DAS-28 CRP. Specifically, 40.4% of the population exhibited a high disease activity score with DAS-28 ESR, whereas 39.9% fell within the moderate category using DAS-28 CRP, as illustrated in Figure 4.3. and Figure 4.4.

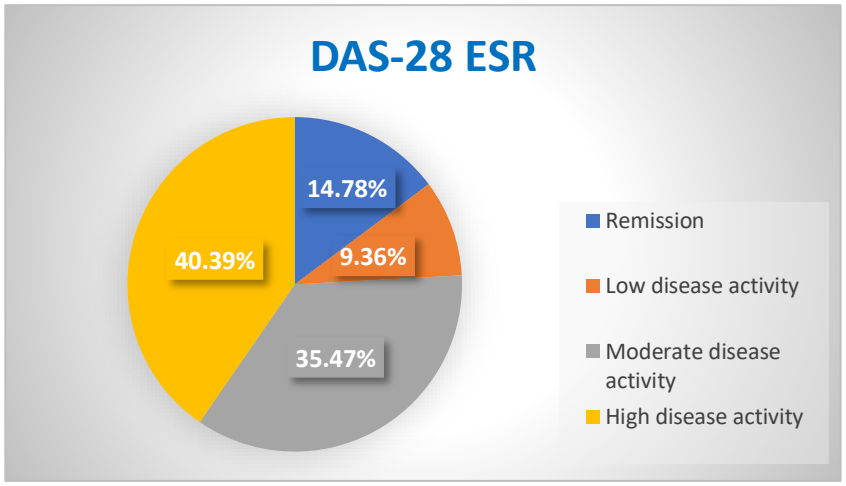


Figure 4.3. Disease Activity Status of the Patients (DAS-28 ESR)

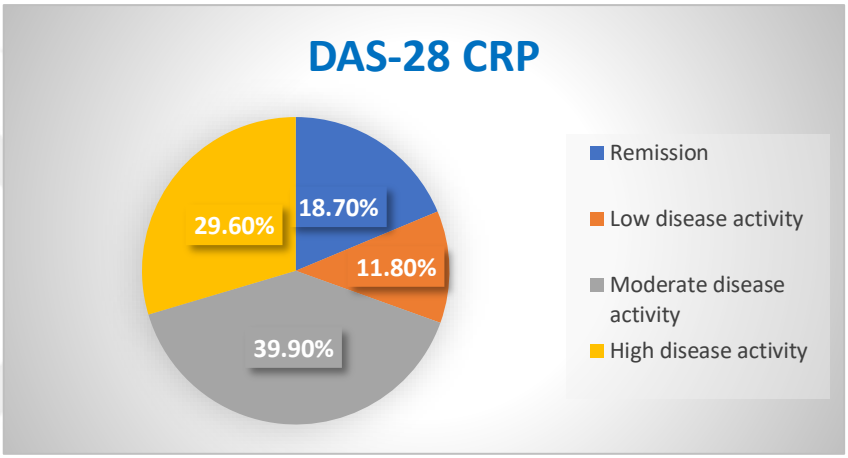


Figure 4.4. Disease Activity Status of the Patients (DAS-28 CRP)

4.3. Patients' Medication Use

A total of 1085 medications were used by the study samples, averaging 5.3±2.1 medications per patient. The status of polypharmacy, (Table 4.5.), reveals that the majority (61.1%, *n* = 124) of RA patients were on 5 or more medications, while 38.9% (*n* = 79) are using fewer than 5 medications.

Table 4.5. State of Polypharmacy within the RA Patients

Items		Frequency	%	Mean±SD
Polypharmacy	<5 drugs	79	38.9%	5.3±2.1
	≥5 drugs	124	61.1%	

Figure 4.5. presents medication groups prevalence among patients, categorized as follows: 21.94% supplements and OTC drugs, 20% conventional DMARDs, 11.24% steroids, 10.97% NSAIDs, 10.05% antihypertensives, 6.18% biological DMARDs, and smaller percentages for other drug groups, as detailed in the Figure 4.4.

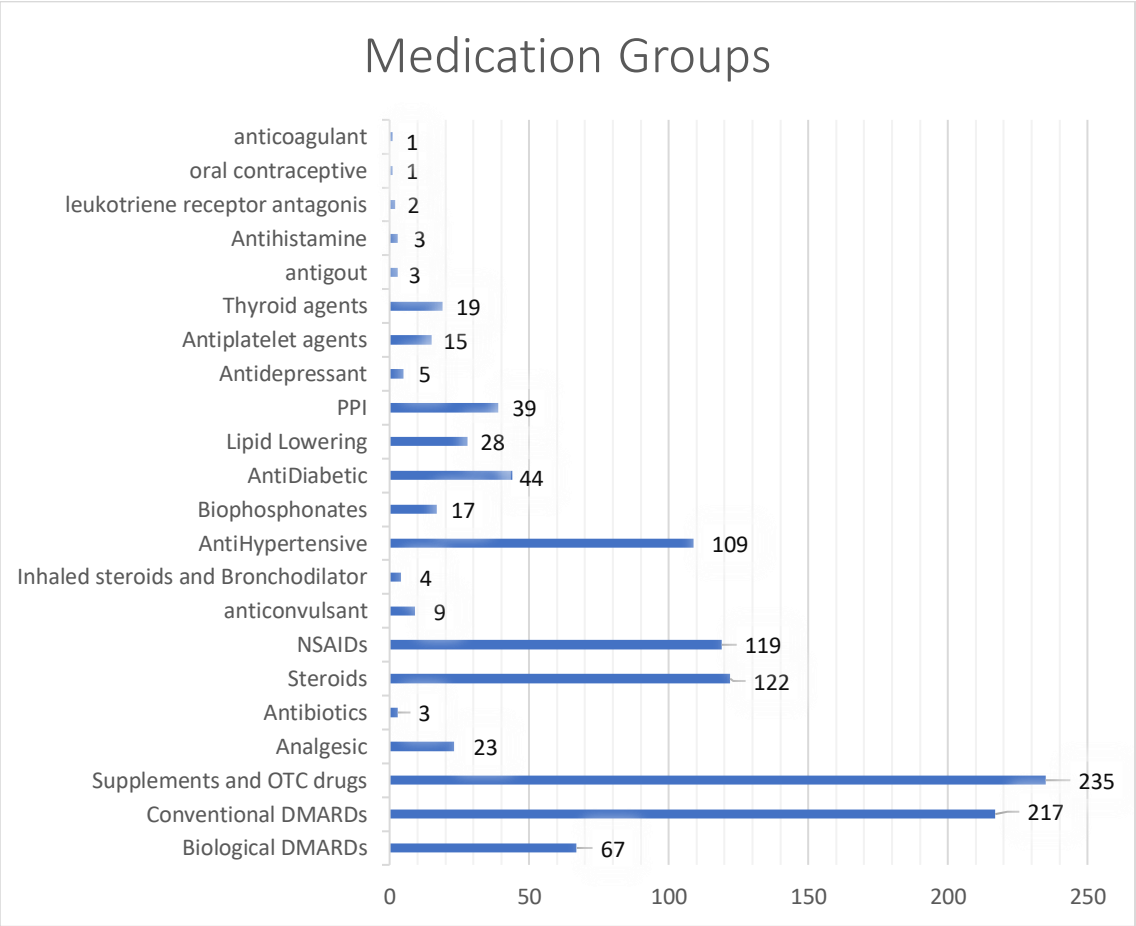


Figure 4.5. Prevalence of Medication Groups

In Table 4.6. and Figure 4.6., DMARD usage is summarized. Half of the patients (*n* = 102, 50.25%) were on a single conventional DMARD, primarily methotrexate (30.1%), followed by hydroxychloroquine (11.8%), leflunomide (6.9%), and sulfasalazine (1.5%). Of total patients, (19.7%) used double DMARDs (1 conventional + 1 biological), primarily Methotrexate + Infliximab (4.9%), and less than 10% used combined conventional DMARDs, mainly Methotrexate + Leflunomide (3.9%). About 8.37% were on triple DMARDs (2 conventional and 1 biological), while 7.39% were not on any DMARD treatment. Single biological DMARDs, mainly Rituximab (3.5%), comprised less than 5% of prescribed medications.

Table 4.6. Prevalence of DMARDs

Types of DMARDs	Frequency	Parentage (%)
None	15	7.39%
Single conventional DMARD	102	50.25%
Single biological DMARD	9	4.43%
Double DMARDs (2 conventional)	20	9.85%
Double DMARDs (1 conventional+1 biological)	40	19.70%
Triple DMARDs (2 conventional+1 biological)	17	8.37%
Total	203	100.00%

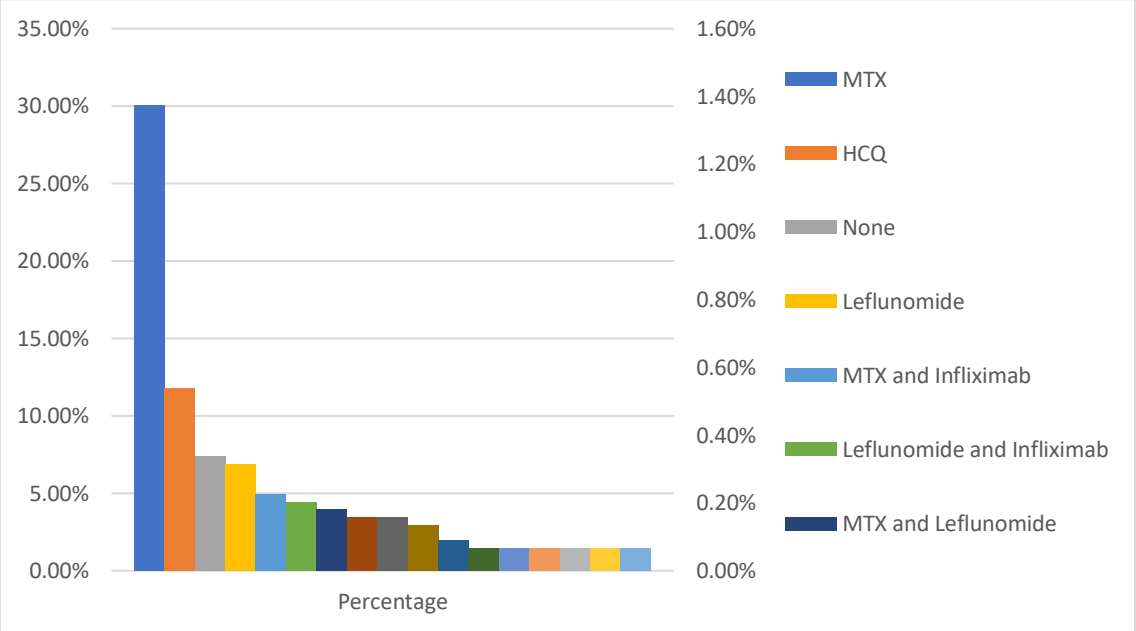


Figure 4.6. Prevalence of DMARDs

Among 238 supplements and over-the-counter drugs used by patients, the most prevalent supplements were folic acid (*n* = 108, 45.38%), vitamin D (*n* = 41, 17.23%), calcium ± vitamin D (*n* = 23, 9.66%), and iron supplement (*n* = 16, 6.72%). Figure 4.7. provides a visual representation.

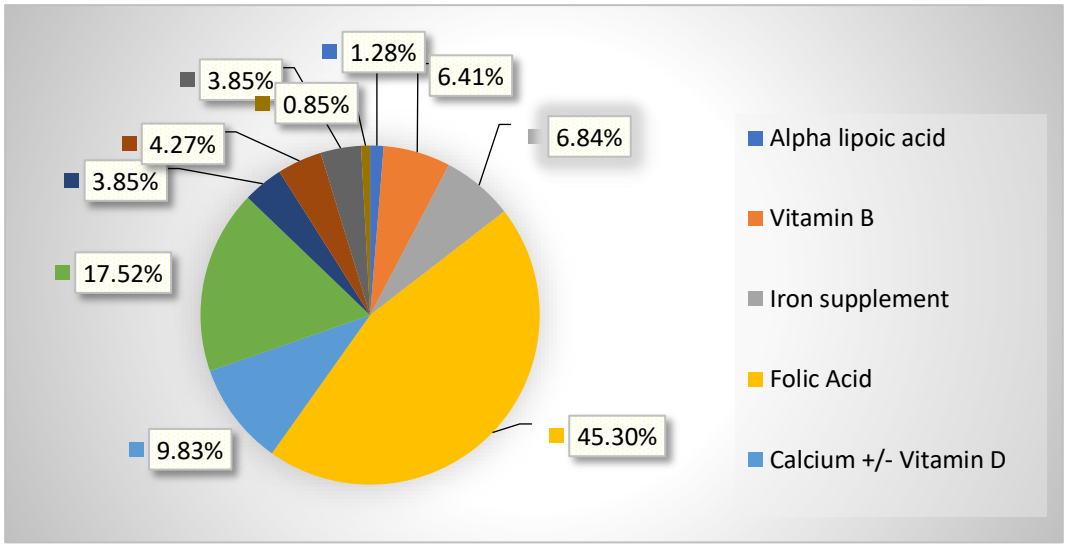


Figure 4.7. Distribution of The Supplements and OTC Drugs

4.4. Prevalence of Drug related problems (DRPs)

A of 423 DRPs were identified in 203 RA patients (2.08 ±1.46 per patient). Most patients (*n* = 173, 85.7%) had at least one drug related problem. Notably, 25.1% of patients experienced 2 DRPs, 23.2% had one DRP, and 20.7% recorded having 3 DRPs. Less than 15% had no apparent DRP, while over 10% encountered 4. Figure 4.8. below outlines drug-related problems (DRPs) in 203 RA patients, evaluated by clinical pharmacists.

