Addis Ababa University, College of Health Sciences

AAU, CHS

Prevalence of Comorbidities in Rheumatoid Arthritis and Associated Risk Factors at Tikur Anbassa Spacialized Hospital, Addis Ababa, Ethiopia

Principal Investigator: Nathan Kefelegn, MD
Advisor: Becky Abdisa, MD, Consultant Internist and Rheumatologist.

A Thesis submitted to Addis Ababa University college of Health Sciences in partial fulfilment of specialty in Internal Medicine

FEB, 2024
Addis Ababa Ethiopia

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I would like thanks First and foremost, to Almighty GOD for his blessings throughout my life and during this proposal development. My special thanks go to my advisor Dr. Becky Abdisa for his invaluable support, and to Addis Ababa University College of Health Science for this opportunity and the support they provided me. I am grateful for all my friends, family and colleagues for their support and encouragement.

Abbreviations and Acronyms

ACR -American College of Rheumatology
ACCP -Anticyclic Citrullinated Peptide
AAU-Addis Ababa university
bDMARDs - biological disease modifying Anti-rheumatic drugs
BMI-body mass index
BP-blood pressure
CHS-Collage of Health science
COMORA-comorbidities in rheumatoid arthritis
COPD-chronic obstructive pulmonary disease
CI-confidence interval
CRP C-Reactive Protein
CVD-cardiovascular disease
csDMARDs- Conventional synthetic disease modifying anti-rheumatic drugs
DAS-28 -28-joint count Disease Activity Score
DM-Diabetes multiuse
DMARD -Disease-Modifying Anti-rheumatic Drug
DRC-Democratic republic of Congo
ESR -Erythrocyte Sedimentation Rate
ETB- Ethiopian Birr
EULAR- European League Against Rheumatism
FBS-Fasting blood sugar
GC -Glucocorticoids
HDL-High density lipoprotein
LDL-Low density lipoprotein
MHAQ-modified health assessment Questioners
MTX- Methotrexate
OR -Odds Ratio
RA -Rheumatoid Arthritis
RF -Rheumatoid Factor
TASH - Tikur Anbessa Specialized Hospital
WHO -World Health Organization

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Summary

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown aetiology characterized by a symmetric polyarthritis and is the most common form of chronic inflammatory arthritis. Comorbidities in RA are defined as one or more additional disorders (or diseases) associated with the primary disease. The prevalence of comorbid conditions with RA varies across countries from 3% to 60%. There is limited literature evidence from Africa and no study at all on the prevalence of comorbidities in RA in Ethiopia.

Objective: The aim of this study to assess the magnitude of comorbidity in Rheumatoid Arthritis patients at Tikur Anbessa Specialized hospital Rheumatology clinic, AAU, Addis Ababa, Ethiopia.

Methods: A hospital based cross-sectional study was conducted at TASH from August to Decembre 30. Data was collected using a structured interviewer administered questionnaire and data extraction form. In this study A total of 275 patients were recruited out of whom 19 patents excluded due to incomplete data and 256 patients involved in this study. Data was analysed using SPSS V27.To identify associated factors in comorbidities of patients with rheumatoid arthritis, bivariable and multivariable analysis was done. Variables with p-value < 0.05 in multivariable analysis was employed as statistically significant.

Result: A total of 275 patients were recruited out of whom 19 patents excluded due to incomplete data and 256 patients analysed. 32% of the study participants were in the age group of 40-49 years with the mean and SD of 47.3±11.14 years respectively. 92.6% were female and 77.3% of the participants were from urban area. 51% of the study participants had between 2-10 years duration of RA with 5.98 years mean duration of disease. RF was done for 195(76%) participant and 77.4% was positive. DAS28-ESR, 45.7% had low activity and moderate activity (33.6%). Two-third of the study participants were taking prednisolone. The study revealed 34% of the study participants have had a one or more comorbidities disease. The commonest comorbidities HTN (33%) DM (28%) dyslipidaemia (15%), ASCVD (7%) and 20 % of the study participants having more than one comorbidity.

Conclusion the aim of this study was to know the prevalence of comorbidity in RA patients and associated factors and this cross-sectional study revealed comparable prevalence comorbidities across the globe with most of the country finding. Even though the prevalence varies from country to country. One of the main aims of the present study was to identify factors that may associate with comorbidities in RA. this may be useful for the identification of patients that may need to be specifically targeted to develop screening tools and hospital-based guideline for early intervention in the routine clinical setting.

1 INTRODUCTION

1.1 Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology, characterized by symmetric polyarthritis, and is the most common form of chronic inflammatory arthritis.

As persistently active RA often results in articular cartilage and bone destruction and functional disability, it is vital to diagnose and treat this disease early and aggressively before damage occurs. RA, a systemic disease, may also lead to a variety of extra-articular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities, which must be managed accordingly (1). Chronic debilitating autoimmune disorders that affect multiple joints are associated with a reduced life expectancy (2). Comorbidities in RA are defined as one or more additional disorders (or diseases) associated with a primary disease (2). The prevalence of comorbid conditions with RA varies across countries from 3% to 60% (3, 4). However, some studies have reported a high prevalence (up to 80%) of one or more comorbid conditions (5). Rheumatoid arthritis (RA) is associated with increased cardiovascular mortality owing to an increased prevalence of comorbidities such as myocardial infarction (MI), stroke, and heart failure (HF) [6, 7]. The adjusted relative risk of MI in women with RA compared to those without RA is estimated to be approximately 2.0, while acute coronary syndromes may present atypically and recur more frequently in patients with RA [7,8]. Increased clinical suspicion may aid in early identification and appropriate management of risk factors in these patients [6]. HTN is the most important modifiable risk factor for cardiovascular disease (CVD) and is more common than cigarette smoking, dyslipidaemia, or diabetes [9]. In the INTERHEART study, which included patients from 52 countries, HTN accounted for 18% of the population-attributable risk of a first MI. HTN increases the risk of both coronary artery and cerebrovascular diseases in the general population [11]. It remains unclear whether HTN is common in RA [12,13]. Aging and obesity are known to be predictors of HTN in the general population. In RA, chronic inflammatory burden may lead to increased arterial stiffness [14]. One physical cause of increased systolic blood pressure (BP) is the potential link between inflammation and HTN. Drugs commonly administered to patients with RA, such as non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase II inhibitors (coxibs) [15], oral steroids [16], and disease-modifying anti-rheumatic drugs (DMARDs), such as leflunomide [17] and cyclosporin [18], may also cause major or minor

increases in BP levels. Comorbidities common to RA, such as insulin resistance [19], dyslipidaemia [20] and renal disease, have also been shown to be associated with essential HTN in the general population [21, 22].

Effective management of RA has improved the survival rate, but the presence of associated comorbidities has a negative impact on the outcome (23,24).

In addition, comorbidities influence treatment choice, outcome, and quality of life and pose major challenges in the adoption of management strategies for RA (25, 26).

Hence, the data on comorbidity and associated factors could be beneficial in customizing management strategies and identifying the determinants of comorbidity. There is limited literature evidence from Africa, and so far, there has been no study on the prevalence of comorbidities in RA in Ethiopia.

