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Psychosocial and Immunological Correlates of Quality of Life in Patients Suffering from Rheumatoid Arthritis

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Objective: *Psychiatric morbidities frequently co-occur with Rheumatoid Arthritis (RA). Psychosocial and immunological correlates of quality of life in patients of RA were assessed including perceived stress, coping pattern.*
Method: *A cross-sectional study on patients of RA attending the Rheumatology Centre was conducted at a tertiary care research and referral hospital for duration of 02 years involving data collection between Jan 2014 to Jan 2015 after obtaining approval by concerned authorities.*
Results: *48.41% of RA patients were above cutoff in GHQ scores indicating caseness for psychiatric morbidity. GHQ scores had strong correlation with perceived stress and pain. Adaptive coping skills are inversely correlated to psychiatric caseness. CRP level is strongly correlated to psychiatric caseness.*
Conclusions: *Female patients in RA possess higher risk to develop psychiatric illness. Early detection andtreatment of psychiatric illnesses has a potential to improve QoL. CRP titres above 10 mg/L should also indicate active psychopathology in RA patients.*

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I. **Introduction**:

Rheumatoid Arthritis (RA) is a chronic inflammatory disease principally involving the musculoskeletal system, but it affects various other systems too. Joint damage and physical disability due to ongoing inflammatory synovitis, usually involves peripheral joints symmetrically. Its autoimmune nature is evidenced by circulating rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody (1-4). Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in active disease indicate ongoing chronic inflammation (5). RA can also be seen in an immune-deficiency paradigm resulting from a specific autoimmune response directed against self-antigenic components and an ongoing inflammatory process (6).Despite an identified autoimmune component, its precise cause remains uncertain (7, 8). A female preponderance also indicates role of hormonal mechanisms (9).

Early studies had linked HLA B27 positivity to increased disease severity and worse functional class and higher ESR in diseases like Spondyloarthritis (10). Genome-wide association studies (GWAS) have related association of non-MHC-related genes to RA susceptibility based on the detection of single-nucleotide polymorphisms (SNPs). By HLA studies in families and twins; it has been estimated that one-third of the genetic risk for RA lies within the locus of the major histocompatibility complex (MHC) on the short (p) arm of chromosome number six (11, 12).The disease-associated HLA-DRB1 alleles encoded in the MHC class II molecules have a *shared epitope (SE);* which is correlated with anti-CCP antibody production and worse disease outcomes*(7, 13)*. Many potential RA-associated genes are also found in regions encoding pathways of T-cell receptor signaling, JAK-STAT signaling and the NF-κB signaling cascades as many available drugs target them. However, the role of RA-associated genes in these pathways and their contribution to the disease is not always clear(14).RA generally progresses throughout life and may damage other systems too. Pain, deformity and resultant restriction in activity level results in progressive disability. The pathogenesis of rheumatoid inflammation is noted to involve many cytokines such as IL-1, TNF, IL-6, IFN-γ, IL-7 etc. There is convincing evidence that cytokines are involved in the physiology and pathophysiology of brain function and interact with different neurotransmitter and neuroendocrine pathways. In chronic inflammatory conditions, a negative feedback loop with pro-inflammatory cytokines stimulate the HPA axis, which results in the secretion of glucocorticoids, which in turn suppress the immune response (15, 16). However, in certain autoimmune disorders such as RA, the counter-regulatory glucocorticoid response is not fully achieved. RA patients show a relative hypo-functioning of the HPA axis despite a high degree of inflammation(17).This may result in increased vulnerability to psychiatric illness as well as diathesis to stress (18-21).

The 2010 ACR-EULAR diagnostic criteria for RA emphasize the role of inflammatory markers CRP and ESR apart from joint involvement and immune markers of RF and anti-CCP antibodies along with disease

duration (22). Psychiatric illnesses are also associated with inflammatory states characterized by high CRP and elevated ESR levels (23). Possible involvement of the immune system in the neurobiological mechanisms that underlie psychiatric disorders has got increasing attention in recent years (24-26). Increased risk for psychological distress and depression in general population is associated with elevated CRP level (27). In past decades, numerous clinical studies have demonstrated dysregulated immune functions in patients with psychiatric disorders (23, 24, 28-37). Immune modulator treatment may also sometimes lead to psychiatric conditions in these patients (38-42). Psychological intervention that decreases emotional distress is known to improve clinician-rated disease activity in RA patients (43). After diagnosis, the patients undergo various modalities of treatment which may involve life-long modifications in lifestyle. Frequent follow-up visits to the medical facilities and regular laboratory tests leads to a restricted routine which may invoke a crippled feeling (29, 44, 45). Risks of partial remission, exacerbation and treatment regimen failure exist(46). Side effects from prolonged medication especially in old age and pregnancy can be troublesome (47). Complications may involve vulnerability to systemic infection or vasculitis aggravating constitutional symptoms: weight loss, fever, fatigue, malaise or depression (48-50). Severe cases may have cachexia and sarcopenia (51). Frequently co-morbidities or complications which includes cardiovascular diseases, osteoporosis, hypoandrogenism, pleuro-pulmonary involvement, Secondary Sjögren's Syndrome and hematologic complications like *Felty's Syndrome* may further deteriorate the quality of life in those with RA(52). Poor outcomes including persistent morning stiffness, fatigue, pain, reduced physical activity and poor quality of life (QoL) are still observed despite modern treatment advances. Reasons for these include poor adherence to medication, insufficient knowledge about the disease and lack of support in coping and effectively self-managing the condition(53, 54). Various factors including poor mobility contribute to difficulties in follow up (55). Poor aerobic fitness is also associated with poor physical, psychological and social health (56). Poor treatment adherence results in high disease activity and a lost window of opportunity for modifying the disease (57). Frustration in absence of a permanent cure leads to perceived stress (43, 58). Inadequate treatment may lead to further socio-economic deficits (59, 60).

