ENDOCRINE PROFILE AND OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfilment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(GENERAL MEDICINE)

JULY, 2020 **DR. PRANAV S KUMAR**

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DECLARATION

I hereby declare that the thesis titled "**ENDOCRINE PROFILE AND OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS**" embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled "**ENDOCRINE PROFILE AND OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS**" is the bonafide work of Dr Pranav S Kumar carried out under our guidance and supervision, in the Department of General Medicine, All India Institute of Medical Sciences, Jodhpur.

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"*Research is to see what everybody else has seen, and to think what nobody else has thought*"

- Albert Szent-Gyorgyi

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Dedicated to my family

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LIST OF ABBREVIATION

ACPA	Anti-Citrullinated Protein Autoantibodies
ACTH	Adrenocorticotropic Hormone
ADL	Activities of Daily Living
AITD	Autoimmune Thyroid Diseases
ATA	Anti Thyroid Antibodies
aTG	Anti Thyroglobulin
aTPO	Anti Thyroid Peroxidase
BMI	Body Mass Index
CDAI	Clinical Disease Activity Index
CRP	C - Reactive Protein
DAS-28	Disease Activity Score-28
DHEAS	Dehydroepiandrosterone Sulfate
EQ-5	European Quality Of Life 5 Dimension
ESR	Erythrocyte Sedimentation Rate
EULAR	European Alliance Of Associations For Rheumatology
GILZ	Glucocorticoid-Induced Leucine Zipper
HADS	Hospital Anxiety And Depression Scale
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HLA	Human Leukocyte Antigen
IHAQ	Indian Health Assessment Questionnaire
IL-1β	Interleukin 1 Beta
KFT	Kidney Function Test
LFT	Liver Function Test
MDHAQ	Multi-Dimentional Health Assessment Questionnaire
MHAQ	Modified Health Assessment Questionnaire
NIH	National Institutes Of Health
NRS	Numerical Ratings Scales
PHQ-9	Patient Health Questionnaire 9

PRL	Prolactin
PROMIS®	Patient-Reported Outcomes Measurement Information System
PROMs	Patient-Reported Outcome Measures
PSQI	Pittsburgh Sleep Quality Index
RA	Rheumatoid Arthritis
RADAI	Rheumatoid Arthritis Disease Activity Index
RAID	Rheumatoid Arthritis Impact Of Disease
SF	Synovial Fluid
SF-36	Short Form 36 Questionnaire
Th1	T Helper 1
Th17	T Helper 17
Th2	T Helper 2
TNF-α	Tumor Necrosis Factor Alpha
TRD	Treatment-Resistant Depression
VAS	Visual Analog Scale

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SUMMARY OF THE PROJECT

Background: Endocrine dysfunction in rheumatoid arthritis is known but its association to disease severity is not clearly studied. PROMs in Indian patients with rheumatoid arthritis and their clinical implication is also a neglected topic.

Aims and objectives:

Primary Objective: To determine the frequency and describe the endocrine dysfunction in rheumatoid arthritis patients.

Secondary Objective: To determine if the endocrine dysfunction is related to disease activity and PROMs.

Methods: In this cross sectional study we enrolled rheumatoid arthritis patients from 13th March 2021 to 31st July 2022 at All India Institute of Medical Sciences (AIIMS), Jodhpur. Patients were assessed clinically, DAS 28 score and various PROMs (VAS for pain, PROMIS® fatigue score, IHAQ disability index, PHQ9 depression score, PSQI for sleep and RAID score) were obtained. Patients were tested for CBC, HsCRP, ESR, Rheumatoid factor, Thyroid function test, Serum cortisol and post ACTH cortisol, prolactin, testosterone and DHEAS.

Results: One hundred and sixty RA patients were enrolled in the study. None of the patients had central hypothyroidism (TSH below the normal range). 13 patients (8.8%) had primary hypothyroidism, only 2 patients (1.3%) had subclinical hypothyroidism. 31 patients (20.9%) had sick euthyroid syndrome. 37 patients (24.34%) had prolactin levels above the normal range (Hyperprolactinemia). Among the 99 patients who had random cortisol values, 36 patients (36.4%) had adrenal insufficiency (random cortisol range below 5 µg/dl). Post ACTH Cortisol levels were available for 71 patients. Out of these 44 patients (61.9%) had adrenal insufficiency (post ACTH cortisol levels below 18 µg/dl). The endocrine parameters could not reliably predict the disease severity categories according to DAS 28 or the various PROMs studied in our patients. All of the PROMs (PROMIS fatigue, IHAQ and RAID score) except PHQ9 and PSQI could predict the disease severity in RA patients however only RAID score could independently predict disease severity. RAID score of 3.1 had a sensitivity of 77.1% and Specificity of 75.0 % in predicting DAS ESR ≥3.2. RAID score of 3.6 had a sensitivity of 71.1 % and Specificity of 70.4 % in predicting DAS CRP ≥3.2. Thus, we would like to propose a RAID score of 3.1 as the cutoff to differentiate the two categories with one needing treatment optimization and other which can be followed up on telemedicine or can be continued with same treatment.

Conclusion: Endocrine dysfunction is prevalent in RA patients but it cannot be used to determine the disease severity. We propose RAID as a patient reported score which can be used for the overall assessment of the patient and manage them as per treat to target principle.

INRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease with predominant articular system involvement presenting as symmetrical, inflammatory, small joint predominant, erosive, polyarthritis with significant peri-articular and extra-articular manifestations. The systemic complications include fatigue, lung involvement, accelerated atherosclerosis, pericarditis, dry eyes, peripheral neuropathy, vasculitis, cutaneous nodules, hematological abnormalities among others (1,2). Endocrine disorders in RA, fatigue and disorders of sleep, physical activity and mood disorders remain less explored in rheumatoid arthritis despite its wide prevalence and effect on patient reported outcomes in the management of the disease.

The prevalence of RA in India is about 0.75%(3), with predominant female preponderance in the age group of 20 to 60 years. Rheumatoid arthritis involves a complex interaction among genotype, environmental triggers, and chance. Twin studies have shown a concordance rates of 15 to 30% among monozygotic twins and 5% among dizygotic twins (4). Genome-wide analysis demonstrate that the disease is caused by immunological regulatory factors (5-8).

Clinical manifestations of RA are varying and includes both articular and extra articular. RA can affect any joint, but characteristically involves metatarsophalangeal, proximal interphalangeal and metatarsophalangeal joints, as well as the wrists and knees. Distal interphalangeal joint, first metatarsophalangeal joint and thoracolumbar spine are generally spared in RA (9-11). Long standing arthritis can lead to characteristic deformities like boutonnieres deformity, swan neck deformity, zigzag deformity among others.

Extra articular manifestations are seen in 40% of patients and are seen in patients with severe active disease and lead to increased morbidity and premature mortality. The chronic inflammatory state of RA has been shown to have causative role in extra articular manifestations like rheumatoid nodules, cardiovascular, respiratory, neurological, vascular, gastrointestinal, renal, and hematologic disease. Extra articular manifestations occur as frequently in males as in female and can occur at any age (2).

Patient Reported Outcome Measures (PROMs) in RA focus on easy, home based, self-assessment of the disease and its morbidity as perceived by the patients. This includes Generic PROMs which are widely used for many other diseases like Visual Analogue Scale (VAS), EQ-5 (European Quality of life 5 dimension), Short Form 36 questionnaire (SF-36), etc. The others are more disease specific PROMs like Health Assessment Questionnaire (HAQ), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Impact of Disease (RAID) (7). The RAID questionnaire comprises seven patient-important domains of disease impact (pain, function, fatigue, sleep disturbance, emotional well-being, physical well-being, coping). RAID was validated as a pooled-weighted score. Its seven unique components may be a useful tool in clinical practice to direct interventions that focus on the patient's experience of the disease (7).

Fatigue in RA: Fatigue is one of the most important patient complaint and affects 40 to 80% of patients(8). Fatigue experienced by patients in RA is different from normal tiredness and is viewed by patients as overwhelming, uncontrollable and often untreatable (9). The pathogenesis and optimal management of fatigue is incompletely understood. It has shown association

with pro inflammatory markers in blood, disease severity and duration, behavioral, sleep, hormonal and psychological factors (10) .

Role of Endocrine system in RA:

For RA the available data support the view that inflammatory and immune system inhibitory mechanisms involving the hypothalamic-pituitary-adrenal axis are deficient.

In various studies it has been noted that the corticosteroid levels appear to be "inappropriately" normal in RA patients even though pro inflammatory mediators in blood such as TNF α, IL1 and IL6 are clearly very high. Additionally, it has been proposed that the prolonged elevation of pro-inflammatory cytokines and interleukins, which inhibit the adrenal gland, is responsible for the irregularity in the nocturnal production of corticosteroids. This could explain why RA patients experience clinical joint symptoms in the morning. To back up these claims, numerous studies were conducted to examine the differences between steroid administration at night and in the morning. The results showed that prednisolone administered at night in low physiological doses had a very favorable impact on the length of morning stiffness and joint pain. The use of corticosteroids in therapy of RA also predisposes patients to adrenal suppression and steroid related side effects.

The current literature is not conclusive as to whether Prolactin (PRL) has a broad pro-inflammatory or anti-inflammatory role in RA, rather it suggests a cell specific response to this hormone. However, PRL/cortisol ratio has found to be positively correlating with the pro-inflammatory status in the body (11). An increased prevalence of autoimmune thyroid diseases (AITD) in patients suffering from RA has been documented. In addition, several authors have described rheumatologic and non-rheumatologic manifestations of AITD most commonly polyarthralgias. Various anti

thyroid antibodies (ATA) have been seen to have positive correlation with DAS 28, ESR (Erythrocyte Sedimentation Rate) and other parameters. Low serum levels of gonadal androgens (androstenedione, testosterone, and dihydrotestosterone) and adrenal androgens (dehydroepiandrosterone sulphate) have been detected in both women and men with RA. Additionally, RA patients have higher levels of testosterone to oestrogen conversion due to peripheral tissues' enhanced aromatase activity, which is stimulated by inflammatory mediators.

As the role of endocrine hormones is wide ranging there are implications for systemic symptoms and PROMs in RA. This study aims to explore the relationship between RA disease activity, PROMs and endocrine profile of patients.

REVIEW OF LITERATURE

Patient-Reported Outcome Measures (PROMs)

Many RA patients still experience severe effects from the disease even when the inflammatory process has been completely controlled, necessitating supplementary therapies (12). This backs up the idea of adopting two distinct goals, one centred on the inflammatory process and the other on the impact of the disease on patients' life. A variety of assessments such as laboratory or imaging, clinician-reported end measures and patient-reported outcome measures (PROMs) are used to determine the severity of the disease and the accompanying disability. Clinician reported outcomes like Disease Activity Score-28 (DAS-28) and Clinical Disease Activity Index (CDAI) are widely used for monitoring the disease progression and treatment response in patients but have a limitation of needing a hospital visit for formal assessment of tender and swollen joint count. Additionally, they place more emphasis on the inflammatory process and place less emphasis on factors that are more important to the patient, such as sleep, weariness, and functional handicap, among other things. (13). For this purpose multiple patient-reported outcome measures (PROMs) have been proposed and validated. We will review some of the existing PROMs in the following paragraphs.

RAID (Rheumatoid Arthritis Impact of Disease):

It is a patient derived weighted score which was designed to assess the impact on RA. This study for the elaboration of a patient derived composite response index for use in clinical trials in RA was funded by EULAR (European Alliance of Associations for Rheumatology) was conducted in Europe and published in 2009 (14). Ten patients suggested 17 domains or areas of health for including into score, then 96 patients

from 10 European countries ranked them according to the degree of importance. The top seven areas of importance were chosen. After significant literature research on psychometric features and professional judgment, instruments were selected for each domain. 505 patients were asked to assign 100 points among the seven domains, and the results were used to determine the relative weight of each domain. The final RAID score with 7 parameters was then calculated using the average relevance ranks of these domains. The RAID score includes seven domains with the following relative weights: pain (21%), functional disability (16%), fatigue (15%), emotional well-being (12%), sleep (12%), coping (12%) and physical well-being (12%). Proposed instruments for measurement of individual parameters include the Health Assessment Questionnaire and Numerical Ratings Scales (NRS).

The study for validation of the score which was backed by EULAR was published in 2011(15). The validation study included 570 patients. Longer questionnaire combinations and NRS questions both scored well; the final RAID score is made up of seven NRS items. The final RAID correlated strongly with patient global (R=0.76) and significantly also with other outcomes (DAS28 R=0.69, short form 36 physical −0.59 and mental −0.55, $p<0.0001$ for all). Reliability was high and sensitivity to change was good compared with DAS28.

Several other studies describe the range and cutoff values of RAID score for various disease activity (7,16). One such study identified the RAID cut-off values for classifying the levels of disease activity in 622 RA patients from Europe (7). Calculating the respective 25th and 75th percentile mean values of RAID allowed for the determination of optimal cut-offs in comparison to external criteria. Based on the distributions of RAID in the different disease activity groups, the study proposed the following cut-off values for Remission: RAID ≤ 3; for Low Disease

Activity (LDA): RAID >3 and ≤4; for Medium Disease Activity (MDA): RAID >4 and ≤6; for High Disease Activity (HAD): RAID >6 (7).

To examine the RAID score's individual parameters, additional research was conducted. RAID score was verified as a pooled-weighted score in one of these studies (12). They concluded that the separate use of the individual NRS of RAID is valid, feasible, reliable, and sensitive to change, representing an opportunity to improve the assessment and treatment of disease impact with minimal questionnaire burden. Table 1 shows the wording of NRS of individual domains included in RAID and the respective instrument of reference.

Fatigue in RA(8–10,10,20–22)**:** The incidence of severe fatigue in RA is from 40-70%. Patients with rheumatoid arthritis perceive their fatigue as overwhelming, unmanageable, and frequently incurable, and perceive it as different from "normal" fatigue which is referred by patients as tiredness. A day without weariness or having energy was listed by 57% of rheumatoid arthritis patients as one of the primary signs of a "good day," which is roughly similar to being pain-free (58%) (23). Patients ranked fatigue second only to pain in terms of importance to reflect remission among the top three domains.

Mechanism of fatigue in RA (8): For a very long time, fatigue has been associated with the main symptoms of the RA including pain and joint symptoms, or drugs used to treat rheumatoid arthritis. Inflammation is viewed to have both direct and indirect role in fatigue in rheumatoid arthritis. Tumor necrosis factor (TNF)- and interleukin (IL)-6 are two inflammatory biomarkers raised in rheumatoid arthritis that have been associated to weariness (IL-6).

Table 1: Wording of NRS of individual domains included in RAID and their respective instrument of reference.

RAID NRS	***Reference instruments***
Pain *Circle the number that best describes the pain that you felt due to your RA during the last week; None (0) to extreme (10)*	*MOS-SF36 Bodily Pain* (17)
Function *Circle the number that best describes the difficulty you had in doing daily physical activities due to your RA during the last week; No difficulty (0) to Extreme difficulty (10)*	*mHAQ* (18)
Fatigue *Circle the number that best describes how much fatigue you felt due to your RA during the last week; No fatigue (0) to Totally exhausted (10)*	MOS-SF36 Vitality (17)
Emotional well-being *Considering your arthritis overall, how would you rate your level of emotional well-being during the past week? Circle the number that best describes your level of emotional wellbeing; Very good (0) to Very bad (10*)	MOS-SF36 Emotional (17)
Physical well-being *Considering your arthritis overall, how would you rate your level of physical well-being during the past week? Circle the number that best describes your level of physical wellbeing; Very good (0) to Very bad (10)*	MOS-SF36 Physical (17)
Sleep *Circle the number that best describes the sleep difficulties you felt due to your RA during the last week; None (0) to Extreme (10)*	MOS Sleep (19)
Coping *Considering your arthritis overall, how well did you cope (manage, deal, make do) with your disease during the last week; Very Well (0) to Very poorly (10)*	Helplessness

However, clinical research on the connection between rheumatoid arthritis's weariness and inflammation has produced mixed results. (24). For instance, a recent comprehensive review found that erythrocyte sedimentation rate (ESR) and fatigue had a weaker association (P = 0.09) but that C-reactive protein (CRP) and fatigue had a stronger correlation (P = 0.006). (25). In the same review, fatigue substantially linked with one clinical indicator of disease activity, DAS28 (P = 0.04), whereas another, swollen and/or tender joint count was not (P = 0.4). A systematic review and meta-analysis found that the impact of biotherapies on fatigue in rheumatoid arthritis is low, which further refutes the idea that inflammation and fatigue are strongly correlated. Most patients who receive anti-TNF medication and go into disease remission nonetheless experience fatigue (26).

There are conceptual explanations for rheumatoid arthritis fatigue (Fig. 1). Hewlett's model, which is the most comprehensive of them, supports the idea that fatigue brought on by rheumatoid arthritis most certainly has a variety of diverse origins as shown in Fig 1 (26).

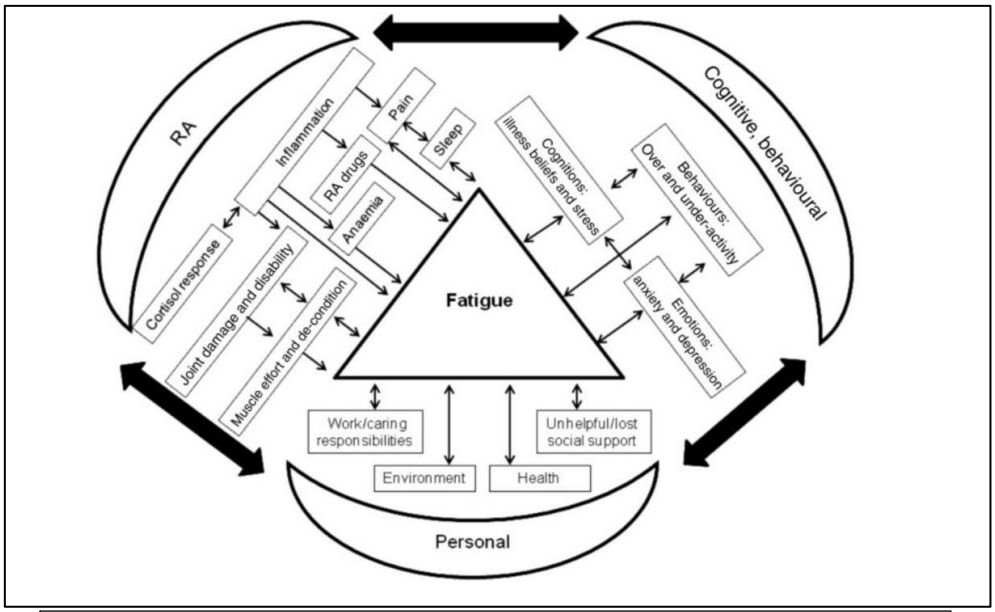


Fig 1: Hewlett Concept model of RA Fatigue.

PROMIS® Fatigue score: (Patient-Reported Outcomes Measurement Information System): The US National Institutes of Health (NIH) initiative, Patient-Reported Outcomes Measurement Information System (PROMIS®, www.nihpromis.org) is a multidisciplinary effort to develop and standardize PRO measures across the spectrum of domains of health-related quality of life applicable for multiple chronic medical conditions. This system was developed based on item response theory to provide a population-normalized metric, with limited floor and ceiling effects, and improved precision compared to most PROs in common use. PROMIS measures are reported as a T score, with the US population mean of 50 for all domains and a change in 10 representing 1 standard deviation across all domains.