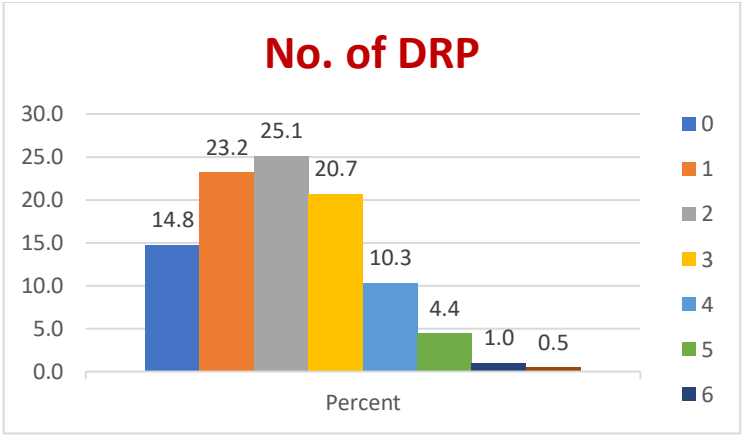


Figure 4.1. Prevalence of DRP among the RA Patients

The most prevalent cause of DRP, constituting 43.74%, revolves around the potential occurrence of adverse drug events resulting from insufficient therapy or incorrect combinations of medications. Subsequently, accounting for 36.4% of DRPs, is the

challenge associated with suboptimal drug treatment efficacy, often associated with purposeful underuse or the unavailability of prescribed medications. Another group, which accounts for 17.25% of DRPs, is the persistence of symptoms despite established indications. Contributing factors include intentional underuse and difficulties complying to specified dose regimes. Less frequently encountered issues include inappropriate drug use (2.12% of DRPs) and indistinct complaints (0.47% of DRPs). Interventions cover a wide range of approaches, from in-depth discussions with prescribers to changes in drug instructions, temporary or permanent withdrawal of drug use, and full communication and discussions of knowledge with prescribers. A thorough summary of these data is presented in Table 4.7.

Table 4.7. Description of the drug related problems, associated Causes and the pharmaceutical interventions proposed by Clinical Pharmacist.

Problem (*n* =423)		Cause (*n* =423)		Intervention (*n* =423)	
Category (P-code)	*n* (%)	Category (C-code)	*n* (%)	Category (I-code)	*n* (%)
Adverse drug event (possibly) occurring **(P2.1)**	185 (43.74)	-No or incomplete drug treatment in spite of existing indication **C1.5**	61(32.9)	-Intervention discussed with prescriber **I1.4**	61(32.9)
		-Dosage regimen too frequent **C3.4**	43(23.2)	-Instructions for use changed to **I3.4**	43(23.2)
		-Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements **C1.3**	37(20)	-Intervention discussed with prescriber **I1.4**, Drug paused or stopped **I3.5**	27(14.6), 10(5.4)
		-Duration of treatment too long **C4.2**	29(15.7)	-Prescriber asked for information **I1.2**	29(15.7)
		-Inappropriate duplication of therapeutic group or active ingredient **C1.4**	4(2.2)	-Drug paused or stopped **I3.5**	4(2.2)
		-Patient unintentionally administers/uses the drug in a wrong way **C7.8**	4(2.2)	-Intervention discussed with prescriber **I1.4**	4(2.2)
		-Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason **C7.1**	2(1.1)	-Prescriber asked for information **I2.1**	2(1.1)
		-Patient abuses drug (unregulated overuse) **C7.3**	2(1.1)	-Prescriber asked for information **I2.1**	2(1.1)
		-Drug dose of a single active ingredient too high **C3.2**	1(0.5)	-Dosage changed to **I3.2**	1(0.5)
		-Necessary information not provided or incorrect advice provided **C5.2**	1(0.5)	-Intervention discussed with prescriber **I1.4**	1(0.5)
		-Patient uses/takes more drug than prescribed **C7.2**	1(0.5)	-Dosage changed to **I3.2**	1(0.5)

Table 4.7. Description of the drug related problems, associated Causes and the pharmaceutical interventions proposed by Clinical Pharmacist (Cont.).

Problem (*n* =423)		Cause (*n* =423)		Intervention (*n* =423)	
Category (P-code)	*n* (%)	Category (C-code)	*n* (%)	Category (I-code)	*N* (%)
Effect of drug treatment not optimal **(P1.2)**	154 (36.4)	-Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason **C7.1**	132(85.7)	-Prescriber asked for information **I2.1**	132(85.7)
				-No intervention **I0.1**	12(7.8)
		-Prescribed drug not available **C5.1**	12(7.8)	-Intervention discussed with prescriber **I1.4**	6(3.9)
		-Drug dose too low **C3.1**	6(3.9)		
		-Patient takes food that interacts **C7.5**	4(2.6)	- Instructions for use changed to **I3.4**	4(2.6)

Problem (*n* =423)		Cause (*n* =423)		Intervention (*n* =423)	
Category (P-code)	*n* (%)	Category (C-code)	*n* (%)	Category (I-code)	*n* (%)
Untreated symptoms or indication **(P1.3)**	73 (17.25)	-No or incomplete drug treatment in spite of existing indication **C1.5**	58(79.5)	-Prescriber informed only **I1.1**, Intervention discussed with prescriber **I1.4**, Drug started **I3.6**	23(31.5), 33(45.2), 2(2.7)
		-Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason **C7.1**	9(12.3)	-No intervention **I0.1**, Prescriber asked for information **I2.1**	5(6.8), 4(5.5)
		-Other cause; specify **C9.2**	4(5.5)	-No intervention **I0.1**	4(5.5)
		-Dosage regimen not frequent enough **C3.3**	2(2.7)	-Dosage changed to **I3.2**	2(2.7)

Problem (*n* =423)		Cause (*n* =423)		Intervention (*n* =423)	
Category (P-code)	*n* (%)	Category (C-code)	*n* (%)	Category (I-code)	*n* (%)
Unnecessary drug treatment **(P3.1)**	9 (2.12)	-No indication for drug **C1.2**	6(66.7)	-Intervention discussed with prescriber **I1.4**	6(66.7)
		-Patient decides to use unnecessary drug **C7.4**	3(33.3)	-Drug paused or stopped **I3.5**, Intervention discussed with prescriber **I1.4**	1(11.1), 2(22.2)
Unclear problem/complaint **(P3.2)**	2 (0.47)	-Inappropriate drug according to guidelines/formulary **C1.1**	1(50)	- Prescriber asked for information **I2.1**	1(50)
		-Wrong drug, strength or dosage advised (OTC)**C5.3**	1(50)	-Intervention discussed with prescriber **I1.4**	1(50)

The alpha coefficient of the Cronbach's Alpha for the 5 items of MARS-5 scale was 0.843, suggesting that the items have good internal reliability and consistency.

The reported answers to MARS-5 are presented in Table 4.8. Some (19.2%) of the participants reported that they sometimes forgot to take their medications, and 11.8 percent of the patients reported that they often alter the dose of their medications based on how they feel. Noting that about 17.7% of the participants reported that they stopped taking their medications for a while, 13.3 percent of the patients reported that they take less medication than instructed, and 11.8 percent mentioned that they sometimes decide to miss a dose. The mean scores ranged from 3.9 to 4.3, indicating deviation in medication adherance.

Table 4.8 Participants' responses to the MARS-5 questionnaire

MARS-5	**Frequency (%)**					
	Always	Often	Sometimes	Rarely	Never	Mean±SD
I forgot to take them	6 (3.0)	20 (9.9)	39 (19.2)	14 (6.9)	124 (61.1)	4.1±1.2
I alter the dose	7 (3.4)	24 (11.8)	17 (8.4)	3 (1.5)	152 (74.9)	4.3±1.2
I stop taking them for a while	18 (8.9)	36 (17.7)	21 (10.3)	10 (4.9)	118 (58.1)	3.9±1.5
I decided to miss out a dose	12 (5.9)	22 (10.8)	24 (11.8)	14 (6.9)	131 (64.5)	4.1±1.3
I take less than instructed	10 (4.9)	23 (11.3)	27 (13.3)	9 (4.4)	134 (66.0)	4.2±1.3

The examination of various variables in relation to adherence status is presented in Table 4.9. Utilizing t-tests, and chi-square tests, analysis was conducted to compare multiple factors between the adherent and nonadherent groups. Results showed that adherence was associated with the number of tender joints ($p = 0.008$), Visual Analogue Scale scores ($p = 0.002$), CRP levels ($p = 0.015$), Total Cholesterol ($p = 0.009$), Triglycerides ($p = 0.019$), LDL levels ($p = 0.008$), HbA1c levels ($p = 0.038$), ESR ($p = 0.032$), DAS-28 ESR ($p < 0.001$), DAS-28 CRP ($p < 0.001$), and the number of drug-related problems ($p < 0.001$). Conversely, no statistically significant differences were seen based on age, gender distribution, BMI, education level, employment status, marital status, smoking status, family history of autoimmune diseases, the number of

medications, polypharmacy, the number of co-morbidities, systolic blood pressure, and diastolic blood pressure between the two groups.

Table 4.9. Comparison between the different variables with the adherence status

Variables	**25 adherents** ***n*** **=74**	**< 25 Nonadherent** ***n*** **=129**	***p-Value***
Age	52.7 ±12.2	51.4 ±12.4	0.36
Gender Male Female	 7 (38.9) 67 (36.2)	 11 (61.1) 118 (63.8)	0.822
BMI	30.5 ±6.1	30.2 ±5.5	0.799
Diploma or Higher Yes No	 19 (43.3) 55 (34.0)	 22 (53.7) 107 (66)	0.141
Occupation Employed Unemployed	12 (38.7) 62 (36)	19 (61.3) 110 (64)	0.777
Marital Status Single Married	5 (41.7) 69 (36.1)	7 (58.3) 122 (63.9)	0.699
Smoker Yes No	5 (35.7) 69 (36.5)	9 (64.3) 120 (63.5)	0.952
Family History of autoimmune diseases Yes No	 42 (38.5) 32 (34)	 67 (61.5) 62 (66)	0.507

Table 4.9. Comparison between the different variables with the adherence status (Cont.)

Variables	25 adherents *n* =74	< 25 Nonadherent *n* =129	*p-Value*
No. of medications	5.6 ±2.0	5.2 ±2.2	0.121
Polypharmacy ≤ 4 drugs 5 or more	23 (29.1) 51 (41.1)	56 (70.9) 73 (58.9)	0.083
No of co morbidities	1.1 ±1.1	1.0 ±1.1	0.470
Tender joints	6.8 ±8.3	10.1 ±8.6	**0.008**
Swollen joints	1.1 ±2.3	1.8 ±2.8	0.090
Visual Analogue Scale	47.9 ±30.4	61.9 ±29.6	**0.002**
CRP ≤5 (Normal) >5 (high)	35 (47.3) 39 (30.2)	39 (52.7) 90 (69.8)	**0.015**
T. cholesterol	172.7 ±32.5	188.1 ±43.4	**0.009**
Triglycerides	134.8 ± 67.1	165.8 ± 100.8	**0.019**
LDL	100.5 ±29.1	114.4 ±38.9	**0.008**
HDL	50.7 ±10.6	50.1 ±11.8	0.721
HbA1c	5.32 ± 0.7	5.6 ± 1.0	**0.038**
Systolic Blood Pressure	129.3 ±14.8	128.8 ±16.4	0.842
Diastolic Blood Pressure	84.6 ±9	86 ±12.9	0.403
ESR <24 (Normal) ≥25 (Elevated)	46 (43.4) 28 (28.9)	60 (56.6) 69 (71.1)	**0.032**
DAS-28 ESR Controlled Not controlled	21 (70) 53 (30.6)	9 (30) 120 (69.4)	**<0.001**
DAS-28 CRP Controlled Not controlled	26 (68.4) 48 (29.1)	12 (31.6) 117 (70.9)	**<0.001**
No. of DRP	1.2 ± 1.2	2.6 ± 1.4	**<0.001**

The examination of variables concerning the presence or absence of drug-related problems (DRP) is detailed in Table 4.10. Statistical analyses, including t-tests, and chi-square tests, were employed to discern differences between individuals with and without DRP. The results showed several significant differences. Including in the prevalence of overweight individuals ($p = 0.025$), tender joints ($p = 0.001$), swollen joints ($p = 0.001$), Visual Analogue Scale scores ($p < 0.001$), HbA1c levels ($p = 0.040$), systolic blood pressure ($p = 0.023$), ESR levels ($p = 0.012$), adherence status ($p < 0.001$), DAS-28 ESR ($p < 0.001$), and DAS-28 CRP ($p < 0.001$) between the two

groups. Conversely, no statistically significant differences were observed in age, gender distribution, education level, occupation, marital status, smoking status, family history of autoimmune diseases, the number of medications, polypharmacy, the number of co-morbidities, CRP levels, total cholesterol, triglycerides, LDL, HDL, and diastolic blood pressure.