1.2 Statement of the problem

The first population-based, cross-sectional observational study assessed multiple comorbidities and their management among a relatively large sample of patients with RA who were enrolled by rheumatologists in 17 participating countries on five different continents. In this study Depression was the most commonly observed comorbidity (15 %); however, its prevalence varied widely among countries (from 2% in Morocco to 33% in the USA). The prevalence of ischemic cardiovascular disease (myocardial infarction or stroke) in 6% of patients ranges from a low of 1% in Morocco to a high of 17% in Hungary. Hepatitis B infection was observed more frequently in Italy (9%) and Taiwan (7%) than in other countries (2.8 %). The prevalence of hepatitis C infection was the highest in Italy (6.6%), Egypt (6.8%), and Taiwan (4.8%). The overall prevalence of past or present gastrointestinal ulcers was 10.8%. Pulmonary diseases, especially COPD, were observed less commonly in Asian countries (Japan, 1.4%; Korea, 1.3%; Taiwan, 0.3%) than in European countries or the USA (Hungary, 8.0%; USA, 7.5%). This study confirms not only the relatively high prevalence of comorbidities among patients with RA but also considerable intercountry variability in the prevalence of these comorbidities (32). So, in this study, the systematic evaluation of RA patients for evidence of comorbidities may uncover previously undiagnosed conditions in some patients. Developing countries are finding an increase in the incidence of RA in the face of ongoing poverty, rampant infectious disease, tuberculosis, increased prevalence of hepatitis B and C, HIV, Immunosuppression associated with the use of glucocorticoids, and poor access to modern healthcare facilities (1). A study conducted at a specialized Tikur anbessa hospital in Ethiopia showed a rheumatoid arthritis prevalence of

18.5% (33). The frequency of comorbidities is not known and is thought to be high because of the late presentation of the patient and the type of drugs being used. To date, no study has been conducted on the prevalence of comorbidities in RA and associated risk factors in Ethiopia; therefore, this study aims to fill the knowledge gap and pave the way for further research. Comorbidities will be studied included diabetes mellitus (DM), hypertension (HTN), cardiovascular disease (CVD), thyroid disease, hypercholesterolemia, psychiatric diseases such as depression and pulmonary disease such as bronchial asthma and chronic obstructive pulmonary disease (COPD), infection such as HBV, HCV, TB, and RVI.
This study aimed to evaluate the demographic characteristics and factors influencing comorbidities, such as age, sex, and disease duration

1.3 Significance of the Study

The findings of this study will be important in determining the comorbidities that usually occur in RA at a Tikur Anbassa Spacialized hospital. Implementing screening measures in place to prevent and treat them in the future. To address the frequently occurring comorbidity in resource-limited setups in our country and elsewhere. Improving the quality of treatment provided to our patients.
This study will help as a baseline study to conduct subsequent research and develop setup-based guidelines

2. Literature Review

RA affects approximately 0.5–1% of the adult population worldwide. There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA live longer. The incidence and prevalence of RA vary based on the geographic location, both globally and among certain ethnic groups within a country. The Native American Yakima, Pima, and Chippewa tribes of North America have reported prevalence rates of approximately 7%. In contrast, many population studies from Africa and Asia show lower prevalence rates of RA in the range of 0.2–0.4%. There are no contemporary estimates of the prevalence of RA in sub-Saharan Africa. Different in different countries, 0.12% in rural SA to 0.6% in DRC (1). Prevalence of comorbid conditions with RA vary across different countries from 3% to 60%. However, some studies have reported a high prevalence (up to 80%) of one or more comorbid conditions (3,4). The prevalence of at least one comorbidity in developed nations ranges from 22% to-31.6%. Depression (27%) and obesity (26%) followed by myocardial infarction (MI) and stroke (5% and 1%, respectively) (3,4). A study from South Korea showed an increased prevalence of MI or angina in patients with rheumatoid arthritis, TB, depression patient (27). Hypertension was the most common comorbidity (35.9%), followed by DM (30.9%), osteoporosis (25.8%), and dyslipidaemia (19.4%) (28). In an Indian study, 40.3% of patients had one or more comorbidities (29). Study from south Africa one comorbidity in 69%, two in 40%, three in 26%, HTN (45.5%), TB (11.1%), Type 2 DM 10.9%and hypercholesterolemia (7.1%) (30). In Egypt, the prevalence of hypertension, depression, and DM is approximately 25 %, 11.4%, and 10.4%, respectively (31). The widely noted COMORA study examined the prevalence of selected comorbidities in 17 participating countries in 5 continents worldwide (32). The prevalence of those comorbidities that were evaluated in this study Depression (past or current symptoms) was the most commonly observed comorbidity (15.0%) however, the prevalence of depression varied widely among countries (from 2% in Morocco to 33% in the USA). There was a history of ischemic cardiovascular disease (myocardial infarction or stroke) in 6.0% of the patients. This prevalence ranged from 1% in Morocco to 17% in Hungary. Hepatitis B infection was observed more frequently in Italy (9 %) and Taiwan (7 %) than in other countries. The prevalence of hepatitis C infection was the highest in Italy (6.6%), Egypt (6.8%), and Taiwan (4.8%). The overall prevalence of past or present gastrointestinal ulcers is 10.8%, ranging from 1% in Morocco to 22% in Egypt. Pulmonary

diseases, especially COPD, are observed less commonly in Asian countries (Japan, 1.4%; Korea, 1.3%; Taiwan, 0.3%) than in European countries or the USA (Hungary, 8.0%; USA, 7.5%).The prevalence of various risk factors that increased the prevalence of cardiovascular disease associated with RA, the most prevalent risk factors were those that predisposed patients to cardiovascular disease, such as increased Framingham Risk Score 42.8%, hypertension 40.4%, and hypercholesterolemia 31.7%. Similar to the prevalence of comorbidities, there was considerable inter-country variability in the prevalence of risk factors. The prevalence of smoking ranged from 3% in Morocco to 48% in Austria. The annual evaluation of cardiovascular risk, including measurement of blood pressure, total serum cholesterol (high-density lipoprotein (HDL) and LDL), blood glucose, and serum creatinine, was performed in 59.4% of the patients. The systematic assessment of certain cardiovascular risk factors in this study allowed their detection in previously undiagnosed patients. Elevated blood pressure was detected in 18% of the patients. Elevated blood glucose levels were detected in 3.7% of the patients without previously diagnosed diabetes mellitus. LDL cholesterol levels above the optimal target were detected in 11.0% of patients who were not previously diagnosed with dyslipidaemia or not receiving lipid-lowering therapy (32).

In India, 85.2% and 79.1% were RF- and ACCP-positive respectively.86.7% commonly used double DMARD and 10.7% of patients had received biologics. In south Africa RF and ACCP were positive in 85.1 % and 80.4 %, respectively Around 2/3 of the patients were given DMARDs. The study which was done at Tikur anbessa specialized hospital, In Ethiopia showed the prevalence of rheumatoid arthritis was 18.5%. Females were mostly affected F:M 4.6:1. A total of 57.8% of the participants were between 35 and 64 years of age. Seropositivity for rheumatoid factor was 47.1% (33). Hence, the data on comorbidity and the associated factors could be beneficial in customizing the management strategies and identifying determinants of comorbidity. There is limited literature evidence from Africa and there is no study in Ethiopia on the prevalence of comorbidities in RA.so the aim of this study was to assess the prevalence of comorbidities in RA patients and its associated factors for early initiation of treatment and patient follow-up at the TASH rheumatoid outpatient clinic.