PROMIS measures are free to use through www.nihpromis.org and the Assessment Center (www.assessmentcenter.net), and international expansion is ongoing. The PROMIS physical function PRO has been reported to date for RA, osteoarthritis, and scleroderma. The responsiveness of the PROMIS - Physical Function was superior to SF-36 and HAQ-DI in a study of RA patients (22).

PROMIS domains use different terms to describe score ranges. One such widely accepted domain classifies fatigue into mild/moderate/severe with T score 50 being the population median. The pictorial depiction of the various fatigue domains is given below in Fig 2. There are also studies regarding what constitutes a meaningful change in T score for the patient (20). A widely accepted score of meaningful change in fatigue promise score is published in (www.healthmeasures.net).

- Improvement: 10 points (patients and clinicians)
- Deterioration: 15 points (patients), 5 points (clinicians)

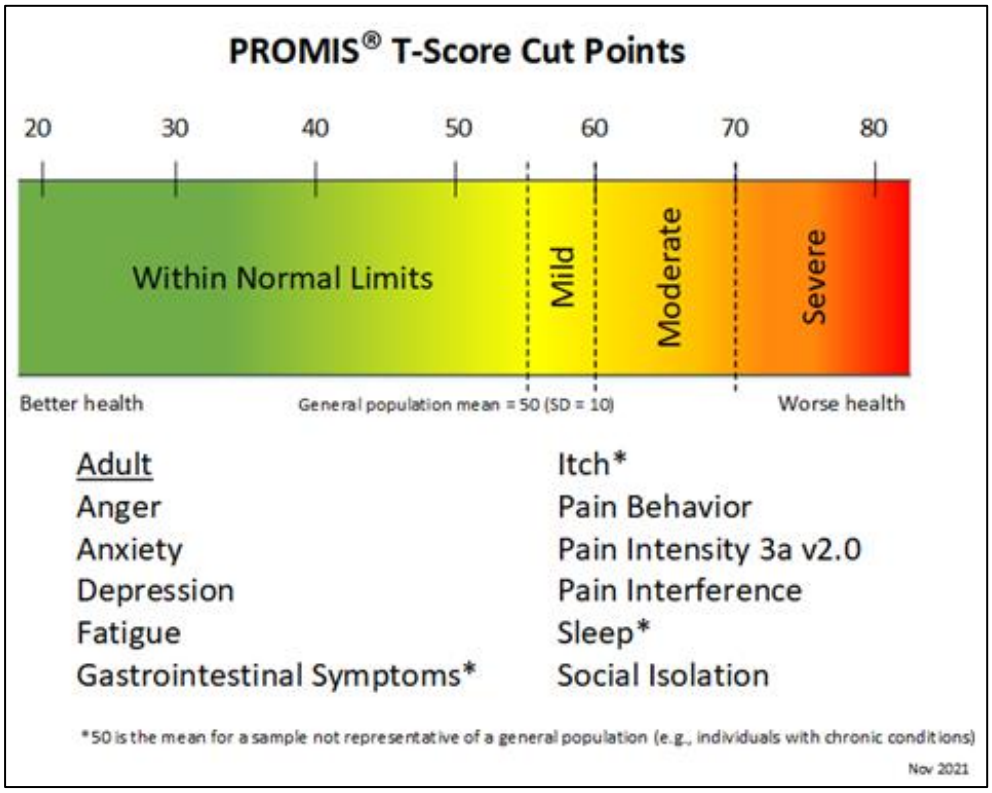


Fig 2: PROMIS T score Cut off values.

Functional Disability in RA: Loss of workdays, increased usage of healthcare services, and a higher prevalence of depression are all linked to disability in RA. Maria Intraigo et al(27) conducted a study on 395 patients of RA in which the prevalence of disability which was defined as HAQ-DI >1.25 (Health Assessment Questionnaire – Disability Index) was 26.6%. Among the determinants of disability, they found female sex, older age, greater disease duration, higher grade of pain, inflammatory markers and the level of disease activity to be positively associated with greater disability. Patients with extra-articular manifestations and comorbidities also had worse functional capacity. For this reason, early diagnosis and treatment of RA patients are crucial to minimizing the disease's negative effects on functional capacity. Additionally, it should be noted that depression is a significant comorbidity

that impairs the quality of life and worsens disability in RA patients, making interventions aimed at treating it an option to improving functional capacity and quality of life in RA patients.

Indian Health Assessment Questionnaire (IHAQ): All outcome studies on rheumatoid arthritis patients now routinely measure functional impairment (RA). The first edition of the Health Assessment Questionnaire-Disability Index (HAQ-DI) was released by 1980 by Fries et al.(28) from Stanford University, USA. Three years later, Pincus et al.(18) published an abridged version ('Modified HAQ' or MHAQ), keeping only eight of the original 20 questions and demonstrating that the MHAQ accurately captured the data obtained. They then released a more comprehensive instrument known as the multi-dimensional HAQ (MDHAQ), in which items from the psychological domain and more complex everyday activities were included to the MHAQ. A Kumar et al.(29) from AIIMS Delhi modified MDHAQ for the Indian context and developed IHAQ-DI (Indian Health Assessment Questionnaire Disability Index).

Eight basic activities of daily living (ADL), six advanced ADL, and four psychological domain items make up the MDHAQ. The following adjustments were made to get the Indian HAQ. One item was added to the eight basic ADL, namely, 'Are you able to squat in the toilet or sit cross-legged on the floor?' due to the distinctiveness and relevance of these two activities to Indian culture and lifestyle. Because the Indian HAQ was designed to measure physical rather than psychological handicap, the psychological domain was left out. The resulting 12 ADL (activity of daily living) IHAQ was compared to the originally suggested 8 ADL-MHAQ by Pincus et al. (18) and it was found to be comparable. In the study by A Kumar et al.(29), when using 12-ADL HAQ, disability index values were higher than when

using 8-ADL MHAQ. The difference was found to be statistically significant (paired t-test, $P<0.001$).

As a result, the Indian HAQ is a valid, accurate, and reliable instrument for assessing functional impairment in RA. It is available in both in English or Hindi. It's ideal for busy rheumatology clinics because it only takes three minutes to finish.

Depression in RA(30,31)**:** Depression is more prevalent in RA patients than in the general population, and it has been linked to greater levels of physical impairment, exhaustion, pain, and health-related quality of life. It has also been linked to higher health care expenses. Therefore, depression may be a helpful area to focus on for therapies targeted at enhancing RA patients' subjective health and quality of life. A Systemic Meta-analysis by Faith Matcham et al.(31) for the prevalence if depression in RA showed that according to the PHQ-9 (Patient Health Questionnaire 9), the prevalence of depression was 38.8% (95% CI 34%, 43%), and prevalence levels according to the HADS (Hospital Anxiety and Depression Scale) with thresholds of 8 and 11 were 34.2% (95% CI 25%, 44%) and 14.8% (95% CI 12%, 18%), respectively. The average age of the sample had the biggest impact on the prevalence of depression.

There is strong proof that depression has a detrimental effect on how RA develops. Depression is linked to a decreased risk of remission as well as a deterioration in health-related quality of life. It also worsens arthritis-related problems, intensifies pain levels, and increases disease activity. Depression is also associated to an increased mortality in RA, with a proportional mortality due to depression of 6.9%. There are numerous causes that can account for these detrimental impacts of depression. Firstly, depression leads to incompliance to treatment. It can also decrease

pain tolerance and ability to participate in physical activity. Additionally, patient reported outcomes may be impacted by cognitive impairment and poor cognitive views associated with depression. Finally, depression may also worsen inflammation, in keeping with the inflammatory hypothesis, aggravating the symptoms of RA. Pharmacology is a key component of the multidisciplinary approach to treating severe depressive disorder. The term "treatment-resistant depression" (TRD) is used for severe depression when there has been a failure of at least two evidence-based, dose-dependent, time-tailored treatment regimens (> 4 weeks).

Higher levels of TNF-, IL-6, IL-8, C-reactive protein (CRP), and macrophage in inflammatory protein1 were found in patients with treatment-resistant depression, and these markers are also linked to less favourable treatment results. (32). TNF and IL6 play a big part in depression among these. There is evidence that several anti-inflammatory medications, like N-acetyl cysteine and minocycline, can effectively cure very severe depression episodes. It is well documented that there is a link between TNF and mood problems. A promising adjuvant therapy for antidepressant medications is infliximab. (33). Infliximab shows a 50% reduction in depression symptoms over the course of the 12-week research.

Sleep in RA (21,36–38)**:** Beyond just affecting the joints, rheumatoid arthritis (RA) is known to affect a variety of bodily functions, including sleep and mood.. It is unclear what causes RA-related depression and poor sleep quality. Patients with arthritis have a higher prevalence of sleep disorders than those in general. In RA, auto-immune synovitis results in the production of inflammatory cytokines such Il-6 that interact with the central nervous system after crossing the blood-brain barrier. This is hypothesized to be the inflammatory cause of sleep disorder. Tocilizumab, an Il-6

antagonist, has been found to dramatically improve disease activity but not depression or sleep disorders, suggesting that mechanisms other than the IL-6 axis are at play.

A study was done by Mark Hughes et al. (36) to understand the correlation between DAS and its components with sleep in RA patients. The subjective DAS components, such as the TJC and VAS, were found to substantially correlate with PSQI (Pittsburgh Sleep Quality Index) among the 200 patients evaluated. However the objective parameters like SJC and ESR, do not have any significant relation to sleep. Additionally, they discovered that neither PHQ9 nor PSQI significantly associated with treatment approaches.

Endocrine parameters in rheumatoid arthritis patients.

Hypothalamic-Pituitary-Adrenal axis in RA(39–48): The study of neuroimmunoendocrinology of the rheumatic diseases had its origins in the Nobel Prize–winning discoveries by Hench and colleagues in 1949 on the dramatic anti-inflammatory effects of corticosteroids in RA(45). In a study by Wilder (38) it was noted that corticosteroids and HPA axis play a central role in RA pathogenesis and natural history of disease. He noted that in a previous Kirwan (46) study along with many other studies it was noted that corticosteroids levels appear to be inappropriately normal in RA patients when pro inflammatory mediators like TNF α,IL 6 and IL 1 were clearly very high. He also suggested that the importance of endogenous corticosteroids in physiological concentrations needed to be re-evaluated. Cutolo Maurixio (39) in 2018 did a review of circadian rhythms and RA. He said that cortisol, whose peak occurs about midnight, has anti-inflammatory effects whereas melatonin, which is present at higher levels at night, is pro-inflammatory. The RA joint clinical symptoms peak in early morning following the peak of melatonin and

proinflammaory markers in the night along with a peak in cortisol levels which also peaks following melatonin peak to counteract the pro inflammatory state. Therefore, it was hypothesized that supplementing with cortisol at night might aid with RA morning symptoms. Supporting this multiple studies noted that night time prednisolone therapy compared to morning prednisolone dose showed very favorable effects on the morning stiffness, joint pain and morning serum concentration of IL 6 (41,42). More recently the most advanced approach for the low dose prednisolone chronotherapy in RA included the modified release prednisone, a timing drug release with administration at 22:00 and releasing prednisone around 2:00 to 3:00 am versus morning release supported the same view.

Prolactin in RA (11,47–51) Rheumatoid arthritis (RA) affects females much more commonly than males. It's possible that hormones like prolactin (PRL) play a role in this phenomena. Women who are lactating after their first pregnancy are more likely to develop RA, which may be related to breastfeeding and the production of PRL. In earlier research, both males and females with RA had higher levels of PRL compared to controls (47,48), although these findings have not been confirmed in all studies (51). The difference in results may be due to multiple factors, one of them being a very small sample size. Additionally, it is not always obvious if morning fasting samples were obtained for PRL testing. Numerous people also believed that prolactin and prolactin-like peptides produced locally by macrophages in the inflamed synovium played a part in the activation of T cell immunity and, consequently, of autoimmune illness. The measured serum prolactin quantities did not correspond to the locally generated prolactin and prolactin-like peptides (48).

Zoli et al (49) measured serum ACTH (Adrenocorticotropic Hormone), Prolactin and Cortisol in 10 postmenopausal patients with RA at multiple times – 06:00, 10:00, 14:00, 18:00, 22:00 and 02:00 hours and interpreted the values. They found that in RA there was down regulation of ACTH and Cortisol secretion but up regulation of Prolactin secretion which induced the pro inflammatory state. Further Prolactin to Cortisol ratio was charted at the various time intervals. It was found that prolactin to cortisol ratio positively correlated with increase in pro-inflammatory cytokines and interleukins. It was also noted that the peak of prolactin and prolactin to cortisol ratio was around 2 am which correlated with peak of pro-inflammatory cytokines and further was associated with early morning joint stiffness due to increased inflammatory activity at night.

Thyroid in RA (52–57) Since the 1960s, evidence between RA and hypothyroidism has been established (54). The incidence of hypothyroidism varies from 12 % to as high as 38.4% (55). One of the generated antibodies' anti-thyroid activities may be the cause of hypothyroidism in RA patients.. One potential explanation for the coexistence of two or more autoimmune illnesses in one person is a genetic factor such as the human leucocyte antigen (HLA) type, which is often HLADR. Thyroid dysfunction may be caused by inflammatory cytokines, according to some studies (55). There has been conflicting evidence linking rheumatoid arthritis's multiple disease activities to hypothyroidism. Elattar et al. (58) found significant association of hypothyroidism with disease activity which was confirmed in Indian population by Joshi et al(55).

Ivaca Lazurova et al (53) in the study autoimmune thyroid disease (AITD) and rheumatoid arthritis stated an increased AITD in RA patients. Additionally, a number of publications have identified rheumatologic and non-rheumatologic signs of AITD, the majority of which are polyarthralgias. In the past, the majority of these symptoms were linked to an underlying thyroid disorder, especially hypothyroidism. Thyroid hormones may not directly affect rheumatic symptoms, but autoimmune processes may be more susceptible to them. Evidence that some rheumatic symptoms can appear in euthyroid patients or that autoimmune thyroiditis patients with hypothyroidism are more likely to experience them than people without the condition supports this. The association between AITD and RA was

In a study by Kozarny et al (52) Anti-thyroid antibodies were positive in 13.3 % of patients with RA (aTPO (anti thyroid peroxidase) in 9.3 %, aTG (anti thyroglobulin) in 8 %, and both aTPO and aTG in 4 %). These findings imply that the presence of ATA may be linked to RA activity.

Androgen in RA(59–64) The increased incidence of RA in female was thought because of the high estrogen which is a pro inflammatory modulator and low testosterone which has anti-inflammatory action. This was supported by many clinical and experimental evidence. At least at the level of the RA synovial tissue, androgens have anti-inflammatory effects, in contrast to the local immune-stimulating effects of oestrogens and their metabolites. (63). However Cutolo et al.(60) found that In female participants who develop RA, neither the genes for hormone receptors nor the plasma levels of androgens appear to have changed considerably. Consequently, they do not appear to be risk factors for the onset of RA. However, the anti-inflammatory effects of adrenal and gonadal androgens are greatly diminished in synovial tissues and

synovial fluid during active RA in both male and female patients, which supports a pro-inflammatory milieu at least in RA joints.

In a study by Lashkari et al (59) they found that DHEAS (dehydroepiandrosterone sulfate) and testosterone were found to be low in RA patients compared to controls. They carried out a case-control research with 59 RA patients and 61 controls who were of similar age, and they discovered that the mean testosterone and DHEAS levels of the RA group were lower than those of the control group.

Estrogen in RA(65,66) Alpizar-Rodriguez et al.(65) reviewed on role on female hormonal factors in RA. He stated that depending on serum concentration, reproductive stage, or ovarian ageing phase, oestrogens affect immune cells differently. Oestrogens promote the Th2 response and the survival of auto-reactive T and B cell clones at levels that range from periovulatory to pregnancy. On the other side, oestrogens may prevent certain cell-mediated reactions, like the development of Th17 cells. Oestrogens bind to ERs, which are distributed differently in different tissues, including the strongest form, 17b-estradiol. A preponderance of ER- β over ER-α has been observed in RA synovial tissue. The production of TNF-α and IL-6 by peripheral blood mononuclear cells is stimulated by inflammation or hypoxia, which can also boost cellular expression of ERβ.

METHODOLOGY

AIM:

To study the endocrine dysfunction in rheumatoid arthritis patients and their relation to disease severity and PROMs (Patient Reported Outcome Measures).

OBJECTIVES:

Primary Objective: To determine the frequency and describe the endocrine dysfunction in rheumatoid arthritis patients.

Secondary Objective: To determine if the endocrine dysfunction is related to disease activity and PROMs.

STUDY SETTING:

Patients attending the Department of Internal Medicine of All India Institute of Medical Sciences, Jodhpur, Rajasthan.

STUDY DURATION:

From 13th March 2021 till 31st July 2022 at the Department of Internal Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan.

STUDY PARTICIPANTS

INCLUSION CRITERIA:

1. Age >18 Years
2. Patient having rheumatoid arthritis according to EULAR ACR criteria (2010).

EXCLUSION CRITERIA:

1. Patients meeting criteria for other connective tissue disorders like SLE, polymyositis or scleroderma.
2. Pregnant females having rheumatoid arthritis.

STUDY DESIGN: Cross-sectional study

The study was conducted after getting the approval of institute's ethics committee in ethical certificate reference number AIIMS/IEC/2021/3370. Written consent was taken from the study participants. Following data were collected

Socio-demographic:

1. Clinical: Name, age and gender, duration of rheumatoid arthritis, details and duration of treatment, associated comorbidities, obstetric history and menstrual history, general physical examination including DAS 28 score, PROMISE fatigue score, PHQ9 depression score, IHAQ functional activity score, PSQI(Pittsburgh Sleep Quality Index) and RAID score
2. Investigations: All patients will undergo the following investigations.
    a. Baseline hematological and biochemical assessment as per routine clinical care including CBC, serum electrolytes, blood glucose, ESR, hsCRP, RA factor/anti CCP, KFT (Kidney Function Test) and LFT (Liver Function Test).
    b. Endocrine assessment:
    1. Thyroid function test (TFT, fT3 and fT4)
    2. Serum Cortisol baseline and 1 hour post ACTH stimulation
    3. Serum Prolactin
    4. Serum Testosterone and DHEA S

METHODOLOGY

Patients were enrolled after being diagnosed with RA according to ACR EULAR criteria (2010).

⇩

All patients underwent baseline investigations as per routine clinical care along with complete medical history, DAS 28 score, PROMIS® fatigue score, PHQ9 depression score, IHAQ disability index, PSQI (Pittsburgh Sleep Quality Index) and RAID score.

⇩

Blood investigations to evaluate endocrine profile were sent.

⇩

Relation between endocrine dysfunction, patient reported outcome measures and disease activity by DAS 28 was reviewed.

SAMPLE SIZE:

Due to the ongoing COVID 19 pandemic the sample size was kept to be dynamic and time bound, all patients presenting to department of medicine from the time of approval of thesis by Institute Ethics Committee to July 31st 2022 were enrolled.

SAMPLE COLLECTION:

All the blood samples were collected according to the standard protocol in sterile vacutainer. They were later centrifuged at 4000 rpm for 8 min and the serum thus separated was stored in vials at -80°C. Adrenal function was assessed by basal cortisol and 1 h post-intramuscular ACTH (adrenocorticotrophic hormone-250 µg) cortisol (67,68).