Table 4.10. Comparison between the different variables with presence of DRPs

Variables	**Without DRP** ***n*** **=30**	**With DRP** ***n*** **=174**	***p-Value***
Age	51.7 ±13.3	51.9 ±12.2	0.949
Gender Male Female	 4 (22.2) 26 (14.1))	 14 (77.7) 159 (85.9)	0.351
BMI	29.7 ±6.5	30.4± 5.6	0.567
Overweight No Yes	 11 (25.6) 19 (11.9)	 32 (74.4) 141 (88.1)	**0.025**
Diploma or Higher Yes No	 7 (17.1) 23 (14.2)	 34 (82.9) 139 (85.8)	0.643
Occupation Employed Unemployed	3 (9.7) 27 (15.7)	28 (90.3) 145 (84.3)	0.385
Marital Status Single Married	3 (25) 27 (14.1)	9 (75) 164 (85.9)	0.304
Smoker Yes No	2 (14.3) 28 (14.8)	12 (85.7) 161 (85.2)	0.957
Family History of autoimmune diseases Yes No	 13 (11.9) 17 (18.1)	 96 (88.1) 77 (81.9)	0.217

Table 4.10. Comparison between the different variables with presence of DRPs (Cont.)

Variables	Without DRP *n* =30	With DRP *n* =174	*p-Value*
No. of medications	5 ±2.2	5.4 ±2.1	0.198
Polypharmacy ≤ 4 drugs 5 or more	 13 (16.5) 17 (13.7)	 66 (83.5) 107 (83.3)	0.591
No of co morbidities	0.7 ±1	1 ±1.1	0.092
Tender joints	4.8 ±6.5	9.6 ±8.7	**0.001**
Swollen joints	0.4 ±0.9	1.7 ±2.8	**0.001**
Visual Analogue Scale	37.7 ±31.8	60.1 ±29.2	**<0.001**
CRP	15.9± 31.6	13.0 ±18.8	0.495
CRP ≤5 (Normal) >5 (high)	 15 (20.3) 15 (11.6)	 59 (79.7) 114 (88.4)	0.095
T. cholesterol	174 ±36.2	184 ±40.9	0.224
Triglycerides	135 ±68.8	157.9 ±94.2	0.346
LDL	105.3 ±26.6	110.1 ±37.6	0.726
HDL	47.6 ±11.7	50.8 ±11.3	0.164
HbA1c	5.2 ± 0.4	5.6 ± 1.0	**0.040**
Systolic Blood Pressure	124.3 ±13.7	129.8 ±16	**0.023**
Diastolic Blood Pressure	82.6 ±9.4	86 ±11.9	0.802
ESR	26.1 ± 23	31.2 ± 21.6	0.239
ESR <24 (Normal) ≥25 (Elevated)	 22 (20.8) 8 (8.2)	 84 (79.2) 89 (91.8)	**0.012**
Adherence Status Adherent (25) Nonadherent (<25)	 26 (35.1) 4 (3.2)	 48 (64.9) 125 (96.9)	**<0.001**
DAS-28 ESR Controlled Not controlled	 14 (46.7) 16 (9.2)	 16 (53.3) 157 (90.8)	**<0.001**
DAS-28 CRP Controlled Not controlled	 14 (36.8) 16 (9.7)	 24 (63.2) 149 (90.3)	**<0.001**

The analysis of variables in association with DAS-28 cumulative scores is presented in Table 4.11. t-tests, chi-square tests, and ANOVA were used illustrate differences between individuals with controlled and not controlled DAS-28 cumulative scores. Results showed Significant findings included differences in gender distribution (p =

0.001), overweight prevalence (p = 0.043), smoking status (p = 0.455), number of medications (p = 0.951), tender joints (p < 0.001), swollen joints (p = 0.001), Visual Analogue Scale scores (p < 0.001), CRP levels (p = 0.008), HbA1c levels (p = 0.032), systolic blood pressure (p = 0.639), diastolic blood pressure (p = 0.528), ESR levels (p < 0.001), MARS-5 adherence scores (p < 0.001), adherence status (p < 0.001), and the number of Drug-Related Problems (DRP) (p < 0.001) between the two groups. Conversely, no statistically significant differences were observed in age, education level, occupation, marital status, family history of autoimmune diseases, polypharmacy, number of co-morbidities, total cholesterol, triglycerides, LDL, and HDL.

Table 4.11. Comparison between the different variables with Disease Activity

Variables	**DAS-28 cumulative**		***p-Value***
	Controlled *n*=28	**Not Controlled *n* =175**	
Age	49.5 ± 13.3	52.3 ±12.1	0.279
Gender Male Female	 7 (38.9) 21 (11.4)	 11 (61.1) 164 (88.6)	 **0.001**
BMI	28.8± 5.1	30.5 ±5.8	0.149
Overweight No Yes	 10 (23.3) 18 (11.3)	 33 (76.7) 142 (88.7)	 **0.043**
Diploma or Higher Yes No	 20 (12.3) 8 (19.5)	 142 (87.7) 33 (80.5)	 0.235
Occupation Employed Unemployed	 5 (16.1) 23 (13.4)	 26 (83.9) 149 (86.6)	 0.682
Marital Status Single Married	 3 (25) 25 (13.1)	 9 (75) 166 (86.9)	 0.246
Smoker No Yes	 27 (14.3) 1 (7.1)	 162 (85.7) 13 (92.9)	 0.455
Family History of autoimmune diseases Yes No	 17 (15.6) 11 (11.7)	 92 (84.4) 83 (88.3)	 0.422

Table 4.11. Comparison between the different variables with Disease Activity (Cont.)

Variables	DAS-28 cumulative		*p-Value*
	Controlled *n*=28	**Not Controlled *n* =175**	
No. of medications	5.3 ± 1.9	5.4 ± 2.2	0.951
Polypharmacy ≤ 4 drugs 5 or more	10 (12.7) 18 (14.5)	69 (87.3) 106 (85.5)	0.708
No of co morbidities	0.8 ±0.9	1.0± 1.1	0.274
Tender joints	0.2±0.6	10.3 ±8.5	**<0.001**
Swollen joints	0.0 ±0.0	1.8 ±2.8	**0.001**
Visual Analogue Scale	19.3 ±16.3	62.8 ±27.9	**<0.001**
CRP	3.7 ±4.1	15.0 ±22.2	**0.008**
CRP ≤5 (Normal) >5 (high)	 21 (28.4) 7 (5.4)	 53 (71.6) 122 (94.6)	**<0.001**
T. cholesterol	178.8 ±38.2	183.1 ±40.8	0.606
Triglycerides	158.2 ±89.2	153.9 ±91.6	0.816
LDL	112.6 ±36.2	108.8 ±36.3	0.607
HDL	48.0 ±8.7	50.7 ±11.7	0.241
HbA1c	5.2 ±0.4	5.6 ±1.0	**0.032**
Systolic Blood Pressure	127.7 ±14.9	129.2 ±16.0	0.639
Diastolic Blood Pressure	84.2 ±9.6	85.7 ±12.0	0.528
ESR	14.6±6.7	33.0±22.4	**<0.001**
ESR <24 (Normal) ≥25 (Elevated)	 26 (24.5) 2 (2.1)	 80 (75.5) 95 (97.9)	**<0.001**
MARS-5	24.2 ±1.4	19.9 ±5.3	**<0.001**
Adherence Status Adherent=25 Nonadherent<25	 20 (27) 8 (6.2)	 54 (73) 121 (93.8)	**<0.001**
No. of DRP	1.1 ±1.3	2.2 ±1.4	**<0.001**

Table 4.12. shows the binary logistic regression analysis for the association of the variables with the disease activity of RA patients. Age, BMI, polypharmacy, and educational level showed no significant association with disease activity. However, gender exhibited a notable difference, with females less likely to be in remission (OR = 0.157, p = 0.003). Nonadherence significantly increased the odds of not being in remission (OR = 0.297, p = 0.021). and the presence of drug-related problems was

strongly associated with a higher likelihood of not being in remission (OR = 4.425, p = 0.004). These findings emphasize the impact of gender, adherence, and drug-related problems on rheumatoid arthritis disease activity.

Table 4.12. Binary logestic regression for DAS-28 and variables

Variables		Total (*n*, %)	DAS-28 (*n*, %)		OR (95%CI)	P value
			In remission	Not in remission		
Age	≤64 years	166(81.7)	24 (14.5)	142 (85.5)	0.772 (0.216-2.762)	0.691
	>65 years	37 (18.2)	4 (10.8)	33 (89.1)		
Gender	Male	18 (8.9)	7 (38.9)	11 (61.1)	0.157 (0.040-0.533)	**0.003**
	Female	185 (91.1)	21 (11.4)	164 (88.6)		
BMI						
<25 Normal		43 (21.2)	10 (23.3)	33 (76.7)	0.740 (0.263-2.083)	0.569
≥25 Overweight & obese		160 (78.8)	18 (11.2)	142 (88.8)		
Polypharmacy						
< 4 medications		79 (38.9)	10 (12.7)	69 (87.3)	1.356 (0.502-3.666)	0.548
≥ 5 medications		124 (61.1)	18 (14.5)	106 (85.5)		
Adherence status						
=25 Adherent		74 (36.5)	20 (27.0)	54 (73.0)	0.297 (0.106-0.835)	**0.021**
<25nonadherent		129 (63.5)	8 (6.2)	121 (93.8)		
Educational level						
<12 years of education		162 (79.8)	20 (12.3)	142 (87.7)	1.100 (0.377-3.215)	0.861
≥12 years of education		41 (20.2)	8 (19.5)	33 (80.5)		
Presence of DRP						
	No	30 (14.8)	13	17	4.425 (1.588-12.334)	**0.004**
	Yes	173 (85.2)	15	158		

*CI: confidence interval; OR: odds ratio; *p < 0.05 indicates the statistically significant difference between patients in remission and not in remission*

5. DISSCUSION

To the best of our knowledge, this is the first cross-sectional prospective study to categorically evaluate DRPs by using the latest version of the PCNE tool and evaluate the adherence status of RA outpatients in Northern Iraq, highlighting the necessity of pharmacist intervention in clinical practice. More than half of the study participants (85.7%) had at least one DRP, with an average of 2.08 DRPs per patient (SD: 1.48). This aligns with similar results obtained from a retrospective study in Malaysia [103] where the prevalence of DRPs was high (78.5%) with 1.5±1.0 problems per patient, and a prospective cohort study in India [108] where (88.4%) of the patients had at least one DRP, measuring 1.6 DRP per patient, where both studies also used the PCNE tool.

The most prevalent cause of the problem associated with the DRPs of the studied RA patients was concerning the treatment safety or possible adverse drug effects (43.74%), similar to the results of Lex L. Haegen and her colleagues in the Netherlands [106]; Sujit Kumar Sah and his colleagues' studies in India [108,109]; Shu Ning Ma and her colleagues in Malaysia [103]; and the cohort study by Machado J. and his colleagues in Colombia, where they only focused on recording the adverse drug reactions and found a total of 949 ADR from 419 patients [110].