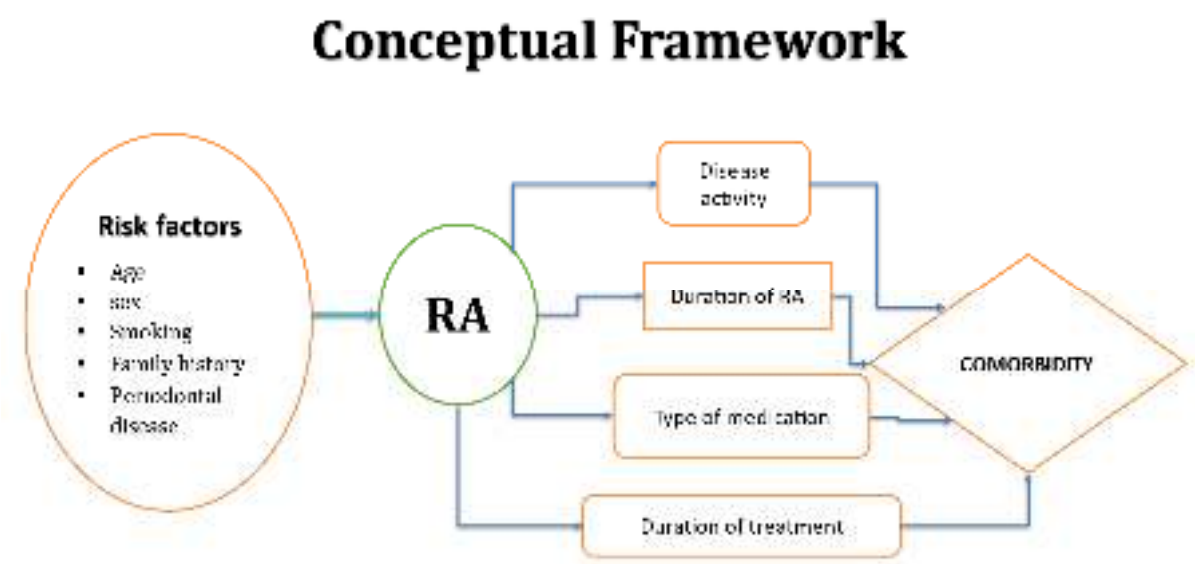

Figure 1 conceptual frame work

3 Objectives

3.1 General objectives

To assess the magnitude of comorbidity in Rheumatoid Arthritis patients at Tikur Anbessa Specialized hospital Rheumatology clinic, AAU, Addis Ababa, Ethiopia October 01 to December 30/2023

3.2 Specific objective

To determine magnitude of comorbidities in rheumatoid arthritis
To identify the risk factors associated with comorbidity in Rheumatoid Arthritis

4. Methodology

4.1 Study Area: The study was conducted in the rheumatology clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Tikur Anbessa Specialized Hospital is the largest tertiary referral hospital in Ethiopia. It is also the main teaching hospital for the College of Health Sciences at Addis Ababa University. The hospital launched a digital recording system in 2018, where the clinical data and other pertinent profiles of the patients were stored and retrieved when needed. It has different clinics that provide services to patients in the country. The Rheumatology clinic is one of the clinics that provides care and follow-up for patients with different rheumatologic problems. It provides services for these patients on two working days of the week, with a daily average of 60–70 cases attending the clinic. The study will be conducted at the rheumatology clinic of the hospital.

4.2 Study Period: The study was conducted from AUG 2023 to DEC2023

4.3 Study Design: A hospital-based cross-sectional study design was used. A cross-sectional study in which patients were diagnosed with RA age > 18 and according to the 2010 ACR criteria (RA classification criteria) will be enrolled in the study. All patients were from those who attended the Rheumatology Outpatient Clinic at Tikur Anbessa-specialized Hospital between AUG 2023 and DEC30,2023 Rheumatology Outpatient Clinic.

4.4 source and study population

The source population comprises all patients with Rheumatoid Arthritis attending the Rheumatology clinic in TASH.

The study population was randomly selected patients with Rheumatoid Arthritis attending the Rheumatology clinic during the study period. We were used digital record of the hospital (I-care) as a sampling frame and patients are randomly selected using a random number generator for the required sample size.

4.5 Sample Size determination: The sample size was calculated using the single population proportion formula. Considering a z value of 1.96 for 95% confidence interval, 50% prevalence of comorbidity in RA and 5% of margin of error, the least sample size (n) required for the study will be calculated using the formula to estimate a single population proportion.

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

Where;

n = required sample size

Zα/2 = critical value for normal distribution at 95% confidence interval= 1.96 (α = 0.05). **P =** Proportion = 50% **d =** margin of error= 5%

n=1.96x1.96x0.5(1-0.5)/0.05x0.05

n=384

The initial sample was adjusted using a correction formula for the study population (population<10,000). The total RA patients attend at Tikur anbessa specialized hospital rheumatology clinic 720.

$$n = \frac{n_0}{1 + \frac{(n_0 - 1)}{N}}$$

Where n is the sample size

N is the population size.

n_o is calculated sample size for infinite population

n=384/1+(384-1)/720
n=250 added 10% non-response rate
the final sample size of 275.

4.6 Sampling Techniques

We were used a simple random sampling technique to select participants. We will list 720 patients from to 1-720 and use the digital record of the hospital (I-care) of the patient as the code number of the patient. Our sampling frame are 720 patients from this randomly select samples by using a random number generator for the required sample size.

4.7 Eligibility criteria

4.7.1 Inclusion criteria

(1) All Rheumatoid arthritis patient who fulfilled the 2010 American College of Rheumatology/ the European League against Rheumatism (EULAR) classification criteria for RA.

(2) Patients 18 years and above.

(3) Patients providing written informed consent

4.7.2 Exclusion criteria

Those patients with concomitant other rheumatologic illness during their follow up period.

Those who do not fulfill the inclusion criteria.

4.8 Variables

4.8.1 Dependent variable

Comorbidity

4.8.2 Independent variable

Age

Sex

Family history

Smoking status

Duration of Illness

Duration of treatment

DAS-28

Drug being administered

BMI

4.9 Data collections instruments and technique

Data was collected by trained General practitioner and residents. Patients' disease activity was assessed using the 28-joint disease activity score based on DAS-28 ESR and Joint count and routine disease activity assessment was done by a consultant Rheumatologists, Residents and general practitioner. Patients was approached at their clinic appointment day, in the follow up clinic. An interviewer administered questionnaire was used instead of self-administered for inclusion of illiterate participants in the study. The MHAQ comprises eight domains, each consisting of two or three questions, where every question can be answered on a 4-level scale regarding the patient's ability to perform an activity of daily living (0 = no difficulty, 1 = some difficulty, 2 = much difficulty and 3 = unable to). The following domains, which cover the main activities of daily life, are as follows: dressing, rising, eating, walking, hygiene, reach, grip, and errands and chores. The MHAQ Calculated by hand or with a calculator by adding all scored item together and dividing by a total number of items answered to obtain the final score. Score interpretations total score between 0.0-3 higher score indicates worse function and greater disability. MHAQ<0.3 =normal, MHAQ<1.3 =mild, MHAQ =1.3 -1.8 moderate and MCQ>1.8 sever (functional loss). First the interview was carried out for each participant and clinical information was extracted from their respective medical records, using data extraction tool.

4.10 Data Quality control

Training was given to data collectors. The collected data was checked for completeness and consistency on each day of data collection. Supervision and monitoring were made every day by the assigned principal investigators.

4.11 Data Analysis

Data were checked manually for completeness and then were entered into Epidata version 3.1 and will be analyzed using SPSS version 27. During the analysis P- value < 0.05 with 95% confidence interval (CI) for OR (odds ratio) will be used in judging the significance of the associations. Univariate and bivariate analysis between dependent and independent variables were performed using binary logistic regression. Multivariable analysis was done to control for possible confounding variable. Data was presented using tables, graphs and charts.

4.12 Operational Definitions

Comorbidity: is defined as the presence of additional one or more disease in RA patients

Depression: is if the patient was diagnosed with standard DSM criteria by a psychiatrist or on follow up.