Coping refers to strategies that individuals use to manage perceived or actual threats involving distraction, passive avoidance, positive reappraisal, direct action, confrontation and information-seeking (61-64). Improving psychological health, motivation, emotional adjustment, coping skills and social support thus plays a significant part in the management of RA(65, 66). Lazarus et al. have identified eight forms of coping that serve as the conceptual foundation for most stress management protocols. These models are based upon two types of cognitive appraisal. The first, Primary Appraisal (PA),refers to evaluation of what is at stake in the encounter. Being diagnosed with a chronic illness such as Rheumatoid Arthritis which if appraised as harmful and threatening (e.g., "Due to RA, I will never be able to do anything I really care about") makes the individual more anxious, depressed and withdrawn. Secondary Appraisal (SA) refers to the evaluation of what can be done about the stressful event (e.g., "Although RA prevents me from doing some physically demanding activities, there are still many other important activities that can be done meaningfully"). More positive outcomes are likely to occur when primary and secondary appraisals are combined to determine whether a particular person-environment transaction is significant for wellbeing; and if significant, whether it is threatening or challenging. Secondary Appraisals depend on several factors including the individuals' repertoire of coping skills, mastery of specific coping, and expectation that their skills will be effective. Secondary Appraisal may be process oriented, contextual or without any a priori assumptions about what constitutes good (adaptive)or bad (dysfunctional) coping (67).Although prevalence of psychiatric illnesses in RA is known, the contribution of psychological factors to quality of life in patients of RA needs exploration. Also, there are limited numbers of studies on whether treatment of these factors will improve quality of life or not. Psychosocial factors do influence the patients' perception of pain and this can influence psychological well-being and social participation (68).Study by Curtis et.al indicated that perceived stress is a better predictor than disease severity for emotionality which could be explained by the coping mechanism of the patients with possible implications for medical care seeking (69).

Catherine et.al stated that patients with chronic diseases such as RA felt that health care professionals did not fully appreciate the psychosocial impact and failed to provide information to meet those needs. Arthur J. Barsky, assessed the benefits of three psychosocial treatments for patients with RA involving cognitive-behavioral therapy (CBT), relaxation response training (RR) and arthritis education (AE). All three groups benefited with small to moderate range difference. Benefits appeared immediately after treatment and were often sustained at long-term follow-up. The benefits were over and above those that can be achieved from medical management (70). Rogers et al reviewed the psycho-neuro-immunology of autoimmune disorders including RA to infer complex bi-directional psycho-neuro-immunological interactions in animal models and felt a need to explore the role of various neurotransmitters and neuromodulators as they may have important therapeutic implications for autoimmune disorders (71).Various studies highlight a negative association between RA and Schizophrenia, often regarded as an epidemiologic puzzle (72-74). Evers AWM et al concluded that early interventions focused on pain-related avoidance factors and social resources for patients at risk may have

beneficial influence on the long-term outcomes in RA (75). Maag TJ et al found a correlation between daily mood scores and the number of antibodies reactive with brain apart from a correlation between cognitive coping styles in RA patients and auto-antibodies (76). As per Skevington et.al, therapies reducing uncertainty and increasing perceptions of control had positive psychological impact on patients. They found cognitive and behaviour modification techniques holding promise to motivate patients to be more active, to comply with medication and improving mental health (77). Aggarwal A et.al concluded that RA has significant impact on the physical and social disability and also resulted in economic burden. Indian patients had good scores for mental and social health indicating good family support systems (78).

Miller et.al in 2001 reviewed the effect of psychosocial interventions on immune response. They found that of the 85 clinical trials that had been conducted thus far, the meta-analysis indicated modest evidence that interventions can reliably alter immune parameters (79). Margaretten described the social contexts and biologic disease state of the individual as contributory factors to develop depression in patients of RA. Depression may be linked to low socio-economic status, gender, age, ethnicity, functional limitation, state of systemic inflammation, pain and poor clinical status as per the study, understanding which may lead to a more comprehensive paradigm to for target interventions to eliminate depression in these patients (80). Faith Matcham in a systematic review on RA patients concluded an increased prevalence of depression in female gender. Depending on the way of measurement, prevalence ranged from 14.8% to 48%. There was a negative association between age and depression (34). Takahiro Tokunaga reported that among RA patients, a significant improvement of depressive state in female gender occurred after treatment initiation with a biologic agent in a setting of similar disease activity level (81).Tanya Covic reported 41.7% RA patients had depression or anxiety with 13.5% anxiety only(82). Abu Al-Fadl Esam Mohammed in his study reported a prevalence of anxiety in 26.9% RA patients with significant correlation of both anxiety and depression scores with bodily pain and disease activity (83).

RA is a chronic debilitating illness which significantly impacts quality of life that may need independent attention to improve treatment efficacy. Psychiatric diseases may additionally contribute to poor outcome; treatment of which has the potential to improve quality of life. This study was undertaken to explore the correlation of the psychosocial and immunological entities in order to formulate newer treatment modalities to further improve outcome of the illness.

Aim and Objectives

The aim of the study was to evaluate the psychosocial and immunological correlates of quality of life in patients suffering from RA. The study made an attempt to achieve following objectives.