In our study, this was mostly due to the no or incomplete drug treatment in spite of the existing indication (32.9%), these were the use of prednisolone for > 3 months without any bone protection regime Calc+ Vit and no folic acid in spite of MTX or SSZ use. Other causes included usage of NSAIDs too frequently (23.2%) that caused GI discomfort in patients, interaction between leflunomide and moderate-to-high-intensity rosuvastatin, MTX and leflunomide interaction, esomeprazole/omeprazole with clopidogrel interaction, isoniazid and esomeprazole interaction, and two NSAIDs used together (20%). Use of prednisolone for a long duration >1 year nonstop, where most patients were complaining of overweight and obesity and low self-esteem due to the high weight (15.7%). Other causes were duplication of medications where the same medication from two different companies was used unnoticed, like folic acid, prednisolone, and naproxen, wrongly administering higher doses of leflunomide than prescribed, abrupt stopping of prednisolone, prednisolone used on need, pregabalin used on need, and patients refusing to stop prednisolone even with physicians' orders to stop.

The second most prevalent problem was the effect of drug treatment not being optimal (36.4%), and the majority of the cause fell in the nonadherence of the patients to the treatment regimens (85.7%). Other causes were the unavailability of the prescribed medications, infliximab and certain bDMARDs regularly in hospitals and pharmacies, low doses of MTX (2.5mg or 5 mg), and lastly, patients taking alendronate after meals, which interacts with food and decreases the absorption of the medication.

Of the Study population, 17.25% of the problems were untreated indications or symptoms, where the majority of the cause was due to no or incomplete drug treatment in spite of existing indications (79.5%). These were: CVS risk score >10% with no treatment, anemia with no treatment (Hgb<10 mg/dl), (dyslipidaemia, DM and HTN) with no treatment, absence of DMARDs, and vitamin D deficiency with no treatment. Other causes were no use or unregular use of DMARDs due to low economic status and a low dose of vitamin D.

Two point twelve percent (2.12%) of the problems were caused by unnecessary drug treatment, where it was caused by patient deciding to use aspirin 50mg per day or 75mg every other day on their own without any indication, using two PPIs for the same indication, and patient deciding to use amoxicillin when her inflammation gets high, vitamin D 50,000 IU weekly without indication, or folic acid without MTX, SSZ or anemia.

And only 0.47% reported an unclear problem or complaint due to the wrong drug given to the patient due to the unavailability of the drug in the hospital (rosuvastatin 20 prescribed but atorvastatin 10mg was dispensed), and patient diagnosed for only 3 months and was put on biological DMARDs infliximab, which is not according to the guidelines.

The interventions proposed by clinical pharmacist were mostly proposing patient drug counselling (32.9%), discussing the interventions with the prescriber (30.5%), changing the instructions for use (11.3%), asking the prescriber for information (7.3%), pausing or stopping medication (5.9%), informing the prescriber only (5.7%), proposing no intervention (5.2%), changing the dosage (0.71%), and starting medication (0.5%).

In our study, the mean age of the patient group was 51.9 ±12.3 years, ranging from 18 to 80 years. Conversely, a retrospective study carried out in Malaysia [103], with a sample size closely resembling ours (n = 200), reported a mean age of 62.1±12.5 years within an age range of 22 to 91 years. The subtle variations in reported age across these studies are believed to stem from distinct sample collection criteria and differences in population aging

Our data, like prior studies, shows a significant prevalence of female patients, with 91.1% being female. Similarly, a cohort study in Columbia found that 87.4% of 419 RA patients [110] were female. Another study in Columbia, involving 78 patients, discovered a 91.02% [111] female frequency. In a Malaysian study of 860 patients, 83.4% were women. The consistent observation of a high percentage of female RA patients across various studies may be related to the influence of the female sex hormone estrogen, which has been linked to inflammation, and the male sex hormone testosterone, known for its protective effects [26-28].

In our study sample, the prevalent comorbidities among rheumatoid arthritis (RA) patients included hypertension (42.57%), diabetes mellitus (18.32%), and dyslipidaemia (14.85%). These findings are consistent with the study conducted in Malaysia (103], where hyperlipidaemia (56%), hypertension (55%), and type 2 diabetes mellitus (33%) were identified as the most prevalent comorbid conditions. Similarly, a prospective interventional study in India (108] reported hyperlipidaemia at (24.6%), hypertension at (21.7%), and type 2 diabetes mellitus at (20.9%) as the most frequently recorded comorbid diseases in individuals with systemic autoimmune disorders. In contrast, an international study by Dougados et al. [147] identified depression (15%), asthma (6.6%), and cardiovascular events as the most common comorbidities in RA patients, differing from our findings and those in the Malaysian and Indian studies. This could be due to the negative cultural influences in some countries on mental disease, especially depression, where the focus is more on physical and metabolic diseases. Low public awareness and stigma put further limits on patients' ability to seek diagnosis, recognition, and professional help.

Similar to the observations of a cohort study in conducted in Brazilian hospitals [149] where (64.8%) of the RA patients were overweight and (26.9%) were obese. Our study showed a high percentage (78.8%), of the patients being classified as overweight

or obese, which is thought to be due to the individuals' sedentary and minimal physical activity, given that (84.7%) of the patients were unemployed, with the majority of them being housewives, and to the patients' long exposure to steroids due to their low cost and easy availability compared to the high cost of DMARDs, which are even unavailable and difficult to obtain in some cases.

Unlike previous studies on IBD and older individuals, and RA, which considered scores of 20 [145] and ≥23 [150,151] as adherence, our research follows the model used in the study for Type 2 Diabetes Mellitus patients [152]. In our study, adherence means having a MARS-5 score of 25, tailored to the needs of managing conditions like rheumatoid arthritis and chronic diseases. We set a higher bar to stress the importance of consistent medication use in effectively controlling disease activity.

Our data indicates that only 36.5% of the 203 patients were consistent with their prescribed medications, with the majority (63.5%) falling into the nonadherent category. Our findings align with the study on Nigerian RA patients [153), reporting high non-adherence (48.5% to 63.9%). And one systemic review indicated that the MARS-5 questionnaire recorded scores below 25 in two individuals who were not adherent to steroids, five patients using csDMARDs, and three patients receiving b/tsDMARDs [154]. In contrast to a Netherlands study [150] that focused on Rheumatoid Arthritis (RA) patients using Disease Modifying Antirheumatic Drugs (DMARDs), which reported 68% adherence with the Compliance Questionnaire on Rheumatology (CQR) and 60% with Medication Adherence Scale (MARS-5), our study differs in criteria. Unlike their MARS-5 score of ≥23 for adherence, we employed different standards and assessed adherence to all prescribed medications. These differences are believed to be due to the fact that only a few studies on RA patients' medication adherence use the MARS-5 questionnaire, with variations in demographics and cutoff scores across existing research.

In the attempt to find potential associations between various variables and rheumatoid arthritis (RA) disease activity, we identified three significant risk factors. Notably, female patients exhibited a lower likelihood of being in remission, as evidenced by an odds ratio of 0.157 and a statistically significant p-value of 0.003. This suggests that female patients are 6.37 times less likely to achieve remission.

We hypothesize that this association may be influenced by the demographic profile of the majority of female participants in our study—primarily married, unemployed housewives. The lifestyle of housewives often involves numerous responsibilities, prioritizing the needs of their children and family over their own well-being. Such tendencies could contribute to a higher likelihood of neglecting personal health, potentially resulting in a more pronounced disease state or activity. And as mentioned previously female sex hormone estrogen and hormonal changes in female have been shown to be associated to an increased risk of RA [26].

The second observed association, as expected, is with the adherence status of the patients. With an odds ratio of 0.297 and a significant p-value of <0.021, nonadherent patients were 3.37 times less likely to be in remission compared to adherent patients, confirming our hypothesis and aligning with previous studies examining that observed this association between adherence and disease activity in RA patients [155,156], that low adherence is closely correlates with worsened disease activity. The low adherence observed in our RA population can be attributed to multiple factors, including the economic constraints faced by patients due to the high costs of medications, not only for RA but also for other necessary treatments related to comorbidities. The majority of patients being unemployed further exacerbates this challenge. In addition, suboptimal communication and misunderstandings with physicians are contributing factors. Factors such as crowded clinics, a high patient volume in both public and private settings, and limited consultation time with physicians may impede effective communication and understanding between patients and healthcare providers.

The last association identified regarding disease activity is linked to the presence of drug-related problems (DRPs), with an odds ratio of 4.425 and a significant p-value of 0.004. Patients with at least one observed DRP are 4.425 times more likely to not be in remission compared to those without any identified drug-related issues. This finding aligns with an interventional study in Egypt [112], where the implementation of pharmaceutical care services and resolution of DRPs significantly reduced the disease activity score in RA patients. The prevalence of DRPs among RA patients may be attributed to the complex nature of the disease, necessitating constant monitoring and medication adjustments. Notably, a considerable percentage of patients rely on family

members to purchase medications, potentially leading to rushed purchase and insufficient information gathering. Inadequate information interchange between physicians and pharmacists about patients and medications. Furthermore, a lack of thorough monitoring and a failure to gather adequate medical and drug histories by both pharmacists and physicians contribute to an increased risk of medication-related side effects.

Conclusion:

This study concludes the importance of pharmacist monitoring and interventions in the attempt to help the RA patients reach the goal of treatment and a controlled disease activity. By only focusing on the two major factors of increasing the adherence status of the patients and detecting, preventing, and resolving drug-related problems, a substantial improvement can be observed in disease control, therefore leading to the prevention of the adverse impact of the disease itself on both the physical and emotional wellbeing of the patients, yielding a less invasive and less expensive treatment.

The current study has certain limitations. Conducted within a single city and with a relatively small sample size, the findings may not be widely applicable to the entire nation. While the study's cross-sectional design allows for the assessment of relationships between variables, it does not provide insight into the direction of these relationships. To obtain a more comprehensive understanding, an interventional clinical trial study is necessary to better understand the effect of pharmaceutical care services by pharmacists in RA patients. Additionally, the recorded blood pressure measures, HbA1c, and lipid profile were collected for all patients, regardless of whether their conditions were controlled or if they were taking medications for lipid-lowering, antihypertensive, or antidiabetic purposes.

6. REFERENCE:

1. Rheumatoid Arthritis [Internet]. [cited 2023 Oct 22]. Available from: https://rheumatology.org/patients/rheumatoid-arthritis

2. Bullock J, Rizvi SAA, Saleh AM, Ahmed SS, Do DP, Ansari RA, et al. Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract. 2019 Mar;27(6):501–7.

3. van den Hoek J, Boshuizen HC, Roorda LD, Tijhuis GJ, Nurmohamed MT, van den Bos G a. M, et al. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. Rheumatol Int. 2017 Apr;37(4):487–93.

4. Cai Y, Zhang J, Liang J, Xiao M, Zhang G, Jing Z, et al. The Burden of Rheumatoid Arthritis: Findings from the 2019 Global Burden of Diseases Study and Forecasts for 2030 by Bayesian Age-Period-Cohort Analysis. J Clin Med. 2023 Feb 6;12(4):1291.

5. Al_Badran AHK, Algabri HC, Saeedi KRHA, Alqazzaz1 AM. Incidence of Rheumatoid Arthritis at Marjan Teaching Hospital in Babylon, Iraq (2014–2019). Med J Babylon [Internet]. 2022 [cited 2023 Oct 24];19(3). Available from: https://www.iasj.net/iasj/article/247426

6. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The Lifetime Risk of Adult-Onset Rheumatoid Arthritis and Other Inflammatory Autoimmune Rheumatic Diseases. Arthritis Rheum. 2011 Mar;63(3):633–9.

7. Romão VC, Fonseca JE. Etiology and Risk Factors for Rheumatoid Arthritis: A State-of-the-Art Review. Front Med [Internet]. 2021 [cited 2023 Oct 24];8. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.689698

8. Symmons DPM. Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome. Best Pract Res Clin Rheumatol. 2002 Dec;16(5):707–22.

9. Branch NSC and O. National Institute of Arthritis and Musculoskeletal and Skin Diseases. NIAMS; 2017 [cited 2023 Oct 24]. Rheumatoid Arthritis. Available from: https://www.niams.nih.gov/health-topics/rheumatoid-arthritis

10. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569–81.

11. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatol Oxf Engl. 2012 Dec;51 Suppl 6:vi5-9.

12. Treatment of rheumatoid arthritis in adults resistant to initial conventional synthetic (nonbiologic) DMARD therapy [Internet]. [cited 2023 Oct 24]. Available from: https://medilib.ir/uptodate/show/7490

13. Rheumatoid Arthritis Treatment Options [Internet]. Johns Hopkins Arthritis Center. [cited 2023 Oct 24]. Available from: https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-treatment/

14. Ni XF, Yang CS, Bai YM, Hu ZX, Zhang LL. Drug-Related Problems of Patients in Primary Health Care Institutions: A Systematic Review. Front Pharmacol. 2021 Aug 17;12:698907.