Duration of illness**:** the period of time since the diagnosis of RA.

Duration of treatment**:** the period of time the patient was on treatment of RA.

Smoker: a patient who has history of smoking of > 100 cigarettes in his life time based on National health interview survey (NHIS)

DM: FBS>125 mg/dl/ HgA1c >6.5 %, or those who started on treatment of DM.

Dyslipidemia**:** Total cholesterol >200 mg/dL HDL-C<40 mg/dl, LDL>100 and TG >150mg/dL based on NCEP-ATPIII guidelines or was on treatment.

Hypertension: ≥140/90 mmHg/ those who started on management will be considered as hypertensive.

Osteoporosis: A patient with BMD of DEXA scan T score <-2.5 or diagnosis with fracture (WHO)

Low dose and High dose corticosteroid**:** patients on prednisolone <7.5mg daily and ≥ 7.5mg daily respectively or equivalent dose based on EULAR

Infection: is defined as an infection that requires hospitalization after the diagnosis of RA.

Health related quality of life**:** the extent to which one's usual or expected physical, emotional, and social wellbeing are affected by a medical condition or its treatment

Disease activity: will be assessed using the standard Disease Activity Score 28 (DAS28). The DAS28 uses a 28 tender joint count (TJC), a 28 swollen joint count (SJC), ESR and a General Health Score (GHS) on a 10-point visual scale to produce an overall continuous

measure of RA disease activity. DAS28 scores can range from 0 to 9.4. Patients were categorized using DAS28 scores into low {DAS28 <= 3.2}, moderate (> 3.2<=5.1) and high {DAS28 > 5.1} disease activity

MHAQ: The MHAQ Calculated by hand or with a calculator by adding all scored item together and dividing by a total number of items answered to obtain the final score. Score interpretations total score between 0.0-3 higher score indicates worse function and greater disability. MHAQ<0.3 =normal, MHAQ<1.3 =mild, MHAQ =1.3 -1.8 moderate and MMAQ>1.8 sever (functional loss).

4.13 Ethical Considerations

Ethical clearance was obtained from institutional review board of College Health Science AAU. Patients were informed about the aim, benefit and possible inconvenience of the study. They were assured the information they gave will be confidential. Before data collection begins, verbal consent was obtained and participants can withdraw at any time if the need arises.

4.14 Dissemination of Results

The findings of the study will be submitted to the department of internal medicine and will be presented as one of the partial fulfillments of specialty certificate in internal medicine. All efforts will be made to publish the results to the local and international journals and to present it in national scientific conferences.

5. Result

5.1 Sociodemographic characteristics of the study participants

In this study a total of 275 patients were recruited, of whom 19 were excluded due to incomplete data. With a 93% response rate, 256 patients were involved in this study. 32% of the study participants were in the age group of 40–49 years, with a mean and SD of 47.3±11.14 years, respectively. Almost all (92.6%) were female, with a female-to-male ratio of 13:1, and 77.3% of the participants were from urban areas. 56.6% of the study participants were married, and 40.6% of the study participants were housewives. Thirty-three percent of the study participants had a primary education level. The majority (44.9%) of the study participants had a normal body mass index, and only 2% of the participants had a smoking history.

Table 1. The sociodemographic characteristics of the study participants having rheumatoid arteritis at TASH,2024.

variable	frequency	Percent
Age of the study participants		
<30	17	6.6
30-39	41	16
40-49	82	32
50-59	74	28.9
≥60	42	16.4
Sex of the study participants		
Male	19	7.4
female	237	92.6
Residence		
Urban	198	77.3
Rural	58	22.7
Marital status		
Single	59	23
Married	145	56.6
Divorced	24	9.4
widowed	28	10.9
Occupation		
Government employee	46	18
Self-employee	69	27
House wife	104	40.6
Farmer	8	3.1
other	29	11.3
Level of education		
Illiterate	56	21.9
Primary	85	33.2
Secondary	42	16.4

Collage and above	73	28.5
Body mass index		
Under weight	23	9
Health weight	115	44.9
Over weight	83	32.4
obese	28	10.9
Severely	5	2
morbidly	2	0.8
Smoking status		
Smoked	5	2
Never smoked	251	98

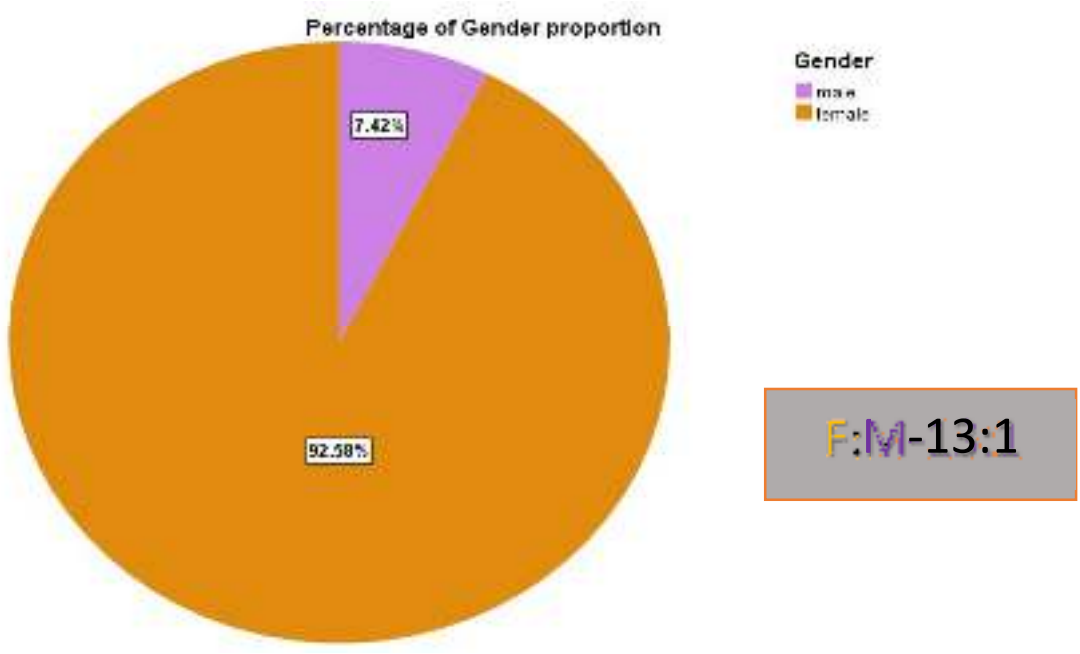

Figure 2 percentage of gender proportion among RA patients

5.2 The study participants characteristics of rheumatoid arteritis

Fifty-one percent of the study participants were in the age range of between 2–10 years of RA disease, with a mean duration of 5.98 years. Among the study participants, RF was done for 195 (76%) patients, and of those, 151 (77.4%) had a positive RF. ACCP was done for 111 patients (43.4%) of whom 94 (84.7%) had positive results. Regarding the disease activity DAS28-ESR result, 45.7% had low activity, followed by moderate activity (33.6%), remission (16.4%), and high activity (4.3%). functional status and disability on daily activities assessment of RA patient by using MHAQ and 2/3 of the participant had have normal activity no limitation on routine activities, were as 30% of participants had mild functional limitation and 4.3% moderate limitation on daily activity.

Table 2. The study participants characteristics of rheumatoid arteritis.

