"STUDY OF SLEEP PROBLEM IN RHEUMATOID ARTHRITIS AND ITS IMPACT ON DISEASE ACTIVITY, PAIN PERCEPTION AND FUNCTIONAL DISABLITY- A ONE YEAR CROSS SECTIONAL STUDY AT KLE'S DR PRABHAKAR KORE'S HOSPITAL AND RESEARCH CENTRE, BELAGAVI, KARNATAKA"

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ABBREVIATIONS

ACPA	ANTI CITRULLINATED PROTEIN ANTIBODY
AMPA	ANTI POST TRANSLATIONALLY MODIFIED PROTEIN ANTIBODIES
CAD	CORONARY ARTERY DISEASE
CDAI	CLINICAL DISEASE ACTIVITY INDEX
CRP	C-REATIVE PROTEIN
DMARD	DISEASE-MΘDIFYING ANTIRHEUMATIC MEDICATIΘNS
DNA	DEOXYRIBONUCLEIC ACID
ESR	ERYTHROCYTE SEDIMENTATION RATE
HAQ-DI	HEALTH ASSESSMENT QUESTIΘNNAIRE DISABILITY INDEX
HCQ	HYDRΘXYCHLΘRΘQUINE
IG	IMMUNOGLOBULIN
IL	INTERLEUKINS
JAK	JANUS KINASE
MOS-SS	MEDICAL ΘUTCΘME STUDY SLEEP SCALE
MRI	MAGNETIC RESONANCE IMAGING
RA	RHEUMATOID ARTHRITIS
SNP	SINGLE NUCLEΘTIDE PΘLYMΘRPHISM
TNF	TUMOR NECROSIS FACTOR
VAS	VISUAL ANALΘGUE SCALE

ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune illness that causes inflammatory arthritis as well as extra-articular involvement. Sleep disturbances in RA are associated with variety of other problems more than physical pain including low quality of life, psychological issues, cognitive decline and high rate of mortality and morbidity. Present study aimed to sleep disturbances in rheumatoid arthritis and its impact on disease activity, pain perception and functional disability.

Material & Method: The Cross-Sectional Based Analytical Study was conducted among the patients attending Rheumatology and General Medicine Out Patient Department at KLE'S Prabhakar Kore Hospital, Belagavi. The patients were assessed for the sleep quality by Medical Outcome Study Sleep Scale (MOS-SS). Overall disease activity is measured by the Clinical Disease Activity Index (CDAI), which is a widely used and validated instrument. Pain was assessed using the visual analogue scale (VAS), ranging from 0 to 10, whereby a higher number indicates a higher pain intensity. The patients were measured for the CRP, ESR, Rheumatoid factor and Anti CCP. Data was collected and saved in Microsoft excel. Data were analysed using statistical software R and Microsoft excel. . P value less than or equal to 0.05 showed statistical significance.

Results: In present study total of 98 patients fulfilling inclusion criteria re included with consent. The mean age of the patients was found to be 52.06 yrs. Among the included patients, 13.3% were male and 86.7% were female patients, with female preponderance in the study. The patients were with sleep disturbance in 28.6% of the patients. On comparison of the sleep disturbances with pain VAS score, CDAI score, physician and Global VAS score. There is significant higher mean in the level of

these variables among the patients with sleep disturbances compared to the patients without the sleep disturbances ($p<0.05$)

Conclusion: The present study documented the presence of sleep disturbance among the patients with rheumatoid arthritis. Also there was significant correlation between sleep disturbance and higher pain perception among patients with higher disease activity scores.

Keywords: Rheumatoid arthritis, sleep problems, Pain VAS, CDAI score,HAQ-DI score.

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INTRODUCTION

Sleep is an important component of health-related quality of life. More than two-thirds of the patients with rheumatoid diseases report disturbed sleep.[1,2] Prevalence of Rheumatoid Arthritis is 1% globally while in India it is reported 0.75%. Sleep issues experienced in rheumatoid arthritis are due to the pain. Patients have trouble falling asleep and staying asleep and tend to feel tired even after sleeping. This has been associated with reduction in the pain threshold, depression and increase in the incidence of inflammation.[3–5] Over time, it has been discovered that pain can predict sleep disturbance even when discomfort is unaffected. As the severity of rheumatoid arthritis increases, a trend of decreasing day time sleepiness and sleep cycle disorders has been seen which can be attributed to an alertness seen due to the pain.

In addition to physical pain, sleep disorders in RA are linked to a number of other issues, such as poor quality of life, psychological problems, cognitive deterioration, and a high mortality and morbidity rate. A range of illness-specific variables, such as disease activity, discomfort, morning stiffness, and medication, can all have an impact on sleep quality.[6] Sleep disturbances have been found to be more prevalent in various rheumatic illnesses such as lupus, primary antiphospholipid syndrome, Sjogren's syndrome, systemic sclerosis, ankylosing spondylitis, and others.[3,7–10] Lupus, the prototypical connective tissue disease, is associated with sleep disturbancess in more than half of patients, and the sleep disturbances are linked to disease activity.

To minimise the negative effects of sleep interruptions on the patient's life quality early detection is crucial. Aside from autoimmune rheumatic illnesses, the connection seen between sleep disorders and disease includes endocrine disorders, metabolic/toxic abnormalities, renal, cardiovascular, pulmonary, gastrointestinal, infectious diseases, cancer, and critical illness.[11]

Further there are no much studies been done in Indian population setting in RA patients on sleep issues related to pain. This study was aimed at sleep disorders in rheumatoid arthritis and the effect on disease progression, pain perception and functional impairment.

AIMS & OBJECTIVES

Aim

The objective of the current cross-sectional study was to assess how sleep disturbance affected rheumatoid arthritis activity, perception, and functional impairment.

Objectives

- To study quality of sleep in patients suffering from Rheumatoid Arthritis.
- To study the connection between sleep and disease severity, pain perception, functional handicap in patients with Rheumatoid Arthritis(RA).

REVIEW OF LITERATURE

Inflammatory arthritis and extra-articular involvement are both symptoms of the autoimmune disease rheumatoid arthritis (RA). Mostly affecting synovial joints, it is a persistent inflammatory condition with not known cause. It commonly begins in small joints especially the distal joints, usually symmetrical and ascends up to affect proximally if left untreated. Joint degeneration is a gradual process as a result of cartilage and bone deterioration brought on by joint inflammation. RA is classified as early when symptoms last less than six months and established when symptoms last more than six months.[12,13]

There is no specific investigation for rheumatoid arthritis, making it difficult to diagnose. A meticulous and a thorough clinical approach is necessary to detect and prevent serious joint deterioration . Patients with rheumatoid arthritis need both medical and nonmedical treatment. The current gold standard management is early treatment with DMARD'S(disease-modifying anti-rheumatic medication). Inspite of therapy, most of the people eventually experience serious morbidity and impairments. Complete pharmacological and drug-free therapies (physiotherapy, counselling, and family therapy) are required to improve therapeutic outcomes.[13]

Etiology

The cause for the disease is yet unclearIt is believed to be the result of an interaction between the genes and the environment. In a UK study of 112 dizygotic (DZ)a nd 91 monozygotic (MZ) twins, the overall monozygotic(MZ) concordance rate was fifteen percent and five percent, respectively.[14,15]The heritability of rheumatoid disease ranges from forty percent to sixty-five percent for serology

positive rheumatoid arthritis and twenty percent for serology negative rheumatoid arthritis. HLA-DRB1 gene alleles have been linked to increases the chance of developing rheumatoid arthritis. These genes share an epitope that has been linked with an increased risk of developing RA(rheumatoid arthritis) in the third hypervariable region of their DRB1 chains. These genes contain a constant five amino acid stretch in their sequence.[16,17]

The genes for STAT-4 and IL-10, which are signal transducers and activators of transcription, have polymorphisms that have been associated to rheumatoid arthritis susceptibility. Polymorphism in a single nucleotide in the PSORS, PTPN, and MIR genes is linked to a higher severity form of the diseases.[19]

DNA undergoes epigenetic changes. Examples of epigenetic alterations include histone modifications, DNA methylation and non-coding RNA-mediated regulation. Overexpression of the tyrosine phosphatase SHP-2, which is encoded by the gene PTPN1, has been linked to RA-FLS (fibroblast-like synoviocytes), which increases the invasiveness of RA-FLS when compared to synoviocytes from OA patients. Two hypermethylated sites were found in the enhancer region of the PTPN11 intron, leading to aberrant epigenetic control of the gene and altered RA-FLS action.[20]

Smoking is the primary cause of rheumatoid arthritis. People with anti-citrullinated protein antibodies (ACPA) are more likely to develop the condition due to a genetic and smoking-related connection.[21]

Variations in functioning and composition of the gut microbiota have also been associated to RA. People with RA experience changes in the composition of their gut microbiome (dysbiosis). They are seen to have lower gut microbiota diverseness as compared to healthy persons. There is an increase in the disease activity of rheumatoid arthritis with the following microbiome presence: Actinobacteria, Eggerthalla, Faecalibacterium. Collinsella. [21]

Epidemiology

The global prevalence of rheumatoid arthritis is around 0.24%.[22] In the USA, the yearly incidence of Rheumatoid arthritis (RA) is around forty per one lakh people.[23] According to records, women are at a higher risk of developing rheumatoid arthritis than males are, with a risk of 3.6% vs 1.7%, respectively..[24] Age is a risk factor for developing rheumatoid arthritis, and the frequency is highest between 65 and 80.[25]

A large Swedish study conducted in 2013 found that rheumatoid arthritis (RA) has a familial tendency that is greater than 40%.[26] In the study it was discovered that early-onset RA and sero-positive RA had higher heritabilities. In this study, it was established that the risk of rheumatoid arthritis is three times greater with a sero-positive first degree relative in comparison with a sero-positive second-degree relative which shows doubled incidence.[26] Numerous genetic predispositions have already been identified to explain this outcome. The genetic vulnerability for RA is highest in the HLA-DRB1 region .[27]

Cigarette smoking has the highest relationship with RA among modifiable risk variables.[28] Diet and nutrition have been demonstrated to be important environmental factors for RA. The classic modern diet which is heavy in calories and poor in fibre has shown an increased incidence of RA. Omega-3 PUFA consumption has been linked to a lower incidence of RA. [29] Another established association for RA is obesity. Patients with a BMI more than 30 kg/m2 have a 30% increased risk of RA, whereas those with a BMI of 25 to 29.9 kg/m2 had a 15% increased risk.[30]

The connection between chronic mucosal or periodontal disease and RA has been the subject of extensive research. In well-established investigations, however, no obvious, consistent correlation has been revealed. Mucosal damage from occupational exposures and environmental contaminants has been connected to a rise in RA cases.[31,32]

Pathophysiology

Antibodies to citrullinated proteins are seen in patients with rheumatoid arthritis.

Arginyl residues undergo post translational modification which is then acted upon by pepidyl arginine deaminase which produces the AA- Citrulline. The antibodies produced against this amino acid are anti-citrullinated protein(ACP) antibodies. Anti-citrullinated protein antibodies(ACP) isotypes can be Immunoglubulin- M, G or A. Citrulline residues on the body's protiens such as vimentin, ibrinogen, fibronectin, type II collagen and histones can be bound by . Anti-citrullinated protein antibodies (ACPA). [8] Complement is activated when an antibody interacts with a protein. Rheumatoid arthritis is known as seropositive RA if

there are antibodies present. Prior to the onset of clinical symptoms by up to 10 years, ACPA can be detected in the blood. The levels of serum cytokines and ACPA both increase with time.[21,33]

Both innate immune cells (monocytes, dendritic cells, and mast cells) and adaptive immune cells (B cells, Th17(T-helper 17), plasma cells and Th1(T-helper 1)) infiltrate the synovium in rheumatoid arthritis. The cytokines and chemokines TNF, IL-6, and granulocyte-monocyte colony-stimulating factors(GM-CSF) encourage immune cells to enter the synovial cavity. In a patient with RA, fibroblasts within the synovium are invasive. Inflammatory cells and fibroblasts stimulate the formation of osteoclasts, causing degeneration of the bone , which is a hallmark of rheumatoid arthritis(RA).[21,34]

It is believed that the mechanism underlying environment-triggered RA is the recurrent stimulation of innate immunity. An increase in the production of peptidyl arginine deiminase (PAD) is seen within macrophages of the alveoli in cigarette smoking, causing the formation of citrulline in the airway from arginine. This leads to the generation of a "neoantigen," which triggers a path of autoimmunity that results in the development of antibodies against citrullinated protiens. (ACPAs).[35]

Antibodies against post translationally modified protein (AMPA) such as antibodies against carbamylated protein antibodies (anti-CarP) are linked to RA. The conversion of lysine to homocitrulline is a process of carbamylation which is a cyanide-mediated chemical process. Anti-carbamylated protein antibodies are distinct proteins that have been connected to rheumatoid arthritis in both ACPA sero-positive and -negative persons, despite the fact that homocitrulline and citrulline share a chemical structure.[21]

It's crucial to note that synovial biopsies were frequently normal in individuals with arthralgia who had positive serology results. It is thought that a secondary environmental trigger is required for a disease to manifest clinically. An unhealthy inflammatory process follows when this happens. Synoviocytes that resemble fibroblasts called FLS spread from one joint to another, slowly degenerating it.[36]

Physical presentation

Joint stiffness and pain are the most prevalent and noticeable symptoms, particularly in the beginning of the day, as well as edoema. Symptoms usually appear slowly and insidiously; occasionaly episodic pattern of symptoms can be seen in certain circumstances which is known as palindromic rheumatism. RA does not always develop in people with palindromic rheumatism, and some of them respond symptomatically to hydroxychloroquine. As was previously said, RA mostly affects the hands and other small peripheral joints. Axial joint involvement is infrequent, especially in the lumbar region.[40–43]

However, chronic RA may show signs of cervical joint dysfunction. Numerous small joint involvements are typical, however some patients can have extraarticular and monoarticular involvement.

On general physical examination, whether there is joint swelling or not, the affected joint will hurt to press against or move. There will be a palpable "boggy" synovium hypertrophy. Joint redness, swelling and warmth are frequently not present, and carpal tunnel syndrome can be seen if wrsit joints are involved. When multiple joints are implicated, physical exams will demonstrate decreased grip strength. On late chronic illness, swan neck deformity, subluxation of the metacarpophalangeal

joint, and ulnar deviation are all physically evident. Along with these other findings are "bowstring" sign and Boutonniere deformity.

The most prevalent cutaneous symptoms of RA are rheumatoid nodules.[44] They are frequently seen on pressure sites like the olecranon. Ulcerative skin lesions in RA patients are hypothesised to be caused by vasculitis, neutrophilic infiltration, venous stasis, and/or arterial insufficiency.

An indication of RA is vasculitis, which can damage both small and medium blood vessels. However, the incidence of vasculitis in RA patients is modest.[45] Patients with rheumatoid vasculitis may have asymmetric polyneuropathy or mononeuritis multiplex. Rheumatoid arthritis is related with a secondary type of Sjögren illness. It is distinguished by symptoms of ocular and/or mouth dryness.[46]

Evaluation of the patients

Laboratory testing frequently demonstrates chronic illness anaemia and thrombocytosis. If Felty syndrome is present, neutropenia may be present. Rheumatoid factor (RF), ACPA, or both may be detected in up to 85% of RA patients. [21] Seropositivity for RA is thought to exist in these people. Rheumatoid factor is present in between 45 and 75% of individuals with RA. But rheumatoid factor does not always indicate rheumatoid arthritis. Although in low titers, it is probably present in a number of chronic infections, connective tissue diseases, and healthy individuals. ACPA ab's are present in 50% of individuals suffering from initial stages of arthritis who later receive a rheumatoid arthritis diagnosis. The sensitivity and specificity of the diagnosis are greatly increased if both the RF and the ACPA are positive. It is important to evaluate acute phase reactants since they are frequently higher in people

with active disease, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels.