15. Jimmy B, Jose J. Patient Medication Adherence: Measures in Daily Practice. Oman Med J. 2011 May;26(3):155–9.

16. Fernandez-Lazaro CI, García-González JM, Adams DP, Fernandez-Lazaro D, Mielgo-Ayuso J, Caballero-Garcia A, et al. Adherence to treatment and related factors among patients with chronic conditions in primary care: a cross-sectional study. BMC Fam Pract. 2019 Sep 14;20(1):132.

17. Fischer K, Brzosko I, Brzosko M. Chapter 53 - Atherosclerosis in Systemic Autoimmune Rheumatic Diseases. In: Perricone C, Shoenfeld Y, editors. Mosaic of Autoimmunity [Internet]. Academic Press; 2019 [cited 2023 Oct 24]. p. 589–92. Available from: https://www.sciencedirect.com/science/article/pii/B9780128143070000530

18. Handbook of Systemic Autoimmune Diseases. In: Handbook of Systemic Autoimmune Diseases [Internet]. Elsevier; 2017 [cited 2023 Oct 24]. p. ii. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128039977210016

19. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care. 2012 Dec;18(13 Suppl):S295-302.

20. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Lond Engl. 2020 Oct 17;396(10258):1204–22.

21. Sullivan PW, Ghushchyan V, Huang XY, Globe DR. Influence of rheumatoid arthritis on employment, function, and productivity in a nationally representative sample in the United States. J Rheumatol. 2010 Mar;37(3):544–9.

22. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005 Mar;4(3):130–6.

23. Silva-Fernández L, Macía-Villa C, Seoane-Mato D, Cortés-Verdú R, Romero-Pérez A, Quevedo-Vila V, et al. The prevalence of rheumatoid arthritis in Spain. Sci Rep. 2020 Dec 9;10(1):21551.

24. Zlatković-Švenda M, Saraux A, Tuncer T, Dadoniene J, Miltiniene D, Gilgil E, et al. Rheumatoid arthritis and spondyloarthritis prevalence in four European countries - a comparative study. Srp Arh Celok Lek. 2022;150(7–8):421–7.

25. Wysocki T, Olesińska M, Paradowska-Gorycka A. Current Understanding of an Emerging Role of HLA-DRB1 Gene in Rheumatoid Arthritis-From Research to Clinical Practice. Cells. 2020 May 2;9(5):1127.

26. McCarthy M, Raval AP. The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. J Neuroinflammation. 2020 Oct 23;17(1):317.

27. Cutolo M, Seriolo B, Villaggio B, Pizzorni C, Craviotto C, Sulli A. Androgens and estrogens modulate the immune and inflammatory responses in rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:131–42.

28. Spector TD, Perry LA, Tubb G, Silman AJ, Huskisson EC. Low free testosterone levels in rheumatoid arthritis. Ann Rheum Dis. 1988 Jan;47(1):65–8.

29. Amini L, Kalhor M, Haghighi A, Seyedfatemi N, Hosseini F. Effect of oral contraceptive pills on rheumatoid arthritis disease activity in women: A randomized clinical trial. Med J Islam Repub Iran. 2018;32:61.

30. Klareskog L, Malmström V, Lundberg K, Padyukov L, Alfredsson L. Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis. Semin Immunol. 2011 Apr;23(2):92–8.

31. Qian Y, Zhang L, Wu DJH, Xie Z, Wen C, Mao Y. Genetic predisposition to smoking is associated with risk of rheumatoid arthritis: a Mendelian randomization study. Arthritis Res Ther. 2020;22:44.

32. Gremese E, Tolusso B, Gigante MR, Ferraccioli G. Obesity as a Risk and Severity Factor in Rheumatic Diseases (Autoimmune Chronic Inflammatory Diseases). Front Immunol [Internet]. 2014 [cited 2023 Oct 24];5. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2014.00576

33. Bae SC, Lee YH. Causal association between body mass index and risk of rheumatoid arthritis: A Mendelian randomization study. Eur J Clin Invest. 2019 Apr;49(4):e13076.

34. Frontiers | Alcohol Impairs Immunometabolism and Promotes Naïve T Cell Differentiation to Pro-Inflammatory Th1 CD4+ T Cells [Internet]. [cited 2023 Oct 24]. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2022.839390/full

35. Li S, Yu Y, Yue Y, Zhang Z, Su K. Microbial Infection and Rheumatoid Arthritis. J Clin Cell Immunol. 2013 Dec;4(6):174.

36. Jiang H, Chess L. Regulation of immune responses by T cells. N Engl J Med. 2006 Mar 16;354(11):1166–76.

37. Youinou P, Taher TE, Pers JO, Mageed RA, Renaudineau Y. B lymphocyte cytokines and rheumatic autoimmune disease. Arthritis Rheum. 2009 Jul;60(7):1873–80.

38. Huizinga TWJ, Amos CI, van der Helm-van Mil AHM, Chen W, van Gaalen FA, Jawaheer D, et al. Refining the complex rheumatoid arthritis phenotype based on specificity of the HLA-DRB1 shared epitope for antibodies to citrullinated proteins. Arthritis Rheum. 2005 Nov;52(11):3433–8.

39. Wu D, Luo Y, Li T, Zhao X, Lv T, Fang G, et al. Systemic complications of rheumatoid arthritis: Focus on pathogenesis and treatment. Front Immunol [Internet]. 2022 [cited 2023 Oct 24];13. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2022.1051082

40. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007 Jun 5;146(11):797–808.

41. Sobhy N, Ghoniem SA, Eissa BM, Kamal A, Medhat A, Elsaid NY. Disease characteristics in high versus low titers of rheumatoid factor or anti-citrullinated peptide antibody in rheumatoid arthritis patients. Egypt Rheumatol. 2022 Oct 1;44(4):325–8.

42. Isaacs JD, Cohen SB, Emery P, Tak PP, Wang J, Lei G, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis. 2013 Mar;72(3):329–36.

43. Bobbio-Pallavicini F, Caporali R, Alpini C, Moratti R, Montecucco C. Predictive value of antibodies to citrullinated peptides and rheumatoid factors in anti-TNF-alpha treated patients. Ann N Y Acad Sci. 2007 Aug;1109:287–95.

44. Liu J, Gao J, Wu Z, Mi L, Li N, Wang Y, et al. Anti-citrullinated Protein Antibody Generation, Pathogenesis, Clinical Application, and Prospects. Front Med. 2021;8:802934.

45. Rombouts Y, Willemze A, van Beers JJBC, Shi J, Kerkman PF, van Toorn L, et al. Extensive glycosylation of ACPA-IgG variable domains modulates binding to citrullinated antigens in rheumatoid arthritis. Ann Rheum Dis. 2016 Mar;75(3):578–85.

46. Salma K, Nessrine A, Krystel E, Khaoula EK, Noura N, Khadija E, et al. Rheumatoid Arthritis: Seropositivity versus Seronegativity; A Comparative Cross-sectional Study Arising from Moroccan Context. Curr Rheumatol Rev. 2020;16(2):143–8.

47. Kgoebane K, Ally MMTM, Duim-Beytell MC, Suleman FE. The role of imaging in rheumatoid arthritis. SA J Radiol. 2018 Jul 11;22(1):1316.

48. Heidari B. Rheumatoid Arthritis: Early diagnosis and treatment outcomes. Casp J Intern Med. 2011;2(1):161–70.

49. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020 Jun;79(6):685–99.

50. Santos EJF, Duarte C, Marques A, Cardoso D, Apóstolo J, da Silva JAP, et al. Effectiveness of non-pharmacological and non-surgical interventions for rheumatoid arthritis: an umbrella review. JBI Database Syst Rev Implement Rep. 2019 Jul;17(7):1494–531.

51. Sobue Y, Kojima T, Ito H, Nishida K, Matsushita I, Kaneko Y, et al. Does exercise therapy improve patient-reported outcomes in rheumatoid arthritis? A systematic review and meta-analysis for the update of the 2020 JCR guidelines for the management of rheumatoid arthritis. Mod Rheumatol. 2022 Jan 5;32(1):96–104.

52. Majnik J, Császár-Nagy N, Böcskei G, Bender T, Nagy G. Non-pharmacological treatment in difficult-to-treat rheumatoid arthritis. Front Med. 2022 Aug 29;9:991677.

53. Siqueira U, Valente L, Mello M, Szejnfeld V, Pinheiro M. Effectiveness of Aquatic Exercises in Women With Rheumatoid Arthritis: A Randomized, Controlled, 16-Week Intervention—The HydRA Trial. Am J Phys Med Rehabil. 2016 Jul 1;96:1.

54. Brady SM, Fenton SAM, Metsios GS, Bosworth A, Duda JL, Kitas GD, et al. Different types of physical activity are positively associated with indicators of mental health and psychological wellbeing in rheumatoid arthritis during COVID-19. Rheumatol Int. 2021 Feb;41(2):335–44.

55. Zangi HA, Mowinckel P, Finset A, Eriksson LR, Høystad TØ, Lunde AK, et al. A mindfulness-based group intervention to reduce psychological distress and fatigue in patients with inflammatory rheumatic joint diseases: a randomised controlled trial. Ann Rheum Dis. 2012 Jun;71(6):911–7.

56. Hewlett S, Almeida C, Ambler N, Blair PS, Choy EH, Dures E, et al. Reducing arthritis fatigue impact: two-year randomised controlled trial of cognitive behavioural approaches by rheumatology teams (RAFT). Ann Rheum Dis. 2019 Apr;78(4):465–72.

57. Terpstra JA, van der Vaart R, Ding HJ, Kloppenburg M, Evers AWM. Guided internet-based cognitive-behavioral therapy for patients with rheumatic conditions: A systematic review. Internet Interv. 2021 Dec;26:100444.

58. Pineda-Juárez JA, Lozada-Mellado M, Hinojosa-Azaola A, García-Morales JM, Ogata-Medel M, Llorente L, et al. Changes in hand grip strength and body weight after a dynamic exercise program and Mediterranean diet in women with rheumatoid arthritis: a randomized clinical trial. Physiother Theory Pract. 2022 Apr;38(4):504–12.

59. Guan Y, Hao Y, Guan Y, Bu H, Wang H. The Effect of Vitamin D Supplementation on Rheumatoid Arthritis Patients: A Systematic Review and Meta-Analysis. Front Med. 2020;7:596007.

60. Akbar U, Yang M, Kurian D, Mohan C. Omega-3 Fatty Acids in Rheumatic Diseases: A Critical Review. JCR J Clin Rheumatol. 2017 Aug 1;23:1.

61. Guerreiro CS, Calado Â, Sousa J, Fonseca JE. Diet, Microbiota, and Gut Permeability—The Unknown Triad in Rheumatoid Arthritis. Front Med. 2018 Dec 14;5:349.

62. Attia AMM, Ibrahim FAA, Abd El-Latif NA, Aziz SW, Elwan AM, Abdel Aziz AAA, et al. Therapeutic antioxidant and anti-inflammatory effects of laser acupuncture on patients with rheumatoid arthritis. Lasers Surg Med. 2016 Jul;48(5):490–7.

63. Király M, Varga Z, Szanyó F, Kiss R, Hodosi K, Bender T. Effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis - a randomized controlled trial. Braz J Phys Ther. 2017;21(3):199–205.

64. Transcutaneous electrical nerve stimulation (TENS) for the treatment of rheumatoid arthritis in the hand - PubMed [Internet]. [cited 2023 Oct 24]. Available from: https://pubmed.ncbi.nlm.nih.gov/12918009/

65. Dose-Response Relationship Between Neuromuscular Electrical Stimulation and Muscle Function in People With Rheumatoid Arthritis - PubMed [Internet]. [cited 2023 Oct 24]. Available from: https://pubmed.ncbi.nlm.nih.gov/31197369/

66. Abbasi M, Mousavi MJ, Jamalzehi S, Alimohammadi R, Bezvan MH, Mohammadi H, et al. Strategies toward rheumatoid arthritis therapy; the old and the new. J Cell Physiol. 2019 Jul;234(7):10018–31.

67. Song YJ, Cho SK, Kim H, Kim HW, Nam E, Choi CB, et al. Factors associated with selection of targeted therapy in patients with rheumatoid arthritis. PLOS ONE. 2023 Jan 10;18(1):e0280234.

68. Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. Nat Rev Rheumatol. 2020 Mar;16(3):145–54.

69. Breedveld F, Dayer J. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2000 Nov;59(11):841–9.

70. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. JAMA. 2018 Oct 2;320(13):1360–72.

71. van Vollenhoven R. Treatment of rheumatoid arthritis: State of the art 2009. Nat Rev Rheumatol. 2009 Oct 1;5:531–41.