1. Assess the nature & extent of psychopathology in patients of RA
2. Ascertain the perceived stress in patients with RA.
3. Evaluate the coping patterns in patients of RA
4. Assess the quality of life in patients with RA
5. Assess various psychological and clinical correlates in patients with RA

II. Material and Method

This cross-sectional study was conducted at a tertiary care research and referral hospital located in a city in western Maharashtra affiliated to the Maharashtra University of Health Sciences (MUHS, Nashik).The sample for the study involved patients of RA attending the Rheumatology Centre. The data was collected between Jan 2014 to Jan 2015 after obtaining approval by concerned authorities.

Inclusion and Exclusion Criteria:

Inclusion Criteria	Exclusion Criteria
1. Age between 18 yrs to 50 yrs 2. Absence of co-morbid immunological disease 3. Absence of known psychological disorder 4.Patients already on immune-modulator treatment	1. Known psychiatric disorder 2. Co-morbid psychiatric diseases 3. Moribund patients 4. Unwilling patients

Variables studied

1. Psychosocial details
2. Immunological parameters by laboratory tests

- ❖ RA Factor
- ❖ CRP
- ❖ ESR
- ❖ Anti CCP antibody

Psychometric Analysis:

The following psychometric instruments were used in this study.

1. GHQ-12 (to assess general psychopathology)
2. Perceived Stress Scale-10 (to assess perceived stress)
3. Brief COPE (to assess the coping skills)
4. Visual Analogue Scale (to assess pain)
5. WHOQOL-BREF (to assess quality of life)

Sample Size Calculation:

Based on the available information in contemporary literature, we assumed that among the patients of RA, a maximum of 50% get affected with altered psychopathology, perceived stress, changed coping pattern & poor quality of life; maintaining a CI of 95%, α =5% and precision of 10%. The formula given below was used for sample size calculation.

$$n \text{ (sample size)} = \frac{Z_{(1-\alpha/2)}{}^2 * (p) * (1-p)}{d^2}$$

Where, $Z^2_{(1-\alpha/2)}$ = confidence interval
p = estimated proportion
d = desired precision

For p=0.50, (1-p) =0.50, d=0.10 or 10%, $Z_{(1-\alpha/2)}$ for α=0.05 was calculated as 1.96. Applying these values to the equation;

$$n \text{ (sample size)} = \frac{(1.96)^2 * (0.5) * (0.5)}{(0.1)^2} = 96.04 \approx 96$$

Out of341 patients visiting the Rheumatology OPD during the study period who met our criteria, 139 had volunteered to participate in the study when they were approached individually. After getting a duly signed informed consent from the participants, they were given a booklet in English. The study population had formal knowledge in English. The booklet contained a specially made psychosocial proforma and questionnaire for psychometric tools. Thus, a wide range of demographic, psychosocial, clinical immunological data was collected.

The study involved no interventional procedures. Data collected from 13 participants was incomplete; hence they were not taken in the final analysis.126 complete data sets were taken for statistical analysis. The psychometric tools are described above. The demographic data involved age, gender, marital status, place of residence (rural or urban), education, profession, family type (nuclear or joint) and religion. Clinical data involved time since diagnosis of RA, compliance to prescribed medication in last 6 months and existing data on positivity of rheumatoid factor (RF), anti-CCP antibody, C-reactive protein, ESR by Westergren method and HLA antigens (84). Apart from the continuous variables, the clinical data of rheumatoid factor (RF), anti CCP antibody, ESR, C-reactive protein and compliance to treatment in last 6 months was assigned values of 0 or 1 (binary variable form).The cutoff for CRP was 10 mg/L, cutoff for ESR for men was 15 mm/hr and for women was 20 mm/hr. Following receipt of the completely filled proforma from the patients administered to them at Rheumatology OPD, the data was collected by the researcher in Microsoft Office Excel Worksheet Version 2010.

Statistical Analysis

Statistical analysis was performed in IBM SPSS software version 21.0. Pearson product-moment correlation coefficient (Pearson *r or* ρ*)* with a 2-tailed significance was calculated among the available continuous variables. Biserial correlation coefficient was calculated (*rbi)* for correlation of nominal variables to other continuous variables. Pearson Chi-square test was done to analyze correlation of psychiatric caseness to the nominal variables. Mann-Whitney test was performed to analyze correlation of psychiatric caseness to continuous variables.

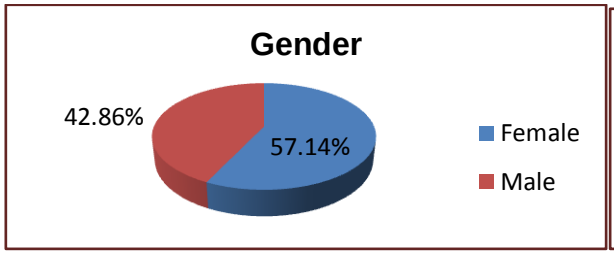
Ethical Clearance, Consent and Funding

The ethical clearance was obtained from the Ethical Committee of the institution attached as Annexure ‘C”. The university had also approved the study procedure as a part of MD curriculum of the researcher subsequent to approval by IEC. Participation in this study was voluntary. The participants were informed about the purpose of the study and were assured about confidentiality of the data. An informed consent form was

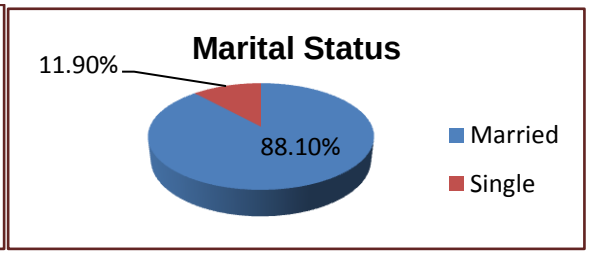
provided to the participants with written certificate of consent was obtained from the participants. The study involved no monetary aid from any organization. All expenses were borne by the researcher. The participants were given no monetary reimbursement or incentive as reflected in the informed consent.