Variable	frequency	Percent
Duration of illness before diagnosis		
≤6months	81	31.6
>6 months -2year	121	47.3
>24-120months	47	18.4
>120months	7	2.7
RA total duration of disease		
<6month	13	5.1
6months-2 years	66	25.8
>2years-10years	131	51.1
>10 years	46	18
RF done		
Yes	195	76.2
no	61	23.8
Result of RF (n=195)		
Positive	151	77.4
negative	44	22.6
ACCP done		
Yes	111	43.4
No	145	56.6
Result of ACCP (n=111)		
Positive	94	84.7
Negative	17	15.3
DAS28-ESR		
Remission	42	16.4
Low activity	117	45.7
Moderate activity	86	33.6
High activity	11	4.3
MHAQ		
normal	165	64.5
Mild functional impairment	77	30.5
Moderate functional impairment	11	4.3

Sever functional impairment	3	1.2

5.3 Medication related characteristics of the study participants

Two-thirds of the study participants were taking prednisolone, and of those who took prednisolone, 74.4% took ≤7.5mg and 79.6% took more than three months. Twenty-seven percent of the study participants used NSAIDs, 30.5% were taking chloroquine, and 85.8% were taking methotrexate. 22.7% had two DMARDs (methotrexate and chloroquine), and no patient received a biological DMARD.

Table 3 Medication related characteristics of the study participants

variable	frequency	Percent
Taking prednisolone		
Yes	168	65.6
No	88	34.4
Dose of prednisolone in mg (n=168)		
≤7.5	125	74.4
>7.5	43	25.6
Duration of prednisolone in month (n=168)		
≤3	34	13.3
>3	135	79.6
NSAID use		
Yes	69	27
No	187	73
Currently chloroquine taking		
Yes	78	30.5
No	178	69.5
Methotrexate		
Yes	218	85.8
no	38	14.2
Dose of methotrexate in mg (n=218)		
≤15	146	67
>15	72	33
Sulfasalazine Taking	2	0.9
Two DMARD		
Yes	59	22.7
No	197	77.3
Three DMARD	1	0.4
Biological DEMARD		
No	256	100

5.4 The prevalence of comorbidities in this study

The findings of the study revealed that86(34%) (95% CI = 27.4, 39.01) of the study participants have had one or more comorbidities, while 170(66%) of the participants haven't. The commonest comorbidities were HTN 28 (33%), followed by DM 24 (28%), dyslipidaemia 13 (15%), and ASCVD 6 (7%). Among ASCVD patients with IHD, the risk factors identified in this patient are HTN and ischemic stroke. Four patients (3.5%) had HTN, one had not identified risk factors, and one had PAD with no risk factors identified. Osteoporosis 5 (6%) risk factors identified in these patients were taking prednisolones. pulmonary disease 7(8%) from this asthma, 3(4.65%), COPD 2(2.32%), post-TB fibrosis 1(1.16%), and gastrointestinal disease 2(2.3%) Peptic ulcer disease 1 (1.16%), and risk factors for this patient were that he was taking NSAID and the other patient had GERD (1.16%). The prevalence of HIV/AIDS in this study was 8 (9%) HBV, 2 (2.32%), and 1 (1.16%), respectively. Psychiatric diseases identified in this study were depression (3.5%), and bipolar 1 (1.66%). Among RA patients with comorbidities, 20% of the patients had more than one comorbidity.