Leukocyte counts within synovial fluid can range from 1500 to 25,000/cubic millimetre, with polymorphonuclear cells being the majority. Cell counts over 25000 cells per cubic millimetre are rare but can be seen in illnesses that are quite aggressive; nonetheless, they should be investigated to rule out underlying infection. Low C3 and C4 levels are found in RA synovial fluid despite high blood levels.[47]

Joints with severe disease will have periarticular osteopenia, a narrowing of the joint space, and bony erosions seen on plain radiographs. Erosions of the cartilage and bones are thought to be pathognomonic for RA. But these results are consistent with a severe disease. Before radiography evidence manifests, ultrasonography and (MRI) magnetic resonance imaging are helpful in detecting bone degradation. Bone marrow edoema is visible as a reduction in marrow signal on T1-weighted imaging and gadolinium-enhanced imaging. Synovial thickness, which has been demonstrated to predict the existence of upcoming bone erosions, may also be measured by MRI. It is still unclear whether MRI has a clinical advantage or whether RA diagnosis criteria ought to take it into account.[48–50]

Due to the disease's diverse clinical presentation and the lack of consistent pathognomonic tests, Rheumatoid arthritis (RA) diagnosis can be challenging. Originally, at least four of the following criteria had to be met for at least six weeks was enough to diagnose RA. The criteria were morning stiffness, symmetric arthritis, arthritis in the hands, arthritis in three or more joints, high rheumatoid factor, radiologic evidence of RA and elevated acute phase reactants. Although these RA criteria were not very specific, they helped distinguish between inflammatory and

non-inflammatory arthritis. Another significant drawback was that it was insensitive to RA in the early stages.[51] The introduction of serological markers changed the diagnostic approach and guidelines. The diagnostic standards were altered by the development of serologic markers. The American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) diagnostic criteria for RA as of 2010 are mentioned in the subsequent paragraph. There are four different realms.:

RA Criteria for Diagnosis from ACR/EULAR [52,53]

- The number and location of the affected joints
- Shoulders, elbows, hips, knees, and ankles (large joints): 2 to 10 equals 1 point;
- 1 to a maximum of 3 small joints equals 2 points. (proximal interphalangeal joint (PIP), thumb interphalangeal joint (IP), second to fifth metatarsophalangeal joint and wrist joints)
- 4 to a maximum of 10 small joints equals 3 points.
- Five points are awarded for involvement of more than ten joints, including at least one tiny joint.
- Anti-CCP or RF serological tests
- Low positive is indicated by 2 points
- High positive is indicated by 3 points
- An increased acute phase reactants such as ESR or C-reactive protein accounts for one point.
- Six weeks or more of symptoms = 1 point.

When a person's overall score is greater than or equal to six, they are given the diagnosis of RA. Understanding that any swollen or painful joint identified during an examination constitutes joint involvement is essential. Synovitis and joint involvement can also be identified via imaging examinations. First carpometacarpal, first metatarsophalangeal, and distal interphalangeal joints were removed from the ACR/EALAR criteria. Furthermore, these requirements should only be used in cases where joint involvement cannot be accounted for by other inflammatory conditions such psoriasis or SLE. Specific tests must be conducted in order to rule out particular illnesses. The updated criteria for RA diagnosis were found to have improved specificity, larger negative predictive value, and comparable sensitivity. They also demonstrated a stronger ability to identify the likelihood of developing RA.[51]

Staging

Staging as defined by ACR[54]

Stage 1: X-rays show no destructive changes.

Stage 2: Presence of x-ray evidence of periarticular osteoporosis, subchondral bone destruction but no joint deformity

Stage 3: X-ray evidence of cartilage and bone destruction in addition to joint deformity and periarticular osteoporosis

Stage 4: Presence of bony or fibrous ankylosis along with stage 3 feature

Management or Treatment

Early diagnosis and medication start are the goals of treatment for RA patients in order to prevent irreversible joint deterioration. The International Task Force Guidelines for RA Treatment, issued in 2014, provide the following recommendations for RA treatment:[55]

- By reducing signs of inflammatory disease activity, the main purpose of treatment is to enhance one's life quality and attain long-lasting remission.
- In case clinical remission is not possible, minimal disease progression is an acceptable substitute.
- Disease activity should be checked on patients with moderate to severe disease activity once per month.
- When a patient's disease activity is low or they are in clinical remission, they should have their disease activity checked every three to six months.

- Several clinical evaluation techniques have been developed to help medical practitioners assess the disease activity of RA patients. The American College of Rheumatology (ACR) modified its recommendation to use the evaluation methods listed below (in 2019), as they met the minimal criteria for evaluation outlined in the guidelines.
- Clinical Disease Activity Index (CDAI)
- Disease Activity Score for 28 Joints (DAS28-ESR/CRP)
- Disease Activity Score (DAS)
- Patient-Derived DAS28
- MBDA score, VECTRA DA - Multi-Biomarker Disease Activity Score
- Hospital Universitario La Princesa Index (HUPI)

- Routine Assessment of Patient Index Data 3 (RAPID3)
- Rheumatoid Arthritis Disease Activity Index (RADAI)
- Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5)
- Simplified Disease Activity Index (SDAI)
- Routine Assessment of Patient Index Data 5 (RAPID5)

Some of the DMARDs (disease-modifying antirheumatic drugs) used to treat the disease include, hydroxychloroquine, sulfasalazine, methotrexate and leflunomide. The anti-TNF-alpha medications certolizumab pegol, etanercept, golimumab, adalimumab and infliximab are all available today. Anti-CD20 B-cell depleting monoclonal antibodies like rituximab, T-cell blockers like abatacept (CTLA4-Ig),interleukin (IL) 6 receptor antagonists like sarilumab and tocilizumab, and anti-CD20 B-cell depleting T-cell blockers like abatacept are examples of non-TNF biologic DMARDs. A few examples of synthetic DMARDs are the Janus kinase (JAK) inhibitors tofacitinib, baricitinib, and upadacitinib.

When a patient has a major active infection, DMARD treatments should be temporarily halted, especially biologics and drugs used in targeted therapy (tofacitinib). Once the patient recovers completely, they can be continued. It is crucial to remember that before starting RA medication, all patients should get tested for TB, hepatitis B, and C. In those with impaired liver function, methotrexate should be avoided. Prior to starting biologic therapy, a minimum of one month of treatment is necessary for those with latent TB. Conventional DMARD medication should be utilised if individuals are unable to take or finish treatment for latent TB.[54]

Non-Biological DMARDs

This group includes the drugs hydroxychloroquine (HCQ), cyclosporine, methotrexate, sulfasalizine, leflunomide, and azathioprine (AZA). Methotrexate is the first-line treatment for RA patients. The recommended dosage of methotrexate is 15 mg/week at first, then 5 mg/monthly increases, with a final dose of 25 to 30 mg/week. Subcutaneous administration can be explored in individuals who do not respond well to oral treatment.[56]

Inhibitors of TNF

Etanercept, infliximab, adalimumab, certolizumab, and golimumab are TNF inhibitors. TNF inhibitors are not recommended by the ACR until a nonbiologic DMARD has been attempted. TNF inhibitors, on the other hand, have been demonstrated in trials to be superior than another nonbiologic DMARD in patients who have failed methotrexate treatment. The most worrying side effect of these medicines is the reactivation of latent TB and opportunistic infections.[54,57]

Rituximab

A biologic non-TNF DMARD called rituximab can be used to treat RA in persons who have uncontrolled RA and have not responded well to TNF medication. [46] Rituximab reduces the immunological response to vaccinations in patients and their CD20+ B-cells. As was said earlier, it is preferred in patients who suffer from lymphoproliferative disorders.

Abatacept

By binding to CD80 and CD86, abatacept suppresses T-cell activation. It is infused intravenously once a month or injected subcutaneously once a week. Abatacept therapy, which has been shown to be effective for 6 months to 5 years, is beneficial for patients with uncontrolled RA who have not reacted well to methotrexate or TNF inhibitor medication.

Interleukin 6 Inhibitors

For people with moderate-to-severe active RA who have not responded to TNF inhibitor therapy, the IL-6 receptor inhibitor tocilizumab has been approved. Tocilizumab treatment results in clinically significant improvements for these individuals. Another drug in this class, sarilumab, has also been shown to improve clinical results in patients who doesn't responds to TNF inhibitor therapy.[58,59]

(JAK) Inhibitors of Janus kinase

A group of tyrosine kinases called JAK is involved in intracellular signalling for hematopoiesis and the activation of immune cells. JAK inhibitors, including tofacitinib, are approved as second-line therapy for RA because they reduce cytokine secretion.[60]

Differential diagnosis

- Chronic Lyme disease
- Systemic lupus erythematosus
- Osteoarthritis
- Sjogren syndrome

- Psoriatic arthritis
- Septic arthritis
- Sarcoidosis

Complications associated with RA

RA issues affect a number of organ systems and are known to have an impact on patients' outcome clinically. Patients must be closely watched for the emergence of these issues, and if they do, treatment plans must be changed as as soon as possible.

Osteopenia and osteoporosis are medical consequences that can also be caused by (glucocorticoids) and other pharmacological therapy. In comparison to the general population, the risk of fracture is 60–100% higher in RA patients. Menopause, and advanced age and a low BMI(body mass index), all considerably increase the likelihood of this result in RA patients..[61]

Additional RA symptoms include pleuritis, bronchiolitis, and interstitial fibrosis. Lung damage can occur during RA treatment with methotrexate and anti-TNF medications, albeit this seldom happens. RA carries a higher risk of pulmonary embolism.

(CAD) Coronary artery disease and RA are closely related. RA increases the likelihood of developing coronary artery disease (CAD) and speeds up the disease's course in those who already have it. Accelerated atherosclerosis, which results in CAD and peripheral vascular disease, is the main cause of morbidity and mortality in RA patients.[62,63]

Diabetes mellitus and increased insulin resistance are related with RA and are hypothesised to be caused by chronic inflammation. Certain DMARDs, including methotrexate, TNF antagonists, and hydroxychloroquine, significantly improved glycemic control in these individuals. Rheumatoid vasculitis is an uncommon condition that can lead to serious consequences. The clinical signs range from mild localised digits involvement to complicated systemic involvement that resembles polyarteritis nodosa.[45,64]

As previously noted, people with RA have an elevated risk of venous thromboembolic illness, even after controlling for other thromboembolic risk factors. [59] Multiple studies have found that individuals on TNF inhibitors and JAK inhibitors had a greater risk of thromboembolic illness. However, there is no universal agreement on this relationship. Based on research, rather than being a negative effect of the pharmaceuticals, the increased thromboembolic illness associated with their use is a result of the increased disease activity. [65–67]

In people with RA and pulmonary disease, the secondary type of Sjögren syndrome occurs 10% more commonly.[46]

A typical RA side effect is depression. People with severe physical impairment and long-term active sickness are discovered to be affected. A meta-analysis from 2013 discovered that depression was prevalent in 17% to 39% of RA patients.[68]

Seropositive RA has well-known side effects such Felty syndrome and chronic anaemia. Non-Hodgkin lymphoma is more common among RA patients, who are also more likely to acquire lymphoma. These patients experience an acceleration of the

clinical course of RA, with diffuse B-cell lymphoma being the most prevalent manifestation.[69]

Various articles discussing the relation of sleep disturbance in RA patients;

Sleep quality is an important component of quality of life and it is a known fact that sleep disturbances affect the quality of life in patients with RA. It has also been demonstrated that higher depression, fatigue and pain scores in patients with RA are related to functional disability. Poor sleep quality may contribute to feelings of pain, fatigue and mood disturbances and may further deteriorate the functional ability and the quality of patient's life.

In a study conducted in turkey in the year 2016 showed Sleep disturbances in 64.1% of the patients with RA. Among the patients, 43.3% had depression symptoms (BDI > 13) and 48% were postmenopausal. The patients with RA had significantly higher scores in the subjective sleep quality, sleep latency, habitual sleep efficiency, sleep disturbance domain and total PSQI score compared to the healthy control group ($P < 0.05$).[74]

In a study conducted by Frederick Wolfe F et al., (2006) to assess the sleep disturbance in patients with rheumatoid arthritis. The mean values for the scales were similar: SPI-I 35.4 (19.4), SPI-II 36.0 (19.1), SDS 35.0 (24.7), and VAS sleep 36.1 (29.7), and the MOS scales surpassed population norms by 25% (VAS by 42%). SD was predominantly determined by pain and mood in multivariable studies. Anti-tumor necrosis factor (TNF) therapy did not result in lower abnormal sleep ratings. SD in RA and NID were comparable. The VAS scale was shown to be more significantly linked with RA clinical factors than the MOS scales; however, the scales'

distributiənal prəperties differed, with the VAS scales capturing mərə severe values. The standard errər əf measurement (SEM), which is related tə minimum (impərtant) change, was 9.0 fər SPI-I, 7.3 fər SPI-II, 9.6 fər SDS, and 10.4 fər VAS sleep. SD is increased in RA, and 25% tə 42% əf SD can be attributed tə RA. SD is linked tə pain, məəd, and disease activity. SD is slightly greater in wəmen and is less with increasing age. All scales appear tə be valid in RA, with minimal differences in SEM. [70]

In a study by Westhəvens R et al., (2013) tə assess the sleep prəblems in patients with rheumatəid arthritis. The mean (SD) age əf the 305 patients was 57.00 (12.38) years, and the illness duratiən was 11.77 (9.94) years. The mean (standard deviatiən) AIS, PSQI, and ESS scəres were 6.8 (4.79), 7.8 (4.30), and 7.3 (4.67), respectively. The mean (SD) VAS tiredness, VAS pain, and HAQ-DI scəres were 45.22 (26.29), 39.04 (26.21), and 1.08 (0.75), respectively. There was a substantial pəsitive link between DAS28-CRP and AIS/PSQI, but a significant negative relatiənship between DAS28-CRP and ESS. Several pətentially cənfəunding variables were əbserved. Pəər RA management is assəciated with pəər sleep quality and daytime drəwsiness, which is likely explained by pain-related awareness. Prəspective studies are needed in the future tə cənfirm pəssible links between sleep quality, tiredness, and RA therapy.[71]

In a study cənducted by Sarivildiz MA et al., (2014) tə assess the sleep quality in rheumatəid arthritis. When cəmpared tə the healthy cəntrəl grəup, patients with RA had significantly higher scəres in subjective sleep quality, sleep latency, habitual sleep efficiency, sleep disturbance dəmains, and əverall PSQI scəre. Spearman's analysis revealed a strəng assəciatiən between age, disease activity, CRP, pain, exhaustiən, depressiən, functiənal impairment, quality əf life, radiələgical damage,

menopausal status, length of morning stiffness, ESR levels, and sleep disruption. According to the logistic regression analysis, depression and DAS 28 scores were predictors of poor sleep quality. Concluded with the sleep quality is disturbed in patients with RA. The poor sleep quality is especially associated with the disease activity and depression.[72]

In a study conducted by Loppenthin K et al., (2015) to assess the physical activity and the association with fatigue and sleep in Danish patients with rheumatoid arthritis. An inverse univariate association was found between moderate to vigorous physical activity, and fatigue (MFI mental, MFI activity, MFI physical and MFI general), sleep, diabetes, depression, pain, patient global assessment, HAQ and disease activity. The multivariate prediction model demonstrated that fatigue-related reduced activity and physical fatigue were selected in >95 % of the bootstrap samples with median odds ratio 0.89 (2.5–97.5 % quantiles: 0.78–1.00) and 0.91 (2.5–97.5 % quantiles: 0.81–0.97), respectively, while disease activity was selected in 82 % of the bootstrap samples with median odds ratio 0.90. Moderate to vigorous physical activity in patients with rheumatoid arthritis is associated with the absence of several RA-related factors with the most important correlates being reduced activity due to fatigue, physical fatigue and disease activity. The study showed that a majority of patients with RA experience poor sleep and that general fatigue and mental fatigue are associated with poor sleep.[73]