SAMPLE PROCESSING:

All hormones were analyzed by chemiluminescent immunoassay (Siemens Advia Centaur© immunoassay system, USA) as per the standard hospital protocol.

Chemiluminescent immunoassay kits supplied by the same company. All Samples were thawed to 30°C before running the assays.

DATA COLLECTION:

Data were collected on the first visit for the baseline assessment using following questionnaires and scales:

1. Socio-demographic proforma (Annexure 2)
2. DAS-28 ESR score and DAS 28- CRP (Annexure 3).
3. Pain VAS (Annexure 4).
4. PROMIS® Fatigue scale (Annexure 5).
5. IHAQ questionnaire for disability (Annexure 6).
6. PHQ-9 depression questionnaire (Annexure 7).
7. PSQI for sleep quality assessment (Annexure 8).
8. RAID score (Annexure 9).

Data were collected regarding symptoms and investigations which were maintained in excel sheet.

STATISTICAL ANALYSIS:

Statistical analysis was carried out using software program SPSS version 25.0. (SPSS Inc. Chicago, USA). All the nominal variables are expressed as mean ± SD, non-nominal variables in median ± Interquartile range and categorical variables as number (%). The Shapiro Wilk test was applied to assess normality of the variables. Binary logistic regression analysis was done to compare the association between various endocrine parameters collected with disease severity by DAS 28, various endocrine parameters collected with PROMs collected and the various PROMs collected with disease severity by DAS 28. Bivariate correlation analysis was done between various PROMs and endocrine parameters and is reported as Pearson correlation co efficient with p value. Multivariate regression model was constructed to see the relation between various PROMs and disease severity by DAS 28. Finally, ROC curve were constructed for RAID score in predicting disease severity as per DAS 28.

Normal laboratory range considered for the Endocrine parameters.

TSH: 0.35-5.50 mIU/L.

Free T3: 2.2-4.2 pg/ml.

Free T4: 0.89-1.76 ng/dl.

Prolactin: 2.8 – 29.2 ng/ml in nonpregnant females and 2.1-17.7 in males.

DHEAS in various groups	Normal Range in µg/dl
Female 18-29 years	80.2 – 339.5
Female 30-39 years	58.7-227.6
Female 40-49 years	46.7-247.6
Female 40-49 years	46.7-247.6
Female 50-59 years	33-212.8
Female >60 years	61.6-124.1
Male 18-29 years	161.2-561.6
Male 30-39 years	124.5-482.7
Male 40-49 years	96.9-391.5
Male 50-59 years	59.7-307.9
Male >60 years	40.8-405.4

Testosterone: 30-100 ng/dl in males and 15-70 ng/dl on females

Random Cortisol: 3.09-16.66 µg/dl

Post ACTH Cortisol < 18 µg/dl were considered to have primary adrenal insufficiency.

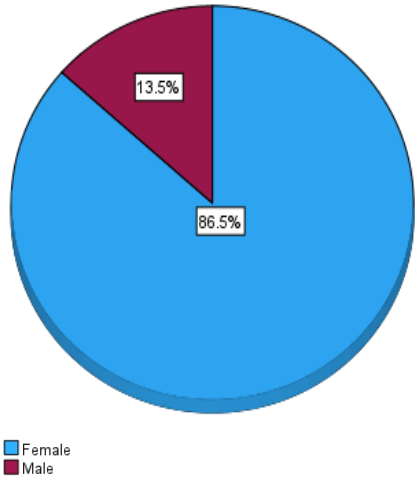
RESULTS

Patient Characteristics

A Total of 160 patients were enrolled after being diagnosed with rheumatoid arthritis according to ACR-EULAR 2010 criteria. Among them 4 had incomplete data and hence 156 were included for the final analysis.

Age and Gender distribution

The mean age of the population under study was 47.02±12.36 years. The youngest being 19 years old and oldest being 76 years. Out of 156 patients, 135 (86.5%) were females and 21 (13.5%) were males as depicted in Fig 3. The age distribution has been depicted in Fig 4.



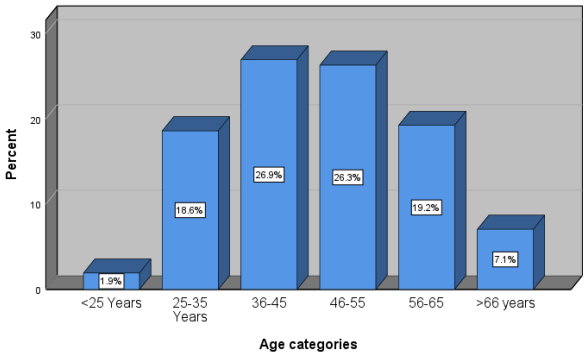


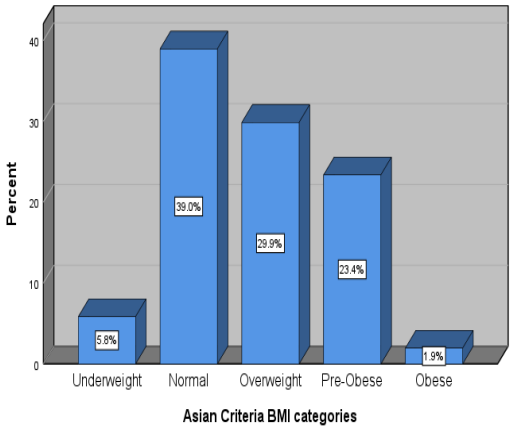
Fig 3. Gender distribution in rheumatoid arthritis patients (N=156).

Fig 4. Age distribution in rheumatoid arthritis patients (N=156).

Clinical Characteristics

Comorbidities: Among 156 patients, 15 had Iron deficiency Anaemia, 4 had hypothyroidism, 2 had ischemic heart disease, 6 had type 2 diabetes mellitus, 5 had hypertension and 12 had osteoarthritis.

Anthropometry: The mean weight of the study population was 61.78±7.58 kilogram (range 38-81). The mean height was 163.15±5.33 cm (range 148-180). The mean BMI (Body Mass Index) was 23.12±2.76 (range 14.20-34.60). Among 154 patients according to Asian BMI criteria 9 (5.8%) were underweight, 60 (39.0%) were having normal BMI, 46 (29.9%) were Overweight, 36 (23.4%) were Pre-Obese and 3 (1.9) were Obese. The BMI distribution is shown in Fig 5.



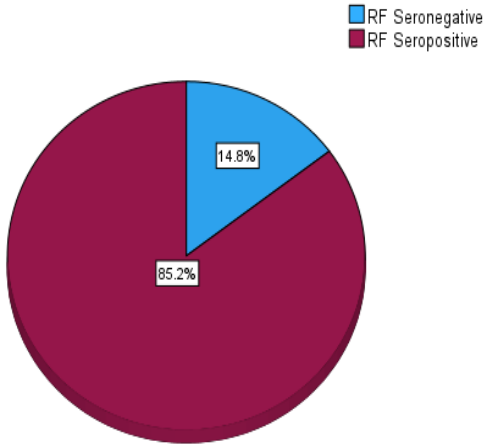


Fig 5. BMI distribution in rheumatoid arthritis patients (N=156).

Fig 6. Distribution of rheumatoid factor positivity in rheumatoid arthritis patients (N=122).

Rheumatoid factor and Anti CCP

Out of 156 patient serum rheumatoid factor values were present in 122 patients and it was positive in 104 (85.4 %) (Fig 6). Similarly, Serum Anti CCP antibodies was present in 41 patients and was positive in 32 patients (78.04 %).

Disease duration: At presentation average disease duration was 28.8±24 months. Among the study population, 25 (16%) patients were having early RA and rest 131(84%) patients had established RA and is being depicted in figure 7.

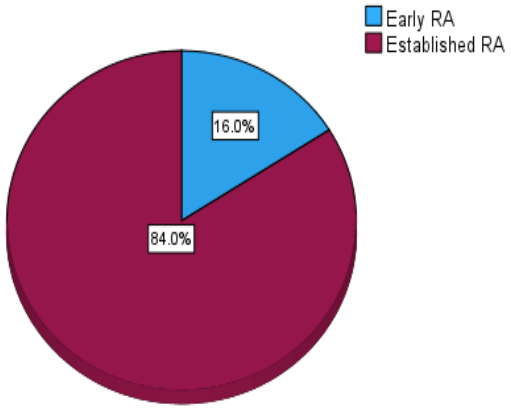


Fig 7. Disease duration in rheumatoid arthritis patients (N=156).

Treatment history

The mean cumulative methotrexate dose taken by the patients at enrolment was 1442.74±1528.72 mg (range 0-11,700). The mean cumulative steroid intake was 280.29±621.9mg (range 0-6000). Steroid use was seen in 64 patients (41.0%) and methotrexate use was present in 124 (79.4%) patients. Among 156 patients, 120 patients (76.92%) had taken some form of alternate medicine and 36 patients (23.07%) had not taken any form of alternate medicines. The clinical characteristics of RA patients have been described in Table 2.

Table 2: Clinical Characteristics of rheumatoid arthritis patients.

Parameter	Mean (±SD)
Age	47.02±12.36 years
Height	163.15±5.33 cm
Weight	61.78±7.58 kilogram
BMI	23.12±2.76 kg/m^2
Rheumatoid Factor Value	89.29±72.29 IU/ml
Cumulative Methotrexate dose	1442.74±1528.72 mg
Cumulative Steroid dose	280.29±621.90 mg

Disease activity

At presentation patients had a mean examiner assessed Tender Joint Count of 5.48±3.89 (range 0-20) Fig 6. Mean swollen Joint count was 3.67±2.70 (range 0-16) Fig 8 & Fig 9. The mean Patient Global Assessment of disease activity was 5.92±1.72 (range 1-9). The Mean Evaluator Global Assessment of disease activity was 4.63±1.54 (range 0-10).

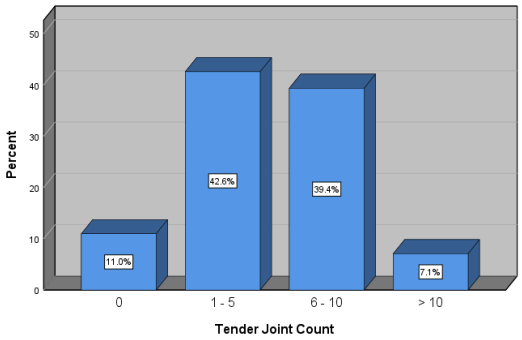


Fig 8. Distribution of Tender Joint Counts in rheumatoid arthritis patients (N=156).

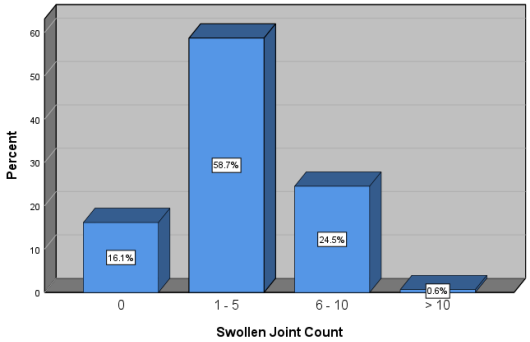


Fig 9. Distribution of Swollen Joint Counts in rheumatoid arthritis patients (N=156).

At Presentation ESR (Erythrocyte sedimentation rate) and CRP (C reactive Protein) was done for all the patients and the corresponding DAS-ESR and DAS-CRP were calculated. The Mean ESR was 50.03±26.66 mm/hour (range 2-116). The mean CRP was 19.78±26.76 mg/L (range 0.4-174.6). The mean DAS-ESR score was 5.10±1.15 (range 1.2-7.70). The mean DAS-CRP score was 4.33±1.14 (range 1.32-6.95).

According to DAS-ESR only 3 (2%) patients were in remission while, 5 (3.3%) were having Low disease activity, 63 (41.4%) were having Moderate disease activity and 81 (53.3%) had High disease activity Fig 10. According to DAS-CRP only 12 (8.3%) patients were in remission while, 12 (8.3%) were having Low disease activity, 89 (61.4%) were having Moderate disease activity and 32 (22.1%) had High disease activity Fig 11. The various Disease severity parameters have been described in Table 3.

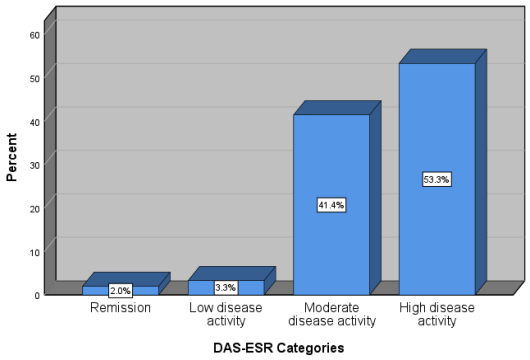


Fig 10. DAS-ESR Categories in rheumatoid arthritis patients (N=156).

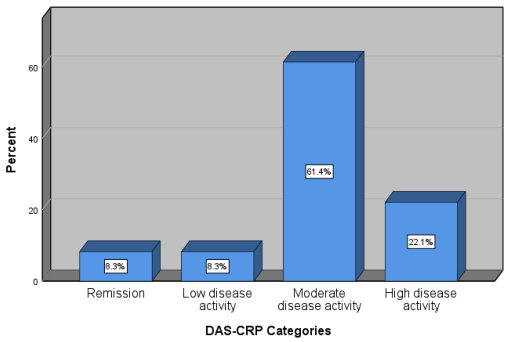


Fig 11. DAS-CRP Categories in rheumatoid arthritis patients (N=156).

Table 3: Disease activity related parameters in rheumatoid arthritis patients.

Parameters	Mean (±SD)
Tender Joint Count	5.48±3.89
Swollen Joint Count	3.67±2.70
ESR	50.03±26.66 mm/hour
CRP	19.78±26.76 mg/L
Patient Global Activity	5.92±1.72
Evaluator Global Activity	4.63±1.541
DAS-ESR	5.10±1.15

Patient Reported Outcome Measures – PROMs

The PROMs measured in the study include VAS (Visual Analogue Score), PROMIS® Fatigue T score, PHQ9 (Patient Health Questionnaire), IHAQ (Indian Health Assessment Questionnaire) and RAID score (Rheumatoid Arthritis Impact of Diseases). Shapiro Wilk test of Normalcy was used for these parameters. Among these only RAID composite score had a normal distribution while rest other parameters were not normally distributed. So the RAID score is reported in Mean with SD while for others Median and Interquartile range is reported.

The median of VAS (Visual Analog Scale) was 6.0 with Interquartile range ±2.0 (range 0-10). The median of PROMIS® Fatigue T score was 55.10 with Interquartile range ±1.60 (range 29.4-71.1). The median IHAQ (Indian Health Assessment Questionnaire) total score was 9.0 with Interquartile range ±8.40 (range 0-34). The median of IHAQ disability index was 0.77 with Interquartile range ±0.70 (range 0-2.8). The median of PHQ9 (Patient Health Questionnaire) was 2.0 with Interquartile range ±3.0 (range 0-12). The median PSQI (Pittsburgh Sleep Quality Index) was 2.0 with interquartile range ±2.0 (range (0-10). The Mean of composite RAID score (Rheumatoid Arthritis Impact of Diseases) was 4.14±1.54 (range 0.42-7.79). The median with interquartile range on PROMs have been given in table 4. The 7 individual RAID parameters are described in the table 5.

Table 4: Patient Reported Outcome Measures in rheumatoid arthritis patients.

Parameters	**Median (±IQR)**
VAS	6.0 (±2.0)
PROMIS® Fatigue T score	55.10 (±1.60)
IHAQ total score	9.0 (±8.40)
IHAQ disabilty index	0.77 (±0.70)
PHQ9	2.0 (±3.0)
PSQI	2.0 (±2.0)
RAID	4.27 (±2.26)

Table 5: RAID Score Parameters in rheumatoid arthritis patients.

RAID individual Parameters	**Median (±IQR)**
Pain	6.0 (±2.0)
Functional Disability	4.0 (±4.0)
Fatigue	6.0 (±4.0)
Sleep	2.0 (±4.0)
Physical well being	4.0 (±4.0)
Emotional well being	2.0 (±3.0)
Coping	2.0 (±2.0)
RAID composite score	4.27 (±2.26)

Fatigue: Among the RA patients in the study 58 (37.2%) were normal when compared to the reference population used by NIH in PROMIS®. Rest 98 (62.8%) had some form of fatigue. Among then 39 (25.0%) had mild fatigue, 57 (36.5%) had moderate fatigue and 2 (1.3%) had severe fatigue. This is depicted graphically in Fig 12.

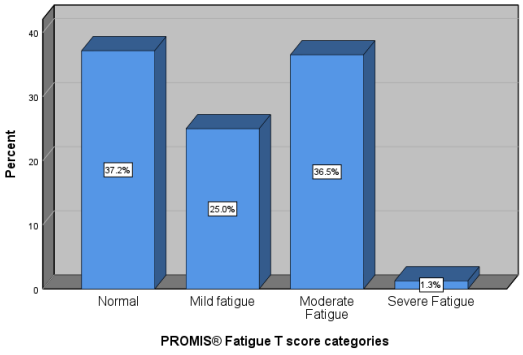


Fig 12. PROMIS® Fatigue T score Categories in RA Patients (N=156).

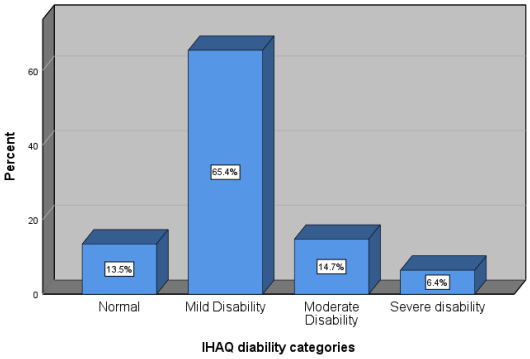


Fig 13. IHAQ disability categories bar graph in rheumatoid arthritis patients (N=156).

Disability: In our RA population under study 21 (13.5%) patients had no disability. Rest 135 (85.5%) had some form of disability. 102 (65.4%) had mild disability, 23 (14.7%) had moderate disability while 10 (6.4%) had severe disability. This is shown in bar graph below Fig 13.

Depression: In our study 22 (14.1%) patients had no depression. Rest 134 (85.9%) had some form of depression according to PHQ9. 112 (71.8%) had minimal depression, 13 (8.3%) had mild depression and 9 (5.8%) had moderate depression. Only 5 patients in the study were treated clinically for depression. The PHQ9 categories and their frequencies are described in Fig14.

RAID score: In our study, according to RAID scores, 36 (23.1%) pateints were in remission, 29 (18.6%) were having low disease activity, 73 (46.8%) were having moderate disease activity and 18 (11.5%) were having high disease activity. This is depicted in Fig 15.

Sleep: Among the study population 130 (83.3%) had good sleep quality whereas 25 (16.0%) had poor sleep quality. This has been depicted in Fig 16

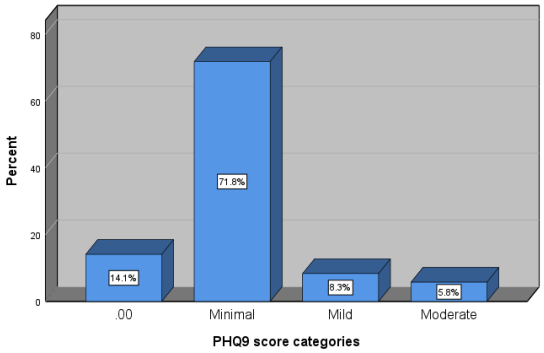


Fig 14. PHQ9 depression score categories in rheumatoid arthritis patients (N=156).