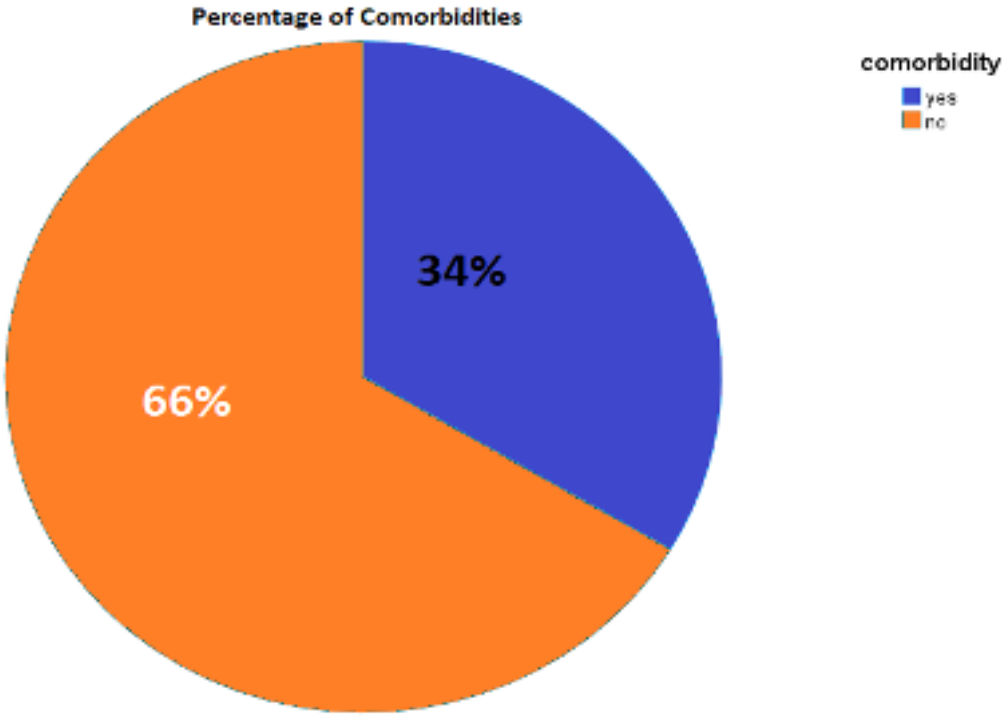

Figure 3 the magnitude of comorbidity among RA patients

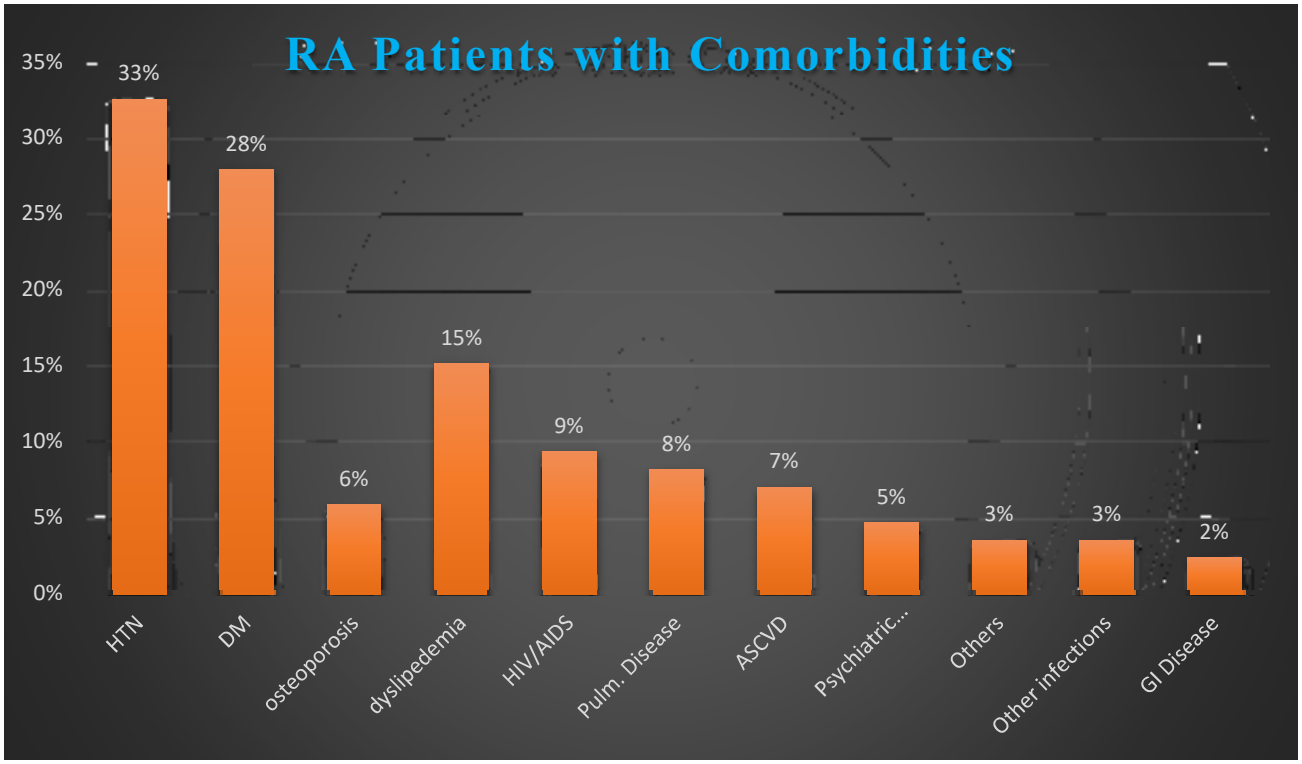

Figure 4. specific comorbidities in RA patients

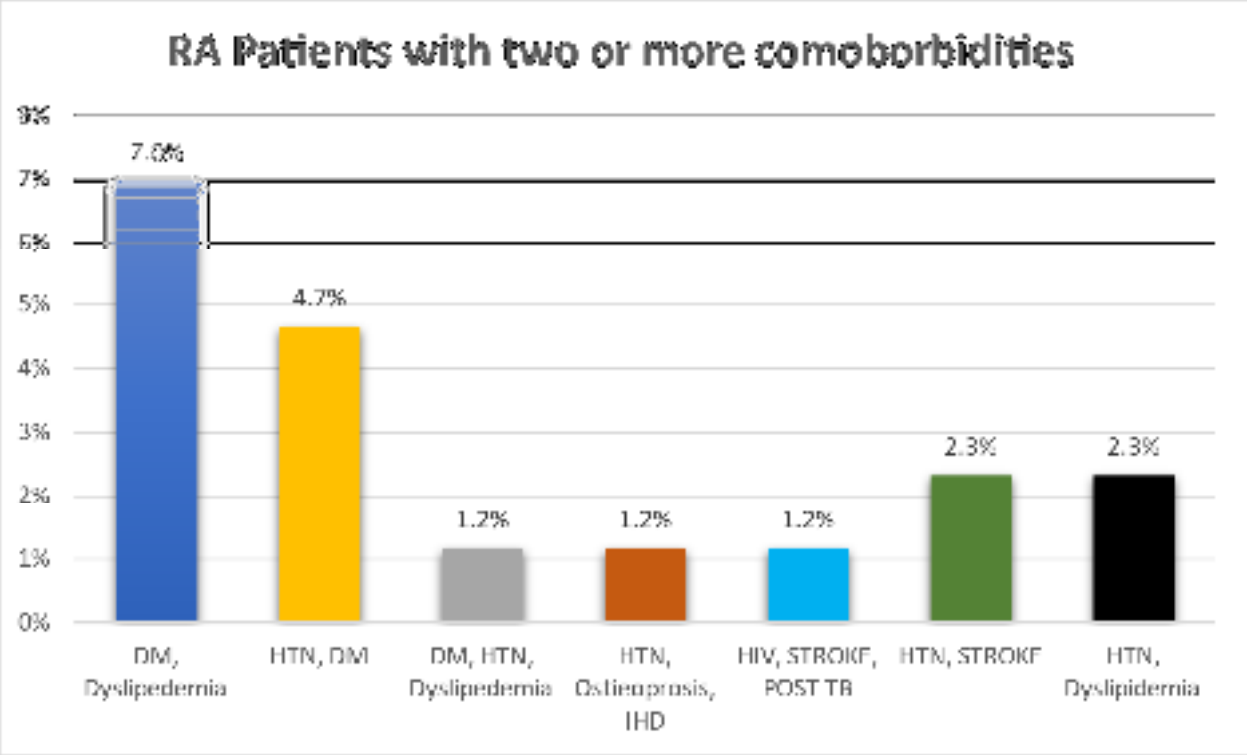

Figure 5. RA patients with more than one comorbidity

Table 4 prevalence comorbidities in rheumatoid arthritis

Variable	frequency	Percent
Hypertension	28	32.5
Diabetes mellitus	24	27.9
Dyslipidemia	13	15
Osteoporosis	5	5.8
ASCVD (n=6)	6	7
IHD (1)	1	1.16
IHD risk factors (n=1) HTN		
Stroke	4	4.65
Stroke risk factor n=3 HTN 1= not identified		
PAD(n=1)	1	1.16
PAD risk factors (not identified)		
Types of pulmonary disease (n=7)	7	8
Asthma	4	4.65
COPD	2	2.32
Post TB Fibrosis	1	1.16
Gastrointestinal disease (n=2)	1	1.16
Peptic ulcer disease	1	1.16
GERD	1	1.16

HIV/AIDS	8	9
HBV	2	2.32
HCV	1	1.16
Other infections	4	3.5
Hypothyroidism	2	2.32
Types of Psychiatric disease (n=4)	4	4.65
Depression	3	3.5
Bipolar	1	1.16
Patients with two or more comorbidities	17	19.77
DM, Dyslipidemia	6	7
HTN, STROKE	2	2.3
HTN, IHD, Osteoporosis	1	1.16
HTN, DM	4	4.7
HTN, Dyslipidemia	2	2.3

5.6 The relation between mean value of the continuous independent variable with comorbidity

The mean age of RA with non-comorbidity participants was 45.56 years, while the mean age of RA with comorbidity participants was 50.71 years, but there was no significant age difference by using the chi-square test at a p-value of 0.063. when the duration of disease increase (RA) was significant in relation to comorbidity disease at a p-value of <0.001.

Table 5 the relationship between comorbid disease and contentious independent variables

Variable	Non-comorbidity	Comorbidity	X2-value	p-value
	Mean ± SD	Mean ± SD		
Age in years	45.56±10.89	50.71±10.9	63.81	0.063
Duration of follow up in years	5.53±4.87	5.96±5.31	47.3	0.003
Total duration of disease in year	5.97±5.16	6.00±5.33	49.9	0.001

5.8. The determinant factor for comorbidity disease among rheumatoid arteritis patients

In this study the strength of the association was measured using an odd ratio and a 95% CI. Accordingly, residence, marital status, level of education, BMI, RF result, dose of prednisolone and methotrexate, and duration of prednisolone were associated with comorbidity disease by bivariate logistic regression. The multivariate logistic regression revealed that study participants who were from rural areas were 4.5-fold more likely to have a comorbidity disease compared to those from urban areas (AOR=4.5, 95%CI=1.17, 17.36 p-value=0.028). and study participants who increased their BMI were 7.6 folds more likely to develop comorbidity compared to healthy weight (AOR = 7.6, 95% CI = 1.46, 25.63 p-value = 0.015). Study participants who took prednisolone > 7.5 mg po/day were 4.3 folds more likely to develop comorbidity disease compared to those who took ≤7.5 mg (AOR=4.3, 95%CI=1.17, 15.39 P-value=0.028), while participants with negative results of RF were 78% less likely to develop comorbidity disease compared to those in the opposite compartment (AOR=0.22, 95%CI=0.05, 0.95 p-value =0.043).