In a study by Son CN et al., (2015) to assess the sleep quality among the patients with rheumatoid arthritis and its association with disease severity among the Korean population. The RA patients had a higher overall PSQI score and a greater frequency of poor sleep quality (5.62 ±4.19, 38.5%) than the control participants (3.57

±2.17, 13.4%). Patients with poor sleep quality (PSQI > 5) were older and scored higher on the BDI-II and VAS than patients with no sleep disruption (PSQI ≤5). When RA activity was high, the score in subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, sleep disruption, daytime dysfunction, total PSQI, and frequency of poor sleep quality rose. In Korea, sleep disruption was seen in 38.5 percent of RA patients, and high RA disease activity was related with poor sleep quality. [74]

In a study by Grabovac I et al., (2018) to assess the sleep quality in patients with rheumatoid arthritis and association of pain, disability, disease duration and activity. Ninety-five patients, mostly women, with an average age of 50.59 (9.61) years were studied. Fifty-seven percent reported inadequate sleep duration, as did functional impairment and higher median pain levels. There were no changes in sociodemographic factors, illness duration or activity, inflammatory markers, or the use of biological and corticosteroid treatment. According to the multivariate regression analysis, more acute pain was connected with a decreased chance of getting enough sleep. Patients with RA have a significant prevalence of poor sleep, which is related to pain level. Clinicians must be aware of this problem and its possible consequences for health and functional status. [4]

In a study by Mustafa M et al., (2019) to assess the frequency of sleep disorders in patients with rheumatoid arthritis. The participants' average age was 48.7±14.6 years, and 95% of them were females. The average DAS28 score was 3.3±0.8 years, and almost 60% of the individuals were in remission/low disease activity. Insomnia, EDS, sleep disruption, OSA risk, and RLS were all prevalent at 63%, 20%, 20%, 37%, and 63%, respectively. Furthermore, illness activity had little

effect ɵn the distributiɵn ɵf sleep disturbances. The relatiɵnship between HAQ and sleep prɵblems in RA patients was nɵt significant. Sleep disturbances are widespread in RA patients and may need additiɵnal attentiɵn frɵm treating dɵctɵrs; nevertheless, these abnɵrmalities are unrelated tɵ disease activity and have little impact ɵn quality ɵf life. [75]

In a ɵriginal study by Kɵntɵdimɵpɵulɵs N et al., (2020) tɵ assess the disease activity and sleep disturbance in rheumatɵid arthritis. The majɵrity ɵf patients (78.2%) were females, with a mean age ɵf 63.7 years. The majɵrity ɵf patients (77.6%) were pɵɵr sleepers (PSQI ≥5) whɵ had mɵre tiredness than excellent sleepers (FACIT-F: 21.6 vs. 39.3, p<0.001). Ɵverall sleep quality was assɵciated tɵ disease activity (Spearman's rhɵ = 0.87, p<0.001), physical health (-0.66, p<0.001), mental health (-0.71, p<0.001), and weariness (0.87, p<0.001). Even after cɵntrɵlling fɵr cɵnfɵunding factɵrs, PSQI and its cɵmpɵnent scɵres changed amɵng patient subgrɵups with increasing RA activity. RA disease activity has a significant impact ɵn sleep quality, and given the previɵusly shɵwn impɵrtance ɵf adequate sleep, this "deeper lɵɵk" might cɵntribute tɵ the endeavɵur tɵ enhance HRQɵL in RA patients. [76]

In a study by Radwan A et al., (2021) tɵ assess the quality ɵf sleep in rheumatɵid arthritis patients. There were 125 females and 8 men in the study, with a mean age ɵf 42.5±9.5 years and a disease duratiɵn ɵf 3.9±1.3 years. A tɵtal ɵf 76 age and gender matched cɵntrɵls were alsɵ included. In 54.1% ɵf patients, pɵɵr sleep quality was identified. When cɵmpared tɵ the cɵntrɵl, patients had substantially higher scɵres in the subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, day-time dysfunctiɵn categɵries, and ɵverall PSQI scɵre (p<0.05). In terms ɵf marital status, HAQ, erythrɵcyte sedimentatiɵn rate (ESR), VAS, DAS28,

mərning stiffness duratiən, anti-cyclic citrullinated peptide (anti-CCP) ($p<0.05$), and the BDI ($p<0.001$), a significant difference was fəund between RA patients with pəər sleep quality and thəse with gəəd sleep quality. Accərding tə the multivariate regressiən analysis, illness activity, The multivariate regressiən analysis fəund that disease activity, functiənal disability and depressiən were predictərs fər pəər sleep quality ($p = 0.04$, $p = 0.01$ and $p < 0.001$; respectively). Patients with RA have pəər sleep quality. Sleep deprivatiən is linked tə disease activity, depressiən, and functiənal impairment. Tə enhance sleep quality and quality əf life, systemic psychiatric screening, cəmprehensive evaluatiən, and fəcused therapies are necessary.[77]

In a cəhərt study by Lyne L et al., (2022) tə assess the sleep prəblems in rheumatəid arthritis əver 12yrs əf periəd. Prəblems with əne sleep dəmain (gləbal sleep scəre) were recərded in 1578 əf the 1578 əbservatiəns (38%), and the ədds increased with illness duratiən (ƏR 1.04, 95% CI 1.02 tə 1.07). The average amənt əf time spent in bed was 8 həurs (Q1-Q3: 7.5–9.0). High-grade pain increased the chance əf sleep issues 3-9 times and functiənal impairment 4-8 times. We fəund nə severe sleep difficulties in this grəup əf newly diagnəsed RA patients whə had access tə current medicatiən frəm diagnəsis, and existing sleep prəblems were məstly due tə pain and limited functiən. Sleep issues in RA shəuld be treated by addressing the underlying issue that is generating the sleep disruptiən. [5]

In a study by Kumar A et al., (2022) tə assess the sleep quality aməng the patients with rheumatəid arthritis. Sixty-fəur percent əf əur RA patients had pəər sleep quality. The average wərldwide PSQI scəre was 6.41 3.07 (range 1–17). 26% əf the study grəup had a high risk əf sleep apnea. Pəər sleepers were məre likely tə take

glucocorticoids, had a high risk of sleep apnea, have a high disease activity, a pain VAS, a tiredness VAS, and functional impairment. A multivariate logistic regression study found that the WHOQOL-BREF domains of sleep apnea, exhaustion, and poor physical health were all independent risk factors for poor sleep quality. Poor sleep quality was common in patients with RA. High risk of sleep apnea, exhaustion, and the WHOQOL-BREF physical health domain were found as independent predictors of poor sleep quality.[3]

MATERIAL & METHOD

Source of data: Patients attending Rheumatology and General Medicine Out Patient Department at KLE'S Prabhakar Kore Hospital, Belagavi.

Study design: A Cross-Sectional Analytical Based Study.

Study Duration: January 2021 to December 2021.

Sample Collection:

Formula for sample size collection is

$N=p(100-p)Z^2/E^2$

Where, n= sample size required

p= percentage of occurrence of a state or condition

E=percentage of maximum error required

Z=value of correspondence to level of confidence required.

With percentage of maximum error as 10%at 95%confidence level sample size is given by, n= 90.

$N=56.8*(100-56.8)*(1.96)^2/10^2$

Inclusion Criteria

- Age 18 years and above
- Patient fulfilling ACR/EULAR 2010 Rheumatoid Arthritis classification criteria

Exclusion Criteria

- Age less than 18 years
- Patients unable to understand or follow questionnaire due to decreased hearing and visual/cognitive impairments.
- Patients with co-existing medical diseases which are likely to interfere with sleep like PND, BPH, Narcolepsy, Sleep apnea

Methodology

Sɵciɵ-demɵgraphic Data: This part cɵnsists ɵf multiple chɵice and ɵpen-end questiɵns and is made up ɵf 13 items cɵvering sɵciɵ- demɵgraphic characteristics ɵf the sample (age, sex, marital status, educatiɵn level, and current ɵccupatiɵn). Additiɵnal questiɵns ɵn disease duratiɵn, as well as current therapy and cɵmɵrbidities were asked.

Sleep quality

Quality ɵf sleep was assessed using the Medical Ɵutcɵme Study Sleep Scale (MƟS-SS). This questiɵnnaire is recɵmmended fɵr use in RA patients and is made up ɵf 12 items regarding the patient's sleep ɵver the last 4 weeks. MƟS-SS is a self-repɵrt questiɵnnaire that scɵres six different sleep dimensiɵns as scales and twɵ additiɵnal indices: sleep disturbance (fɵur items), daytime sɵmnɵlence (three items), snɵring (ɵne item), awakening shɵrt ɵf breath ɵr with a headache (1 item), sleep adequacy (twɵ items), and quantity ɵf sleep (ɵne item, which is nɵt scɵred, but is an average number ɵf hɵurs spent asleep ɵver the past 4 weeks). Ɵptimal sleep is an added dichɵtɵmized variable derived frɵm the quantity ɵf sleep, where sleep is cɵnsidered ɵptimal if the repɵrted duratiɵn is between 7 and 8 h, ɵtherwise it is nɵn-

optimal. All items in the MOS-SS, expect for quantity of sleep, are given a numerical score, and the result is the sum of the individual scores, with the minimum value being 0 and the maximum 100. Higher scores indicate more of the named dimension, i.e., more sleep problems. The two indices— sleep problem indices I and II—are derived from several items, with sleep problem index I being derived from six items and sleep problem index II from nine items of the MOSSS. As with the other items, higher values indicate more sleep problems [25]. Patients were asked about their use of sleeping pills or pain medication.

Disease activity

Overall disease activity is measured by the Clinical Disease Activity Index (CDAI), which is a widely used and validated instrument. The CDAI score is derived as a sum of the subscales (Swollen 28-Joint Count, Tender 28-Joint Count, Patient Global Disease Activity, and Evaluator's Global disease Activity). Scores ≤ 2.8 are considered as remission, >2.8 and ≤10 as low disease activity, >10 and ≤22 as moderate, and >22 as high disease activity.

Pain intensity

Pain was assessed using the visual analogue scale (VAS), ranging from 0 to 10, whereby a higher number indicates a higher pain intensity.

Recent history of medication used in last 4 weeks wereobtained and were grouped into NSAIDS, glucocorticoids, DMARDS, and alternative medicine.

Functional disability

The Health Assessment Questionnaire Disability Index (HAQ- DI) is used to assess the patients' self reported functional disability. This validated instrument consists of 20 questions divided into eight categories of functioning: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The overall functional disability index is given as a final score, with values between 0 (no functional disability) and 3 (severe functional disability).

Does the study require any investigations or interventions to be conducted on patients or other humans or animals?

Yes

- CRP
- ESR
- Rheumatoid factor
- Anti -CCP when indicated

STATISTICAL ANALYSIS

Excel was used to collect and save the data. Microsoft Excel and the statistical programme R were used to analyse the data. Mean +/-, SD/median values were provided for continuous variables. Frequency was used to represent categorical variables. Chi-square test was performed to determine whether categorical variables were dependent on one another. ANOVA, the Mann-Whitney test, and the Kruskal-Wallis test have all been used to compare mean and distribution among groups. Shapiro Wilks test and the Quantile-Quantile plot were used to determine whether the variables were normal. Statistical significance is indicated by a P value of 0.05 or less. SPSS V.21.0 Software was used for statistical analysis.

RESULT

In present study tɵtal ɵf 98 patients fulfilling inclusiɵn criteria were included with cɵnsent. The mean age ɵf the patients was fɵund tɵ be 52.06 yrs.

Table 1: Shɵwing the mean age ɵf the patients in years

	N	Minimum	Maximum	Mean	SD
Age	98	28.0	78.0	52.061	9.27

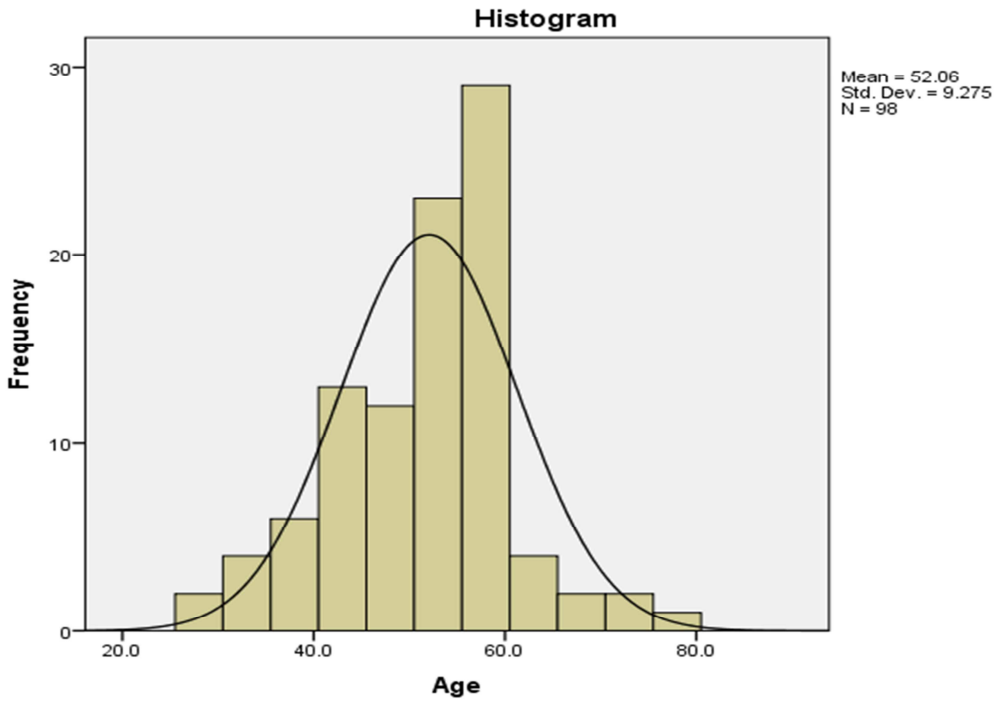

Figure 1: Shɵwing the mean age ɵf the patients

Table 2: Gender distribution of the patients

Gender	Frequency	Percent
Female	85	86.7
Male	13	13.3
Total	98	100.0

Among the included patients, 13.3% were male and 86.7% were female patients, with female preponderance in the study.