III. Result

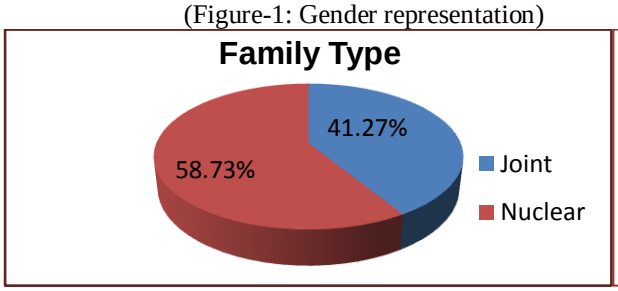
Minimum and maximum age of study subjects were 20 and 50 yrs respectively with a range of 30 yrs. Mean age of the participants was 37.68 yrs with standard deviation of 8.49 yrs (Table-1). Females constituted 57.14% and males 42.86% (Figure-1). Among four categories, 47.62% were educated till 10th standard (Figure-2). 88.1% were married (Figure-3). 58.7% lived in nuclear families (Figure-4). Minimum and maximum times since diagnosis of RA were 1 and 27 yrs respectively with mean time since diagnosis of RA was 4.651 yrs (SD-3.54 yrs) (Table-1).67.46% were positive for rheumatoid factor (RF) (Figure-5). 67.46% were found positive for anti CCP antibody (Figure-6).With gender-matched ACR/EULAR criteria, (men-15 mm/hr and women-20 mm/hr as cutoff; 56.35% had raised ESR (Figure-7). With cutoff level of 10 mg/L as per ACR/EULAR Remission criteria, 48.41% had raised C-reactive protein. 51.59% were negative for this inflammatory marker (Figure-8).As per Visual Analogue Scale, 10 had no pain, 48 had mild pain, 52 had moderate pain and 16 had severe pain; which were assigned values 0, 1, 2 and 3 respectively (Figure-9). 73.81% were regular with medication and in previous 6 months(Figure-10).



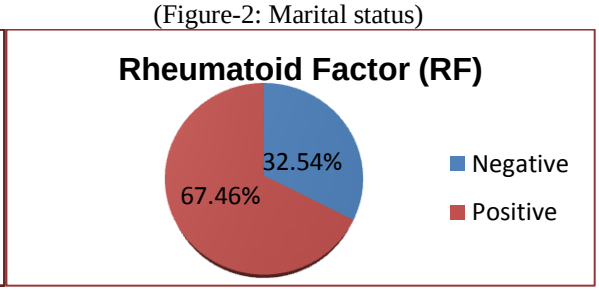
(Figure-1: Gender representation)



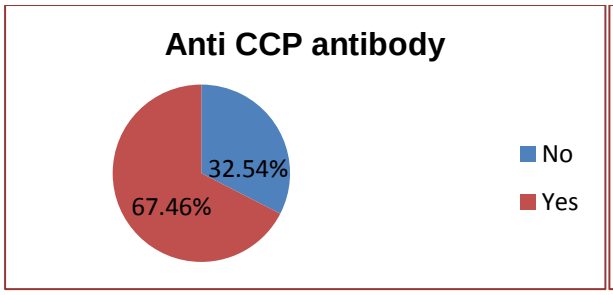
(Figure-2: Marital status)



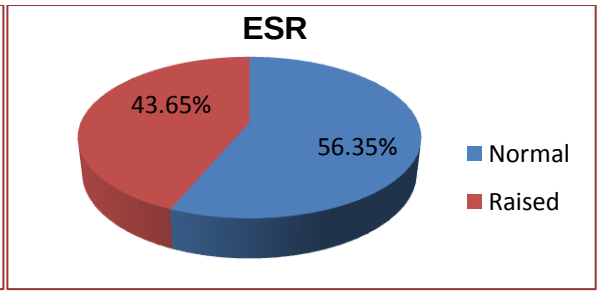
(Figure-3: Family Type)



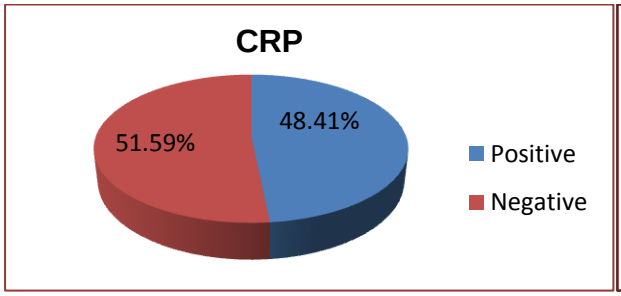
(Figure-4: RF)



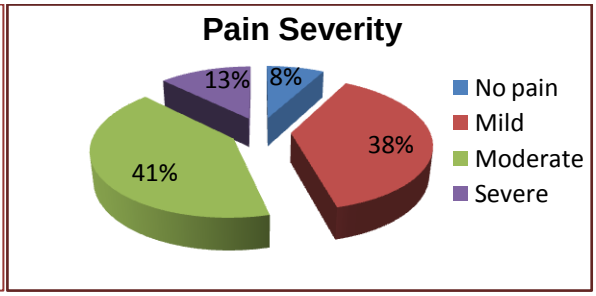
(Figure-5: Anti CCP Antibody)