Table 6 the association of bivariate and multivariate logistic regression between comorbidity disease and independent variable among RA patients, TASH 2024

variable	Presence of comorbid disease		p-value	COR with 95%CI	P-value	AOR with 95%CI
	yes	No				
Age in years						
18-30	4	13	1		1	
30-39	8	33	0.731	0.79(0.20, 3.07)	0.110	0.10(0.007, 1.66)
40-49	25	57	0.568	1.4(0.42, 4.81)	0.427	0.33(0.02, 5.15)
50-59	26	48	0.363	1.8(0.52, 5.95)	0.711	0.59(0.04, 9.37)
>=60	22	20	0.050	3.6(1.00, 12.78)	0.597	2.3(0.11, 47.46)
Residence						
Urban	54	144	1		1	
rural	**31**	**27**	**0.000**	**3.1(1.68, 5.59)**	**0.028**	**4.5(1.17, 17.36)**
Marital status						
Single	14	45	1		1	
Married	49	96	0.161	1.6(0.82, 3.28)	0.133	0.31(0.06, 1.44)
Divorced	8	16	0.371	1.6(0.57, 4.54)	0.201	0.28(0.04, 1.99)
widowed	14	14	0.016	3.2(1.24, 8.34)	0.550	0.46(0.04, 5.95)
Level of education						
Illiterate	24	32	0.002	3.5(1.56, 7.07)	0.334	2.2(0.45, 10.57)
Primary	33	52	0.005	2.9(1.39, 6.15)	0.411	1.8(0.42, 8.23)
Secondary	15	27	0.034	2.6(1.07, 6.12)	0.833	1.2(0.17, 9.29)
Collage and above	13	60	1		1	
Body mass index						
Under weight	3	20	1		1	
Health weight	35	80	0.100	2.9(0.81, 10.46)	0.948	0.92(0.07, 12.31)
Over weight	30	53	0.044	3.8(1.04, 13.76)	0.308	3.9(0.28, 56.63)
obese	**17**	**18**	**0.009**	**6.3(1.58, 25.09)**	**0.015**	**7.6(1.46, 25.63)**
The result of RF						
Positive	55	96	1		1	
Negative	**4**	**40**	**0.002**	**0.18(0.06, 0.51)**	**0.043**	**0.22(0.05, 0.95)**
Dose of prednisolone in mg						
≤7.5	41	84	1		1	
>7.5	**22**	**21**	**0.034**	**2.1(1.06, 4.34)**	**0.028**	**4.3(1.17, 15.39)**
Duration of prednisolone medication in months						
≤3	8	26	1		1	
>3	54	79	0.070	2.2(0.94, 5.28)	0.678	1.4(0.31, 5.97)
Methotrexate						
Yes	66	152	1			
No	19	19	0.019	2.3(1.15, 4.63)	0.130	3.2(0.71, 14.28)

6. Discussion

In this study the prevalence of comorbidity in RA patients was revealed to be 34%. The commonly observed comorbidities are HTN (33%), followed by DM (28%), dyslipidaemia (15%), and ASCVD (7%). Among the ASCVD patients, IHD (1.16%) and ischemic stroke (3.5%). Other comorbidities identified in this study were osteoporosis (6%), pulmonary disease (8%) from asthma (4.65%), COPD (2.32%), and the prevalence of HIV/AIDS in this study (9%). other comorbidities in this study Gastrointestinal disease, psychiatric disease, HBV, HCV, and hypothyroidism are ≤5%. prevalence comorbidities in RA across the globe vary between 3 and 60% (3, 4). study from South Korea HTN 35.9%, osteoporosis 25.5%, and dyslipidaemia 19.4% (28). When we compare with our study, HTN and dyslipidaemia were almost comparable, as osteoporosis was low in our case. In the study that was done in India on the prevalence of comorbidities in RA patients, 40.3% of patients had one or more comorbidities. from this HTN was 20.7% and DM 14.4% (28) and when we see this study in terms of comorbidity occurrence, there is a visible difference from our study. study takes place in Morocco, and the prevalence of ASCVD is 1% and 6%, respectively, and in our study, it was 7%. COPD In Asian countries, Japan is 1.4% and Korea is 1.3%. Taiwan: 0.3%, and Europe and the USA Hungary 8% and the USA 7.5% in our study 2.23%; prevalence of depression is 15%, but which varies in different countries; 2% in Morocco and 33% in the USA. Study in South Africa HTN 45.5%, TB 11%, and DM 10.9% (30) were as prevalent in Egypt as HTN 25%, depression 11.9%, and DM 10.9% (31). In one study, a review of the medical records of 3623 patients with HIV/AIDS at a university hospital in Taiwan identified a concomitant diagnosis of RA in six (0.16%) cases (34). Among these, five patients developed arthritis after the initiation of HAART, with an average time to onset of arthritis of 67 months. Regarding functional status and disability of RA patients, assessing daily activity by using MHAQ from RA patients without comorbidity, 121 (71.2%) had no functional limitation on daily activity, 45 (26.5%) were mildly affected, and 4 (2.4%) were moderately affected, but in this study, there was no severe functional limitation of activity among RA patients without comorbidity. 29 (42.6%) mildly affected 4 (5.9%) moderately affected 1 (1.5%), severely affected, and among RA patients with more than one comorbidity 3 (16.7%) mildly affected Three (16.7%) were moderately affected, while 11.1% were severely affected (functional loss). So far, studies done over the past 20 years across the globe on the impact of comorbidity on RA patients' functional status and disability showed a negative impact, and when the number of comorbidities and age increased, the degree of functional disability also increased

In India, 85.2% and 79.1% of patients were RF and ACCP positive, respectively. In south Africa, RF and ACCP were positive at 85.1% and 80.4%, respectively. In our study, RF was done for 191 (74.6%) patients; from this, 151 (77.4%) were positive, and ACCP was done for 111 patients; 94 (84.7%) were positive. When we compare the studies done in India and South Africa, they are almost comparable. In India, commonly used double DMARD, and 10.7% had received biological DMARD. As in our study, only 23% of study participants were taking double conventional DMARD, and there is no patient taking biologic DMARD. In this study, the strength of the association was measured using an odd ratio and a 95% CI. In this study, the multivariate logistic regression revealed that study participants who were from rural areas were 4.5 times more likely to have a comorbidity disease compared to those from urban areas (AOR = 4.5, 95% CI = 1.17, 17.36, P = 0.028). study a rural RA population in northern New York against a national population-based dataset of RA patients, among the RA comorbidities, the prevalence of diastolic hypertension is significantly higher in rural RA patients (46.4%) compared with the national counterpart (24.2%), and COPD prevalence was the most prominent between the rural (11.8%) and national (3.5%) datasets (35). and study participants who were obese were 7.6-fold more likely to develop comorbidity compared to healthy weight (AOR = 7.6, 95% CI = 1.46–25.63, P = 0.015). Study participants who took prednisolone > 7.5 mg po/day were 4.3 folds more likely to develop its comorbidity disease compared to those who took ≤7.5 mg (AOR=4.3, 95%CI=1.17, 15.39P=0.028). So far, there have been a number of studies done on RA with comorbidities. Almost all of the studies found patients who were taking prednisolone >7.5 mg and had a long duration > 3 months were highly likely to develop comorbidities. In our study, participants taking prednisolone > 7.5 mg/day developed comorbidity with a statistically significant p-value <0.023. other study in one study, in order to evaluate which factors were independently associated with the presence of HTN, variables that retained significance were age (OR ¼ 1.05, CI: 1.02–1.07, P < 0.001), BMI (OR ¼ 1.06, CI: 1.003–1.121, P ¼ 0.038), and use of a dose >7.5 mg of prednisolone (OR ¼ 2.39, CI: 1.02–5.6, P ¼ 0.045) (35). The other interesting finding in this study was that patients with negative results of RF had a 78% lower likelihood of developing comorbidity disease compared to those in the opposite compartment (AOR=0.22, 95%CI=0.05, 0.95P=0.043). but other studies done on this comorbidity were noted in 49% of seropositive RA and in 45% of seronegative RA without any significant difference (p = 0.6). (36)

7.Strength & limitations of the study

7.1 Strength In this study- a simple random sampling technique by using a random number generator for the required sample size was used, and this was believed to make the studied population more or less representative. The response rate in the present study was high, which may imply the high level of motivation of the study participant.