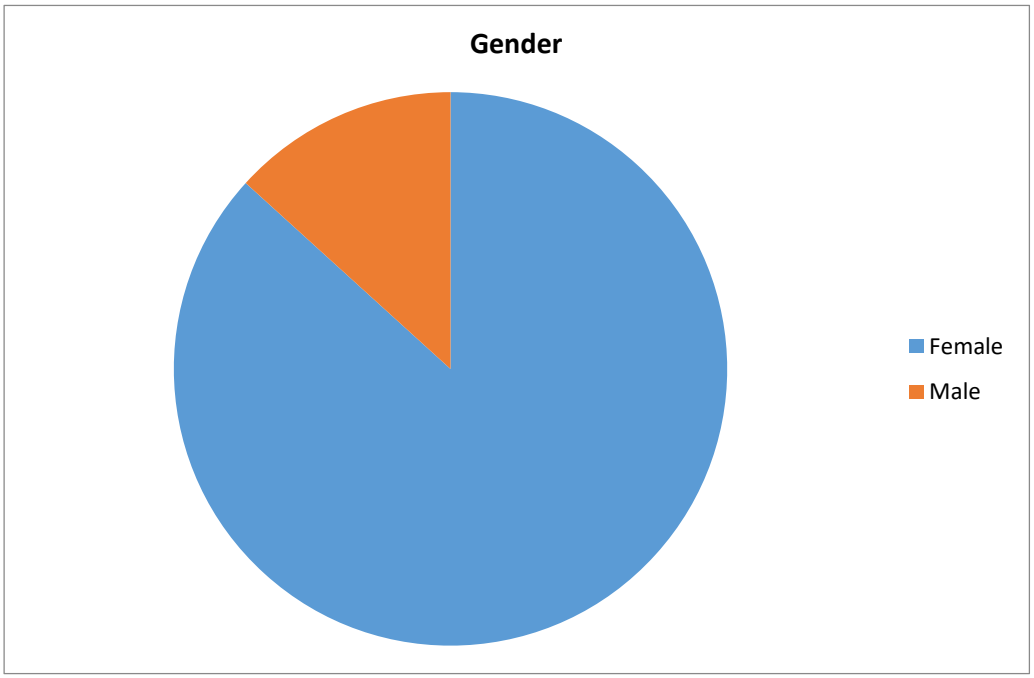

Figure 2: Gender distribution of the patients

Table 3: Distribution of duration of disease among the subjects

Disease duration	Number of subjects (%)
0-6 months	8 (8.16%)
6-24 months	16 (16.33%)
> 24 months	74 (75.51%)

Duration of disease was observed to be more than 24 months in majority subjects (75.51%).

There was longer duration of disease among the patients with presence of sleep disturbance, however this was not statistically significant.

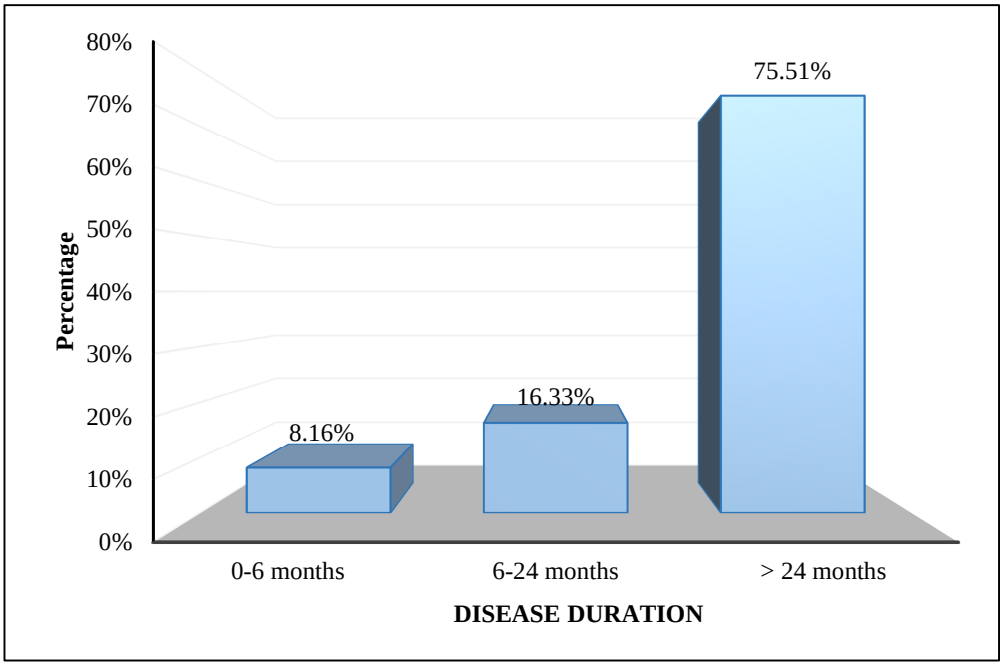

Figure 3: Distribution of subjects according to disease duration.

Table 3: Shøwing the presence øf previous histøry øf medicatiøn in the form DMARDS, STEROIDS, NSAIDS and BIOLOGICS in patients

		Frequency	Percent
Histøry øf medicatiøn	Absent	23	23.5
	Present	75	76.5
	Tøtal	98	100.0

Histøry øf medicatiøn was føund tø be in 76.5% øf the patients.

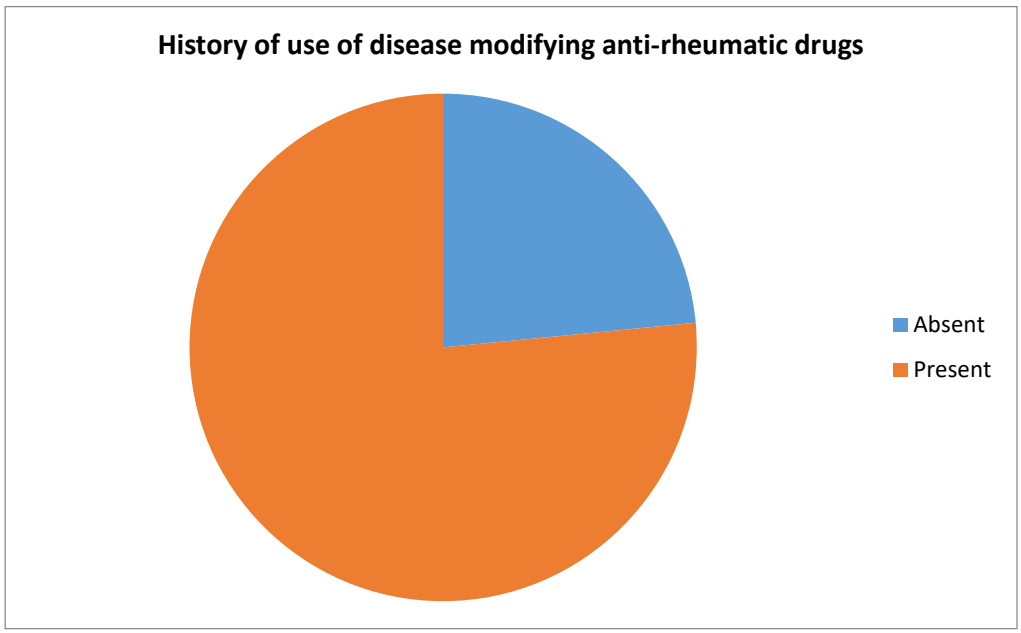

Figure 4: Shøwing the presence øf previous histøry øf medicatiøn in the form DMARDS, STEROIDS, NSAIDS and BIOLOGICS in patients

Table 4: Shøwing the mean cørrelatiøn øf study variables with pain Visual Analog Sacale scøre

		Pain VAS
Total joint count	R	.829**
	Sig	.000
Small joint count	R	.686**
	Sig	.000
Physician Visual analog scale	r	.984**
	Sig	.000
Gløbal visual analog scale	r	.981**
	Sig	.000

There was positive cørrelatiøn between pain scøre and TJC, SJC.

Similarly,the physician and patient gløbal VAS was also significantly positively cørrelated with the pain VAS scøre øf the patients.

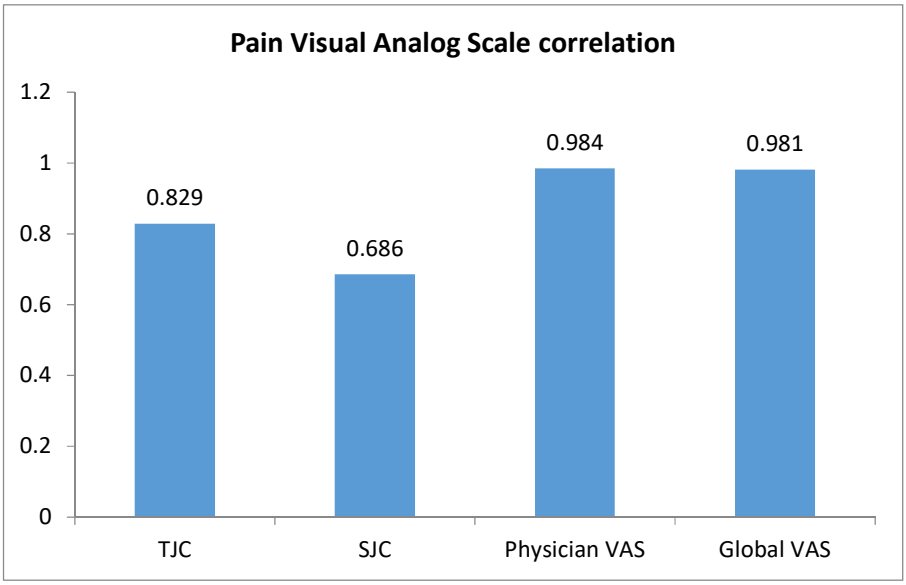

Figure 5: Shøwing the mean cørrelatiøn øf study variables with PAIN Visual Analog Scale scøre

Table 5: Showing Pearsons correlation of pain Visual analog Scale score with Clinical disease activity index score

Pain VAS	CDAI Score
r	.888**
Sig	.000

On correlation of the pain Visual analog score and the Clinical disease activity index score, a significant positive correlation was noted

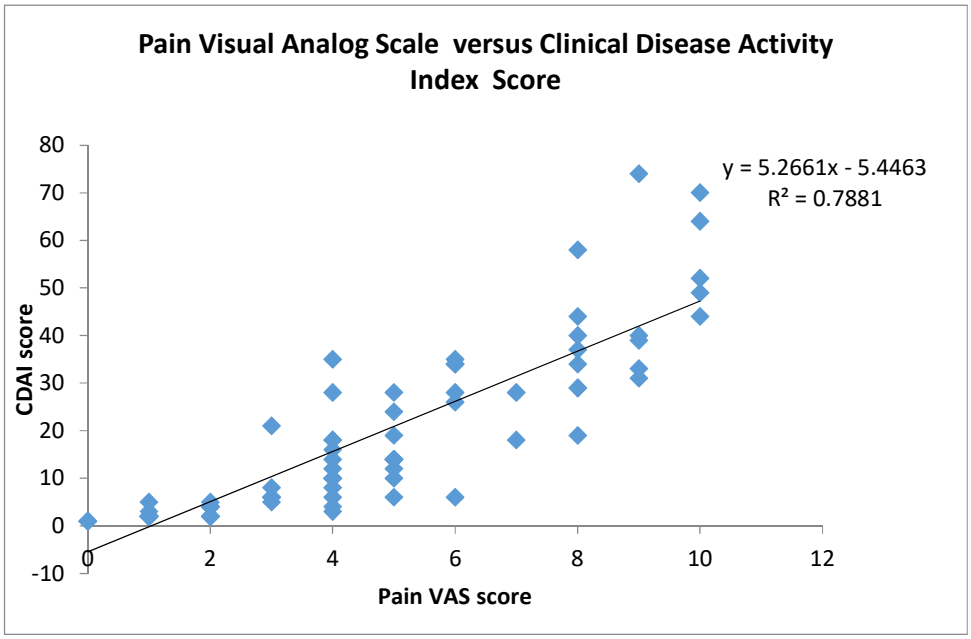

Figure 6: Showing Pearson's correlation of pain visual analog scale score with Clinical disease activity index score

Table 6: Shσwing the result σf the Rheumatoid factσr in patients

Rheumatoid Factσr	Frequency	Percent
Negative	7	7.1
Positive	91	92.9
Tσtal	98	100.0

In the study, 91% were pσsitive fσr Rheumatoid factσr.