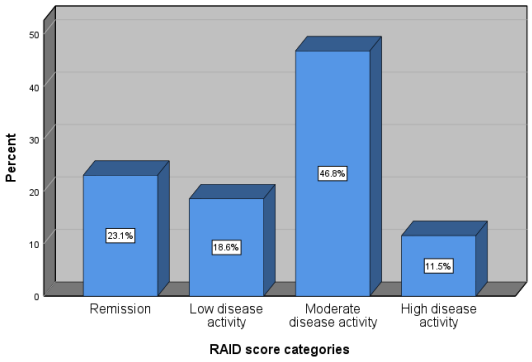


Fig 15. RAID score categories in rheumatoid arthritis patients (N=156).

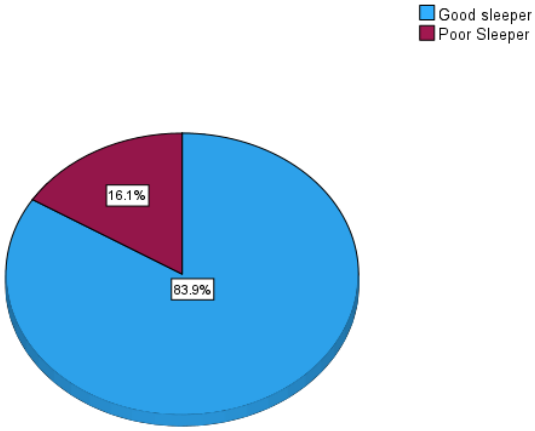


Fig 16. Sleep quality in rheumatoid arthritis patients (N=156).

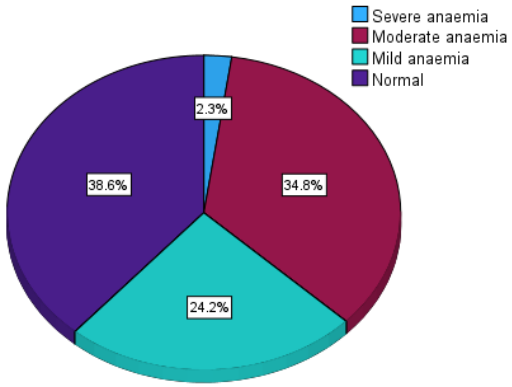


Fig 17. Anaemia according to WHO criteria in rheumatoid arthritis.

Anaemia in rheumatoid arthritis patients

Haemoglobin levels was available for 132 patients. The mean haemoglobin was 11.38±1.57 (range 8.9(7.3-16.2)). According to WHO criteria 3 patients (2.3%) had severe anaemia, 46 patients (34.8%) had moderate anaemia, 32 patients (24.2%) had mild anaemia and 51 patients (38.6%) had normal Haemoglobin value. The hemoglobin groups are shown in Fig 17.

Description of Endocrine Laboratory Parameters.

Shapiro Wilk test of Normalcy showed that all the endocrine parameters in the study population had a Non-Normal distribution. Hence their median and interquartile range is reported.

Thyroid function test (TFT)

Out of 156 patients 4 were known cases of hypothyroid at enrolment on Levothroxine supplementation. All the hypothyroid patients had TSH values in the normal range. Out of the remaining 152 patients, 148 had TFT reports. None of the patients had central hypothyroidism (TSH below the normal range). 13 patients (8.8%) had primary hypothyroidism (low fT4 and TSH >5.5 mIU/L). Only 2 patients (1.3%) had subclinical hypothyroidism (fT4 normal with TSH >5.5mIU/L). 31 patients (20.9%) had sick euthyroid syndrome. Among them 13 patients (8.9%) had low fT3 and low fT4, 14 patients (9.5%) had low fT3 and normal fT4 and rest 4 patients (2.7%) had low fT3 with increased fT4. The thyroid disorders in the RA patients under study is shown in table 6.

Table 6. Thyroid disorders in rheumatoid arthritis patients (N=148).

Thyroid Abnormality	No of Patients (%)
Primary hypothyroidism	13 (8.8%)
Subclinical hypothyroidism	2 (1.3%)
Sick Euthyroid cases low fT3 and low fT4 low fT3 and normal fT4 low fT3 with increased fT4	31 (20.9%) 13 (8.9%) 14 (9.5%) 4 (2.7%)

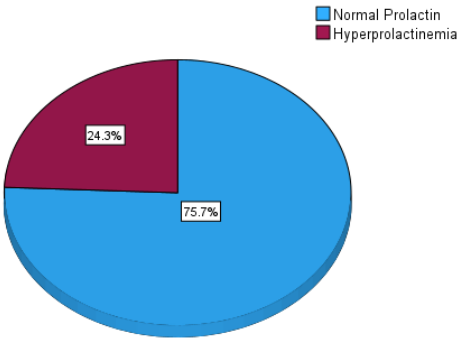
Among 148 patients 133 patients (89.9%) had TSH within the normal range (0.35-5.50 mIU/L). The median TSH value was 2.03 mIU/L with interquartile range of ±2.15 mIU/L. The TSH range was from 0.46 to 70.49 mIU/L.

Out of 148 samples the median fT4 value was 1.45 ng/dl with interquartile range of ±0.87 ng/dl. The fT4 range was from 0.36 to 9.31 ng/dl. 11 patients (7.4%) had Free T4 level below the range. In 54 (36.7%) of patients fT4 was above the normal range.

Out of 104 samples of the median fT3 value was 2.60 pg/ml with interquartile range of ±1.22 pg/ml. The fT3 range was from 0.523 to 4.502 pg/ml. 31 patients (30.4%) had Free T3 level below the normal range. Only 1 (0.96%) had fT3 above the normal range.

Prolactin

Among the study population, 152 patients had serum prolactin levels. None of the patients had prolactin below the normal range. Thirty seven patients (24.34%) had prolactin levels above the normal range (Hyperprolactinemia) Fig 18. Rest 115 (75.7%) had prolactin in the normal range. The median of serum prolactin was 14.13 ng/ml with an interquartile range of ±20.37ng/ml. The range being 3.78-377.36 ng/ml. The mean of prolactin levels in various disease categories is shown in Fig 19. The percentage of patients with hyperprolactinemia in each disease category is shown in Fig 20 and 21.



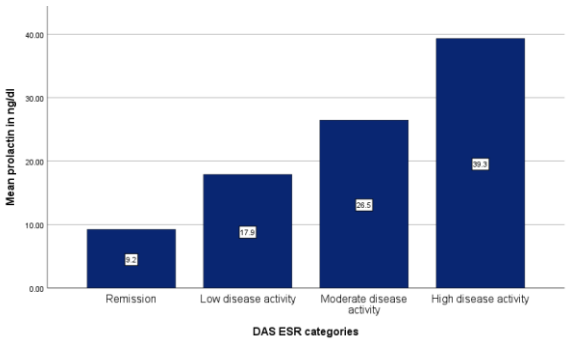


Fig 18. Hyperprolactinemia in rheumatoid arthritis patients.

Fig 19. Mean of prolactin levels in various DAS ESR categories in rheumatoid arthritis patients (N=152).

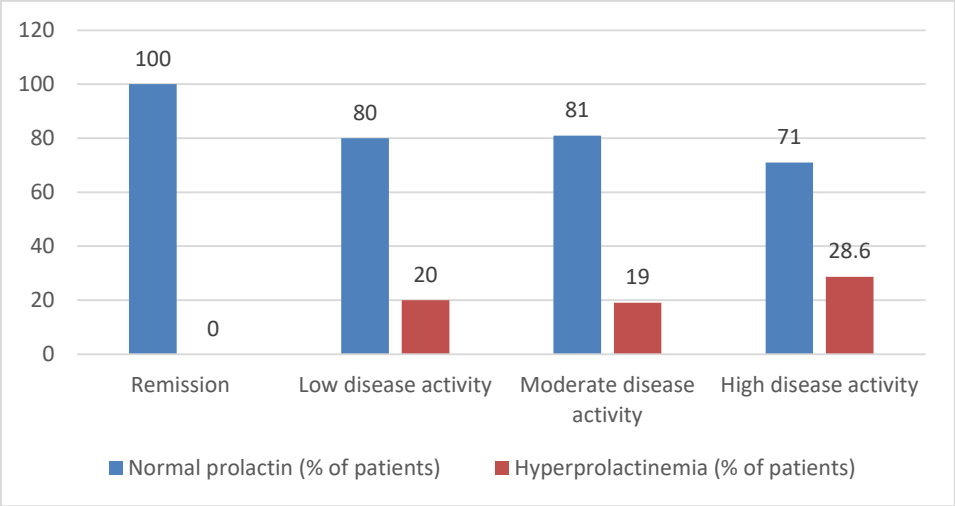


Fig 20. Percentage of patients with Hyperprolactinemia in various DAS ESR categories in rheumatoid arthritis patients (N=152).

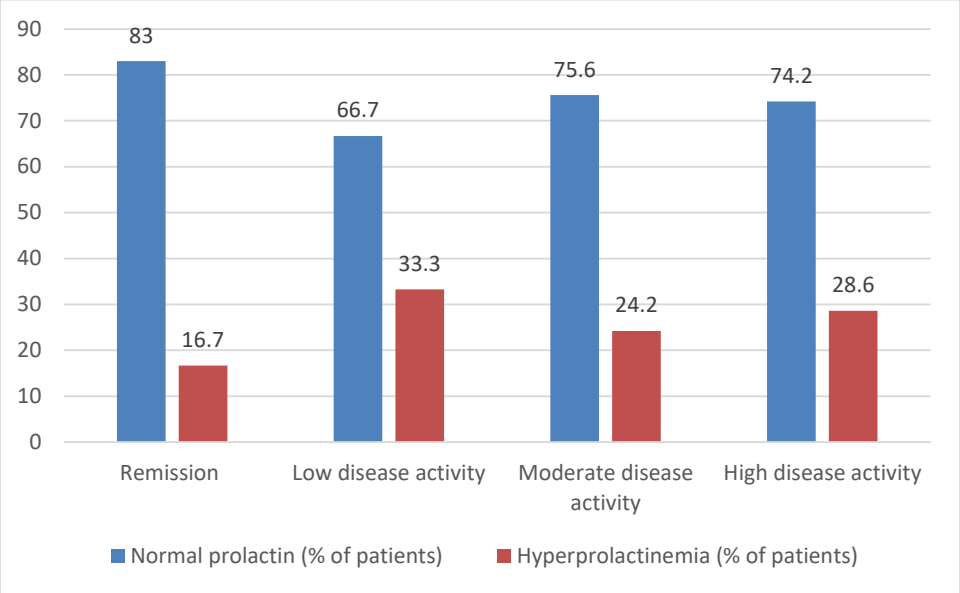


Fig 21. Percentage of patients with normal prolactin and Hyperprolactinemia in various DAS CRP categories in rheumatoid arthritis patients (N=152).

DHEAS

Out of 156 patients, 147 patients had serum DHEAS levels. Out of the total 147 patients, 88 (56.4 %) had DHEAS levels below the normal range. Only one female had DHEAS above normal range.

The median of serum DHEAS among 127 female patients was 39.17 µg/dl with an interquartile range of ±53.51 µg/dl. The range was from 1.0 to 335.6 µg/dl. Out of 126 females, 73 (57.5%) had a DHEAS level below the normal range (Fig 22). The median of serum DHEAS among 20 male patients was 40.43 µg/dl with an interquartile range of ±71.05 µg/dl. The range was from 5.5 to 162.4 µg/dl. Out of 20 males, 15 (71.4%) had a DHEAS level below the normal range (Fig 23). The percentage of patients with low DHEAS in various disease categories in shown in Fig 24 and 25.

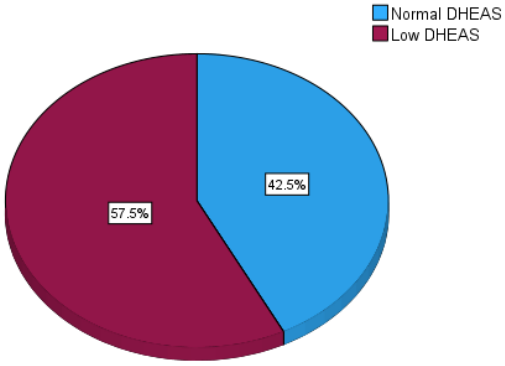


Fig 22. DHEAS in female rheumatoid arthritis patients (N=126).

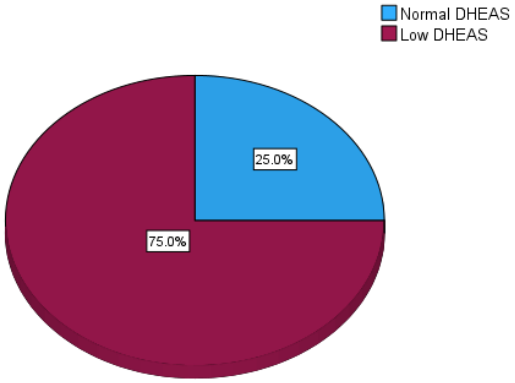


Fig 23. DHEAS in male rheumatoid arthritis patients (N=20).

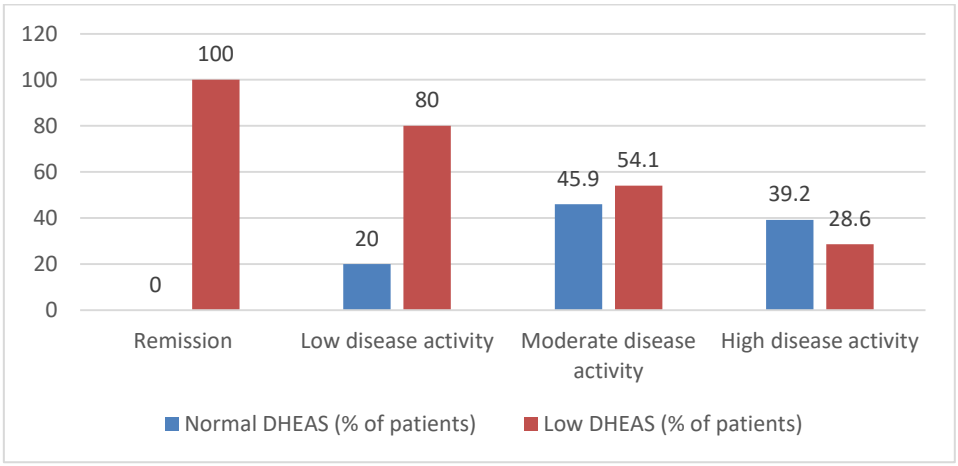


Fig 24. Percentage of patients with normal and low DHEAS in various DAS ESR categories in rheumatoid arthritis patients (N=147).

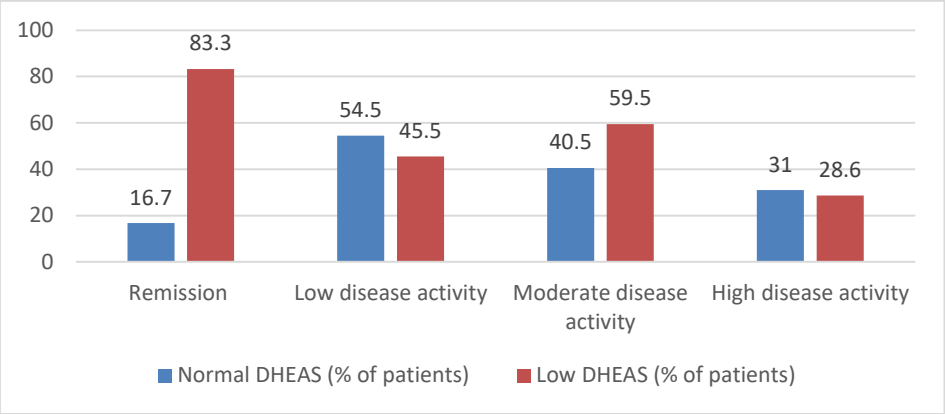


Fig 25. Percentage of patients with normal and low DHEAS in various DAS CRP categories in rheumatoid arthritis patients (N=147).

Testosterone

Among the study population, 153 patients had serum Testosterone levels and 86 patients (56.6%) had serum testosterone levels below the normal range and 14 (9.2%) had testosterone above the normal range and rest 44 (34.2%) had normal testosterone. The median serum Testosterone levels among 132 female patients was 13.33 ng/dl with an interquartile range of ±15.49 ng/dl (range 7.0- 486.86). Among 132 females, 73 (55.7%) had testosterone levels below the normal range and 14 (10.7%) had testosterone above the normal range and rest 44 (33.6%) had normal testosterone (Fig 26). The median serum Testosterone levels among 21 male patients was 191.84 ng/dl with an interquartile range of ±426.30 ng/dl (range 7.0- 529.70). Among 21 males, 13 (61.9%) had testosterone below the normal range while the rest 8 (38.1%) had normal testosterone (Fig 27). The percentage of patients with normal and low testosterone in various disease categories is shown in Fig 28 and 29.

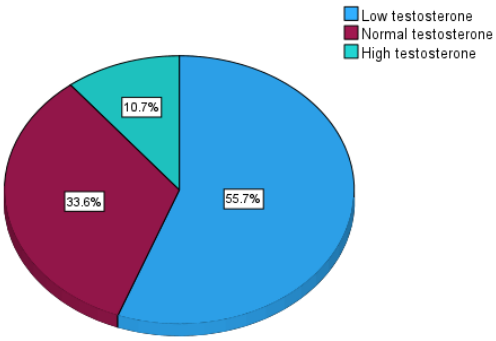


Fig 26. Serum testosterone in female rheumatoid arthritis (N=132).

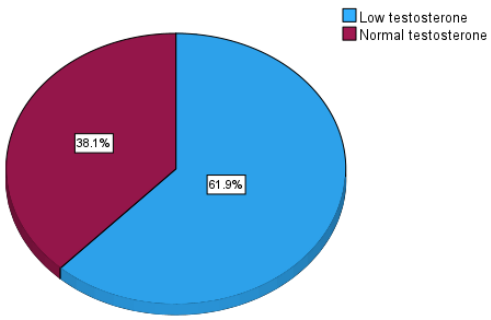


Fig 27. Serum testosterone in male rheumatoid arthritis (N=21).

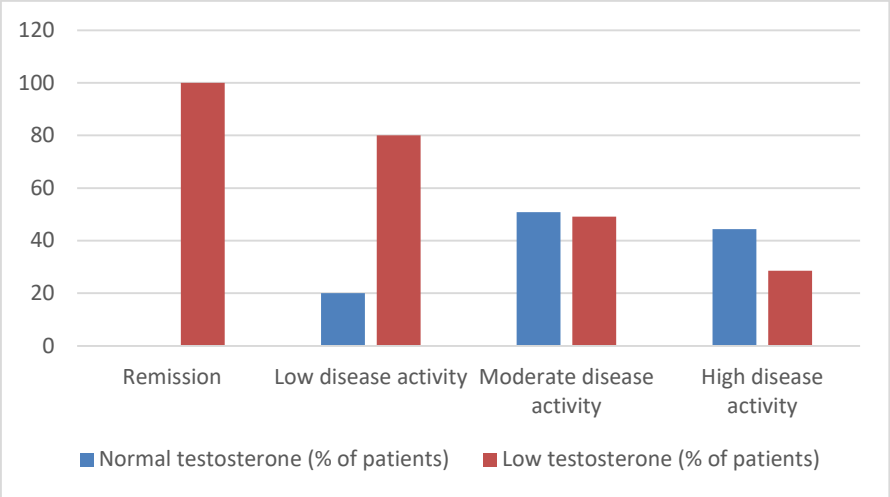


Fig 28. Percentage of patients with normal and low testosterone in various DAS ESR categories in rheumatoid arthritis patients (N=153).