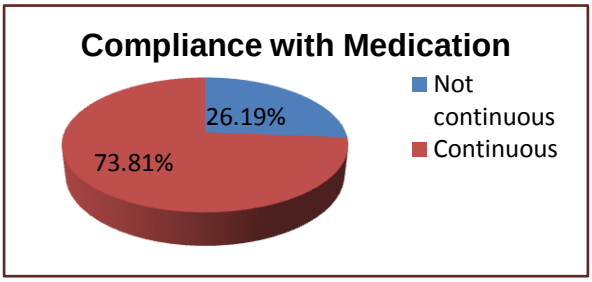
(Figure-6: ESR)

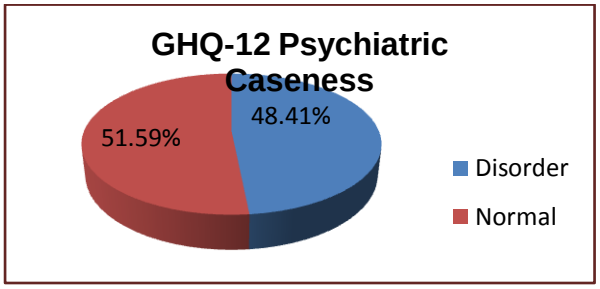


(Figure-7: CRP)



(Figure-8: Pain Severity)





(Figure-9: Treatment Compliance) (Figure-10: GHQ-12)

The mean score of GHQ-12 was 2.667 (SD-1.33). 48.41% fulfilled psychiatric caseness with scores above cutoff of 2 (i.e. 3 or more) (Figure-10). Domain-wise scores were calculated as per the 3-dimensional model adopted from "The factor structure of the twelve item General Health Questionnaire (GHQ-12): the result of negative phrasing?" by Hankins M (85). The individual domains were also calculated. Mean dysphoria/ anxiety was 1.22 (SD-0.9). Mean social dysfunction was 1.214 (SD-0.87). Mean loss of confidence has a mean of 0.23 (SD-0.49) (Table-1).

Domain-wise scores for WHOQOL-BREF were obtained. Physical health had mean 22.76 (SD-3.38), psychological health had mean 19.99 (SD-3.53), social QoL had mean 11.03 (SD-1.43) and environmental QOL had mean 29.2 (SD-4.2). The scores were transformed into scales 0-20 and 0-100 to match with normative data. Total score and domain wise scores were obtained in PSS-10. Total score had a mean of 15.45 (SD-3.39). Minimum and maximum values were 6 and 28 respectively. Domain-1 (items 4, 5, 7 and 8) had a mean of 6.4 with SD 1.74. Domain-2 (items 1, 2, 3, 6, 9 and 10) had a mean of 9.048 (SD-2.28) (Table-1).

	N	Mean	Std. Error of Mean	Median	Mode	Std. Deviation	Variance	Skewness	Std. Error of Skewness	Kurtosis	Std. Error of Kurtosis	Range	Minimum	Maximum
Age	126	37.683	0.757	38.00	50	8.49	72.12	-0.21	0.22	-1.00	0.43	30	20	50
Disease duration of RA (years)	126	4.651	0.316	4.000	3	3.54	12.57	2.71	0.22	12.41	0.43	26	1	27
QOL Domain-1 (Physical)	126	22.762	0.301	23.000	23	3.38	11.40	-0.73	0.22	0.30	0.43	15	13	28
QOL Domain-2 (Psychological)	126	19.992	0.314	20.000	20	3.53	12.44	-0.19	0.22	-0.34	0.43	15	12	27
QOL Domain-3 (Social)	126	11.032	0.127	11.000	10	1.43	2.03	0.67	0.22	-0.11	0.43	7	8	15
QOL Domain-4 (Environmental)	126	29.214	0.375	30.000	32	4.21	17.74	-0.40	0.22	-1.17	0.43	15	21	36
Total WHOQOL score	126	83.000	1.001	83.500	89	11.23	126.18	-0.35	0.22	-0.69	0.43	45	57	102
GHQ Domain-1 (Dysphoria/anxiety)	126	1.222	0.080	1.000	1	0.90	0.81	0.47	0.22	0.16	0.43	4	0	4
GHQ Domain-2 (social dysfunction)	126	1.214	0.078	1.000	1	0.87	0.76	1.40	0.22	2.66	0.43	4	0	4
GHQ Domain-3 (confidence loss)	126	0.230	0.044	0.000	0	0.49	0.24	2.08	0.22	3.62	0.43	2	0	2
GHQ-Total score	126	2.667	0.119	2.000	2	1.33	1.78	1.17	0.22	2.52	0.43	7	0	7
PSS Domain-1	126	6.405	0.155	7.000	7	1.74	3.01	-0.11	0.22	0.93	0.43	10	1	11
PSS Domain-2		9.048	0.203	9.000	10	2.28	5.18	0.25	0.22	2.30	0.43	16	1	17
PSS Total score		15.452	0.302	16.000	15	3.39	11.51	0.11	0.22	2.35	0.43	22	6	28

(Table-1: Continuous Variables)