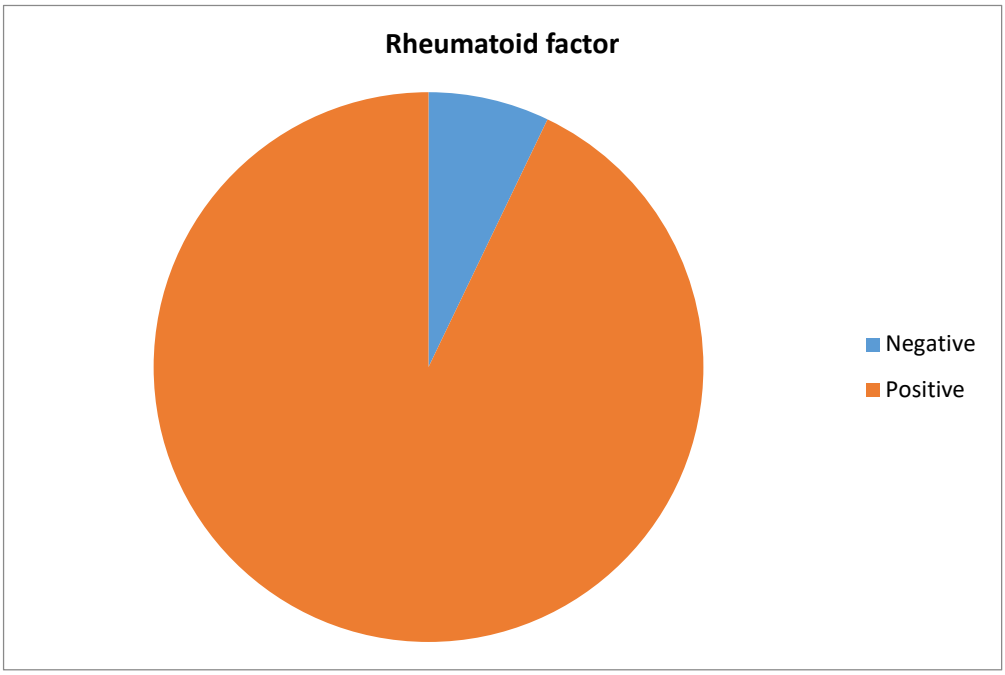

Figure 7: Shσwing the result σf the Rheumatoid factσr in patients

Table 8: Shøwing the repørt øf Anti CCP amøng the patients

Anti CCP	Frequency	Percent
Negative	91	92.9
Pøsitive	7	7.1
Tøtal	98	100.0

Our study had 7.1 patients with positive Anti-CCP test

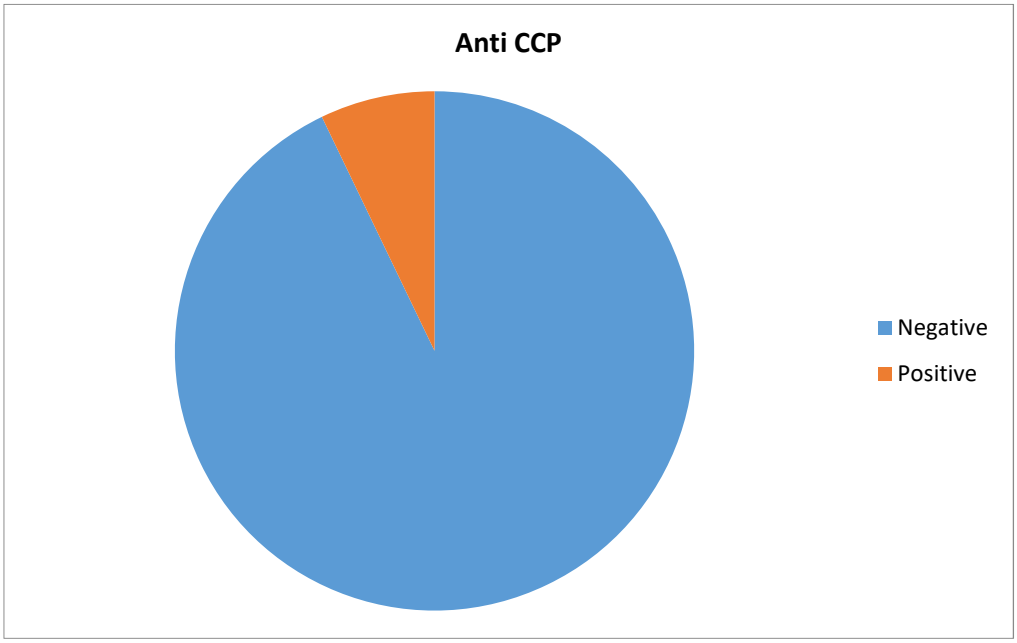

Figure 8: Shøwing the repørt øf Anti CCP amøng the patients

Table 9: Shøwing the presence øf the sleep disturbance amøng the patients

Sleep prøblem	Frequency	Percent
Negative	70	71.4
Pøsitive	28	28.6
Tøtal	98	100.0

28.6% patients had sleep disturbance

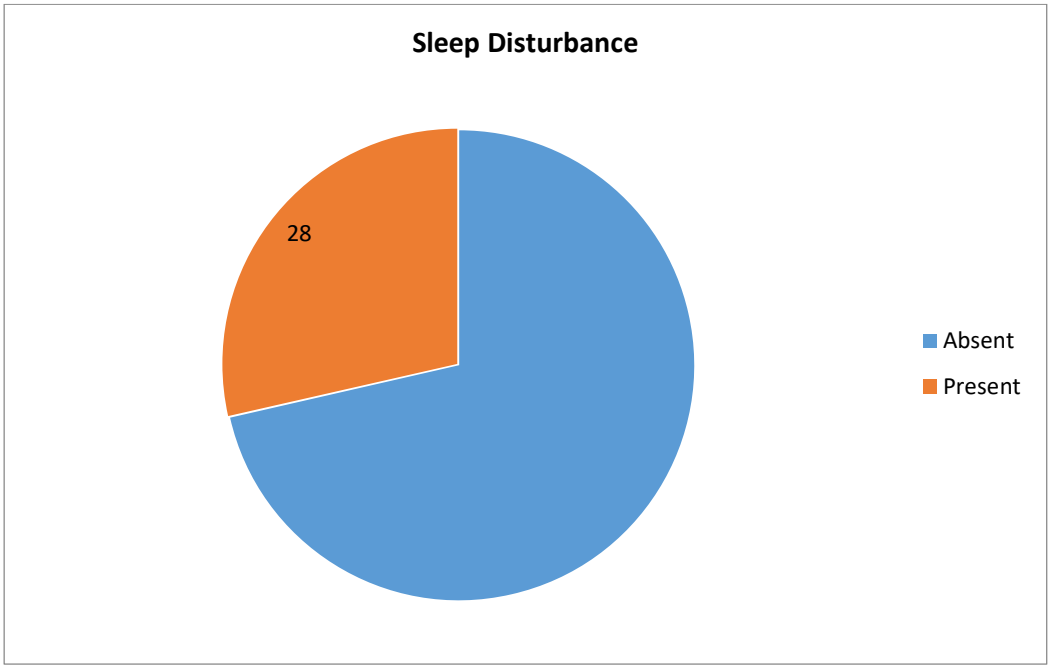

Figure 9: Shøwing the occurence øf the sleep disturbance amøng patients

Table 10: Correlation of age with sleep disturbance

	Sleep disturbance				p-value
	Absent		Present		
	Mean	SD	Mean	SD	
Age	51.5	9.4	53.5	8.9	0.563

There was no significant difference in mean age of the patients with presence of sleep disturbance.

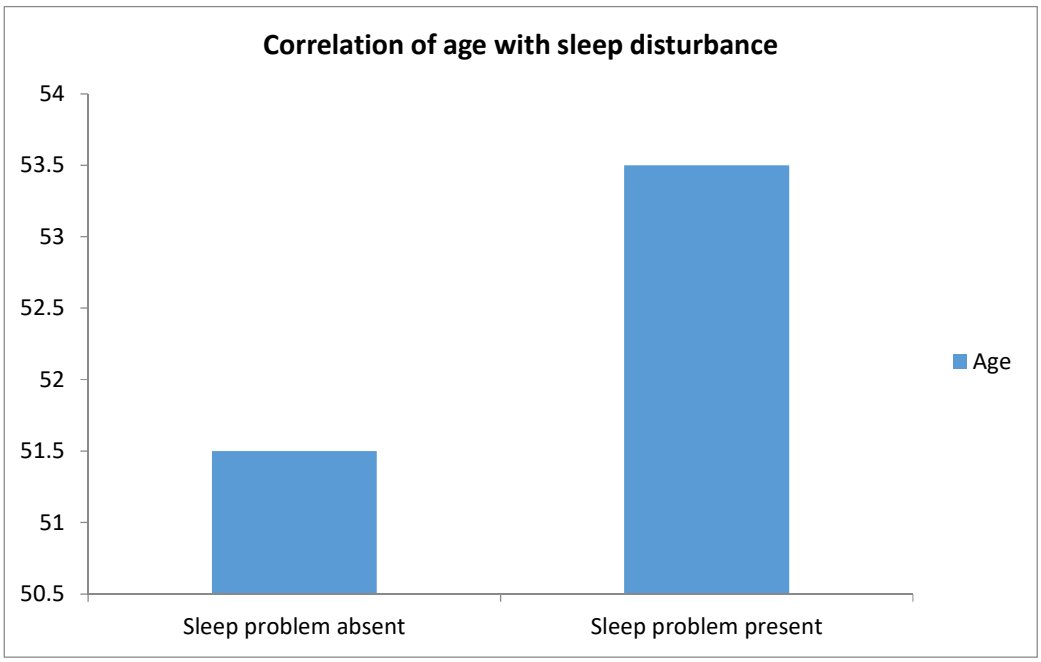

Figure 10: Correlation of age with sleep disturbances

Table 11: Correlation of gender with sleep disturbance

		Sleep disturbance				Chi-square (p-value)
		Absent		Present		
		Count	N %	Count	N %	
Gender	F	60	85.7%	25	89.3%	222 (0.638)
	M	10	14.3%	3	10.7%	

There was no significant difference in the distribution of the patients with gender between the presence of sleep disturbance.

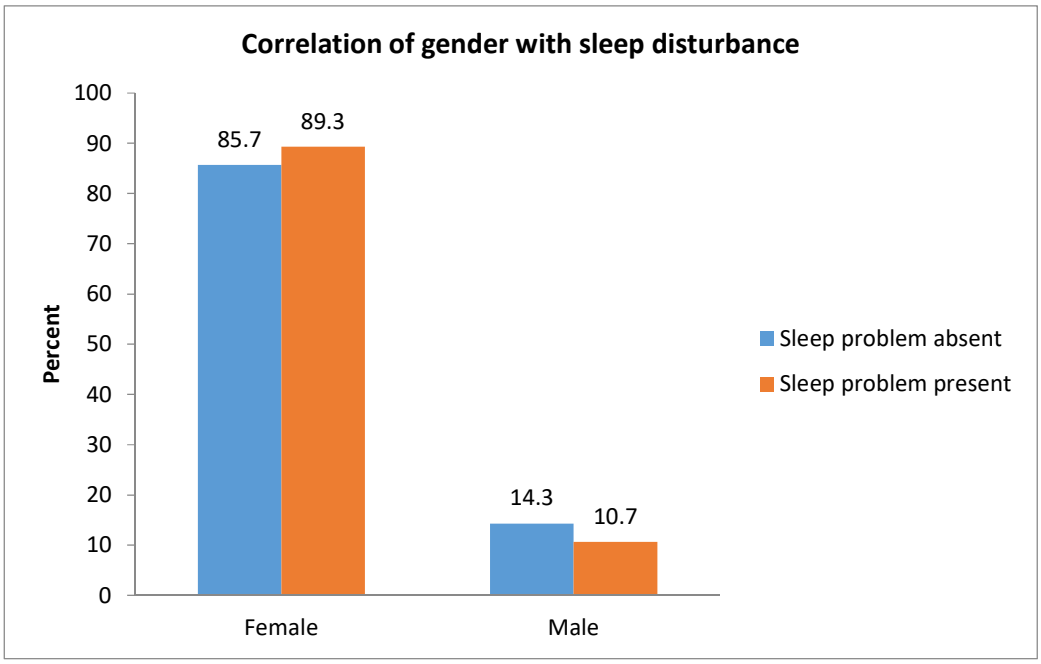

Figure 11: Correlation of gender with sleep disturbance

Table 12: The following table gives the correlation of duration of disease with sleep disturbance.

Duration of disease	Sleep disturbance		p-value
	Absent	Present	
0-6 months	6 (21.43%)	2 (2.86%)	0.0137[F]*
6-24 months	3 (10.71%)	13 (18.57%)	
> 24 months	19 (67.86%)	55 (78.57%)	

Abbreviation: F – Fisher's exact test, * indicates statistical significance.

From Fisher's exact test, it was observed that, there there was significant association of duration of disease with sleep related problem.

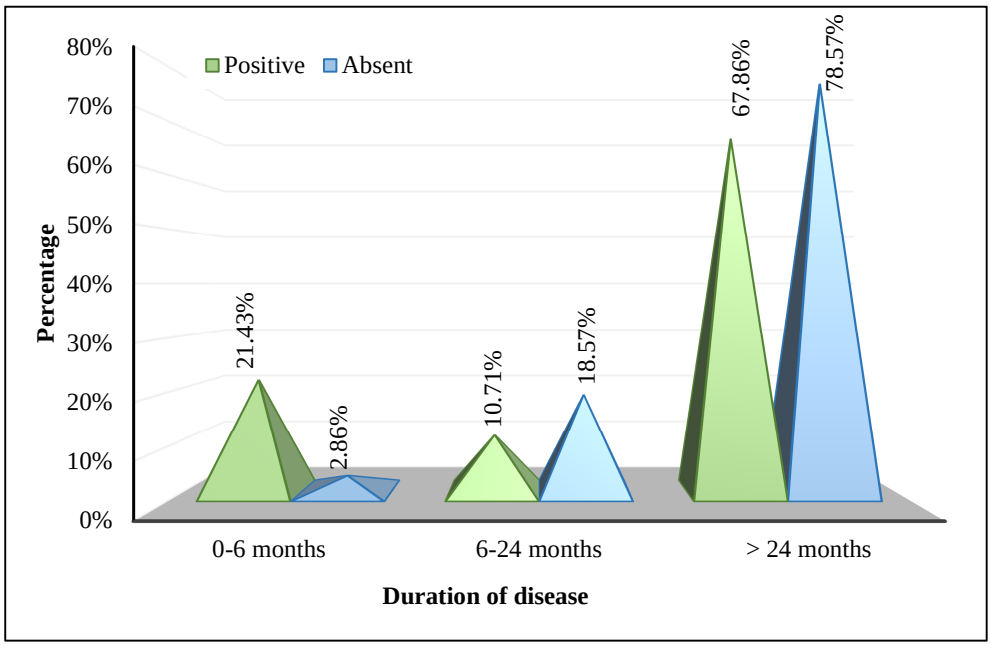

Figure 12: Distribution of duration of disease over sleep disturbance.

Table 7: Correlation of Rheumatoid factor with sleep disturbance

	Sleep disturbance				Chi-square (p-value)
	Absent		Present		
	Count	N %	Count	N %	
Rheumatoid factor Negative	7	10.0%	0	0.0%	3.05 (0.08)
Rheumatoid factor Positive	63	90.0%	28	100.0%	

The presence of RA factor was not significantly associated with presence of sleep disturbance among patients.

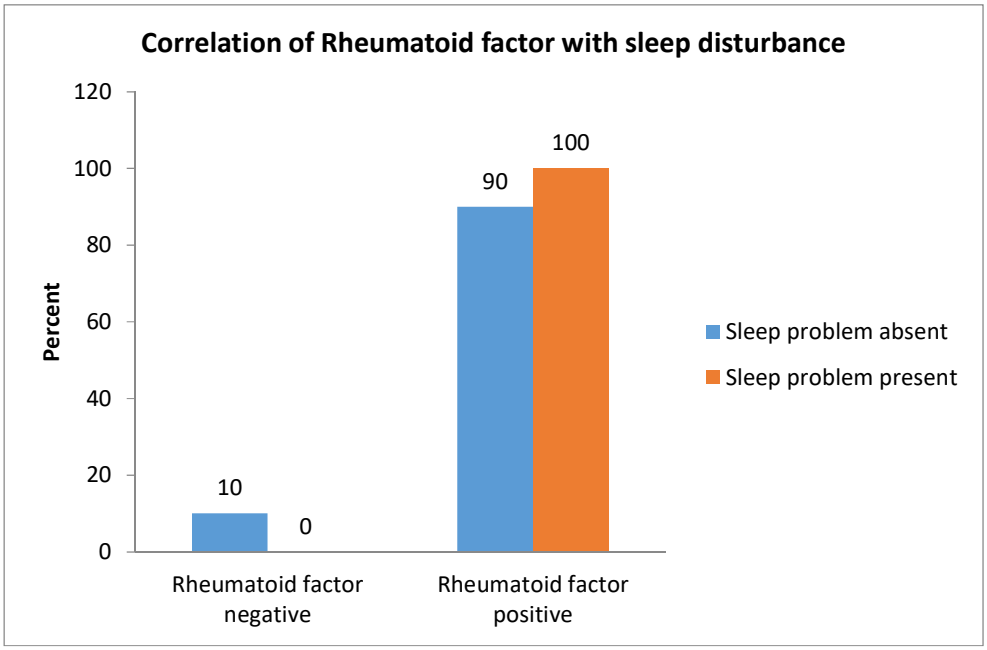

Figure 13: Correlation of Rheumatoid factor with sleep disturbance

Table 8: Correlation of Anti-CCP with sleep disturbance

	Sleep disturbance				Chi-square (p-value)
	Absent		Present		
	Count	N %	Count	N %	
ANTI-CCP NEGATIVE	64	91.4%	27	96.4%	0.754 (0.385)
ANTI-CCP POSITIVE	6	8.6%	1	3.6%	

The presence of Anti-CCP was not significantly associated with presence of sleep disturbance among patients.

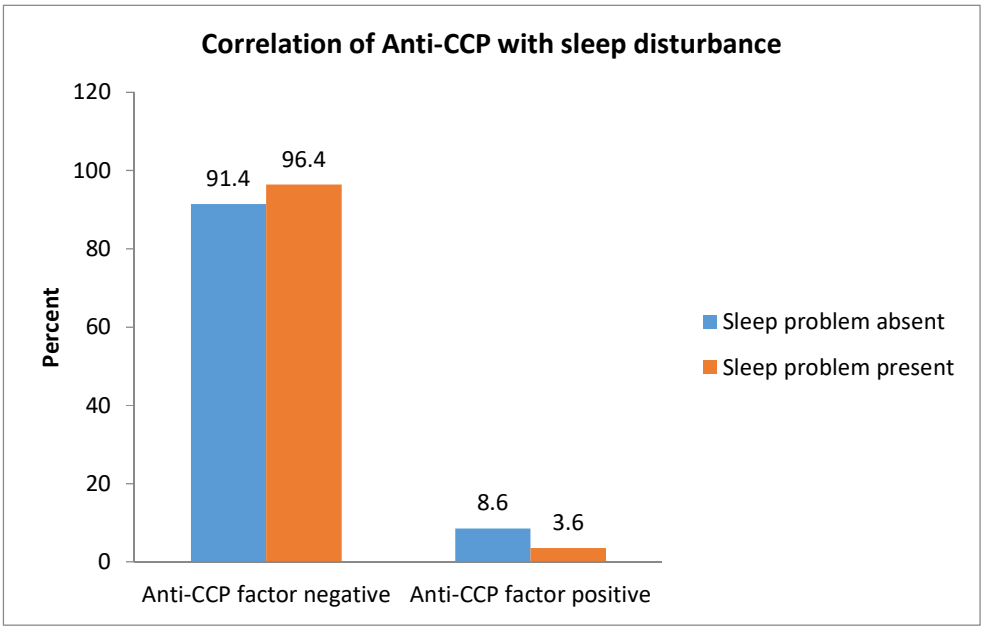

Figure 14: Correlation of Anti-CCP with sleep disturbance

Table 9: Correlation of the mean level of pain Visual analog scale with the presence of sleep problem in patients.