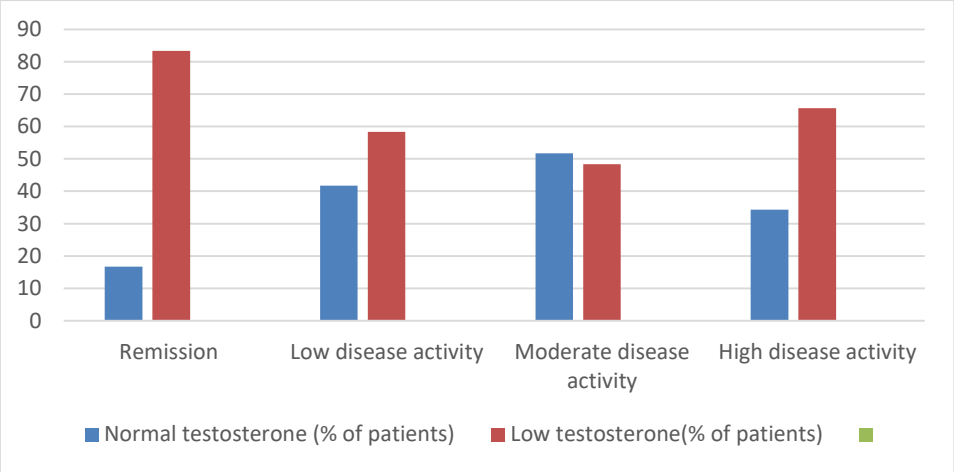


Fig 29. Percentage of patients with normal and low testosterone in various DAS CRP categories in rheumatoid arthritis patients (N=153).

Cortisol

Random cortisol levels were available for 99 patients. The median of random cortisol was 5.89 µg/dl with an interquartile range of ±5.34 µg/dl (range 0.32-22.06). Among the 99 patients who had random cortisol values, 36 patients (36.4%) had adrenal insufficiency (random cortisol range below 3 µg/dl) and the rest 63 patients (63.6%) had normal adrenal function Fig 30.

Post ACTH Cortisol levels were available for 71 patients. Out of these 44 patients (61.9%) had adrenal insufficiency (post ACTH cortisol levels below 18 µg/dl) Fig 31.

Percentage of patient with adrenal insufficiency in various disease categories is shown in Fig 32 and 33.

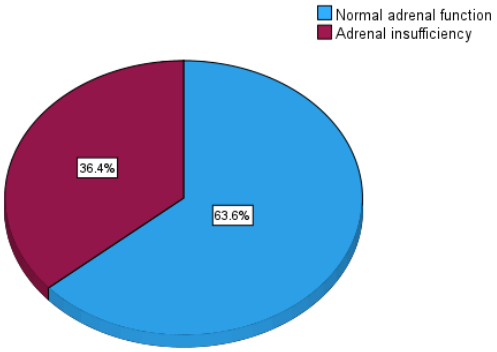


Fig 30. Adrenal insufficiency (cortisol <3 µg/dl) in rheumatoid arthritis (N=99).

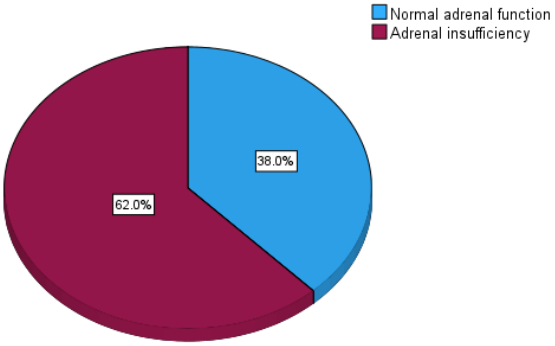


Fig 31. Primary adrenal insufficiency (post ACTH cortisol <18) in rheumatoid arthritis (N=71).

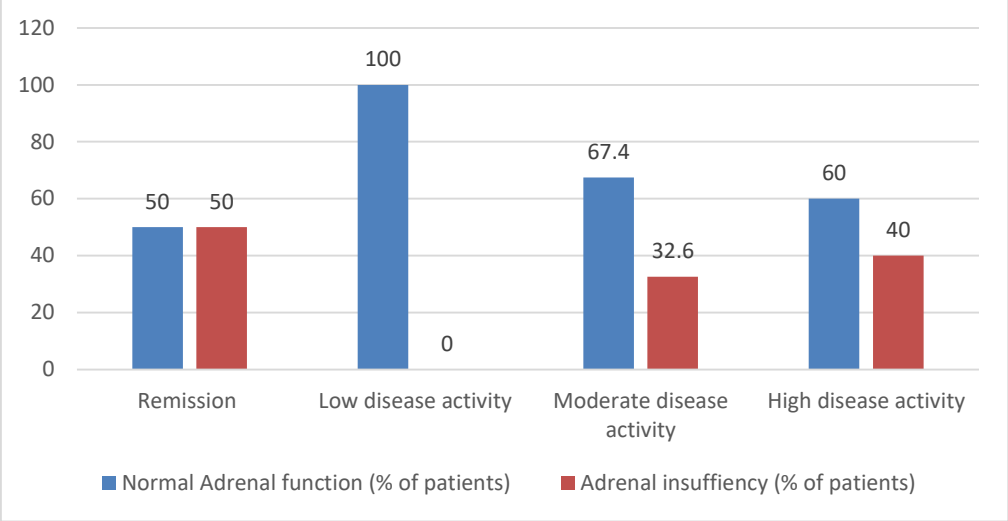


Fig 32. Percentage of patients with normal adrenal function and adrenal insufficiency in various DAS ESR categories in rheumatoid arthritis patients (N=99).

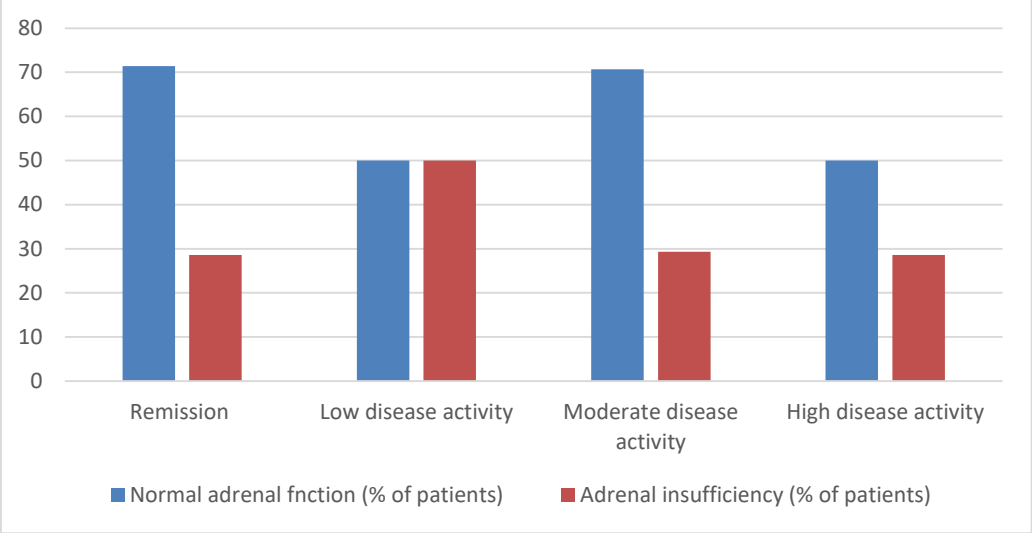


Fig 33. Percentage of patients with normal adrenal function and adrenal insufficiency in various DAS CRP categories in rheumatoid arthritis patients (N=99).

Relationship between Disease activity and Endocrine parameters.

Relationship between High disease activity and endocrine parameters.

Binary logistic regression analysis was done with dependant variable as high DAS (DAS ESR >5.1) and covariates being Prolactin, DHEAS, Testosterone, Random Cortisol, Post ACTH Cortisol and TSH values. The results have been reported in the form of odds ratio with confidence interval and p value in Table 7. None of the endocrine parameters could predict high DAS ESR (>5.1) as outcome.

Table 7: Binary Logistic Regression analysis showing relationship between high DAS ESR and Endocrine parameters.

Endocrine parameters	ODDs RATIO (95% C.I.)	p value
TSH	1.042 (0.966-1.123)	0.289
T4	1.047 (0.807-1.358)	0.730
T3	1.549 (0.941-2.551)	0.086
Prolactin	1.004 (0.997-1.010)	0.245
DHEAS	0.991 (999-1.005)	0.691
Testosterone	1.002 (0.999-1.005)	0.196
Random Cortisol	0.990 (0.906-1.081)	0.818
Post ACTH Cortisol 30min	1.017 (0.964-1.073)	0.533

Binary logistic regression analysis was done with dependant variable as high DAS (DAS CRP>5.1) and Covariates being Prolactin, DHEAS, Testosterone, Random Cortisol, Post ACTH Cortisol and TSH values. The results have been reported in the form of odds ratio with confidence interval and p value in Table 8. None of the endocrine parameters could predict high DAS CRP (>5.1) as outcome.

Table 8: Binary Logistic Regression analysis showing relationship between high DAS CRP and Endocrine parameters.

Endocrine parameters	ODDs RATIO (95% C.I.)	p value
TSH	1.038 (0.989-1.090)	0.130
T4	0.879 (0.599-1.291)	0.511
T3	1.173 (0.612-2.248)	0.630
Prolactin	0.996 (0.986-1.005)	0.394
DHEAS	0.997 (0.988-1.006)	0.488
Testosterone	0.997 (0.988-1.006)	0.735
Random Cortisol	0.975 (0.877-1.083)	0.638
Post ACTH Cortisol 30min	1.016 (0.953-1.082)	0.631

Relationship between Low disease activity and remission with Endocrine parameters.

We grouped remission and low disease activity category into a combined category. Binary logistic regression analysis was done with dependant variable as the combined category including remission and low disease activity (DAS ESR <3.2) and Covariates being Prolactin, DHEAS, Testosterone, Random Cortisol, Post ACTH Cortisol and TSH values. The results have been reported in the form of odds ratio with confidence interval and p value in Table 9. None of the endocrine parameters could predict the combined category including low disease activity and remission combined.

Table 9: Binary Logistic Regression analysis showing relationship between combined low disease and remission DAS ESR (<3.2) and Endocrine parameters.

Endocrine parameters	ODDs RATIO (95% C.I.)	p value
TSH	0.808 (0.482-1.357)	0.421
T4	1.163 (0.752-1.798)	0.498
T3	0.971 (0.345-2.733)	0.955
Prolactin	0.976 (0.928-1.026)	0.342
DHEAS	0.989 (0.968-1.010)	0.301
Testosterone	0.978 (0.927-1.032)	0.416
Random Cortisol	0.944 (0.705-1.264)	0.699
Post ACTH Cortisol 30min	1.040 (0.833-1.226)	0.638

We grouped remission and low disease activity category into a combined category. Binary logistic regression analysis was done with dependant variable as the combined category including remission and low disease activity (DAS CRP <3.2) and Covariates being Prolactin, DHEAS, Testosterone, Random Cortisol, Post ACTH Cortisol and TSH values. The results have been reported in the form of odds ratio with confidence interval and p value in Table 10. None of the endocrine parameters could predict the combined category including low disease activity and remission combined.

Table 10: Binary Logistic Regression analysis showing relationship between combined low disease and remission DAS CRP (<3.2) and Endocrine parameters.

Endocrine parameters	ODDs RATIO (95% C.I.)	p value
TSH	0.890 (0.706-1.122)	0.325
T4	0.911 (0.626-1.326)	0.627
T3	0.731 (0.397-1.347)	0.315
Prolactin	0.998 (0.989-1.007)	0.634
DHEAS	0.997 (0.988-1.007)	0.543
Testosterone	0.998 (0.994-1.003)	0.435
Random Cortisol	0.898 (0.764-1.055)	0.191
Post ACTH Cortisol 30min	0.970 (0.895-1.052)	0.467

Relationship between Moderate and high disease activity with endocrine parameters

We grouped moderate and high disease activity category into a combined category. Binary logistic regression analysis was done with dependant variable as the combined category including moderate and high disease activity (DAS ESR ≥3.2) and Covariates being Prolactin, DHEAS, Testosterone, Random Cortisol, Post ACTH Cortisol and TSH values. The results have been reported in the form of odds ratio with confidence interval and p value in Table 11. None of the endocrine parameters could predict the combined category including combined moderate and high disease activity category.

Table 11: Binary Logistic Regression analysis showing relationship between combined moderate and high DAS ESR (≥3.2) and Endocrine parameters.

Endocrine parameters	ODDs RATIO (95% C.I.)	p value
TSH	1.237 (0.737-2.077)	0.421
T4	0.860 (0.556-1.330)	0.498
T3	1.030 (0.366-2.899)	0.955
Prolactin	1.025 (0.974-1.077)	0.342
DHEAS	1.011 (0.990-1.033)	0.301
Testosterone	1.022 (0.969-1.079)	0.416
Random Cortisol	1.059 (0.791-1.418)	0.699
Post ACTH Cortisol 30min	0.961 (0.816-1.133)	0.638

We grouped moderate and high disease activity category into a combined category. Binary logistic regression analysis was done with dependant variable as the combined category including moderate and high disease activity (DAS CRP ≥3.2) and Covariates being Prolactin, DHEAS, Testosterone, Random Cortisol, Post ACTH Cortisol and TSH values. The results have been reported in the form of odds ratio with confidence interval and p value in Table 12. None of the endocrine parameters could predict the combined category including combined moderate and high disease activity category

Table 12: Binary Logistic Regression analysis showing relationship between combined moderate and high DAS ESR (≥3.2) and Endocrine parameters.

Endocrine parameters	ODDs RATIO (95% C.I.)	p value
TSH	1.123 (0.891-1.416)	0.325
T4	1.098 (0.754-1.598)	0.627
T3	1.368 (0.742-2.520)	0.315
Prolactin	1.002 (0.993-1.011)	0.634
DHEAS	1.003 (0.994-1.012)	0.543
Testosterone	1.002 (0.997-1.006)	0.191
Random Cortisol	1,114 (0.948-1.309)	0.191
Post ACTH Cortisol 30min	1.030 (0.950-1.117)	0.467

Relationship between PROMs (Patient Reported Outcome Measures) and Endocrine parameters.

Bivariate correlation analysis was done between PROMIS® Fatigue T score and various endocrine parameters and the results are reported in table 13 as Pearson Correlation with 95% confidence interval and p value. There was no significant correlation between any of the endocrine parameters and PROMIS® Fatigue T score.

Table 13: Bivariate correlation analysis between PROMIS® Fatigue T score and endocrine parameters

Correlation between	Pearson Correlation	p value	95% CI	
			Lower	Upper
PROMIS® T score & Prolactin	.003	.967	-.156	.162
PROMIS® T score & free T4	-.047	.575	-.207	.116
PROMIS® T score & free T3	-.011	.910	-.203	.182
PROMIS® T score & TSH	.018	.825	-.143	.179
PROMIS® T score & DHEAS	.047	.575	-.116	.207
PROMIS® T score & Testosterone	.011	.890	-.148	.170
PROMIS T score - Random Cortisol	.127	.210	-.072	.317
PROMIS T score - Post ACTH Cortisol	.126	.296	-.111	.349

Bivariate correlation analysis was done between IHAQ disability index and various endocrine parameters and the results are reported in table 14 as Pearson Correlation with 95% confidence interval and p value. There was no significant correlation between any of the endocrine parameters and IHAQ disability index.

Table 14: Bivariate correlation analysis between IHAQ-Disability index and endocrine parameters

Correlation between	Pearson Correlation	p value	95% CI	
			Lower	Upper
IHAQ- Disability index & Prolactin	-.036	.660	-.194	.124
IHAQ- Disability index & free T3	.035	.672	-.127	.196
IHAQ- Disability index & free T4	.058	.560	-.136	.248
IHAQ- Disability index & TSH	.023	.777	-.138	.184
IHAQ- Disability index & DHEAS	-.096	.249	-.254	.067
IHAQ- Disability index & Testosterone	.089	.275	-.071	.244
IHAQ- Disability index & Random Cortisol	.241	.016	.046	.419
IHAQ- Disability index & Post ACTH Cortisol	-.064	.598	-.293	.172

Bivariate correlation analysis was done between PHQ 9 Depression score and various endocrine parameters and the results are reported in table 15 as Pearson Correlation with 95% confidence interval and p value. There was no significant correlation between any of the endocrine parameters and PHQ 9 Depression score.

Table 15: Bivariate correlation analysis between PHQ9 Depression score and endocrine parameters.

Correlation between	Pearson Correlation	p value	95% CI	
			Lower	Upper
PHQ9 & T4	-.013	.874	-.175	.149
PHQ9 & T3	-.056	.569	-.246	.138
PHQ9 & TSH	.068	.412	-.094	.227
PHQ9 & Prolactin	-.136	.094	-.289	.024
PHQ9 & DHEAS	.095	.255	-.068	.253
PHQ9 & Testosterone	.095	.241	-.064	.250
PHQ9 & Random Cortisol	.060	.556	-.139	.254
PHQ9 & Post ACTH Cortisol	-.091	.451	-.318	.145

Bivariate correlation analysis was done between PSQI (Pittsburgh Sleep Quality Index) and various endocrine parameters and the results are reported in table 16 as Pearson Correlation with 95% confidence interval and p value. There was no significant correlation between any of the endocrine parameters and PSQI (Pittsburgh Sleep Quality Index).

Table 16: Bivariate correlation analysis between PSQI and endocrine parameters.

Correlation between	Pearson Correlation	p value	95% CI	
			Lower	Upper
PSQI & T4	.040	.634	-.123	.201
PSQI & T3	.009	.927	-.184	.201
PSQI & TSH	.107	.196	-.056	.265
PSQI & Prolactin	-.065	.429	-.222	.096
PSQI & DHEAS	-.054	.517	-.215	.109
PSQI & Testosterone	.132	.105	-.028	.285
PSQI & Random Cortisol	.073	.474	-.127	.268
PSQI & Post ACTH Cortisol	-.141	.241	-.362	.095

Bivariate correlation analysis was done between RAID composite score and various endocrine parameters and the results are reported in table 17 as Pearson Correlation with 95% confidence interval and p value. There was no significant correlation between any of the endocrine parameters and RAID score.

Table 17: Bivariate correlation analysis between RAID score and endocrine parameters.

Correlation between	Pearson Correlation	p value	95% CI	
			Lower	Upper
RAID score & T4	.003	.969	-.159	.165
RAID score & T3	.078	.430	-.116	.267
RAID score & TSH	.120	.147	-.042	.276
RAID score & Prolactin	-.095	.245	-.250	.065
RAID score & DHEAS	.014	.871	-.149	.175
RAID Score & Testosterone	.036	.662	-.124	.193
RAID score & Random Cortisol	.152	.132	-.046	.340
RAID score & Post ACTH Cortisol	-.040	.742	-.271	.195

Relationship between PROMs (Patient Reported Outcome Measures) and Disease severity.