Coping Strategy domains	N	Mean	Std. Error of Mean	Median	Mode	Std. Deviation	Variance	Skewness	Std. Error of Skewness	Kurtosis	Std. Error of Kurtosis	Range	Minimum	Maximum
Self-distraction	126	6.206	0.108	7.000	7	1.21	1.46	-0.65	0.22	-0.41	0.43	5	3	8
Active coping	126	5.984	0.153	6.000	4	1.72	2.94	-0.06	0.22	-1.73	0.43	4	4	8
Denial	126	3.190	0.107	3.000	2	1.20	1.45	0.94	0.22	0.77	0.43	6	2	8
Substance use	126	2.492	0.073	2.000	2	0.82	0.67	1.54	0.22	1.39	0.43	3	2	5
Emotional	126	5.770	0.114	6.000	6	1.28	1.63	0.09	0.22	-0.93	0.43	4	4	8
Disengagement	126	3.294	0.118	3.000	2	1.33	1.76	0.61	0.22	-0.78	0.43	5	2	7
Venting	126	4.992	0.128	5.000	6	1.43	2.06	-0.17	0.22	-1.07	0.43	5	2	7
Instrumental	126	5.675	0.123	6.000	6	1.38	1.92	-0.42	0.22	-0.52	0.43	6	2	8
Reframing	126	4.595	0.137	5.000	5	1.54	2.37	0.13	0.22	-0.62	0.43	6	2	8
Self-blame	126	4.151	0.115	4.000	3	1.29	1.67	0.21	0.22	-0.95	0.43	5	2	7
Planning	126	5.730	0.139	6.000	4	1.56	2.44	-0.03	0.22	-1.31	0.43	5	3	8
Humour	126	3.365	0.104	3.000	3	1.16	1.35	0.52	0.22	-0.72	0.43	4	2	6
Acceptance	126	5.056	0.123	5.000	4	1.38	1.91	0.47	0.22	-0.26	0.43	6	2	8
Religion	126	5.714	0.115	6.000	6	1.30	1.68	-0.10	0.22	-0.42	0.43	6	2	8
Total coping Score	126	66.214	0.514	66.000	66	5.77	33.24	0.64	0.22	0.24	0.43	30	56	86

(Table-2: Coping Skill)

Statistical Analysis:

The statistical analysis was done using SPSS software version 21.0. Since the data was found not to be distributed normally, non-parametric tests were used. Pearson product-moment correlation coefficient (Pearson *r or* ρ*)* with a 2-tailed significance was calculated among the available continuous variables. Biserial correlation coefficient was calculated (*rbi)* for correlation of nominal variables like RF, anti CCP antibody, ESR, CRP, pain severity and compliance to treatment to other continuous variables (interval or ratio scale).

GHQ score had correlation with PSS score (r= 0.731, p<0.01), environmental quality of life (r= -0.678, p<0.01), psychological quality of life (r= -0.649, p<0.01), mobility (r= -0.581, p<0.01), planning (r= -0.563, p<0.01), self-blame (r= 0.546, p<0.01), behavioural disengagement (r= 0.531, p<0.01), venting (r= 0.526, p<0.01), using emotional support (r= 0.523, p<0.01) and physical quality of life (r= -0.498, p<0.01).Perceived stress had correlation with psychological QoL(r= -0.660, p<0.01), environmental quality of life (r= -0.592, p<0.01), planning (r= -0.573, p<0.01), social quality of life (r= -0.551, p<0.01), physical quality of life (r= -0.494, p<0.01) and self-blame (r= -0.487, p<0.01).

Among the biomarkers, C-reactive protein had correlation with active coping (r= -0.567, p<0.01), planning (r= -0.566, p<0.01), self-blame (r= 0.521, p<0.01), self-distraction (r= 0.496, p<0.01), positive reframing (r= -0.567, p<0.01), behavioural disengagement (r= 0.480, p<0.01) and venting (r= 0.451, p<0.01).Rheumatoid Factor had correlation with anti CCP antibody (r= -0.482, p<0.01), positive reframing (r= -0.305, p<0.01) and active coping (r= -0.274, p<0.01). Anti-CCP antibody had conflicting correlations with some variables, but not strong enough apart from that with Rheumatoid Factor. Those were treatment compliance (r= 0.318, p<0.01), self-blame (r= -0.274, p<0.01) and venting (r= -0.274, p<0.01).

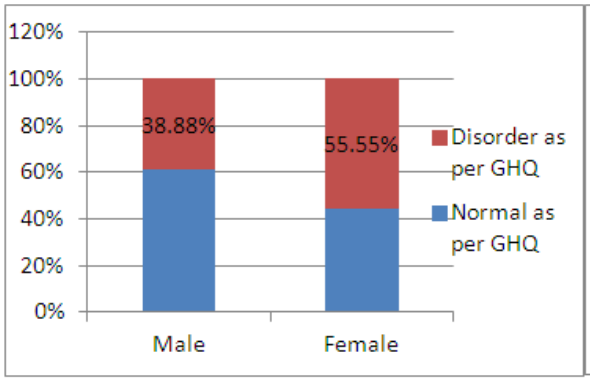
Pain had correlation with GHQ score (r= 0.515, p<0.01), psychological quality of life (r= -0.465, p<0.01), perceived stress (r= -0.465, p<0.01), treatment compliance (r= -0.438, p<0.01), planning (r= -0.385, p<0.01), self-blame (r= 0.357, p<0.01) and C-reactive protein (r= 0.350, p<0.01).The sum of all domains of WHOQOL-BREF was found to have correlation to mobility (r= 0.698, p<0.01), GHQ score (r= -0.672, p<0.01), perceived stress (r= -0.648, p<0.01), planning (r= 0.633, p<0.01), self-blame (r= -0.593, p<0.01), venting (r= -0.590, p<0.01) and behavioural disengagement (r= -0.580, p<0.01).