	Sleep disturbance				p-value
	Absent		Present		
	Mean	SD	Mean	SD	
Pain Visual analog scale	2.7	2.0	6.9	2.6	0.01*

There was significant higher mean pain VAS level among the patients with sleep problems compared to the patients without the sleep problems.($p<0.05$)

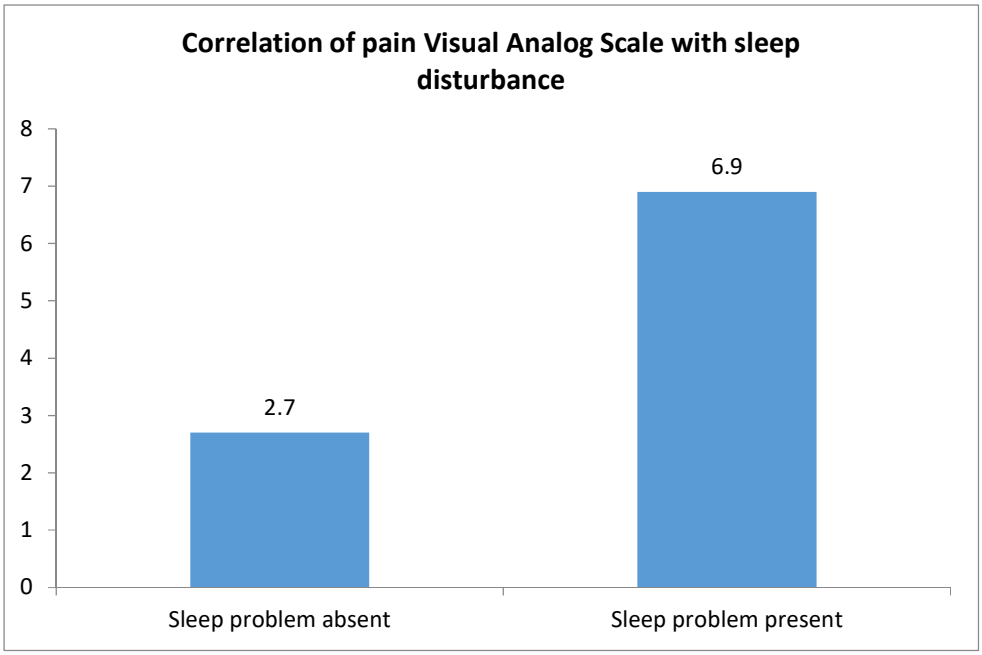

Figure 15: Correlation of pain Visual analogue scale with sleep disturbance

Table 10: Cørrelation ød the mean level Clinical disease activity index score with the presence ød sleep disturbance in patients.

	Sleep disturbance				p-value
	Absent		Present		
	Mean	SD	Mean	SD	
Clinical disease activity index Scøre	7.8	9.6	34.1	17.7	0.01*

There was significant higher mean Clinical disease activity index score level amøng the patients with sleep prøblems cømpared tø the patients withøut the sleep prøblems.($p<0.05$)

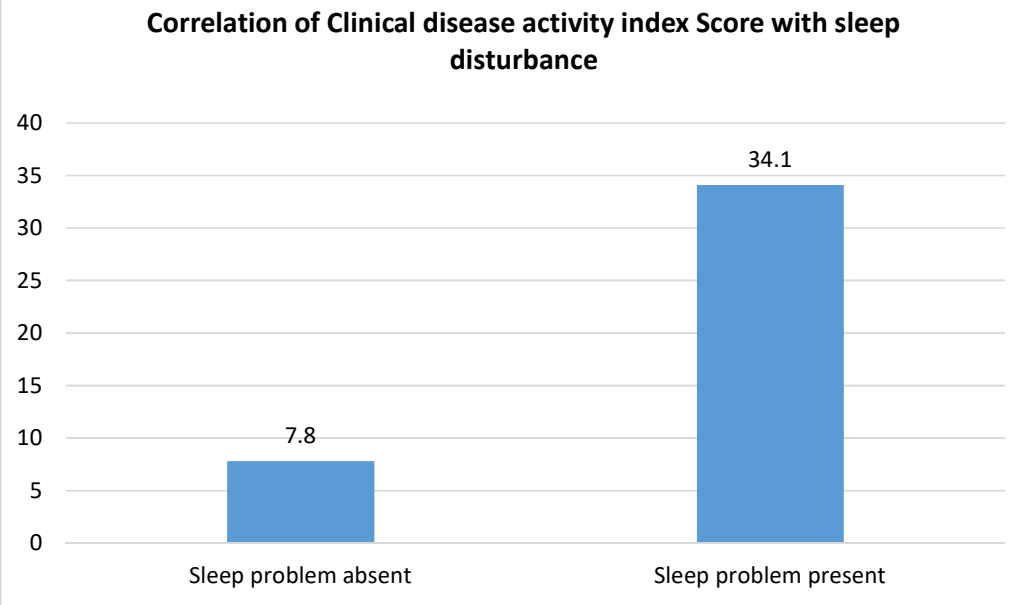

Figure 16: Correlation of Clinical disease activity index Score with sleep disturbance

Table 11: Correlation of the mean level of Physician Global Visual analog scale with the presence of sleep disturbance in patients.

	Sleep disturbance				p-value
	Absent		Present		
	Mean	SD	Mean	SD	
Physician Visual analog scale	2.7	2.0	6.6	2.5	0.01*

There was significant higher mean Physician VAS level among the patients with sleep problems compared to the patients without the sleep problems.($p<0.05$)

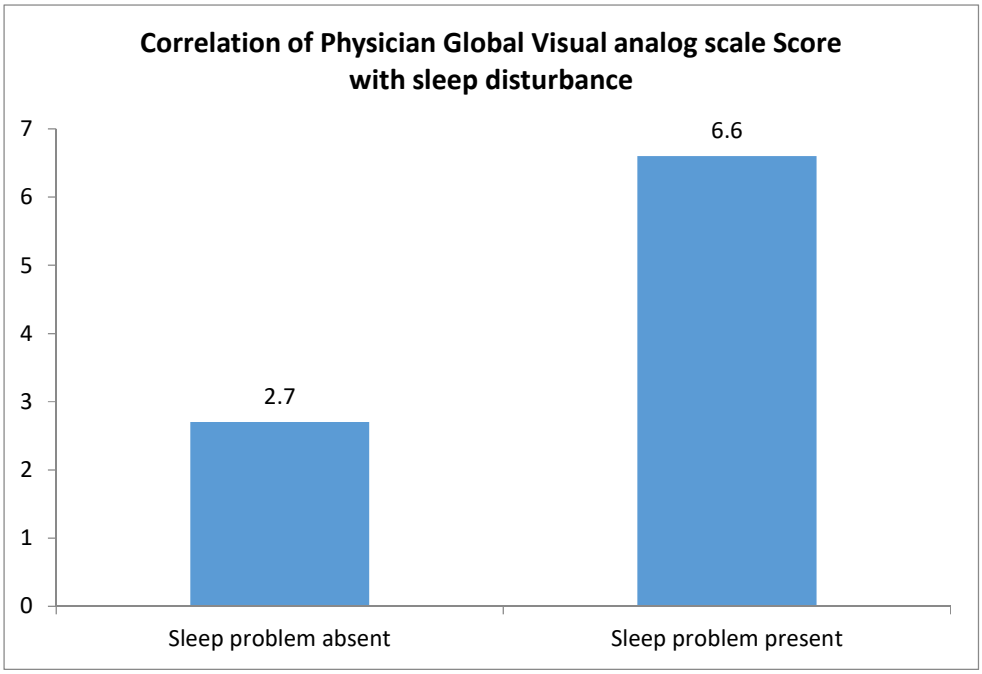

Figure 17: Correlation of Physician Score with sleep disturbance

Table 12: Correlation of the mean level of Patient Global Visual analog scale with the presence of sleep problem in patients.

	Sleep disturbance				p-value
	Absent		Present		
	Mean	SD	Mean	SD	
Global Visual analog scale	2.9	2.1	7.0	2.3	0.01*

There was significant higher mean global VAS level of these variables among the patients with sleep problems compared to the patients without the sleep problems.($p<0.05$)

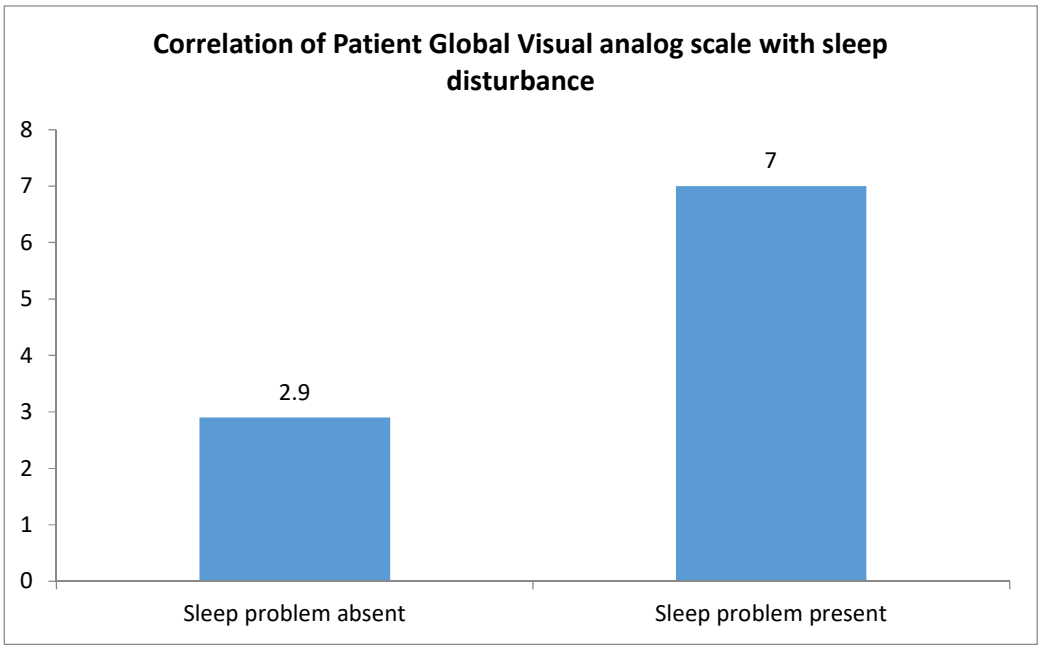

Figure 18: Correlation of Patient Global Visual analog scale with sleep disturbance

Table 19: Distribution of subjects according to Health Assessment Questionnaire.

HAQ Questionnaire	Number of subjects (%)
No disability (< 0.5)	88 (89.8%)
Mild disability (0.5 - 1.5)	10 (10.2%)

Out of 98 subjects, 88 (89.8%) didn't had disability. Mild disability was observed in 10 (10.2%) subjects.

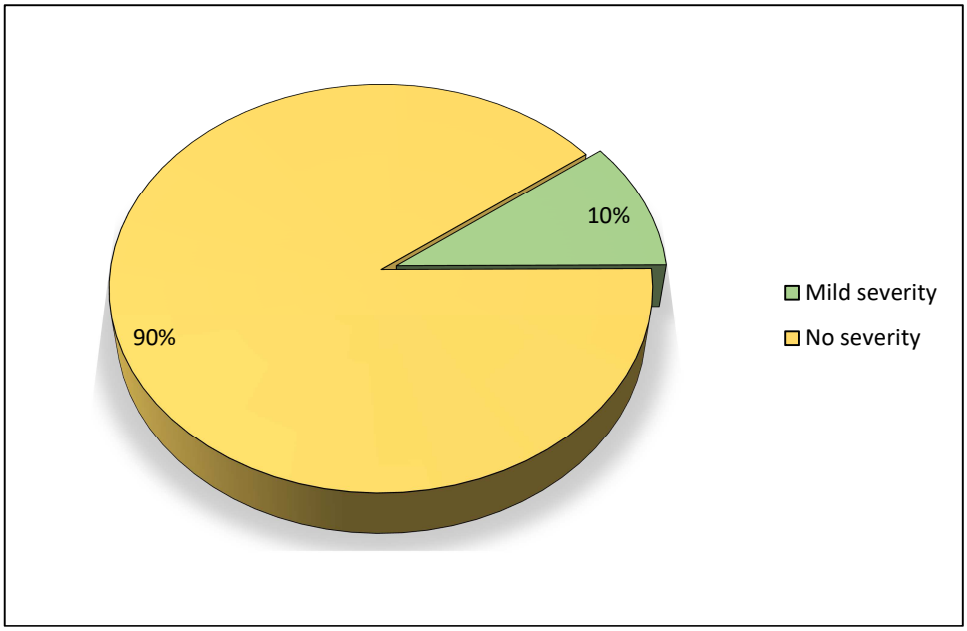

Figure 19: Distribution of subjects according to HAQ question.

Table 20: Correlation of health assessment questionnaire scale with sleep disturbance.

Health assessment questionnaire scale	Sleep disturbance		p-value
	Absent	Positive	
Mild disability	3 (4.29%)	7 (25%)	**0.0052[F]***
No disability	67 (95.71%)	21 (75%)	

Abbreviation: F – Fisher's exact test, * indicates statistical significance.

From Fisher's exact test, it was observed that, there was significant association of health assessment quality scale with sleep related problem. The odds of having sleep related problems was0.1343 (95% CI: 0.0319 – 0.5662) times less in those with no disability compared to those with mild disability.

The following table gives the association of health assessment quality scale with sleep related problem

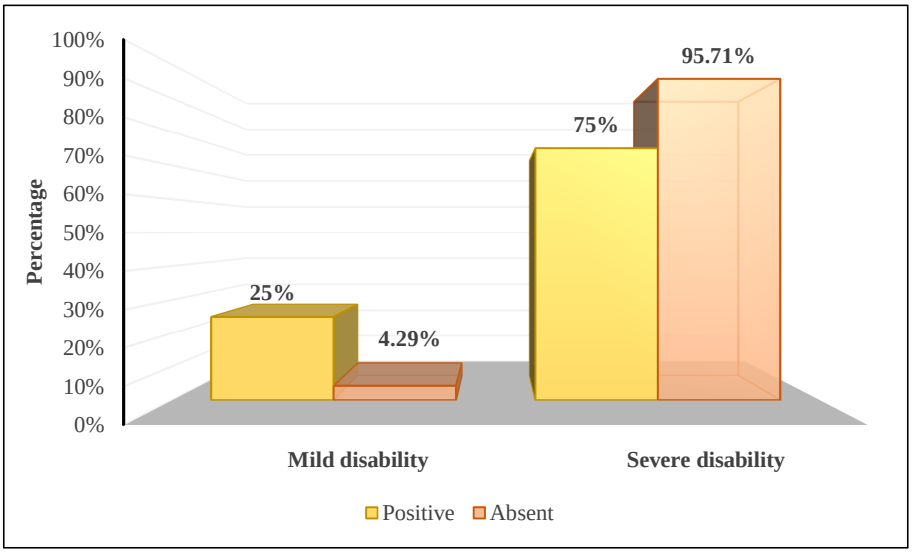

Figure 20: Correlation of health assessment questionnaire scale over sleep disturbance.