Relationship between High disease activity and PROMs.

Binary logistic regression analysis was done with dependant variable as high DAS (DAS ESR >5.1) and Covariates being PROMIS® Fatigue T score, IHAQ disability index, PHQ-9 depression score, PSQI sleep score and RAID score. The results have been reported in the form of odds ratio with confidence interval and p value in Table 18.

Table 18: Binary Logistic Regression analysis showing relationship between high DAS ESR and PROMs.

PROMs	ODDs RATIO (95% C.I.)	p value
PROMIS® Fatigue T score	1.050 (1.016-1.086)	0.004
IHAQ disability index	2.377 (1.236-4.572)	0.009
PHQ-9 depression score	1.043 (0.925-1.175)	0.492
PSQI sleep score	1.055 (0.908-1.126)	0.484
RAID composite score	1.714 (1.343-2.188)	<0.001
RAID Pain	2.407 (1.761-3.289)	<0.001
RAID Functional disability	1.406 (1.184-1.670)	<0.001
RAID fatigue	1.245 (1.074-1.442)	0.004
RAID Sleep	1.114 (.979-1.268)	0.100
RAID physical well being	1.283 (1.105-1.489)	0.001
RAID emotional well being	1.127 (0.956-1.329)	0.155
RAID coping	1.217 (1.031-1.436)	0.020

Binary logistic regression analysis was done with dependant variable as high DAS (DAS CRP >5.1) and Covariates being PROMIS® Fatigue T score, IHAQ disability index, PHQ-9 depression score, PSQI sleep score and RAID score. The results have been reported in the form of odds ratio with confidence interval and p value in Table 19. It was noted that all of the PROMs except PHQ9 depression score and PSQI sleep score could predict high DAS CRP (>5.1) as outcome.

Table 19: Binary Logistic Regression analysis showing relationship between high DAS CRP and PROMs.

PROMs	ODDs RATIO (95% C.I.)	p value
PROMIS® Fatigue T score	1.084 (1.030-1.140)	0.002
IHAQ disability index	2.535 (1.236-5.199)	0.011
PHQ-9 depression score	1.130 (0.99301.287)	0.063
PSQI sleep score	1.113 (0.936-1.322)	0.226
RAID composite score	1.844 (1.330-2.557)	<0.001
RAID Pain	2.621 (1.663-4.132)	<0.001
RAID Functional disability	1.297 (1.064-1.581)	0.010
RAID fatigue	1.349 (1.093-1.665)	0.005
RAID Sleep	1.132 (0.972-1.316)	0.105
RAID physical well being	1.306 (1.072-1.592)	0.008
RAID emotional well being	1.328 (1.093-1.613)	0.004
RAID coping	1.259 (1.035-1.533)	0.022

Relationship between Remission and PROMs.

Binary logistic regression analysis was done with dependent variable as remission DAS (DAS ESR<2.6) and Covariates being PROMIS® Fatigue T score, IHAQ disability index, PHQ-9 depression score, PSQI sleep score and RAID composite score. The results have been reported in the form of odds ratio with confidence interval and p value in Table 20. It was noted that only RAID pain score could predict remission DAS ESR (<2.6) as outcome.

Table 20: Binary Logistic Regression analysis showing relationship between remission DAS ESR and PROMs.

PROMs	ODDs RATIO (95% C.I.)	p value
PROMIS® Fatigue T score	0.969 (0.884-1.061)	0.496
IHAQ disability index	0.399 (0.041-3.882)	0.429
PHQ-9 depression score	0.481 (0.192-1.206)	0.119
PSQI sleep score	1.242 (0.851-1.813)	0.262
RAID composite score	0.505 (0.253-1.010)	0.054
RAID Pain	0.446 (0.257-0.774)	0.004
RAID Functional disability	0.609 (0.334-1.112)	0.106
RAID fatigue	0.885 (0.578-1.356)	0.574
RAID Sleep	1.040 (0.706-1.532_	0.844
RAID physical well being	0.655 (0.399-1.074)	0.094
RAID emotional well being	0.699 (0.356-1.370)	0.297
RAID coping	0.70 (0.388-1.286)	0.255

Binary logistic regression analysis was done with dependant variable as remission DAS (DAS CRP<2.6) and Covariates being PROMIS® Fatigue T score, IHAQ disability index, PHQ-9 depression score, PSQI sleep score and RAID composite score. The results have been reported in the form of odds ratio with confidence interval and p value in Table 21. It was noted that all of the PROMs except PHQ9 depression score, PSQI sleep score, RAID emotional well-being score and RAID coping score could predict remission DAS CRP (<2.6) as outcome.

Table 21: Binary Logistic Regression analysis showing relationship between remission DAS CRP and PROMs.

PROMs	ODDs RATIO (95% C.I.)	p value
PROMIS® Fatigue T score	0.917 (0.869-0.967)	0.002
IHAQ disability index	0.039 (0.006-0.273)	0.001
PHQ-9 depression score	0.821 (0.605-1.115)	0.207
PSQI sleep score	1.000 (0.3-1.293)	1.000
RAID composite score	0.423 (0.273-0.656)	<0.001
RAID Pain	0.492 (0.360-0.674)	<0.001
RAID Functional disability	0.488 (0.324-0.735)	<0.001
RAID fatigue	0.690 (0.533-0.893)	0.005
RAID Sleep	0.826 (0.638-1.069)	0.147
RAID physical well being	0.577 (0.425-0.784)	<0.001
RAID emotional well being	0.693 (0.478-1.005)	0.053
RAID coping	0.730 (0.529-1.008)	0.056

Multivariate regression model for predicting high disease activity with PROMs.

We ran a multivariate regression model to predict high disease activity (DAS ESR >5.1) from the various PROMs collected in the study which are PROMIS® Fatigue T score, PHQ9 (Patient Health Questionnaire), IHAQ (Indian Health Assessment Questionnaire) and RAID score (Rheumatoid Arthritis Impact of Diseases). The result is depicted in table 22. It was noted that PHQ9, PSQI sleep score and RAID score could independently predict high DAS ESR (>5.1) as outcome (Table 22).

Similarly we ran a multivariate regression model to predict high disease activity (DAS CRP >5.1) from the various PROMs collected in the study. The result is depicted in table 23. It was noted that only RAID score could independently predict high DAS CRP (>5.1) as outcome (Table 23).

Table 22. Multivariate regression analysis for predicting high DAS ESR (>5.1) with PROMS in rheumatoid arthritis patients.

PROMs	ODDs ratio (95%CI)	p value
PROMIS® Fatigue T score	0.979 (0.930-1.031)	0.429
IHAQ Disability index	1.148 (0.481-2.740)	0.755
PHQ9 depression score	0.768 (0.643-0.919)	0.004
PSQI Sleep score	0.743 (0.586-0.943)	0.015
RAID score	3.278 (1.954-5.500)	<0.001

Table 23. Multivariate regression analysis for predicting high DAS CRP (>5.1) with PROMS in rheumatoid arthritis patients.

PROMs	ODDs ratio (95%CI)	p value
PROMIS® Fatigue T score	1.024 (0.959-1.095)	0.476
IHAQ Disability index	1.004 (0.394-2.559)	0.994
PHQ9 depression score	0.916 (0.764-1.098)	0.343
PSQI Sleep score	0.801 (0.586-1.096)	0.166
RAID score	2.332 (1.239-4.388)	0.009

We ran a multivariate regression model to predict remission DAS (DAS ESR <2.6) from the various PROMs collected in the study. The result is depicted in table 24. It was noted that none of the PROMs could independently predict remission DAS ESR (<2.6) as outcome (Table 24).

We ran a multivariate regression model to predict remission DAS (DAS CRP <2.6) from the various PROMs collected in the study. The result is depicted in table 25. It was noted that only PSQI sleep score and RAID score could independently predict remission DAS CRP (<2.6) as outcome (Table 25).

Table 24. Multivariate regression analysis for predicting remission DAS ESR (<2.6) with PROMS in rheumatoid arthritis patients.

PROMs	ODDs ratio (95%CI)	p value
PROMIS® Fatigue T score	1.119 (0.923-1.357)	0.252
IHAQ Disability index	1.993 (0.093-42.822)	0.660
PHQ9 depression score	0.524 (0.117-2.356)	0.399
PSQI Sleep score	1.397 (0.983-1.985)	0.062
RAID score	0.308 (0.079-1.211)	0.092

Table 25. Multivariate regression analysis for predicting remission DAS CRP (<2.6) with PROMS in rheumatoid arthritis patients.

PROMs	ODDs ratio (95%CI)	p value
PROMIS® Fatigue T score	1.014 (0.921-1.115)	0.783
IHAQ Disability index	0.195 (0.018-2.146)	0.182
PHQ9 depression score	1.289 (0.958-1.733)	0.094
PSQI Sleep score	1.359 (1.003-1.842)	0.048
RAID score	0.308 (0.131-0.723)	0.007

ROC curve for RAID score in predicting high disease severity and remission.

ROC curve was constructed for RAID score in predicting high disease severity according to DAS ESR (>5.1). Area under the curve obtained was 0.713 with 95% CI (0.631-0.795) and p value of < 0.0001. RAID score of 4.0 had a sensitivity of 76.2% and specificity of 62.5 % in predicting high disease activity as per DAS ESR (>5.1). The ROC curve is shown in Fig 34.

Similarly, ROC curve was obtained for RAID score in predicting high disease severity according to DAS CRP (>5.1). Area under the curve obtained was 0.733 with 95% CI (0.642-0.825) and p value of <0.0001. RAID score of 4.5 had a sensitivity of

71.9% and Specificity of 62.1 % in predicting high disease activity as per DAS CRP (>5.1). The ROC curve is shown in Fig 35.

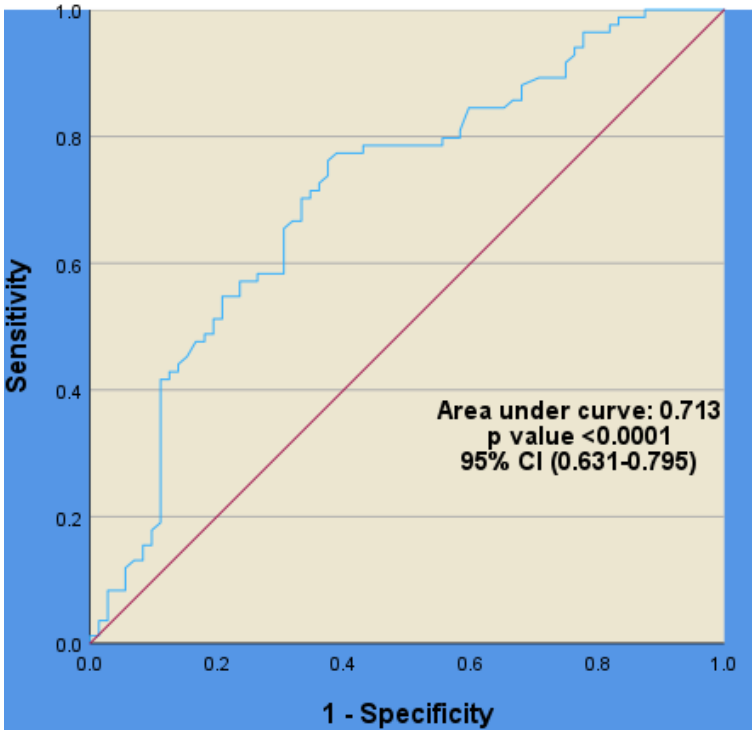


Fig 34. ROC curve for RAID score in predicting high DAS ESR (>5.1) in rheumatoid arthritis patients (N=156).

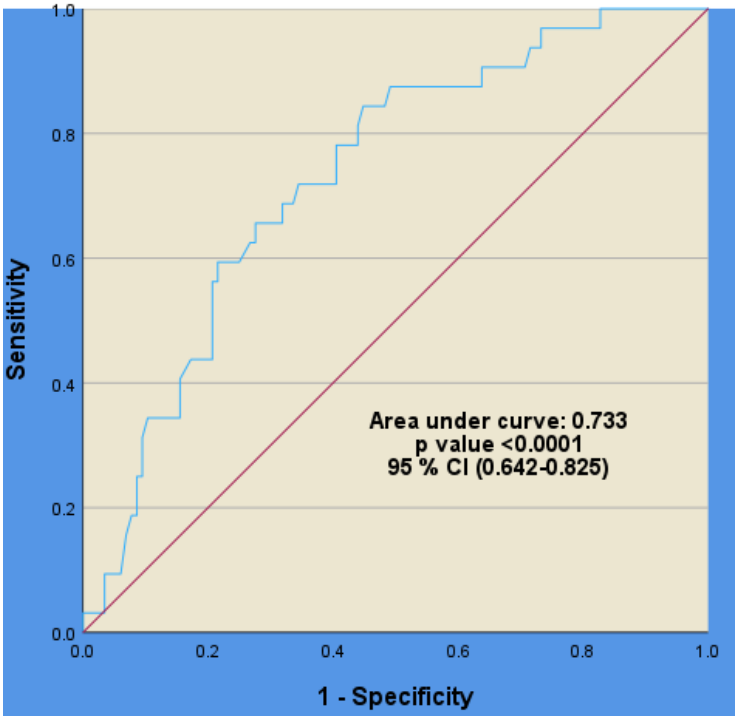


Fig 35. ROC curve for RAID score in predicting high DAS CRP (>5.1) in rheumatoid arthritis patients (N=156).

ROC curve was constructed for RAID score in predicting remission according to DAS ESR (<2.6). Area under the curve obtained was 0.785 with 95% CI (0.620-0.949) and p value of 0.052. RAID score of 3.1 had a sensitivity of 75.7% and Specificity of 75.0 % in predicting remission as per DAS ESR (<2.6). The ROC curve is shown in Fig 36.

ROC curve was constructed for RAID score in predicting remission according to DAS CRP (<2.6). Area under the curve obtained was 0.822 with 95% CI (0.721-0.924) and p value of <0.0001. RAID score of 3.1 had a sensitivity of 78.0 % and Specificity of 64.3 % in predicting remission as per DAS CRP (<2.6). The ROC curve is shown in Fig 37.

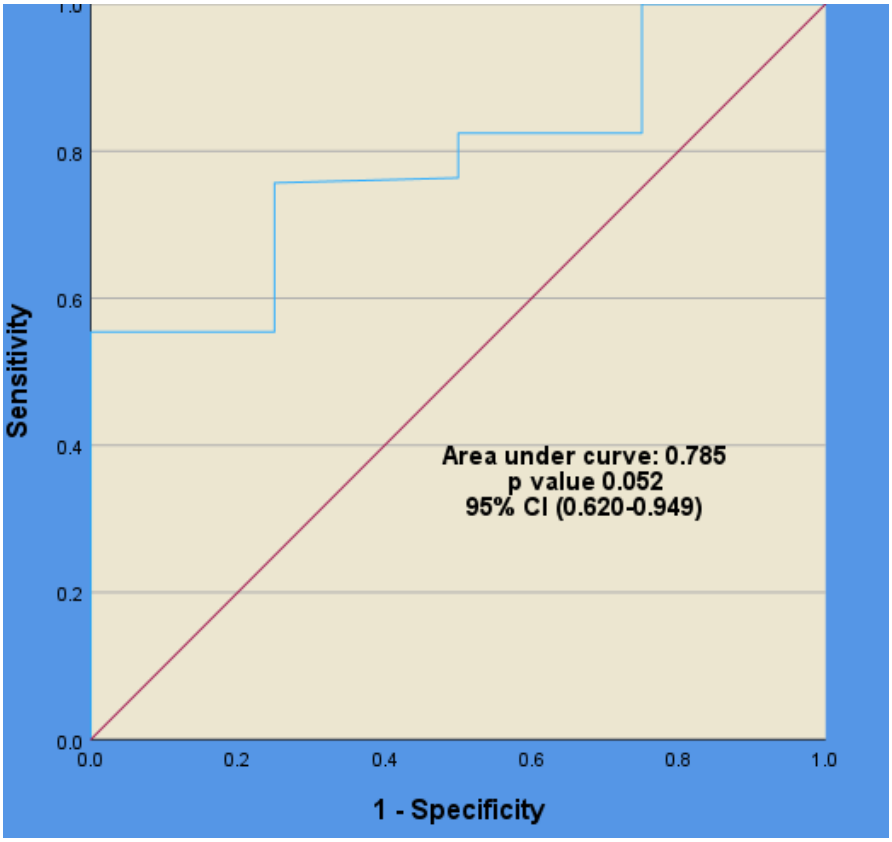


Fig 36. ROC curve for RAID score in predicting remission DAS ESR (<2.6) in rheumatoid arthritis patients (N=156).

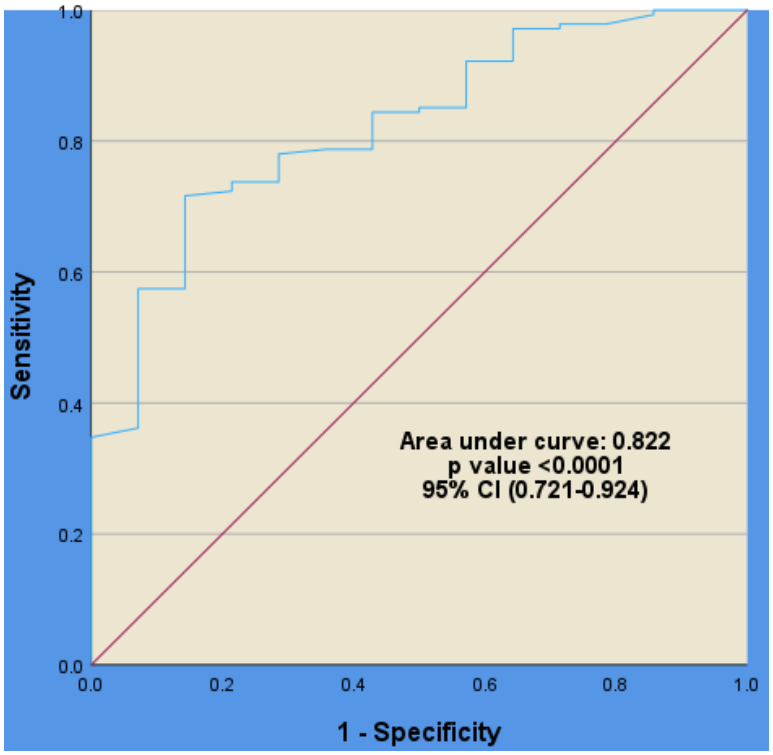


Fig 37. ROC curve for RAID score in predicting remission DAS CRP (<2.6) in rheumatoid arthritis patients (N=156).

ROC curve for RAID score in predicting the new combined disease categories.

Remission and Low disease activity was combined into a single category. ROC curve was constructed for RAID score in predicting this combined category of moderate and high disease activity according to DAS ESR (≥3.2) who need treatment optimisation (Fig 38). Area under the curve obtained was 0.781 with 95% CI (0.577-0.984) and p value of 0.008 (Fig 47). RAID score of 3.1 had a sensitivity of 77.1% and Specificity of 75.0 % in predicting DAS ESR ≥3.2.