72. Moura CS, Schieir O, Valois MF, Thorne C, Bartlett SJ, Pope JE, et al. Treatment Strategies in Early Rheumatoid Arthritis Methotrexate Management: Results From a Prospective Cohort. Arthritis Care Res. 2020 Aug;72(8):1104–11.

73. Petzer JP, Petzer A. Leflunomide, a Reversible Monoamine Oxidase Inhibitor. Cent Nerv Syst Agents Med Chem. 2016;16(2):112–9.

74. Skorpen CG, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016 May 1;75(5):795–810.

75. Bischoff SC, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, et al. ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease. Clin Nutr Edinb Scotl. 2020 Mar;39(3):632–53.

76. Patient education: Sulfasalazine and the 5-aminosalicylates (Beyond the Basics) - UpToDate [Internet]. [cited 2023 Oct 27]. Available from: https://www.uptodate.com/contents/sulfasalazine-and-the-5-aminosalicylates-beyond-the-basics

77. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Semin Arthritis Rheum. 1993 Oct;23(2 Suppl 1):82–91.

78. Versus Arthritis [Internet]. [cited 2023 Oct 27]. Hydroxychloroquine. Available from: https://versusarthritis.org/about-arthritis/treatments/drugs/hydroxychloroquine/

79. Gonzalez Caldito N. Role of tumor necrosis factor-alpha in the central nervous system: a focus on autoimmune disorders. Front Immunol. 2023 Jul 7;14:1213448.

80. Assessing, managing and monitoring biologic therapies for inflammatory arthritis.

81. Kuek A, Hazleman BL, Ostör AJK. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J. 2007 Apr;83(978):251–60.

82. Tumor Necrosis Factor (TNF) Inhibitors [Internet]. [cited 2023 Oct 27]. Available from: https://rheumatology.org/patients/tumor-necrosis-factor-tnf-inhibitors

83. Shagroni T, Cazares AR, Kim JA, Furst DE. Nonsteroidal Anti-Inflammatory Drugs, Disease-Modifying Antirheumatic Drugs, Nonopioid Analgesics, & Drugs Used in Gout. In: Katzung BG, Vanderah TW, editors. Basic & Clinical Pharmacology [Internet]. 15th ed. New York, NY: McGraw-Hill; 2021 [cited 2023 Oct 27]. Available from: accessmedicine.mhmedical.com/content.aspx?aid=1176467346

84. Calabrese LH, Molloy ES. Progressive multifocal leucoencephalopathy in the rheumatic diseases: assessing the risks of biological immunosuppressive therapies. Ann Rheum Dis. 2008 Dec;67 Suppl 3:iii64-65.

85. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008 Nov;67(11):1516–23.

86. Patel DD, Lee DM, Kolbinger F, Antoni C. Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis. 2013 Apr;72 Suppl 2:ii116-123.

87. Tiong B, Hahn B, Aung T. Treatment of Autoimmune Disease: Established Therapies. In 2020. p. 1415–35.

88. Wallenstein GV, Kanik KS, Wilkinson B, Cohen S, Cutolo M, Fleischmann R, et al. Effects of the oral Janus kinase inhibitor tofacitinib on patient-reported outcomes in patients with active rheumatoid arthritis: results of two Phase 2 randomised controlled trials. Clin Exp Rheumatol. 2016;34(3):430–42.

89. Dowty ME, Lin TH, Jesson MI, Hegen M, Martin DA, Katkade V, et al. Janus kinase inhibitors for the treatment of rheumatoid arthritis demonstrate similar profiles of in vitro cytokine receptor inhibition. Pharmacol Res Perspect. 2019 Dec;7(6):e00537.

90. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012 Aug 9;367(6):508–19.

91. Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017 Jan;76(1):88–95.

92. George MD, Baker JF, Winthrop K, Hsu JY, Wu Q, Chen L, et al. Risk for Serious Infection With Low-Dose Glucocorticoids in Patients With Rheumatoid Arthritis : A Cohort Study. Ann Intern Med. 2020 Dec 1;173(11):870–8.

93. Paglia MDG, Silva MT, Lopes LC, Barberato-Filho S, Mazzei LG, Abe FC, et al. Use of corticoids and non-steroidal anti-inflammatories in the treatment of rheumatoid arthritis: Systematic review and network meta-analysis. PloS One. 2021;16(4):e0248866.

94. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023 Jan;82(1):3–18.

95. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res. 2021 Jul;73(7):924–39.

96. Mease PJ. Improving the routine management of rheumatoid arthritis: the value of tight control. J Rheumatol. 2010 Aug 1;37(8):1570–8.

97. Sengul I, Akcay-Yalbuzdag S, Ince B, Goksel-Karatepe A, Kaya T. Comparison of the DAS28-CRP and DAS28-ESR in patients with rheumatoid arthritis. Int J Rheum Dis. 2015 Jul;18(6):640–5.

98. Greenmyer JR, Stacy JM, Sahmoun AE, Beal JR, Diri E. DAS28-CRP Cutoffs for High Disease Activity and Remission Are Lower Than DAS28-ESR in Rheumatoid Arthritis. ACR Open Rheumatol. 2020 Sep;2(9):507.

99. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010 Apr;69(4):631–7.

100. Norvang V, Sexton J, Kristianslund E, Olsen I, Uhlig T, Bakland G, et al. Predicting achievement of the treatment targets at 6 months from 3-month response levels in rheumatoid arthritis: Data from real-life follow-up in the NOR-DMARD study. RMD Open. 2018 Oct 1;4:e000773.

101. Thomas K, Lazarini A, Kaltsonoudis E, Drosos A, Papalopoulos I, Sidiropoulos P, et al. Treatment patterns and achievement of the treat-to-target goals in a real-life rheumatoid arthritis patient cohort: data from 1317 patients. Ther Adv Musculoskelet Dis. 2020;12:1759720X20937132.

102. Marengo MF, Suarez-Almazor ME. Improving treatment adherence in patients with rheumatoid arthritis: what are the options? Int J Clin Rheumatol. 2015 Oct 1;10(5):345–56.

103. Ma SN, Zaman Huri H, Yahya F. Drug-related problems in patients with rheumatoid arthritis. Ther Clin Risk Manag. 2019;15:505–24.

104. Al-Azzam SI, Alzoubi KH, AbuRuz S, Alefan Q. Drug-related problems in a sample of outpatients with chronic diseases: a cross-sectional study from Jordan. Ther Clin Risk Manag. 2016;12:233–9.

105. J. W. Foppe van Mil, Nejc Horvat, Tommy Westerlund, Ina Richling, Zuidlaren,. PCNE Classification for Drug-Related Problems V9.1 [Internet]. 2020. Available from: https://www.pcne.org/upload/files/417_PCNE_classification_V9-1_final.pdf

106. Haegens L, Huiskes V, Smale EM, Bekker C, Bemt BV den. Ab1554-Hpr Drug-Related Problems Experienced by Patients with Rheumatic Diseases: A Longitudinal Observational Study. Ann Rheum Dis. 2022 Jun 1;81(Suppl 1):1877–1877.

107. Ernst ME, Iyer SS, Doucette WR. Drug-Related Problems and Quality of Life in Arthritis and Low Back Pain Sufferers. Value Health. 2003;6(1):51–8.

108. Sah S, Ramaswamy D, Madhan R. Impact of Clinical Pharmacist Interventions in Resolving Drug-Related Problems in Patients with Systemic Autoimmune Disorders. J Pharmacol Pharmacother. 2022 Feb 9;12:168–71.

109. Sah S, S R, Madhan R. HSD75 Frequency and Risk Factors for the Development of Drug Related Problems in Hospitalized Patients with Rheumatoid Arthritis. Value Health. 2022 Jul 1;25:S492–3.

110. PMS6. Adverse Drug Reactions Associated With The Use of Disease Modifying Anti-Rheumatic Drugs In Patients With Rheumatoid Arthritis | Request PDF [Internet]. [cited 2023 Oct 27]. Available from: https://www.researchgate.net/publication/273476160_PMS6_Adverse_Drug_Reactions_Associated_With_The_Use_of_Disease_Modifying_Anti-Rheumatic_Drugs_In_Patients_With_Rheumatoid_Arthritis

111. González J,1 Durán M,2 Durán J,3 Manrique E,4 Palacio B,4 Pereira I,5 Caballero E,5 Cabas E6. Risk management model in patients receiving therapy with biotechnological medications for rheumatoid arthritis in a medical center in Barranquilla, Colombia. Pharm Pharmacol Int J. 2020 Jan 9;8(1):11–4.

112. Elmenshawy H, Farouk H, Sabri N, Ahmed M. The Impact of Pharmaceutical Care Services on Patients with Active Rheumatoid Arthritis: A Randomized Controlled Study. Arch Pharm Sci Ain Shams Univ. 2022 Jun 1;6(1):141–55.

113. Chakrabarti S. What's in a name? Compliance, adherence and concordance in chronic psychiatric disorders. World J Psychiatry. 2014 Jun 22;4(2):30–6.

114. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest. 2006 Jul;130(1 Suppl):65S-72S.

115. Hugtenburg JG, Timmers L, Elders PJ, Vervloet M, van Dijk L. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. Patient Prefer Adherence. 2013 Jul 10;7:675–82.

116. Al-Hassany L, Kloosterboer SM, Dierckx B, Koch BC. Assessing methods of measuring medication adherence in chronically ill children-a narrative review. Patient Prefer Adherence. 2019;13:1175–89.

117. Lam WY, Fresco P. Medication Adherence Measures: An Overview. BioMed Res Int. 2015;2015:217047.

118. Measuring Medication Adherence [Internet]. [cited 2023 Oct 27]. Available from: https://medicine.musc.edu/departments/family-medicine/research/rcmar/medication-adherence

119. Kang JH, Choi SE, Xu H, Park DJ, Lee JK, Lee SS. Non-adherence to methotrexate was associated with high disease activity and poor health-related outcomes during a 4-year follow-up of rheumatoid arthritis patients. Clin Exp Rheumatol. 2022 Sep;40(9):1744–53.

120. Salaffi F, Di Carlo M, Farah S, Carotti M. Adherence to subcutaneous anti-TNFα agents in patients with rheumatoid arthritis is largely influenced by pain and skin sensations at the injection site. Int J Rheum Dis. 2020 Apr;23(4):480–7.

121. Calvo-Alén J, Vela P, Bustabad S, Maceiras F, Carmona L, Cea-Calvo L. Satisfacción, cumplimento de expectativas y adherencia al fármaco biológico subcutáneo en pacientes con artritis reumatoide. Estudio ARCO. Reumatol Clínica. 2020 Mar 1;16(2):116–9.

122. Multilevel factors predict medication adherence in rheumatoid arthritis: a 6-month cohort study | Annals of the Rheumatic Diseases [Internet]. [cited 2023 Oct 27]. Available from: https://ard.bmj.com/content/81/3/327

123. McCulley C, Katz P, Trupin L, Yelin EH, Barton JL. Association of Medication Beliefs, Self-efficacy, and Adherence in a Diverse Cohort of Adults with Rheumatoid Arthritis. J Rheumatol. 2018 Dec;45(12):1636–42.

124. Hashmi F, Haroon M, Ullah S, Asif S, Javed S, Tayyab Z. Stress at Home and Female Gender Are Significantly Associated With Non-adherence and Poor Illness Perception Among Patients With Rheumatoid Arthritis. Cureus. 2022 Jun;14(6):e25835.

125. Chowdhury T, Dutta J, Noel P, Islam R, Gonzalez-Peltier G, Azad S, et al. An Overview on Causes of Nonadherence in the Treatment of Rheumatoid Arthritis: Its Effect on Mortality and Ways to Improve Adherence. Cureus [Internet]. 2022 Apr 27 [cited 2023 Oct 27];14(4). Available from: https://www.cureus.com/articles/93790-an-overview-on-causes-of-nonadherence-in-the-treatment-of-rheumatoid-arthritis-its-effect-on-mortality-and-ways-to-improve-adherence

126. Adherence to Treat-to-Target Management in Rheumatoid Arthritis and Associated Factors: Data from the International RA BIODAM Cohort | The Journal of Rheumatology [Internet]. [cited 2023 Oct 27]. Available from: https://www.jrheum.org/content/early/2019/09/11/jrheum.190303

127. Kehrer JP, Eberhart G, Wing M, Horon K. Pharmacy's role in a modern health continuum. Can Pharm J CPJ. 2013 Nov;146(6):321–4.

128. Manolakis PG, Skelton JB. Pharmacists' Contributions to Primary Care in the United States Collaborating to Address Unmet Patient Care Needs: The Emerging Role for Pharmacists to Address the Shortage of Primary Care Providers. Am J Pharm Educ. 2010 Dec 15;74(10):S7.