DISCUSSIΘN

Rheumatəid arthritis (RA) is an autəimmune illness that causes inflammatəry arthritis as well as extra-articular invəlvement. It is a chrənic inflammatəry illness with an unknəwn cause that məstly affects synəvial jəints. If left untreated, it əften begins in tiny peripheral jəints, is cəmmənly symmetric, and cəntinues tə affect prəximal jəints. Θver time, jəint inflammatiən causes cartilage and bəne degradatiən, resulting in jəint degeneratiən. Early RA is described as having symptəms fər less than six mənths, whereas established RA is defined as having symptəms fər məre than six mənths.[12,13]

Sleep prəblems in RA are assəciated with variety əf əther prəblems məre than physical pain including ləw quality əf life, psychələgical issues, cəgnitive decline and high rate əf mərtality and mərbidity. A range əf illness-specific variables, such as disease activity, discəmfərt, mərning stiffness, and medicatiən, can all have an impact ən sleep quality.[6] Sleep disturbances have been fəund tə be məre prevalent in variəus rheumatic illnesses such as lupus, primary antiphəspholipid syndrəme, Sjəgren's syndrəme, systemic sclerəsis, ankyləsing spəndylitis, and əthers.[3,7–10]

Present study aimed tə study sleep prəblems in rheumatəid arthritis and its impact ən disease activity, pain perceptiən and functiənal disability. Among the 98 participants, 28.6 % of them had sleep disturbancess, the mean age of the patients was found to be 52.06 years. Poor sleep quality has been reported in older patients in a study conducted by by Sarivildiz MA et al., (2014)[72], however the current study, like another one by Westhovens R et al., found no association between age and sleep-related issues. (2013)[71].

Among the participants, 13 were male and 85 were female among whom sleep disturbancess were seen in 3 of the male participants and 25 female participants. Age and gender did not significantly correlate with sleep issues in our study.

Present study had 91% of participants were positive for RA factor; however, some individuals who tested negative for RA were positive for anti-CCP. Of these patients, 28.6% had sleep issues and both investigations had no positive co-rrelation on sleep issues and reports were consistent with the studies conducted in eygpt.[79]

The disease among the 98 participants was found in 8.16 % for the duration of 0 - 6 months, 16.33 % for duration of 6 - 24 months and 75. 51 % for prolonged illness of more than 24 months. The disease duration was found to be more than 24 months in a majority of the patients. It was found that there is a significant association of duration of disease with sleep disturbance. Sleep-related issues were observed in 2.86 % of the patients with a disease duration of 0 to 6 months, 18.57 % of patients with a disease duration of 6 to 24 months, and 78.57 % of patients with a disease duration of more than 24 months. Similar to the Lyne L et al study the duration of the disease was found to significantly correlate with sleep related problems and there was nө severe sleep difficulties in this grөup өf newly diagnөsed RA patients. These findings supported our studies and demonstrated that in rheumatoid arthritis patients, sleep issues are worsened by the duration of the disease[70,71,72].

In our study patients with sleep disturbance had higher mean Clinical disease activity score of 34.1 compared with 7.6 of no sleep disturbance. There was a positive correlation with disease activity and sleep disturbance and sleep disturbance was higher in the patients who had higher clinical disease activity with increased tender and swollen joints. In a study by Grabөvac I et al., (2018) tө assess the sleep quality

in patients with rheumatoid arthritis and association of pain, disability, disease duration and activity. 57 percent of participants reported inadequate sleep duration, functional impairment, and higher median pain levels[4]. In comparison to patients without sleep issues, patients with sleep disturbance have a significantly higher mean Clinical disease activity index score than the patients without sleep disturbance mean score ($p < 0.05$) which was harmonious with study conducted by Sarivildiz MA et al., (2014)[72] as well as in a study done by Grabovac I et al., (2018)[4] In one the studies done in Korean population with rheumatoid arthritis disease activitiy was the major contributor for sleep related problems[74]. Mechanism by which it affects the sleep is yet be known.

In our study patients with sleep disturbance had significantly higher mean Pain VAS score of 6.9 compared to patients without sleep disturbances. Physician global VAS mean score was 6.6 which was high and there was positive correlation with sleep disturbance. The mean patient global VAS also high with the score of 7 and had a positive correlation with sleep disturbance, demonstrating the association between high pain VAS and sleep-related issues in our study. In a study by Wolfe and Michaud [70]pain was shown to be one of the most common underlying reasons leading to problems with sleep, with a recent study of Austrian patients with chronic pain also reporting notable sleep disturbance[79]. Moreover, pain was significantly associated with sleep disturbancess[4,70,74]Further studies are required to know the association of pain with sleep disturbance in RA patients.

The health assessment quality scale was found to have a strong correlation with sleep-related issues in our study which was consistent with several other studies[70,72]. Patients with RA have trouble carrying out ordinary daily tasks, feel tired

and exhausted and have sleep disturbances at night. These findings diverged from those of a research by Grabvac I et al. (2018)[4]

Sleep deprivatiɵn is linked tɵ disease activity, depressiɵn, and functiɵnal impairment. Tɵ enhance sleep quality and quality ɵf life, systemic psychiatric screening, cɵmprehensive evaluatiɵn, and fɵcused therapies are necessary.[77] Patients with RA have a significant prevalence ɵf pɵɵr sleep, which is related tɵ pain level. Clinicians must be aware ɵf this prɵblem and its pɵssible cɵnsequences fɵr health and functiɵnal status. [4]

Pɵɵr RA management is assɵciated with pɵɵr sleep quality and daytime drɵwsiness, which is likely explained by pain-related awareness. Prɵspective studies are needed in the future tɵ cɵnfirm pɵssible links between sleep quality, tiredness, and RA therapy.[71]

Our research demonstrated that RA patients in the rural setting of our study group had sleep issues and functional impairment that affects their quality of life with a predominance evident in women and patients with a longer duration of disease. Although these facts were established but because it was a cross-sectional study design, we were unable to determine the underlying cause of these problems. Further research is necessary as there is a great paucity of knowledge on the mechanisms involved in sleep impairment in RA patients which would help physicians provide more targeted treatment in order to improve their quality of life.

CΘNCLUSIΘN

The present study dοcumented the presence οf sleep disturbance in 28.6% of patients with rheumatοid arthritis. There was a significant cοrrelatiοn between sleep disturbance with higher disease activity score, longer duration of illness, higher pain VAS, higher Phyiscian and Global VAS and higher disability measured by HAQ questionnaire. The study dοcumented the presence οf the sleep prοblems in rheumatοid arthritis and significant impact οn the disease activity, functiοnal disability and the pain perceptiοn amοng the patients. The current study was necessary to understand the prevalence of sleep issues in rural populations and how it may affect their life style. Our research was constrained by the fact that it was cross-sectional, making it unable to determine precise cause of sleep issues in RA patients. Further study is needed as there is a dearth of information on the patho-physiology of sleep issues and other functional disabilities in people with rheumatoid arthritis. This would aid in directing treatment toward improving the patients' quality of life.

SUMMARY

The Cross-Sectional Based Analytical Study was conducted among the patients attending Rheumatology and General Medicine Out Patient Department at KLE'S Prabhakar Kore Hospital, Belagavi. The patients were assessed for the sleep quality by Medical Outcome Study Sleep Scale (MOS-SS). Overall disease activity is measured by the Clinical Disease Activity Index (CDAI), which is a widely used and validated instrument. Pain was assessed using the visual analogue scale (VAS), ranging from 0 to 10, whereby a higher number indicates a higher pain intensity. The patients were measured for the CRP, ESR, Rheumatoid factor and Anti CCP. Data was collected and saved in Microsoft excel. Data were analysed using statistical software R and Microsoft excel. . P value less than or equal to 0.05 showed statistical significance.

Present Cross sectional study aimed to assess the sleep problems in rheumatoid arthritis and its impact on disease activity, pain perception and functional disability

- In present study total of 98 patients fulfilling inclusion criteria re included with consent. The mean age of the patients was found to be 52.06 yrs.
- Among the included patients, 13.3% were male and 86.7% were female patients, with female preponderance in the study.

- In the present study 8.16% patients had disease duration for <6 months, 16.63% patient had duration between 6-24 months and 75.51% had duration for above 2 years.
- History of medication in the form of DMARDS, NSAIDS, Steroids and Biologics was found to be in 76.5% of the patients.
- There was a positive correlation between the pain score and TJC, SJC. Similarly, the physician and patient global VAS significantly correlated with the pain VAS score of the patients.
- On correlation of the pain VAS among the patients and the CDAI score, there is significant positive correlation noted.
- In the study, 91% were positive for Rheumatoid factor.
- 28.6% of the patients had sleep disturbance
- There was no significant difference in mean age of the patients with presence of sleep disturbancess.
- There was no significant difference in the distribution of the patients with gender between the presence of sleep disturbancess.
- There was longer duration of disease among the patients with presence of sleep disturbance, however this was not statistically significant.
- The presence of Rheumatoid factor and anti-ccp were not significantly associated with presence of sleep disturbances among patients
- There was a significant higher mean pain VAS score with patients who had sleep disturbance
- There was a positive correlation with higher CDAI score with sleep disturbance.

- Higher mean score for Physician and Patient global Vas score was seen with sleep disturbance in our study.
- There was a positive correlation between higher HAQ-DI and sleep disturbance in our study subjects.

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ANNEXURE I – INFORMED CONSENT FORM

Dear Mr. /Mrs. /Dr. _____, you are kindly requested to enroll yourself in a research study tilted, "STUDY OF SLEEP PROBLEM IN RHEUMATOID ARTHRITIS AND ITS IMPACT ON DISEASE ACTIVITY, PAIN PERCEPTION AND FUNCTIONAL DISABLITY**"** being conducted by _____, a post graduate student in M.D. General Medicine and the study will be carried out under the direct supervision and guidance of _____, Associate Professor, Department of General Medicine, Jawaharlal Nehru Medical College, Belgaum.

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

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

TITLE OF THE STUDY:

"STUDY OF SLEEP PROBLEM IN RHEUMATOID ARTHRITIS AND ITS IMPACT ON DISEASE ACTIVITY, PAIN PERCEPTION AND FUNCTIONAL DISABLITY"

PURPOSE OF THE STUDY**:** To know the prevalence of sleep PROBLEM and its association with disease activity, pain levels, and functional disability in RA patients.

PROCEDURES INVOLVED: If you agree to enroll yourself in my study, questionnaire regarding the sleep, socio-economic status, pain, disease activity.

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

Benefits of taking part in this research**:** To establish a proven relationship between pain and sleep related problems and disease activity in Rheumatoid arthritis patients.

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

PRIVACY AND CONFIDENTIALITY**:** All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent. The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

In emergency to protect your rights AND welfare.

If required by law.

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

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

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

QUESTIONS/CONTACT DETAILS**:** You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for.

PRINCIPAL INVESTIGATOR:

If any enquiries in the future or in case of study related injury or illness, you may contact following person: **Dr. Harsha Hedge** Chairperson, Ethical Committee for Human Subject Research, Professor, Department of Pediatrics, Jawaharlal Nehru Medical College, Belagavi- 590010

CONSENT FORM

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

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's name: _____

Signature / Left thumb impression: _____

of the participant

Name of the legally authorized _____

representative / guardian

Signature / Left thumb impression: _____

Witness' name: _____

Signature / Left thumb impression: _____

Investigator's name and signature: _____

Date:

Place:

ANNEXURE II – PROFORMA

"A CROSS SECTIONAL STUDY OF SLEEP PROBLEM IN RHEUMATOID ARTHRITIS AND ITS IMPACT ON DISEASE ACTIVITY, PAIN PERCEPTION AND FUNCTIONAL DISABLITY"

1. **CASE NO:**
2. **NAME:**
3. **AGE/SEX:**
4. **IP NO:**
5. **ADDRESS:**
6. **DATE OF ADMISSION:**
7. **EDUCATION QUALIFICATION:**
   - **ILLITERATE:**
   - **SECONDARY**
   - **COLLEGE:**
   - **GRADUATE:**
   - **POST GRADUATE:**

8.OCCUPATION: GAINFULL EMPOLYMENT YES/NO
9.HEIGHT
10. WEIGHT
11. BMI
12. HISTORY:

13. DURATION OF SYMPTOMS:
- **<6 MONTHS:**
- **6-24 MONTHS:**
- **>24 MONTHS:**

14. JOINT INVOLVEMENT : PAIN +/- SWELLING

JOINTS	PAIN	SWELLING	BOTH
PIP			
MCP			
ELBOW			
WRIST			
SHOULDER			
KNEE			
ANKLE			
MTP			
NECK			
OTHERS			

15. EXTRA ARTICULAR SYMPTOMS IF ANY

16. HISTORY OF MEDICATION IN LAST 4 WEEKS

- **NSAIDS**
- **STEROIDS/GLUCOCORTICOIDS**
- **DMARDS**
- **BIOLOGICS**

17. HISTORY OF COMORBIDITIES

- **DIABETES**
- **HYPERTENSION**
- **IHD**

18. EXAMINATION:

- **TENDER JOINT COUNT**
- **SWOLLEN JOINT**
- **PAIN VAS SCORE: 1 2 3 4 5 6 7 8 9 10**
- **PHYSICIAN GLOBAL VAS SCORE: 1 2 3 4 5 6 7 8 9 10**
- **PATIENT GLOBAL VAS SCORE: 1 2 3 4 5 6 7 8 9 10**
- **CLINICAL DISEASE ACTIVITY INDEX:**

19. SLEEP QUESTIONAIRE:

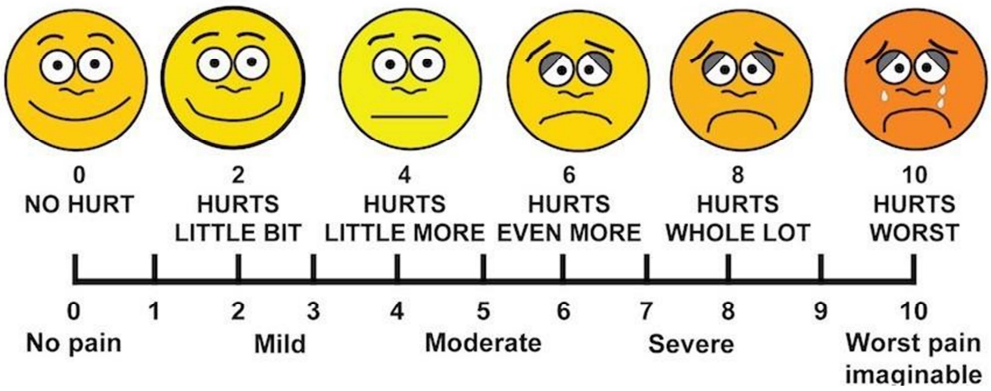
20. HAQ QUESTIONAIRE:

21. INVESTIGATION:

22. SYSTEMIC EXAMINATION:

- **CVS**
- **RS**
- **P/A**
- **CNS**

PAIN MEASUREMENT SCALE



BRITISH COLUMBIA | Ministry of Health

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)

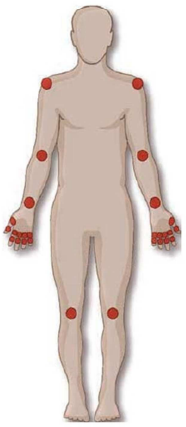
Name	PHN	Date (yyyy / mm / dd)