ROC curve was constructed for RAID score in predicting this combined category of moderate and high disease activity according to DAS CRP (≥3.2) who need treatment optimisation (Fig 39). Area under the curve obtained was 0.734 with 95% CI (0.624-0.843) and p value of <0.0001 (Fig 48). RAID score of 3.6 had a sensitivity of 71.1 % and Specificity of 70.4 % in predicting DAS CRP ≥3.2.

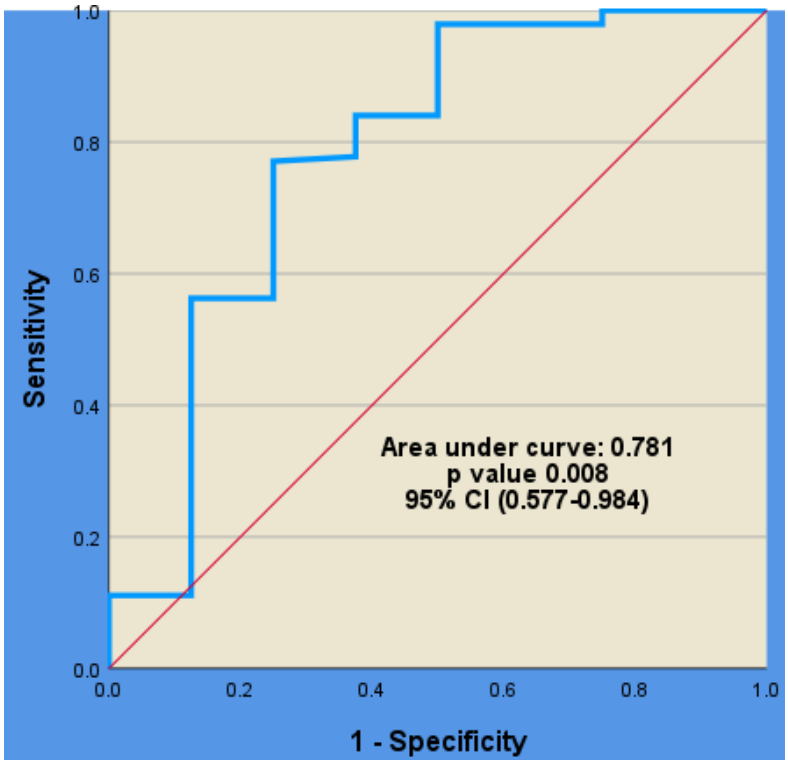


Fig 38. ROC curve for RAID score in predicting DAS ESR ≥3.2 (N=156).

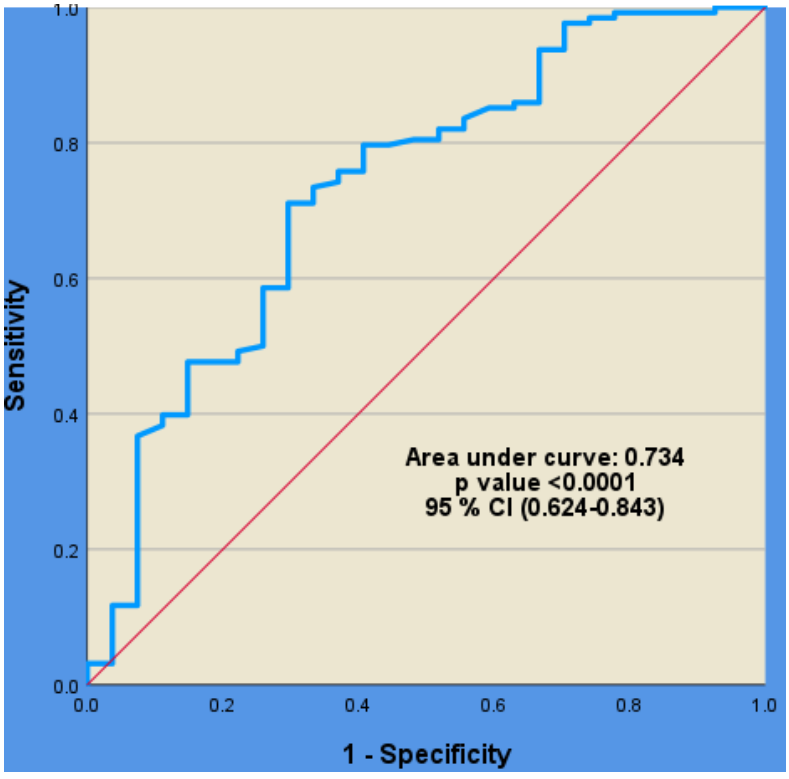


Fig 39. ROC curve for RAID score in predicting DAS CRP ≥3.2 (N=156).

DISCUSSION

One hundred and fifty-six patients were included in this study. The mean age of the population was 47.02±12.36 which was comparable to the previous available data of 30 to 50 years (3,69). A substantial number of patients, 19 (18.6%) were in the age group 25-35 years which was similar to other studies which found RA presenting at an earlier age in Indian population suggesting that RA causes significant disability in young and productive age groups (3,70). Among the study population, 135(86.5%) were females and 21 (13.5%) were males. Female to male ratio was 6.4. Worldwide RA sex ratio between males and females is 3:1 (71). However previous Indian studies have showed similar sex ratio in Indian population. Diggikar et al (72), Premkumar et al (73) and Yadav et al (74) have shown female proportion in RA of 84%, 77.3% and 86% respectively.

Among 156 patients included in the study, 15 had Iron deficiency anemia, 4 had hypothyroidism, 2 had ischemic heart disease, 6 had type 2 diabetes mellitus, 5 had hypertension and 12 had osteoarthritis. The prevalence of comorbidities in our patient was much less those expressed in previous studies like Yadav et al (74).

Average disease duration was 28.8±24 months which was lower than 3.97 years ± 3.93 years as mentioned in study by Yadav et al (74). Twenty-five (16%) patients were having early RA and rest 131(84%) patients had established RA. The lower average is likely due to a larger number of newly diagnosed RA patients.

Among the study population 64 patients (41.0%) had history of steroid use with mean cumulative steroid intake of 280.29±621.9mg. This was less compared to the study by Kumar et al.(70) in which the prevalence of steroid use was 66.3%. One hundred twenty-four patients (79.4%) were taking methotrexate with a mean cumulative methotrexate dose of 1442.74±1528.72 mg which is comparable to previous Indian studies (70,73).

The mean weight of the study population was 61.78±7.58 kilogram (range 38-81). The mean height was 163.15±5.33 cm (range 148-180). The mean BMI was 23.12±2.76 (range 14.20-34.60). Among 154 patients according to Asian BMI criteria 9 (5.8%) were underweight, 60 (39.0%) were having normal BMI, 46 (29.9%) were Overweight, 36 (23.4%) were pre-Obese and 3 (1.9) were Obese. The trend of higher

prevalence of obesity in rheumatoid arthritis patients compared to healthy population was seen in in other studies (75).

Out of 156 patient serum rheumatoid factor values were present in 122 patients and it was positive in 104 (85.4 %). Similarly, Serum Anti CCP antibodies was present in 41 patients and was positive in 32 patients (78.04 %). The number of seronegative RA patients are marginally more than other Indian studies (70,73).

The mean DAS-CRP score was 4.33±1.14 (range 1.32-6.95). According to DAS-ESR only 3 (2%) patients were in remission while, 5 (3.3%) were having Low disease activity, 63 (41.4%) were having Moderate disease activity and 81 (53.3%) had High disease activity. According to DAS-CRP only 12 (8.3%) patients were in remission while, 12 (8.3%) were having Low disease activity, 89 (61.4%) were having Moderate disease activity and 32 (22.1%) had High disease activity. Our study had significant number of patient with high disease activity compared to western studies (70,76). However, the disease severity in our study population matched a study which calculated DAS 28 in untreated patients from eastern India (77). The high disease activity in our patients can be attributed to multiple factors. Since our study was done post COVID-19 pandemic many of the patients had difficulty in their regular follow up and were off treatment. Also, since the patients were studied in a tertiary care center there were more patients with high disease severity. It was also hypothesized that post COVID-19 infection there was a flare in autoimmune illness, which need to be confirmed by additional studies (78).

The median of PROMIS® Fatigue T score was 55.10 (IQR ±1.60). Among the RA patients in the study 58 (37.2%) were normal when compared to the reference population used by NIH in PROMIS®. Rest 98 (62.8%) had some form of fatigue. Among then 39 (25.0%) had mild fatigue, 57 (36.5%) had moderate fatigue and 2 (1.3%) had severe fatigue. PROMIS® Fatigue score which was calculated using a computer adaptive test was used by Bacalo et al. (79) in RA patients in their treat to target project. They reported a mean PROMIS® Fatigue T score of 42.3±5.9. However, they used CDAI (Clinical disease Severity Index) instead of DAS 28 score as a clinician measured outcome. The higher mean of fatigue score in our study was most probably due to more patients with moderate and high disease activity. To our knowledge, there is no Indian study which measured fatigue with PROMIS® in RA patients.

The median of IHAQ disability index was 0.77 (IQR ±0.70). In our RA population under study 21 (13.5%) patients had no disability. Rest 135 (85.5%) had some form of disability. In a study by Intriago et al. (27) in Ecuadorian RA patients the mean HAQ-DI was 0.8±0.9, with a prevalence of disability of 26.6% which was defined as HAQ DI > 1.25 (corresponding to our moderate and severe disability). Kumar A et al. (29) validated a Indian adaptation of HAQ which we used in our study. They found the Baseline HAQ values for English and Hindi groups were 1.21±0.48 and 1.5±0.49 untreated RA patients. After treatment, the HAQ values changed to 0.81±0.47 and 0.65±0.55, respectively. These after treatment values were comparable our results.

The median of PHQ9 (Patient Health Questionnaire) was 2.0 (IQR ±3.0). In our study, 22 (14.1%) patients had no depression. Rest 134 (85.9%) had some form of depression according to PHQ9. 112 (71.8%) had minimal depression, 13 (8.3%) had mild depression and 9 (5.8%) had moderate depression. Only 5 patients in the study were treated clinically for depression. The findings were similar to other studies on depression in RA patients (31,36). This also highlights the load of untreated depression in patients with RA which contributes significantly to patient morbidity and functional status.

The mean of composite RAID score (Rheumatoid Arthritis Impact of Diseases) was 4.14±1.54 (range 0.42-7.79). According to RAID scores, 36 (23.1%) pateints were in remission, 29 (18.6%) were having low disease activity, 73 (46.8%) were having moderate disease activity and 18 (11.5%) were having high disease activity while applying the cutoff described by Salffi et al. (7) for European pateints.

There was higher prevalence of anemia in Indian patients when compared to western population which was also seen in the previous study by Agarwal et al. (80).

The incidence of hypothyroidism in our study population is slightly lower compared to the previous Indian and western studies (55,58). However, the number of patients with sick euthyroid were substantially higher owing to the larger percentage of patient with moderate and high disease activity.

Among 152 patients with serum prolactin values, 37 patients (24.34%) had prolactin levels above the normal range (Hyperprolactinemia) The mean prolactin levels the various disease severity subgroups gradually increased with severity however it was

not found to be statistically significant. We used the binary logistic regression to look for the association between serum prolactin values and disease severity score and also various PROMs and found no statistical significance. Previous studies had conflicting results with respect to prolactin levels in various disease severity in RA. The prolactin levels increase at the local site which is the synovium being produced by the activated macrophages which however isn't adequately represented by serum prolactin values. Additionally doing a serial prolactin value had shown some diurnal variation in prolactin with respect to disease inflammation in joints. It was seen that the Prolactin level peaks at around 2 am early morning along with a fall in cortisol. These two changes occur just before the peak of joint inflammation and early morning stiffness. This phenomenon could not be explored by our study as we had collected only single serum prolactin sample (11,47,49,51).

Out of 126 females, 73 (57.5%) had a DHEAS level below the normal range. Out of 20 males, 15 (71.4%) had a DHEAS level below the normal range. Similarly among 132 females, 73 (55.7%) had testosterone levels below the normal range and among 21 males, 13 (61.9%) had testosterone below the normal range. However there was no correlation between DHEAS and testosterone with disease severity and PROMs. This is in accordance to other studies which hypothesized low androgen levels in inflammatory condition which probably occurred at the local tissue level and was not able to be appreciated from serum values of DHEAS(60–62).

Among the 99 patients, who had random cortisol values, 36 patients (36.4%) had adrenal insufficiency (random cortisol range below 3 µg/dl). Post ACTH Cortisol levels were available for 71 patients. Out of these 44 patients (61.9%) had adrenal insufficiency (post ACTH cortisol levels below 18 µg/dl). The adrenal insufficiency in our study is higher compared to the other studies. However it was similar when compared to studies with RA patients on chronic low dose oral steroids (81,82).

There was no relation between serum cortisol values and disease activity as per binary logistic regression. It was hypothesized that the cortisol being an anti-inflammatory hormone were low in patients with high disease activity in RA. This was seen in studies which did serial measurements of cortisol in RA and found that the cortisol levels dips in the night maximum at 2 am where there is peak inflammation and increases later as due to stress mediated release during early morning(11,44,49). This

however could not be assessed in our study which took only a single sample of cortisol.

We noted that the endocrine dysfunction in RA patients occur at a higher frequency than general population. This included hypothyroidism (clinical and subclinical), sick euthyroid state, low androgen levels (low DHEAS and low testosterone), hyperprolactinemia and adrenal insufficiency. However, the endocrine dysfunction did not vary significantly with disease activity in RA. This can be explained by understanding that the flares in disease activity in RA is multifactorial and mostly occurs locally. Probably only in chronically untreated or inadequately treated RA patients will this inflammation be significant enough to cause significant variation in endocrine parameters. So, we would like to recommend that though endocrine dysfunction should be suspected and clinically looked for and if needed be confirmed by laboratory tests, they cannot be used to predict the disease severity or PROMs. Hence there is no role in using endocrine parameters for guiding the treatment of RA as per treat to target system.

The various PROMs collected in the study were VAS (Visual Analogue Score), PROMIS® Fatigue T score, PHQ9 (Patient Health Questionnaire), IHAQ (Indian Health Assessment Questionnaire) and RAID score (Rheumatoid Arthritis Impact of Diseases). These were obtained by the standardized and validated questionnaire under the supervision of a trained doctor. It was noted that all of the PROMs except PHQ9 depression score, PSQI sleep score and RAID emotional well-being score could predict high DAS 28 (>5.1) as outcome. This is in accordance with multiple studies which recognized depression and sleep as the unmet needs in RA patients who were in remission with their inflammatory activity controlled but experienced some form of morbidity in the form of depression and sleep disturbances (7,8,12,16,79,83,84). The cause for this is multifactorial including multiple associated co morbidities, long duration of RA treatment with remission and relapses, extra articular complications of RA which respond differently to DMARDs, associated other connective tissue diseases, ineffective patient support system, patient education, age, gender among others.

It was noted that only RAID pain score could predict remission DAS ESR (<2.6) as outcome. This discrepancy was probably due to very low number of patients in remission according to DAS ESR which were only 3 patients.

It was noted that all of the PROMs except PHQ9 depression score, PSQI sleep score, RAID emotional well-being score and RAID coping score could predict remission DAS CRP (<2.6) as outcome. Even though only 12 patients were in remission according to DAS CRP the PROMs measured could predict the outcome reliably expect depression and sleep which were considered as unmet needs in RA inflammatory treatment as noted above.

We attempted a multivariate regression model to predict high disease activity (DAS ESR >5.1) from the various PROMs collected in the study. It was noted that PHQ9, PSQI sleep score and RAID score could independently predict high DAS ESR (>5.1) as outcome. Similarly, we ran a multivariate regression model to predict high disease activity (DAS CRP >5.1) from the various PROMs collected in the study. It was noted that only RAID score could independently

predict high DAS CRP (>5.1) as outcome (7). RAID being a composite score measuring both inflammatory target and unmet needs like sleep and depression it was able to independently predict high DAS as outcome. It also has the added benefit of being able to be calculated at the comfort of home or while waiting in OPD to be seen by the treating doctor.

We ran a multivariate regression model to predict remission DAS (DAS ESR <2.6) from the various PROMs collected in the study. It was noted that none of the PROMs could independently predict remission DAS ESR (<2.6) as outcome. This was again due to very low number of patients (3 patients) in remission according to DAS ESR.

We ran a multivariate regression model to predict remission DAS (DAS CRP <2.6) from the various PROMs collected in the study. It was noted that only PSQI sleep score and RAID score could independently predict remission DAS CRP (<2.6) as outcome. This is in accordance with the finding above where RAID was the only parameter to independently predict High DAS ESR or high DAS CRP (7).

ROC curve was constructed for RAID score in predicting high disease severity according to DAS ESR (>5.1). Area under the curve obtained was 0.713 with 95% CI

(0.631-0.795) and p value of < 0.0001. RAID score of 4.0 had a sensitivity of 76.2% and specificity of 62.5 % in predicting high disease activity as per DAS ESR (>5.1). Similarly, ROC curve was obtained for RAID score in predicting high disease severity according to DAS CRP (>5.1). Area under the curve obtained was 0.733 with 95% CI (0.642-0.825) and p value of <0.0001. RAID score of 4.5 had a sensitivity of 71.9% and Specificity of 62.1% in predicting high disease activity as per DAS CRP (>5.1). The RAID cutoff for HDAS is relatively low in our population when compared to the western studies which reported a RAID >6 for HDAS. This can be probably due the majority of patients who were in HDAS in our study. We also hypothesized that Indian patients have a higher threshold and greater acceptance oftheir symptoms and PROMs which is probably reflected by the low RAID score for HDAS with respect to western studies(7,16). To our best knowledge there is no Indian study comparing the RAID score cutoff for various disease activity according to RAID.

ROC curve was constructed for RAID score in predicting remission according to DAS ESR (<2.6). Area under the curve obtained was 0.785 with 95% CI (0.620-0.949) and p value of 0.052. RAID score of 3.1 had a sensitivity of 75.7% and Specificity of 75.0 % in predicting remission as per DAS ESR (<2.6). ROC curve was constructed for RAID score in predicting remission according to DAS CRP (<2.6). Area under the curve obtained was 0.822 with 95% CI (0.721-0.924) and p value of <0.0001. RAID score of 3.1 had a sensitivity of 78.0 % and Specificity of 64.3 % in predicting remission as per DAS CRP (<2.6). The RAID score corresponding to remission DAS in our study was very similar to the European study which reported a RAID cutoff of 3 for remission. There is however no data for the same in Indian population.

We suggest that patients may be categorized into those who needed hospital visit and treatment optimization in the form of increasing the drug, confirming their adherence or addressing additional issues and those who could be followed by telemedicine and managed at the comfort of home. We found that combining HDAS and MDAS disease category into a single category which needed hospital visit for treatment optimization would be reasonable. Also combining the Remission and LDAS category into a single category who could be followed up with telemedicine was

deemed appropriate. This is in according to EULAR guidelines given by international task force in treating RA where they stated that “While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease” (84). Hence we divided DAS into 2 categories one with DAS ≥3.2 and other with DAS <3.2. We tried to get the RAID cutoff in determining these two outcomes.

ROC curve was constructed for RAID score in predicting DAS ESR (≥3.2). Area under the curve obtained was 0.781 with 95% CI (0.577-0.984) and p value of 0.008 (Fig 47). RAID score of 3.1 had a sensitivity of 77.1% and Specificity of 75.0 % in predicting DAS ESR ≥3.2. Similarly, ROC curve was constructed for RAID score in predicting DAS CRP (≥3.2). Area under the curve obtained was 0.734 with 95% CI (0.624-0.843) and p value of <0.0001 (Fig 48). RAID score of 3.6 had a sensitivity of 71.1 % and Specificity of 70.4 % in predicting DAS CRP ≥3.2.