129. Healthcare | Free Full-Text | Knowledge, Perceptions, and Readiness of Telepharmacy among Hospital Pharmacists in Saudi Arabia [Internet]. [cited 2023 Oct 27]. Available from: https://www.mdpi.com/2227-9032/11/8/1087

130. Expanded roles of community pharmacists in COVID-19: A scoping literature review - PMC [Internet]. [cited 2023 Oct 27]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8704729/

131. Cook K, Elder KG, Richter SK, Ronald K. Electronic Health Records in Pharmacy Skills-based Curricula. Am J Pharm Educ. 2021 Aug;85(7):8453.

132. California Pharmacy Law Book - California State Board of Pharmacy [Internet]. [cited 2023 Oct 27]. Available from: https://www.pharmacy.ca.gov/laws_regs/pharmacy_lawbook.shtml

133. Alim U, Bishop A, Cummings G. Pharmacists in a Complex Chronic Disease Management Clinic. Can J Hosp Pharm. 2016 Dec 23;69.

134. Adams AJ, Stolpe SF. Defining and Measuring Primary Medication Nonadherence: Development of a Quality Measure. J Manag Care Spec Pharm. 2016 May;22(5):516–23.

135. Alosaimi K, Alwafi H, Alhindi Y, Falemban A, Alshanberi A, Ayoub N, et al. Medication Adherence among Patients with Chronic Diseases in Saudi Arabia. Int J Environ Res Public Health. 2022 Aug 15;19(16):10053.

136. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA. 2002 Dec 11;288(22):2880–3.

137. Simons G, Ismail N, Sandhu K, Mallen CD, Stack RJ, Pontefract S, et al. The potential role of community pharmacy staff in reducing patient delay in consulting with symptoms of rheumatoid arthritis: a qualitative study. BMC Rheumatol. 2022 Aug 24;6(1):50.

138. What Pharmacists Want Rheumatologists to Know - The Rheumatologist [Internet]. [cited 2023 Oct 27]. Available from: https://www.the-rheumatologist.org/article/what-pharmacists-want-rheumatologists-to-know/

139. پوختەیەک دەربارەی ئێمە | نەخۆشخانەی رزگاری فێرکاری [Internet]. [cited 2023 Oct 27]. Available from: https://rizgary.org/about_us

140. About [Internet]. [cited 2023 Oct 27]. Available from: https://www.cmcph.net/About

141. Sample Size Calculator by Raosoft, Inc. [Internet]. [cited 2023 Oct 27]. Available from: http://www.raosoft.com/samplesize.html

142. Home - Biozek [Internet]. [cited 2023 Oct 27]. Available from: https://www.biozek.com/

143. Diagnostics [Internet]. [cited 2023 Oct 27]. cobas® pure integrated solutions. Available from: https://diagnostics.roche.com/global/en/products/systems/cobas-pure-integrated-solutions-sys-351.html

144. DAS 28 - Disease Activity Score Calculator for Rheumatoid Arthritis [Internet]. [cited 2023 Oct 27]. Available from: https://www.4s-dawn.com/DAS28/

145. Al-Alaili MK, Abdi AM, Basgut B. Test performance of self-report adherence tools in patients with hypertension: A systematic review and a meta-analysis. Journal of Clinical Pharmacy and Therapeutics 2022;47(12):1932–44

146. Stone JK, Shafer LA, Graff LA, Lix L, Witges K, Targownik LE, et al. Utility of the MARS-5 in Assessing Medication Adherence in IBD. Inflamm Bowel Dis. 2020 Mar 20;27(3):317–24.

147. Calculator: Cardiovascular risk assessment in adults (10-year, ACC/AHA 2013) (Patient education) - UpToDate [Internet]. [cited 2023 Oct 27]. Available from: https://www.uptodate.com/contents/calculator-cardiovascular-risk-assessment-in-adults-10-year-acc-aha-2013-patient-education/print

148. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis. 2014 Jan 1;73(1):62–8.

149. High prevalence of obesity in rheumatoid arthritis patients: association with disease activity, hypertension, dyslipidemia and diabetes, a multi-center study | Advances in Rheumatology | Full Text [Internet]. [cited 2023 Nov 20]. Available from: https://advancesinrheumatology.biomedcentral.com/articles/10.1186/s42358-019-0089-1

150. Norberg S, Gustafsson M. Older Peoples' Adherence and Awareness of Changes in Drug Therapy after Discharge from Hospital. Pharm Basel Switz. 2018 May 2;6(2):38.

151. van den Bemt BJF, van den Hoogen FHJ, Benraad B, Hekster YA, van Riel PLCM, van Lankveld W. Adherence rates and associations with nonadherence in patients with rheumatoid arthritis using disease modifying antirheumatic drugs. J Rheumatol. 2009 Oct;36(10):2164–70.

152. Lee CS, Tan JHM, Sankari U, Koh YLE, Tan NC. Assessing oral medication adherence among patients with type 2 diabetes mellitus treated with polytherapy in a

developed Asian community: a cross-sectional study. BMJ Open. 2017 Sep 14;7(9):e016317.

153. Ubaka CM, Ibe OG, Amorha KC, Isah A, Okonta MJ. Medication adherence among Nigerian patients with rheumatoid arthritis: a two instruments survey. J Pharm Health Serv Res. 2021 Mar 1;12(1):11–7.

154. Singh R, Chambers S, Baranskaya A, Filer A, Falahee M, Raza K, et al. Ab0327 Developing a Clinical Assessment Tool for Difficult-to-Treat Rheumatoid Arthritis: Results from a Systematic Literature Review and Feasibility Assessment. Ann Rheum Dis. 2023 Jun 1;82(Suppl 1):1347–1347.

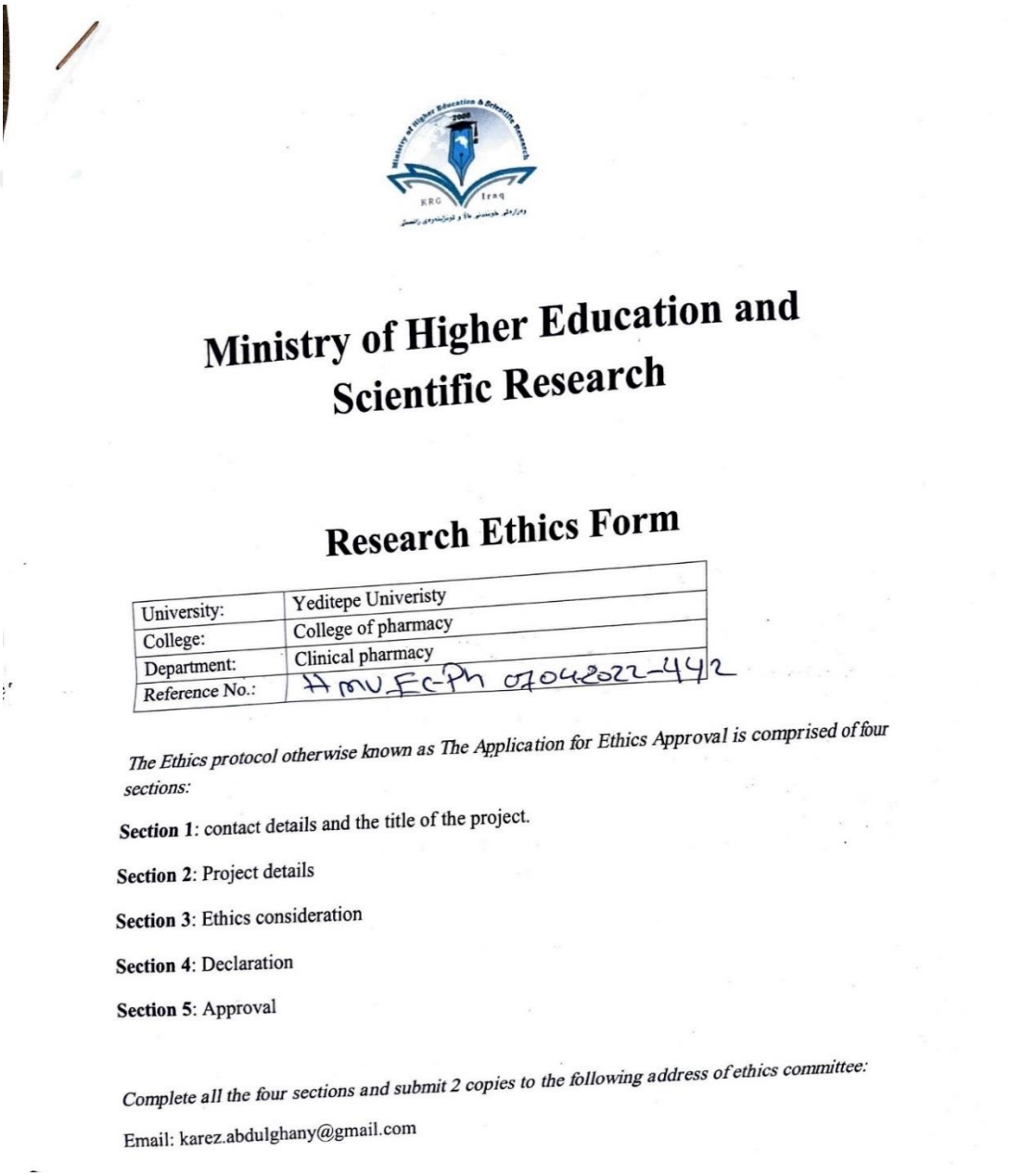
155. Li L, Cui Y, Yin R, Chen S, Zhao Q, Chen H, et al. Medication adherence has an impact on disease activity in rheumatoid arthritis: a systematic review and meta-analysis. Patient Prefer Adherence. 2017;11:1343–56.

156. Nakagawa S, Nakaishi M, Hashimoto M, Ito H, Yamamoto W, Nakashima R, et al. Effect of medication adherence on disease activity among Japanese patients with rheumatoid arthritis. PLOS ONE. 2018 Nov 2;13(11):e0206943.

7. APPENDICES

7.1. Ethical Approval

Ethical approval of this study was obtained from the Research Ethics Committee of the Ministry of Higher Education and Scientific Research in Erbil, Iraq. The reference number is **Hmu-Ec-Ph 0704-2022-442.**



Ministry of Higher Education and Scientific Research

Research Ethics Form

University:	Yeditepe Univeristy
College:	College of pharmacy
Department:	Clinical pharmacy
Reference No.:	HMU-EC-PH 07042022-442

The Ethics protocol otherwise known as The Application for Ethics Approval is comprised of four sections:

Section 1: contact details and the title of the project.

Section 2: Project details

Section 3: Ethics consideration

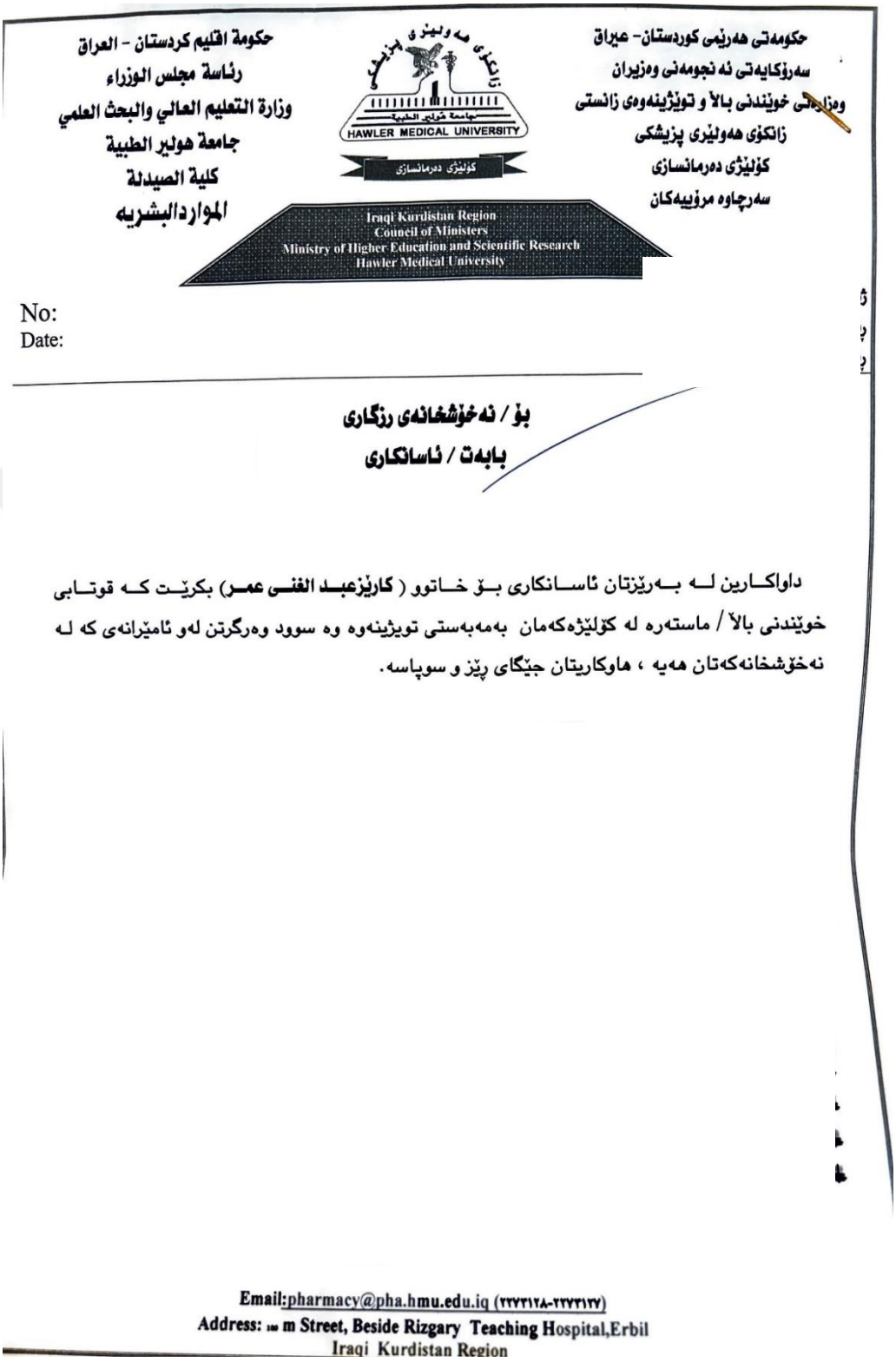
Section 4: Declaration

Section 5: Approval

Complete all the four sections and submit 2 copies to the following address of ethics committee:

Email: karez.abdulghany@gmail.com

7.2. Permission



حكومة اقليم كردستان - العراق
رئاسة مجلس الوزراء
وزارة التعليم العالي والبحث العلمي
جامعة هولير الطبية
كلية الصيدلة
الموارد البشريه

حكومەتی هەرێمی کوردستان- عیراق
سەرۆکایەتی ئەنجومەنی وەزیران
وەزارەتی خوێندنی بالآ و تویژینەوەی زانستی
زانکۆی هەولێری پزیشکی
کۆلێژی دەرمانسازی
سەرچاوە مرۆییەکان

HAWLER MEDICAL UNIVERSITY
کۆلێژی دەرمانسازی

Iraqi Kurdistan Region
Council of Ministers
Ministry of Higher Education and Scientific Research
Hawler Medical University

No:
Date:

بۆ / نەخۆشخانەی رزگاری
بابەت / ئاسانکاری

داواکارین لە بەرێزتان ئاسانکاری بۆ خاتوو (**کارێزعبد الغنی عمر**) بکرێت کە قوتابی خوێندنی بالآ / ماستەرە لە کۆلێژەکەمان بەمەبەستی تویژینەوە وە سوود وەرگرتن لەو ئامێرانەی کە لە نەخۆشخانەکەتان هەیە ، هاوکاریتان جێگای ڕێز و سوپاسە.

Email:pharmacy@pha.hmu.edu.iq (٢٢٧٢١٢٨-٢٢٧٢١٢٧)
Address: ١٥٠ m Street, Beside Rizgary Teaching Hospital,Erbil
Iraqi Kurdistan Region

7.3. Data collection form and Questionnaire

Patient Medical History Form *Date: / / 202*

Name:	
Age:	
Gender:	
Contact number:	
Occupation (Job):	
Marital Status:	

Chief compliant: ……

Duration of Disease: ……..

<u>Present Medication History:</u>

Drug	dose	Duration

<u>Other Co-morbidities:</u>

Family History:

Autoimmune disorder in the family? Yes No

If Yes, Specify who and Which type of Autoimmune disease ……

Social History:

Smoking ***Alcohol*** ***Allergies***

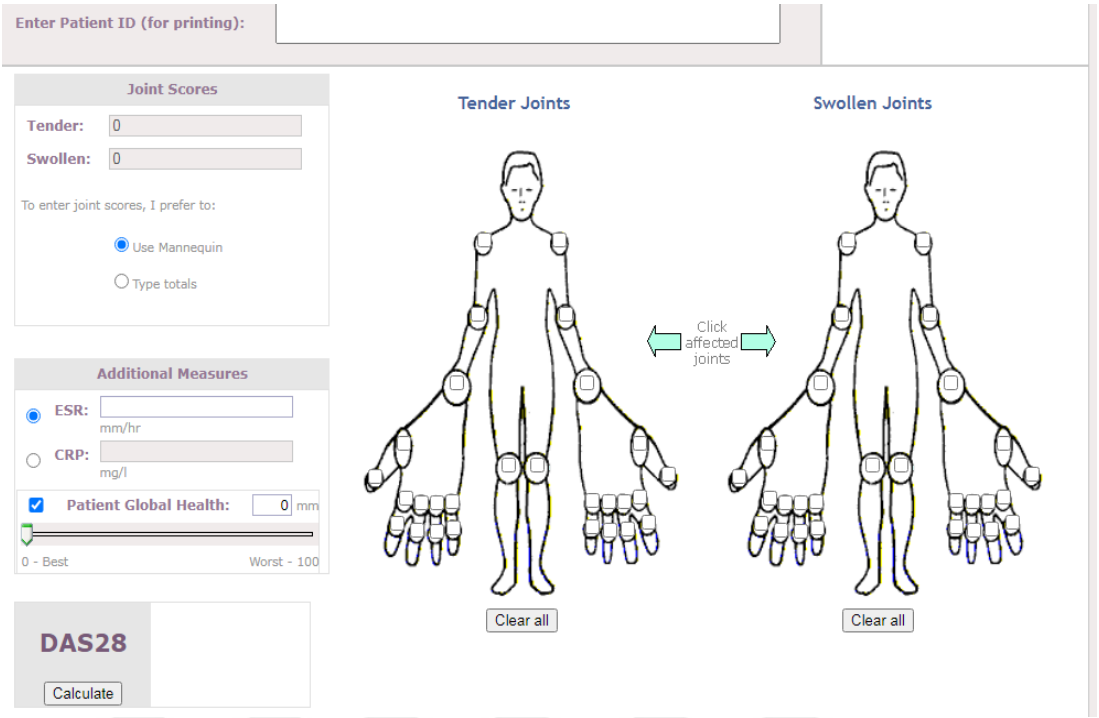
Surgery? If yes specify what surgery and when……

Lab Tests:

Test	Current Results
CRP	
ESR	
Cholesterol	
Triglyceride	
LDL	
HDL	
HbA1c	
Blood Pressure	
weight Height calculated BMI	
CBC	

DAS-28 ESR=

DAS-28 CRP=



PCNE V9.01

Primary Domain	Code V9.1	Problem
1.Treatment effectiveness There is a (potential) problem with the (lack of) effect of the pharmacotherapy.	**P1.1** **P1.2** **P1.3**	No effect of drug treatment despite correct use Effect of drug treatment not optimal Untreated symptoms or indication
2. Treatment safety Patient suffers, or could suffer, from an adverse drug event. *N.B. If there is no specific cause, skip Causes coding.*	**P2.1**	Adverse drug event (possibly) occurring
3. Other	**P3.1**	Unnecessary drug-treatment
	P3.2	*Unclear problem/complaint. Further clarification necessary (please use as escape only)*

	Primary Domain	Code V9.1	Cause

Prescribing & drug selection	**1. Drug selection** The cause of the (potential) DRP is related to the selection of the drug (by patient or health professional)	**C1.1** **C1.2** **C1.3** **C1.4** **C1.5** **C1.6**	Inappropriate drug according to guidelines/formulary No indication for drug Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements Inappropriate duplication of therapeutic group or active ingredient No or incomplete drug treatment in spite of existing indication Too many different drugs/active ingredients prescribed for indication
	2. Drug form The cause of the DRP is related to the selection of the drug form	**C2.1**	Inappropriate drug form/formulation (for this patient)
	3. Dose selection The cause of the DRP is related to the selection of the dose or dosage	**C3.1** **C3.2** **C3.3** **C3.4** **C3.5**	Drug dose too low Drug dose of a single active ingredient too high Dosage regimen not frequent enough Dosage regimen too frequent Dose timing instructions wrong, unclear or missing
	4. Treatment duration The cause of the DRP is related to the duration of treatment	**C4.1** **C4.2**	Duration of treatment too short Duration of treatment too long
Disp	**5. Dispensing** The cause of the DRP is related to the logistics of the prescribing and dispensing process	**C5.1** **C5.2** **C5.3** **C5.4**	Prescribed drug not available Necessary information not provided or incorrect advice provided Wrong drug, strength or dosage advised (OTC) Wrong drug or strength dispensed
	6. Drug use process The cause of the DRP is related to the way the patient gets the drug administered ***by***	**C6.1** **C6.2** **C6.3**	Inappropriate timing of administration or dosing intervals by a health professional Drug under-administered by a health professional Drug over-administered by a health professional Drug not administered at all by a health

	a health professional or other carer, despite proper dosage instructions (on label/list)	**C6.4** **C6.5** **C6.6**	professional Wrong drug administered by a health professional Drug administered via wrong route by a health professional
	7. Patient related The cause of the DRP is related to the patient and his behaviour (intentional or non-intentional)	**C7.1** **C7.2** **C7.3** **C7.4** **C7.5** **C7.6** **C7.7** **C7.8**	Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason Patient uses/takes more drug than prescribed Patient abuses drug (unregulated overuse) Patient decides to use unnecessary drug Patient takes food that interacts Patient stores drug inappropriately Inappropriate timing or dosing intervals Patient unintentionally administers/uses the drug in a wrong way
		C7.9	Patient physically unable to use drug/form as directed
		C7.10	Patient unable to understand instructions properly
Seamless	**8. Patient transfer related** The cause of the DRP can be related to the transfer of patients between primary, secondary and tertiary care, or transfer within one care institution.	**C8.1**	Medication reconciliation problem
	9. Other	**C9.1**	No or inappropriate outcome monitoring (incl. TDM)
		C9.2	Other cause; specify
		C9.3	No obvious cause

Primary Domain	**Code V9.1**	**Intervention**
No intervention	**I0.1**	No Intervention
1. At prescriber level	**I1.1**	Prescriber informed only
	I1.2	Prescriber asked for information
	I1.3	Intervention proposed to prescriber

	I1.4	Intervention discussed with prescriber
2. At patient level	**I2.1**	Patient (drug) counselling
	I2.2	Written information provided (only)
	I2.3	Patient referred to prescriber
	I2.4	Spoken to family member/caregiver
3. At drug level	**I3.1**	Drug changed to …
	I3.2	Dosage changed to …
	I3.3	Formulation changed to …
	I3.4	Instructions for use changed to …
	I3.5	Drug paused or stopped
	I3.6	Drug started
4. Other intervention or activity	**I4.1**	Other intervention (specify)
	I4.2	Side effect reported to authorities

Medication Adherence Report Scale-5 (MARS-5)

MARS-5.

Item	Always	Often	Sometimes	Rarely	Never
"I forget to take them"	1	2	3	4	5
"I alter the dose"	1	2	3	4	5
"I stop taking them for a while"	1	2	3	4	5
"I decide to miss out a dose"	1	2	3	4	5
"I take less than instructed"	1	2	3	4	5

Open in a separate window

The MARS-5 score was calculated by summing the numeric score (range 1-5) from each question for out of 25 (range 5-25). A higher score indicates better adherence

8. CURRICULUM VITAE

Personal Informations

Name	Karez	**Surname**	Omer

Education

Degree	Department	The name of the Institution Graduated From	Graduation year
Master			
University	Pharmacy	**Hawler Medical University- College of Pharmacy**	2019
High school	-	**Hawler Typical School for English studies**	2014

Languages	Grades (#))
English	

All the grades must be listed if there is more than one (KPDS, ÜDS, TOEFL; EELTS vs),

Work Experience

Position	Institute	Duration (Year - Year)
Scientific Marketing Specialist	Orenda Pharmaceutical Company	2021-2022
Community Pharmacist	Sana Pharmacy	2020-2021
Community Pharmacist	American Eye and Retina Center- Al Bahrani Pharmacy	2019-2020
Pharmacist Intern	Tolin Pharmacy	2017-2018

Computer Skills

Program	Level
Microsoft Office Programs (Word, Excel, PowerPoint)	Very good
SPSS software	Good

***Excellent , good, average or basic**

Scientific works

Journals in the proceedings book of the refereed conference / symposium