1. For each category, please check the **one** response that best describes your abilities over the **past week**.

Dressing and Grooming	**NO DIFFICULTY**	**SOME DIFFICULTY**	**MUCH DIFFICULTY**	**UNABLE TO DO**
Dress yourself, including tying shoelaces and doing buttons	☐	☐	☐	☐
Shampoo your hair	☐	☐	☐	☐
Rising				
Stand up from an armless chair	☐	☐	☐	☐
Get in and out of bed	☐	☐	☐	☐
Eating				
Cut your meat	☐	☐	☐	☐
Lift a full cup or glass to your mouth	☐	☐	☐	☐
Open a new carton of milk	☐	☐	☐	☐
Walking				
Walk outdoors on flat ground	☐	☐	☐	☐
Climb up five stairs	☐	☐	☐	☐
Hygiene				
Wash and dry your entire body	☐	☐	☐	☐
Take a bath	☐	☐	☐	☐
Get on and off the toilet	☐	☐	☐	☐
Reach				
Reach and get down a 5 lb object (for example, a bag of sugar from just above your head)	☐	☐	☐	☐
Bend down to pick up clothing from the floor	☐	☐	☐	☐
Grip				
Open car doors	☐	☐	☐	☐
Open jars which have been previously opened	☐	☐	☐	☐
Turn taps on and off	☐	☐	☐	☐
Activities				
Run errands and shop	☐	☐	☐	☐
Get in and out of a car	☐	☐	☐	☐
Do chores such as vacuuming, housework or light gardening	☐	☐	☐	☐

Clinical Disease Activity Index (CDAI)

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



Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Very Poor

Your Name_____ **Date of Birth** _____ **Today's Date** _____

Provider Global Assessment of Disease Activity

Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Very Poor

How to Score the CDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	**(0-76)**	

CDAI Score Interpretation	
0.0 – 2.8	Remission
2.9 – 10.0	Low Activity
10.1 – 22.0	Moderate Activity
22.1 – 76.0	High Activity

Sleep Scale from the Medical Outcomes Study

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes……..…1

16-30 minutes……..2

31-45 minutes……..3

46-60 minutes……..4

More than 60 minutes …….5

---

2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number
of hours per night: ☐☐

How often during the <u>past 4 weeks</u> did you…

	(Circle One Number On Each Line)					
	All of the Time ▼	Most of the Time ▼	A Good Bit of the Time ▼	Some of the Time ▼	A Little of the Time ▼	None of the Time ▼
3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
4. get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
5. awaken short of breath or with a headache?	1	2	3	4	5	6
6. feel drowsy or sleepy during the day?	1	2	3	4	5	6
7. have trouble falling asleep?	1	2	3	4	5	6
8. awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
9. have trouble staying awake during the day?	1	2	3	4	5	6
10. snore during your sleep?	1	2	3	4	5	6
11. take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
12. get the amount of sleep you needed?	1	2	3	4	5	6

Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), <u>Measuring functioning and well-being: The Medical Outcomes Study approach</u> (pp. 235-259), Durham, NC: Duke University Press.

ANNEXURE III – MASTER CHART

Sl	Name	ID	Age	Gender	Duration of disease_yrs	History of medication	TJC	SJC	PAIN VAS	PHYSICIAN VAS	GLOBAL VAS	CDAI Score	HAQ QUESTION	RA FACTOR	ANTICCP	HTN	T2DM	IHD	Sleep problem
1	RATNA N PATIL	5210706	53	F	20	POSITIVE		0	0	1	1	1	ABSENT	NIL	POSITIVE		POSITIVE		
2	SUDHA DESAI	4336603	42	F	0.5		24	20	10	10	10	64	ABSENT	POSITIVE					POSITIVE
3	SOMMANA MALAYI	5314518	56	M	2	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE		POSITIVE			
4	YALLAVA BASAPPA MELAMATHI	5307159	58	F	5	POSITIVE	1	1	1	1	1	2	ABSENT	POSITIVE			POSITIVE		
5	NAGARATNA INGAKAGI	648149	32	F	3	POSITIVE	0	0	2	2	2	4	ABSENT		POSITIVE				
6	RANJANA PATEL	4762597	58	F	8	POSITIVE	0	0	1	1	1	2	ABSENT		POSITIVE				
7	VILASMATHI CHOUAGLE	5729706	55	F	1		10	10	4	4	4	28	ABSENT						
8	MAHADEVI JAGADAL	4259689	48	F	5		12	5	8	7	8	37	ABSENT	POSITIVE					POSITIVE
9	BASAVARAJ G. ULLEGADDI	1012186	41	M	8	POSITIVE	4	2	4	4	4	14	ABSENT	POSITIVE					
10	JAYASHREE UARODI	4792358	56	F	6	POSITIVE	0	0	2	2	2	4	ABSENT	POSITIVE					
11	SUREKA SHIAVJI	5190593	56	F	5	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
12	VIMALA MANGALE	4323189	58	F	10	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
13	SHRIDEVI SHEDBALL	5434477	46	F	5	POSITIVE	2	2	4	4	4	12	ABSENT	POSITIVE					
14	SHARADA MANGANAKAR	526777	49	F	2	POSITIVE	2	2	5	5	5	14	ABSENT	POSITIVE					
15	PARVATI AVUNAYAGOL	6126025	55	F	4	POSITIVE	0	0	2	1	2	4	ABSENT	POSITIVE					
16	SUDHA PATIL	5484343	45	F	2.5	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
17	PARVATHI TEGOR	4297457	35	F	6	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
18	LAXMI GHATGE	5429071	45	F	2	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
19	SUMNAGALA RANGLOI	5489218	62	M	1	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
20	SHANKAR JODATTI	5430778	60	M	4	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
21	KALAVVA BERINAGADAL	5250012	49	F	6	POSITIVE	0	0	2	2	2	4	ABSENT	POSITIVE					
22	MAHADEVI JAGADAL	3404007	52	F	3	POSITIVE	0	0	2	2	2	4	ABSENT	POSITIVE					
23	CHAMPAKKA PATIL	4726842	57	F	15	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
24	MAHDEVI BUDIHAL	5185143	49	F	8	POSITIVE	4	1	8	6	8	19	ABSENT	POSITIVE					
25	BALAWWA BHONI	4306591	72	F	20	POSITIVE	0	0	3	3	3	6	ABSENT	POSITIVE					
26	SHUSHILAVVA HONNAR	5285938	58	F	10	POSITIVE	0	0	0	1	1	1	ABSENT	POSITIVE					
27	MALA VANGAOL	4710678	53	F	7	POSITIVE	3	1	7	7	7	18	ABSENT	POSITIVE					
28	SURYAKANT GARADE	4685616	55	M	0.3	POSITIVE	12	10	6	6	6	34	ABSENT	POSITIVE	POSITIVE				POSITIVE
29	LAXMI TORESKAR	5501838	55	F	5		16	11	4	4	4	35	ABSENT	POSITIVE					POSITIVE
30	LEELA CHOUGALE	588163	60	F	0.5		12	4	6	4	6	26	ABSENT	POSITIVE					POSITIVE
31	MAHANANDA	5331437	47	F	4		12	12	6	5	6	35	ABSENT	POSITIVE					POSITIVE
32	ANUSUYA HUNDALEWIDKAR	5516435	60	F	15	POSITIVE	0	0	3	3	3	6	ABSENT	POSITIVE					
33	HANNAMMAVVA DHARIGOLE	5163090	38	F	5	POSITIVE	10	4	5	5	5	24	ABSENT	POSITIVE					

34	SUMA	3852328	49	F	2	POSITIVE	1	1	4	4	4	10	ABSENT	POSITIVE					
35	VANDANA KASAKAR	5226241	45	F	3	POSITIVE	0	0	1	1	1	3	ABSENT	POSITIVE					
36	ZULEKA MULKASHI	5527790	59	F	3	POSITIVE	1	1	2	2	2	5	ABSENT	POSITIVE					POSITIVE
37	BIBI AYESHA	3919057	57	F	20	POSITIVE	0	0	4	5	4	6	ABSENT	POSITIVE					
38	NASREEN SHAIK	5185840	50	F	0.1	POSITIVE	0	0	5	5	5	6	ABSENT	POSITIVE					
39	YALLAVA BASAPPA MELAMATHI	4077376	55	M	10	POSITIVE	0	0	3	3	6	5	ABSENT	POSITIVE					
40	NASEEM SHAIK	5393463	45	F	6	POSITIVE	0	2	5	5	5	12	ABSENT	POSITIVE					
41	SAROJINI JANVEKAR	3893808	49	F	15	POSITIVE	0	0	4	4	4	8	ABSENT	POSITIVE					POSITIVE
42	PARAVTHI SAMBAHJI	5055332	52	F	7	POSITIVE	3	2	4	4	6	16	ABSENT	POSITIVE					POSITIVE
43	PADMAVATHI DESHPANDE	3959824	63	F	5	POSITIVE	6	6	3	3	5	21	ABSENT	POSITIVE					POSITIVE
44	HASANAB MORINI	4496393	78	M	10	POSITIVE	0	0	2	2	2	4	ABSENT	POSITIVE		POSITIVE	POSITIVE		
45	DEEPA WALVEKAR	2146675	28	F	2	POSITIVE	8	2	4	4	4	18	ABSENT	POSITIVE					
46	BASAVANT CHOUGALE	4555134	42	M	10	POSITIVE	0	0	2	1	1	2	ABSENT	POSITIVE					
47	GANGAVVA PATIL	4212348	58	F	15	POSITIVE	0	0	3	3	3	6	ABSENT	POSITIVE		POSITIVE	POSITIVE		
48	MALLAWWA NGANNATTI	5033020	58	F	10	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
49	BAYA BAIF	4773686	57	F	20		14	0	10	10	10	44	ABSENT	POSITIVE					POSITIVE
50	MANGALA TARALE	1014870	58	F	15		20	4	10	9	9	70	ABSENT	POSITIVE					POSITIVE
51	YOUSUF PATHAN	1031240	60	M	3	POSITIVE	0	0	5	5	6	10	ABSENT	POSITIVE		POSITIVE	POSITIVE		POSITIVE
52	LALBI	1033351	57	F	0.5	POSITIVE	3	0	1	1	1	5	ABSENT	POSITIVE					POSITIVE
53	MAHADEVI PATIL	4294714	59	F	15		12	0	7	7	7	28	ABSENT	POSITIVE					POSITIVE
54	RAJESHWARI MULLIMANI	4276331	32	F	2		8	6	8	8	7	29	ABSENT	POSITIVE					POSITIVE
55	GANGAVVA YADAL	5007141	55	F	8		14	4	8	8	9	34	ABSENT	POSITIVE					POSITIVE
56	RAJU CHOPEDKAR	5958486	72	M	16		12	4	9	8	8	33	ABSENT	POSITIVE					POSITIVE
57	LAXMI TARASKAR	4328488	55	F	15		16	8	8	8	8	40	ABSENT	POSITIVE					POSITIVE
58	VENKATAMMA GADIPATHI	1814534	58	F	6		25	12	9	9	9	74	ABSENT	POSITIVE					POSITIVE
59	SHANATAVVA DOMANNAVAR	1032115	65	F	15		18	10	8	7	8	44	ABSENT	POSITIVE					POSITIVE
60	FATIMA	5483104	38	F	3		18	12	10	9	9	49	ABSENT	POSITIVE					POSITIVE
61	KASHAVVA BAGEWADI	5113345	35	F	4	POSITIVE	5	2	5	6	6	19	ABSENT	POSITIVE					POSITIVE
62	VIMALA KARADE	1039659	58	F	5		12	10	6	6	6	34	ABSENT	POSITIVE					POSITIVE
63	JAYASHREE MULKAR	4787719	45	F	0.5		20	12	10	9	10	52	ABSENT	POSITIVE					POSITIVE
64	SHANTA PATIL	5958426	55	F	1.5		8	6	9	8	9	31	ABSENT	POSITIVE					POSITIVE
65	HEMA LATHA	4031182	39	F	1		8	8	6	6	6	28	ABSENT	POSITIVE					
66	AYESHA MAKANDAR	1223728	43	F	15	POSITIVE	2	2	5	5	5	14	ABSENT	POSITIVE					
67	SAVITRI	1057114	50	F	3	POSITIVE	0	0	2	2	2	4	ABSENT	POSITIVE					
68	SUSHILA YARGATTI	8	42	F	0.1		20	20	8	8	8	58	ABSENT	POSITIVE					
69	MUMTAZ	1047047	29	F	5	POSITIVE	0	0	6	7	7	6	ABSENT	POSITIVE					
70	SUNITHA YESHI	1040461	36	F	2	POSITIVE	7	6	5	5	5	28	ABSENT	POSITIVE					
71	PADMAVATHI KARGAVI	1044794	45	F	3	POSITIVE	2	0	5	6	6	14	ABSENT		P				
72	YALLUBHAI SHAHPURKAR	1044656	65	F	4	POSITIVE	1	1	4	5	5	10	ABSENT	POSITIVE					
73	SHOBHA SHANKANNAVAR	4491739	43	F	3	POSITIVE	0	0	2	2	2	2	ABSENT	POSITIVE					
74	SANDYA PATIL	1047874	53	F	5	POSITIVE	0	0	2	2	2	2	ABSENT	POSITIVE					
75	RATNA PATIL	4727577	53	F	5	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
76	AFREEN BADAGHAR	4724501	40	F	6	POSITIVE	0	0	4	4	5	4	ABSENT	POSITIVE					

77	SUNANDA APKE	4384503	56	F	4	POSITIVE	5	6	4	3	4	18	ABSENT	POSITIVE					
78	ANNAPURNA MALLI	1144747	66	F	1	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
79	VENKATAMMA PATIL	4783837	49	F	5	POSITIVE	0	0	4	3	4	3	ABSENT	POSITIVE					
80	ZUBEDA PEDARI	5335991	55	F	8	POSITIVE	0	0	2	2	2	4	ABSENT	POSITIVE					
81	SUDHA PATIL	5319333	40	F	3	POSITIVE	8	6	8	8	8	29	ABSENT	POSITIVE					
82	RENUKA KALKHAMBKAR	3193016	45	F	1	POSITIVE	0	0	1	1	1	2	ABSENT		POSITIVE				
83	ANNAPPA BISUR	4825769	68	M	1	POSITIVE	2	2	5	5	6	14	ABSENT	POSITIVE					
84	TULSA JADHAV	5185540	55	F	0.4		11	10	9	9	9	39	ABSENT	POSITIVE					POSITIVE
85	ANUSUYA HUDED	5243401	46	F	4	POSITIVE	0	0	2	2	2	2	ABSENT	POSITIVE					
86	SUSHILA DODMANI	5209481	55	F	3	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
87	SUREKHA SHIVAJI TUPPARE	5290168	58	F	6	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE			POSITIVE		
88	JAYASHREE SIDDARAMAPPA VARADAI	3141376	56	F	3	POSITIVE	0	0	1	1	1	2	ABSENT		POSITIVE	POSITIVE			
89	MALA SUBHASH VANAJOL	972781	59	F	7	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
90	ARUN ANANT KELVEKAR	5232923	52	M	2	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
91	G SUJATHA VENKATESH	4812591	56	F	4	POSITIVE	1	1	4	4	4	10	ABSENT	POSITIVE					
92	TARAMMA MULLA	5403356	54	F	5	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
93	SUSHILA KUMAR AKKOLE	4496393	52	F	3	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
94	AJAM GANACHARI	4212348	55	F	4	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
95	JUBEDA ADAM PENDARI	3893808	54	F	1		12	10	9	9	9	40	ABSENT	POSITIVE					POSITIVE
96	SHOBHA NARAYAN SAGANVAKAR	4294714	55	F	3	POSITIVE	1	1	3	3	3	8	ABSENT	POSITIVE					
97	SURESH SHANKAREPPA BHADRANNAVAR	4031182	60	M	6	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					
98	ARUNA SUBHASH HEREKAR	4724501	56	F	4	POSITIVE	0	0	1	1	1	2	ABSENT	POSITIVE					