Thus, we would like to propose a RAID score of 3.1 as the cutoff to differentiate the two categories with one needing treatment optimization and other which can be followed up on telemedicine or can be continued with same treatment.

The advantages of using RAID score for this purpose is multiple.

Firstly, it is simple, easy to calculate, and a patient reported outcome which doesn’t need a formal examination to determine tender and swollen joint count and blood test for determining the level of inflammatory markers. Therefore, it can be calculated by the patient at home and he can take a decision to whether visit the OPD or follow up with telemedicine. It can also be calculated by the patient while he is waiting for his turn in a busy OPD. Measuring RAID score is also in accordance with the first overarching principle described in EULAR recommendation of RA treatment which reads as this, “The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist”.

It is also important to note that sleep and depression have been proven both in our study and multiple western study as the unmet needs while treating the patient with inflammatory control as the main target and keeping DAS 28 as the primary method to measure disease activity. RAID score however incorporates both sleep and emotional well-being as a separate score with 12% importance to each of these

parameters in calculation the composite RAID score. Using this will help to identify such patients with unmet needs and address them appropriately.

RAID score is cost effective, simple, time saving and a very efficient way to assess disease activity in patients with RA.

However, we need to objectively measure the inflammatory activity and the extent of disease at the begging of starting our treatment and frequently till the target of inflammatory control is achieved. Once this is achieved patient can primarily monitored frequently with RAID score and periodically have a physical assessment of overall status with clinician reported score recording.

Further need of study with regard to use of RAID in monitoring extra-articular features of RA is also warranted.

CONCLUSION

Among the 156 patients included in the study, none of the patients had central hypothyroidism (TSH below the normal range). 13 patients (8.8%) had primary hypothyroidism, only 2 patients (1.3%) had subclinical hypothyroidism. 31 patients (20.9%) had sick euthyroid syndrome. Among them 13 patients (8.9%) had low fT3 and low fT4, 14 patients (9.5%) had low fT3 and normal fT4 and rest 4 patients (2.7%) had low fT3 with increased fT4.

Thirty seven patients (24.34%) had prolactin levels above the normal range (Hyperprolactinemia). The mean level of serum prolactin increased as the disease severity increased but it was not statistically significant

Out of the total 147 patients, 88 (56.4 %) had DHEAS levels below the normal range. Out of 127 females, 73 (57.5%) had a DHEAS level below the normal range. Out of 20 males, 15 (71.4%) had a DHEAS level below the normal range.

Among 86 patients (55.1%) had serum testosterone levels below the normal range. Among 132 females, 73 (54.1%) had testosterone levels below the normal range. Among 21 males, 13 (61.9%) had testosterone below the normal range.

Among the 99 patients who had random cortisol values, 36 patients (36.4%) had adrenal insufficiency (random cortisol range below 5 µg/dl). Post ACTH Cortisol levels were available for 71 patients. Out of these 44 patients (61.9%) had adrenal insufficiency (post ACTH cortisol levels below 18 µg/dl).

The endocrine parameters could not reliably predict the disease severity categories according to DAS 28 or the various PROMs studied in our patients. This can be explained by understanding that the flares in disease activity in RA is multifactorial and mostly occurs locally. Probably only in chronically untreated or inadequately treated RA patients will this inflammation be significant enough to cause significant variation in endocrine parameters. So, we would like to recommend that though endocrine dysfunction should be suspected and clinically looked for and if needed be confirmed by laboratory tests, they cannot be used to predict the disease severity or PROMs. Hence there is no role in using endocrine parameters for guiding the treatment of RA as per treat to target system.

All of the PROMs (PROMIS fatigue, IHAQ and RAID score) except PHQ9 and PSQI could predict the disease severity in RA patients however only RAID score could independently predict disease severity.

RAID score of 3.1 had a sensitivity of 77.1% and Specificity of 75.0 % in predicting DAS ESR ≥3.2. RAID score of 3.6 had a sensitivity of 71.1 % and Specificity of 70.4 % in predicting DAS CRP ≥3.2. Thus, we would like to propose a RAID score of 3.1 as the cutoff to differentiate the two categories with one needing treatment optimization and other which can be followed up on telemedicine or can be continued with same treatment.

Advantages of RAID score being a patient self-reported score over clinician reported scores

Firstly, it is simple, easy to calculate, and a patient reported outcome which doesn't need a formal examination to determine tender and swollen joint count and blood test for determining the level of inflammatory markers. RAID score incorporates sleep and emotional well-being which are considered the unmet needs when RA patients are followed up with DAS 28 score only. RAID score is cost effective, simple, time saving and a very efficient way to assess disease activity in patients with RA. It can be done at the comfort of home or while waiting to see the doctor in a busy OPD.

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IEC CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3535 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3370**

Project title: **"Endocrine profile and outcomes in patients with rheumatoid arthritis"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Pranav S Kumar**
Guide:	**Dr. M.K.Garg**
Co-Guide:	**Dr. Maya Gopalakrishnan & Dr. Kamla Kant Shukla**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

APPENDIX-1

All India Institute of Medical Sciences

Jodhpur, Rajasthan

Informed Consent Form

Title of Thesis/Dissertation: Endocrine dysfunction in patients with Rheumatoid arthritis

Name of PG Student : Dr. Pranav S Kumar 8660978838

Patient/Volunteer Identification No.: _____

I,_____S/o or D/o_____ give my full, free, voluntary consent to be a part of the study **"ENDOCRINE PROFILE AND OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS "**, the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions. I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason. I understand that the information collected about me and any of my medical records may be looked at by responsible individual from _____(Company Name) or from regulatory authorities. I give permission for these individuals to have access to my records.

Date : _____ _____

Place : _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date : _____ _____

Place : _____ Signature of PG Student

Witness 1
Signature
Name: _____
Address : _____

Witness 2
Signature
Name: _____
Address : _____

APPENDIX-2

अखिल भारतीय आयुर्विज्ञान संस्थान
जोधपुर, राजस्थान
सूचित सहमति प्रपत्र

थीसिस का शीर्षक: रूमेटाइड गठिया के रोगियों में अंतःस्रावी प्रोफ़ाइल का मूल्यांकन

पीजी छात्र का नाम: **डॉ** प्रणव एस कुमार दूरभाष।संख्या : 8660978838

रोगी / स्वयंसेवीपहचानसंख्या.: _____

मैं,_____पुत्र /पुत्री_____

निवासी_____मेरीपूर्ण, नि: शुल्क, स्वैच्छिक सहमति देता हु निम्नलिखित अध्ययन का हिस्सा बनने के लिए

जिसकी प्रक्रिया और प्रकृति मेरी पूरी संतुष्टि के लिए मेरी अपनी भाषा में मुझे समझाया गया है।मैं पुष्टि करता हूं कि मेरे पास प्रश्न पूछने का अवसर था।

मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और किसी भी कारण के बिना ,किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं।

.मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्र की गई जानकारी एम्स जोधपुर से या नियामक प्राधिकरणों से जिम्मेदार व्यक्ति द्वारा देखी जा सकती है। मैं इन व्यक्तियों के लिए अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

यदि आवश्यक हो तो भविष्य के संदर्भों और अध्ययनों के लिए, एकत्र किए गए नमूने कड़े परिस्थितियों में संग्रहित किए जाएंगे।

दिनांक: _____ **_____**
स्थान : _____ **हस्ताक्षर/बाएंअंगूठेकीछाप**

यह प्रमाणित करने के लिए कि उपर्युक्त सहमति मेरी उपस्थिति में प्राप्त की गई है।

तारीख :_____ **_____**
स्थान: _____ **हस्ताक्षरपीजी छात्र**

साक्षी 1
हस्ताक्षर

नाम: _____
स्थान : _____

साक्षी 2
हस्ताक्षर

नाम: _____
स्थान : _____

APPENDIX-3

PATIENT INFORMATION SHEET

Name of the patient: **Patient ID.:**

ENDOCRINE PROFILE AND OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS

You are participating in a study to understand the endocrine dysfunction found in a condition called rheumatoid arthritis.

1. We will be collecting information regarding your age, gender, duration of your disease and the treatment you have received along with ongoing symptoms.
2. Study procedure: We will be collecting your blood sample to do your routine tests as well as few tests, which are done as part of our study along with the following questionnaire PROMISE fatigue score, PHQ9 depression score, IHAQ functional activity score, PQSI sleep index and RAID score.
3. Likely benefit: If you have an underlying lung disease, we can treat it early which will be of benefit to you.
4. Confidentiality : All the data collected from you will be highly confidential.
5. Risk: Enrollment in the above study poses no substantial risk to you. You can withdraw from the study any point of time without any consequences to yourself.

   For further information / questions, the following personnel can be contacted:

   Dr Pranav S Kumar, Junior Resident, Department of Internal Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan. Ph: 8660978838

APPENDIX-4

रोगी सूचना पत्र

रोगी का नाम: रोगी आईडी:

रूमेटाइड गठिया के रोगियों में अंतःस्रावी प्रोफ़ाइल का मूल्यांकन

आप रूमेटाइड अर्थराइटिस नामक स्थिति में पाई जाने वाली एंडोक्राइन विकार को समझने के लिए एक अध्ययन में भाग ले रहे हैं

1. हम आपकी आयु, लिंग, आपकी बीमारी की अवधि और चल रहे लक्षणों के साथ आपके द्वारा प्राप्त उपचार के बारे में जानकारी एकत्र करेंगे।
2. अध्ययन प्रक्रिया: हम आपके नियमित परीक्षण के साथ-साथ कुछ परीक्षण करने के लिए आपके रक्त का नमूना एकत्र करेंगे, जो निम्नलिखित प्रश्नावली प्रॉमिस थकान स्कोर, PHQ9 अवसाद स्कोर, IHAQ कार्यात्मक गतिविधि स्कोर, PQSI स्लीप इंडेक्स और RAID स्कोर के साथ हमारे अध्ययन के हिस्से के रूप में किया जाता है।
3. गोपनीयता: आपसे एकत्र किया गया सभी डेटा अत्यधिक गोपनीय होगा।
4. जोखिम: उपरोक्त अध्ययन में नामांकन से आपको कोई खास खतरा नहीं है। आप किसी भी समय अध्ययन से स्वयं को बिना किसी परिणाम के वापस ले सकते हैं।

अधिक जानकारी/प्रश्न के लिए निम्नलिखित कर्मियों से संपर्क किया जा सकता है।

डॉ. प्रणव एस कुमार, जूनियर रेजिडेंट, आंतरिक चिकित्सा विभाग, अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान। फोन: 8660978838

ANNEXURE 1: ACR-EULAR CRITERIA FOR DIAGNOSIS OF RHEUMATOID ARTHRITIS

Parameter	Criteria	Score*
Joint involvement	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negativity for RF and anti-CCP	0
	Low level of RF or anti-CCP	2
	High level of RF or anti-CCP	3
Acute-phase reactants	Normal CRP level and ESR	0
	Abnormal CRP level or ESR	1
Duration of symptoms	<6 wk	0
	≥6 wk	1

CCP = cyclic citrullinated peptide; **CRP** = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **RF** = rheumatoid factor; **wk** = week.
*A total score of more than 6 indicates a diagnosis of rheumatoid arthritis.

Annexure 2: Socio-demographic Proforma

Name			
Date Of Birth/Age			
Phone number			
Address			
Disease Duration		Date of Enrolment	
RA Diagnosed By			
BMI			
Smoking history		CURRENT/PREVIOUS/NEW	
Tender Joints (Annexure 3)			
Swollen Joints(Annexure 3)			
DAS 28 with date of assessment			
Patient Global Assessment			
Evaluator Global Assessment			
Pain By Vas (Annexure 4)			
PROMIS® fatigue score (Annexure 5)			
IHAQ functional activity score (Annexure 6)			
PHQ9 depression score (Annexure 7)			
PSQI(Pittsburgh Sleep Quality Index) (Annexure 8)			
RAID score (Annexure 9)			
ESR			

HsCrp		
Ra Factor		
Anti Ccp		
Erosions On Hand X Ray (date of xray)	YES/NO	
Cumulative Methotrexate Dose		
Cumulative Steroid Dose		
CURRENT STEROID DOSE IN MG Of PREDINISOLONE with date		
Intake > 3 Months	YES/NO	
Past DMARD Use (Names)		
Ongoing/Recent Dmard Used	Name of DMARD	
	Start date	
	Stop date	
Target for the Patient		
Date for target achievement		
Shared decision making	YES ☐ NO ☐	

ANNEXURE 3: DAS-28 Score

DAS28 form

Patient name …… Date of Birth __ /__/____

Observer name …… Date __ /__/____

		Left		Right	
		Swollen	Tender	Swollen	Tender
Shoulder					
Elbow					
Wrist					
MCP	1				
	2				
	3				
	4				
	5				
PIP	1				
	2				
	3				
	4				
	5				
Knee					
Subtotal					
Total		Swollen		Tender	

How active was your arthritis during the past week?
(Please mark the degree of activity on the scale below by placing a vertical line |)

Not active at all ——————————————— **Extremely active**

Swollen Joint Count (0-28)	
Tender Joint Count (0-28)	
ESR	
VAS disease activity (0-100mm)	

DAS28 = 0.56*√(t28) + 0.28*√(sw28) + 0.70*Ln(ESR) + 0.014*VAS	

ANNEXURE 4: PAIN VAS

ANNEXURE 5

PROMIS®: FATIGUE SCALE

	Never	Rarely	Sometimes	Often	Always
How often did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did you Experience extreme exhaustion?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did you run out of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did fatigue limit you at work (include work at home)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often were you too tired to think clearly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
ow often were you too tired to take a bath or shower?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did you have enough energy to exercise strenuously?	☐ 5	☐ 4	☐ 3	☐ 2	☐

ANNEXURE 6

Indian Health assessment Questionnaire

	Activity of daily living (ADL): Are you able to:	Without any difficulty (0)	With some difficulty (1)	With much difficulty (2)	Unable to do (3)
1.	Dress yourself, including tying sari/salwar/dhoti/ pyjama and doing buttons?	–	–	–	–
2.	Get in and out of bed?	–	–	–	–
3.	Lift a full cup or glass to your mouth?	–	–	–	–
4.	Walk outdoors on flat ground?	–	–	–	–
5.	Wash and dry your entire body?	–	–	–	–
6.	Squat in the toilet or sit cross-legged on the floor?	–	–	–	–
7.	Bend down to pick up clothing from the floor?	–	–	–	–
8.	Turn a tap on and off?	–	–	–	–
9.	Get in and out of autorickshaw/manual rickshaw/car?	–	–	–	–
10.	Walk three kilometres?	–	–	–	–
11.	Shop in a vegetable market?	–	–	–	–
12.	Climb a flight of stairs?	–	–	–	–

$$\text{Disability Index} = \frac{\text{Sum of all scores}}{12}.$$

ANNEXURE 7

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

S. NO.	**Over the last two weeks, how often have you been bothered by the following problems?**	**Not at all (0)**	**Several days (1)**	**More than half days (2)**	**Nearly every day (3)**
1.	Little interest or pleasure in doing things				
2.	Feeling down, depressed, or hopeless				
3.	Trouble falling asleep or sleeping too much				
4.	Feeling tired or having little energy				
5.	Poor appetite or overeating				
6.	Feeling bad about yourself or that you are a failure or have let yourself or your family down				
7.	Trouble concentrating on things				
8.	Moving or speaking so slowly that other people have noticed or the opposite being so restless or fidgety that you have been moving around a lot more than the usual				
9.	Thoughts that you would be better off dead or of hurting yourself				
10.	If you checked off any problems, how difficult these problems made it for you to do your work, take care of things at home or get along with other people	Not difficult at all ——— Somewhat difficult ——— Difficult ——— Extremely difficult ———			

ANNEXURE 8

SLEEP QUALITY ASSESSMENT (PSQI)

During the past month

1. When have you usually gone to bed (Time)?

2. How long (in minutes) has it taken you to fall asleep each night?

3. What time have you usually gotten up in the morning?

4. A. How many hours of actual sleep did you get at night?

   B. How many hours were you in bed?

5.	During the past month, have you had trouble sleeping because you	Not during the past month(0)	Less than once a week(1)	Once or twice a week(2)	Three or more times a week(3)
a.	Cannot get to sleep within 30 minutes				
b.	Wake up in middle of night or early morning				
c.	Have to get up to use the bathroom				
d.	Cannot breathe comfortably				
e.	Cough or snore loudly				
f.	Feel too cold				
g.	Feel too hot				
h.	Have bad dreams				
i.	Have pain				
j.	Other reasons				
6.	During the past month how often have you taken medicine (prescribed or over the counter) to help you sleep?				
7.	During the past month how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8.	During the past month how much of a problem has it been for you to keep up enthusiasm to get things done?				
9.	During the past month how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

ANNEXURE 9: RAID SCORE

1. Pain

Circle the number that best describes the pain you felt due to your rheumatoid arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

2. Functional disability assessment

Circle the number that best describes the difficulty you had in doing daily physical activities due to your rheumatoid arthritis during the last week.

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

3. Fatigue

Circle the number that best describes how much fatigue you felt due to your rheumatoid arthritis during the last week.

No fatigue	0	1	2	3	4	5	6	7	8	9	10	Totally exhausted

4. Sleep

Circle the number that best describes the sleep difficulties (i.e., resting at night) you felt due to your rheumatoid arthritis during the last week.

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

5. Physical well-being

Considering your arthritis overall, how would you rate your level of physical well being during the past week? Circle the number that best describes your level of physical well-being.

Very good	0	1	2	3	4	5	6	7	8	9	10	Very bad

6. Emotional well-being

Considering your arthritis overall, how would you rate your level of emotional well being during the past week? Circle the number that best describes your level of emotional well-being.

Very good	0	1	2	3	4	5	6	7	8	9	10	Very bad

7. Coping

Considering your arthritis overall, how well did you cope (manage, deal, make do) with your disease during the last week?

Very well	0	1	2	3	4	5	6	7	8	9	10	Very poorly

RAID SCORING AND CALCULATION RULES

The RAID is calculated based on 7 Numerical rating scales (NRS) questions. Each NRS is assessed as a number between 0 and 10. The 7 NRS correspond to pain, function, fatigue, sleep, emotional well-being, physical well-being, and coping/self-efficacy.

1. Calculation

RAID final value =
(pain NRS value (range 0-10) x 0.21) + (function NRS value (range 0-10) x 0.16) + (fatigue NRS value (range 0-10) x 0.15) + (phys well being NRS value (range 0-10) x 0.12) + (sleep NRS value (range 0-10) x 0.12) + (emotional well being NRS value (range 0-10) x 0.12) + (coping NRS value (range 0-10) x 0.12).

Thus, the range of the final RAID value is 0-10 where higher figures indicate worse status.

2. Missing data imputation

If one of the 7 NRS values composing the RAID is missing, the imputation is as follows:
a. calculate the mean value of the 6 other (non-missing) NRS (range, 0-10)
b. impute this value for the missing NRS
c. Then, calculate the RAID as explained above.

If 2 or more of the NRS are missing, the RAID is considered as missing value (no imputation).