Duration of disease had a correlation with physical quality of life (r= -0.339, p<0.01) and psychological quality of life (r= -0.325, p<0.01).Adherence to treatment (treatment compliance) was correlated to self-blame (r= -0.548, p<0.01), venting (r= -0.522, p<0.01), pain (r= -0.438, p<0.01), GHQ score (r= -0.435, p<0.01) and mobility (r= -0.434, p<0.01).

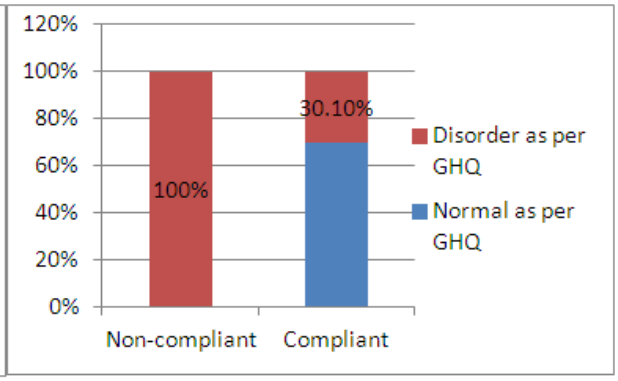
Correlations as Per GHQ Category

The entire study population was categorized into two separate groups based on the GHQ score to perform Mann-Whitney U test and Pearson Chi Square tests to differentiate the values of all clinical and psychosocial parameters among the above two groups based on GHQ scores. In Mann-Whitney U test, groups

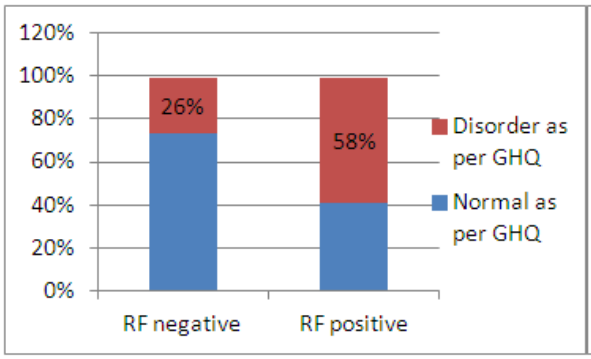
of potential psychiatric cases and normal participants based on GHQ-12 score differed significantly on perceived stress ($p<0.01$), self-distraction ($p<0.01$), active coping ($p<0.01$), denial ($p<0.01$), using emotional support ($p<0.01$), behavioural disengagement ($p<0.01$), venting ($p<0.01$), using institutional support ($p<0.01$), positive reframing ($p<0.01$), self-blame ($p<0.01$), planning ($p<0.01$), humour ($p<0.01$), religion ($p<0.01$), substance use ($p<0.05$), mobility ($p=0.000$), physical quality of life ($p<0.01$), psychological quality of life ($p<0.01$), social quality of life ($p<0.01$), environmental quality of life ($p<0.01$) , duration of disease($p<0.01$) and pain ($p<0.01$)). The p-value was calculated as an asymptotic 2-tailed significance. Two groups based on GHQ-12 score differed significantly when compared to each other for compliance to medication ($p<0.01$), RF ($p<0.01$), CRP ($p<0.01$), anti CCP antibody ($p<0.01$) and gender ($p<0.05$). ESR difference among the two groups was not statistically different. The p-value was calculated as an asymptotic 2-tailed significance. We also compared the 3 individual factors of GHQ-12 separately to the two groups based on the total GHQ score. Factor-1 (dysphoria/ anxiety) and Factor-2 (social dysfunction) differed significantly ($p<0.01$in each). However, domain 3 (loss of confidence) did not have a statistically significant difference among the two groups ($p>0.05$).38.88% male and 55.55% female participants fulfilled psychiatric caseness (score 3 or above in GHQ-12) (Figure-11). All participants not adherent to medication for RA in last 6 months were detected to have psychiatric caseness as per GHQ-12 (Figure-12).58% participants who tested positive for RF had psychiatric caseness (Figure-13). 80% participants with CRP level more than 10 mg/L had psychiatric caseness (figure-14).Only 37.6% of participants tested positive for anti-CCP antibody scored 3 or above in GHQ-12 satisfying for a psychiatric caseness.



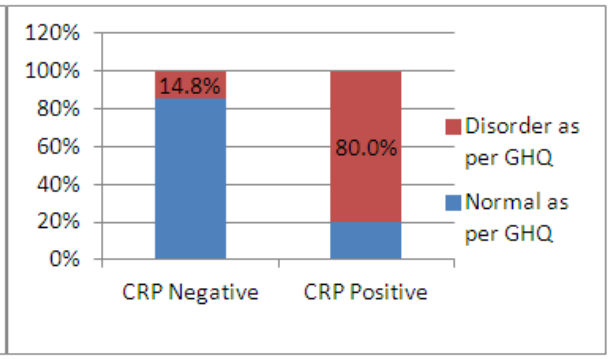
(Figure-11: Gender difference in caseness)



(Figure-12: treatment compliance in caseness)



(Figure-13: RF in caseness)



(Figure-14: CRP in caseness)

IV. Discussion

The result of the study indicated at a high prevalence of psychiatric morbidity (48.1%) in patients suffering from Rheumatoid Arthritis as measured by GHQ 12 with a cut off of 3 (Figure-10). This may be due interplay of multiple factors such as ongoing inflammation that may also involve neuro-inflammation, a suppressed HPA axis, high pro-inflammatory cytokines identical to psychiatric illnesses, multiple co-morbidities, complications of RA, exacerbations in RA, side effects of immune-modulator treatment, treatment failure, poor compliance to treatment, pain, deformity, poor quality of life including poor mobility, high stress level, use of dysfunctional coping skills with long term physical, psychosocial and economic consequences including loss of job. Indeed, pain as measured by the VAS correlated with psychiatric caseness, stress, quality of life compliance with medication, planning, self-blame and CRP. In a systematic review on RA patients, Faith Matcham reported prevalence of depression ranged from 14.8% to 48%(34). Mary Margaretten had mentioned

prevalence of major depressive disorders in 13% to 42% of RA patients (80). In a similar study by Magdalena C, depression and anxiety disorders among patients with RA ranges from 14% to 42%(32). Tanya Covic had found prevalence of anxiety in 13.5% and depression or anxiety in 41.7% of RA patients(82).

In two of his studies, Michael EBhad highlighted an increased risk of development of schizophrenia in autoimmune diseases and vice versa (30, 35). The result of the current study are thus in line with existing literature. This study noted an increased prevalence of psychiatric caseness in females (55.55%) as compared to males (38.88%) (Figure-11). This is in line with the existing literature on female preponderance to develop psychiatric illness among those suffering from RA (34, 80).In this study, high level of perceived stress was found in people suffering from RA. Also, the stress was positively correlated with pain, use of emotional support, behavioural disengagement, venting and self-blame. The same had high negative correlation with planning, positive reframing, active coping, compliance to treatment, mobility and all domains of quality of life. Difference in perceived stress was significantly different in participants with a psychiatric caseness as compared to those without.

Treharne GJ in 2 of his studies had reported that increased stress in patients of RA is related to not using active coping strategies and a poor outcome (86, 87). Curtis R had mentioned perceived stress as a better predictor of positive and negative emotionality (88). Positive outcomes are likely in stressful situations if primary and secondary appraisals converge to determine whether a person-environment transaction is significant for wellbeing and if so, whether it's challenging or threatening. A wide array of individual coping skills, acquiring mastery of specific coping skills and being certain about its effectiveness is key to adequate secondary appraisal. In this study, stress and psychiatric caseness had strong correlations with dysfunctional coping strategies (denial, self-blame, behavioural disengagement and venting) and negative correlation with adaptive coping strategies (active coping, planning, positive reframing and humour). This corresponds to the findings of Michal Ziarko who inferred that dysfunctional coping increases risk of depression in patients of RA(89). In this study, the subpopulation of non-cases as per GHQ-12 score had significantly higher score in all the domains of quality of life than those who satisfied psychiatric caseness. The quality of life was associated with moderate correlation with better mobility, absence of psychopathology, less stress, better planning and less dysfunctional coping (self-blame, venting and behavioural disengagement). The scores compared to contemporary study on patients of Rheumatoid Arthritis and other chronic diseases had similar scores in physical and psychological domains(90-96). Social and environmental domains obtained a higher score; which may be attributable to the characteristics of the study population. Among the immunological and inflammatory markers, C-reactive protein was associated with higher psychiatric morbidity (Figure-15) and dysfunctional coping. This is in agreement with contemporary studies since CRP is associated with various psychiatric morbidities(27, 97, 98).

Anti-CCP antibody had negative correlation with Rheumatoid Factor and it was associated with less psychiatric morbidity (Figure-16), less dysfunctional coping and increased compliance to treatment. This can be attributed to the high sensitivity and specificity of this immune marker, and an observation that it is usually the last one among the biomarkers of Rheumatoid arthritis to be undetectable with continued treatment (1, 99-102).

V. **Conclusion**

On the basis of the above findings of this study involving psychosocial correlates of quality of life in patients suffering from Rheumatoid Arthritis, the following conclusions were made.

1. About half of RA patients require psychiatric consultation since they are at risk of developing psychiatric morbidities. Female patients need special attention since they are more prone for psychiatric caseness.
2. C-reactive protein is correlated to psychiatric morbidity and poor QoL, probably because it is a better indicator of acute inflammation state. CRP titres above 10 mg/L should raise suspicion of an active psychopathology in RA patients. Circulating anti-CCP antibody did not appear to correlate with quality of life or psychiatric morbidities, probably because it is detectable early during inflammation and is also the last one to disappear even after active inflammation has subsided.
3. Early detection and treatment of psychiatric morbidities in patients of RA has got a potential to improve quality of life since there is a strong correlation between disease progression, psychiatric caseness and poor quality of life.
4. Psychological measures also have a potential to have a salutary effect on pain as evidenced by high correlation between psychiatric caseness and pain. Secondarily, quality of life can also be positively influenced by these measures. Better coping skills could help patients manage their illness better with improved outcomes. Psychotherapy has the potential to play a significant role in improving coping style and reduce dysfunctional coping.

Strengths:

1. Robust correlation between psychiatric caseness and QoL was documented.
2. Potential improvement of QoL for RA patients with psychosocial intervention was identified.

Limitations:

1. Only caseness was detected, not actual diagnostic screening or interview was used, which could have given actual case findings.
2. Those screened were not given a psychiatric evaluation of diagnostic which could give a true account of the prevalence of psychiatric illness.

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