7.2 Limitations- The study design was a single-centre cross-sectional study, and hence it is challenging to conclude regarding causality and alternative explanations of the findings and also difficult to know the comorbidities exactly when they occurred. Since the intention of the study was to know the magnitude of comorbidities in RA patients and their associated factors, it was difficult to know which statistically significant factors were more associated with a specific type of comorbidity.

8. Conclusion & recommendation

The aim of this study was to determine the prevalence of comorbidity in RA patients and associated factors, and this cross-sectional study revealed comparable prevalence comorbidities across the globe with most of the country's findings, Even though the prevalence varies from country to country. one of the main aims of the present study was to identify factors that may be associated with comorbidities in RA. This may be useful for the identification of patients that may need to be specifically targeted to develop screening tools and hospital-based guidelines for early intervention in the routine clinical setting.

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Annexes

Annex 1: Assurance of Principal Investigators

My name is Nathan Kefelegn. I am the principal investigator. I put my signature below to confirm that I take over the responsibility for the scientific, ethical and technical conduct of the research project and for provision of progress reports for all stakeholders of the research project.

Signature: _____ Date: ----------

Contact Address of PIs:

Phone number: +251912877660

Email: kefelegnnathan@gmail.com

TASH, ADDIS ABABA, ETHIOPIA

Annex 2: information and consent sheet

Information sheet

Dear participant,

The purpose of this study is to assess the prevalence of comorbidities in Rheumatoid arthritis and associated risk factors. Since the findings of this study are very important in determining future decisions in early detection of comorbid disease and initiation of treatment. I kindly request your genuine participation.

You have full right to participate throughout, or to discontinue at any time, or never participate in the study.

The information you give will be used only for the purpose of this study confidentially.

Thank you for your valuable time.

Consent form

I, the undersigned, have heard the information in the information sheet and understood the purpose and significance of the study.

I agree to participate in the research voluntarily with the hope of contributing to the effort to assess the prevalence of comorbidity in Rheumatoid arthritis and associated risk factors of rheumatoid arthritis patients.

Signature---------- date----------

Annex 3: Questionnaire

English version

I care No._____ Date of interview ___

interviewer name_____

SECTION 1

Sociodemographic

Serial number	QUESTIONS	Response & CODING	REMARK
101	sex	1.male 2.femal	
102	age	In year	
103	Where is your residence?	1-urban 2-rural	
104	What is your current marital status**?**	1. Single 2. Married 3. Divorced 4. Widowed	
105	What is your occupation?	1. Government Employee 2. Self-employed 3. House wife 4. Farmer 5. Others (specify)…….	
105	What is your level of education?	1. No formal education 2. Primary school 3. Secondary school 4. Higher education	
106	What is your average household monthly income?	……in Birr	
107	The patient BMI	1.Underweight (<18.5) 2.Health weight (18.5-24.9) 3.overweight (25-29.9) 4.obese (30-34.9) 5.severelyobese (35-39.9) 6.morbidly obese (>=40)	
108	The RA duration of illness prior to diagnosis?	1.<=6 months 2.>6 months	
109	Total duration of disease?	1.<6 months 2.6 months-10 year	
110	Rheumatoid factor done for the patient	1.yes 2.no	
111	If the answer for Q110 yes what was the result?	1.postive 2.negative	
112	ACCP done	1.yes	

		2.no	
113	If the answer for Q112 yes What was the result?	1.postive 2.negative	
114	DAS-28-ESR	1.<2.6(remission) 2.2.6-<3.1(low activity) 3.3.1-<5.1(moderate activity) 4.>=5.1 (high activity)	
115	Smoking status	1.smoker 2.never smoke	
	Prednisolone currently taking?	1.yes 2.no	
116	If the answer for Q 111 yes dose of prednisolone?	1.<=7.5mg 2. >7.5mg	
117	If the answer for Q 111 yes duration of prednisolone?	1.< =3 months 2.> 3 months	
118	Currently NSAID USE?	1.yes 2.no	
119	Do you taking chloroquine?	1.yes 2.no	
120	Do you taking Methotrexate?	1.yes 2.no	
121	Dose of MTX	1.<=15mg 2.>15mg	
122	Two DMARD	1.yes 2.no	
123	Any biological DEMARD	1.yes 2.no	

SECTIONS 2 Comorbidities and risk factors

SER.NO	QUESTIONS	RESPONSE &CODING	REMARK
201	Is the Patient having comorbidity?	1.yes 2.no	
202	If the answer yes for Q 201 which comorbidity? More than one answer possible	1.atheroscelorosis cardiovascular disease 2.pulmonary disease 3.Gastrointestinal disease 4.HTN 5.Diabetesmilituse 6.dyslipedemia	

		7.infection 8.psychiatric disease 10.others specify.	
203	Which Atherosclerosis cardiovascular disease (ASCVD) identified?	1-IHD 2.stroke 3.PAD 4.Other specify	
204	If the answer for Q 203 IHD what modified risk factors identified? More than one answer possible	1.smoking 2.HTN 3.DM 4.Dyslipedemia 5.Other specify	
205	If the answer for Q 203 stroke what modified risk factors identified? More than one answer possible	1.smoking 2.HTN 3.DM 4.Dyslipedemia 5.Other specify	
206	If the answer for Q 203 PAD what modified risk factors identified? More than one answer possible	1.smoking 2.HTN 3.DM 4.Dyslipedemia 5.Other specify	
207	Is the patient having HTN?	1.yes 2.no	
208	If the answer for Q206 yes	1.known HTN 2.Newly diagnosis	
209	Is the patient having DM?	1.yes 2.no	
210	If the answer for Q 208 yes	1.known 2. newly diagnosis	
211	Is the patient having dyslipidaemia	1.yes 2.no	
212	If the answer for Q 210 yes	1.known 2.new	
213	If the patient having Gastrointestinal disease which one is identified?	1.PUD 2.IBD 3.Others specify	
214	If the answer for Q 212 PUD Which risk factor identified	1.h. pylori 2.NSAID 3.steroid 4.others specify	
215	If the patient having pulmonary disease which one is identified	1-asthma 2.COPD 3.Others specify	
216	If the patient having infectious disease which one is identified?	1.Hepatitis B virus 2.hepatitis C virus	

	More than one answer possible	3.RVI 4.other specify	
217	Previous or current psychiatric diseases?	1-depression 2.bipolars 3.scizophernia 4.others specify	

SECTION 3-Modified Health Assessment Questionnaire (MHAQ)

In this section we are interested in learning how your illness affects your ability to function in daily life Please check the response which best describes your usual abilities over one week

Serial no	Questions	Without any difficulty	With some difficulty	With much difficulty	Unable to do
301	Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
302	Get in and out of bed?	0	1	2	3
303	Lift a full cup or glass to your mouth?	0	1	2	3
304	Walk outdoors on flat ground?	0	1	2	3
305	Wash and dry your entire body?	0	1	2	3
306	Bend down to pick up clothing from the floor?	0	1	2	3
307	Turn taps on and off?	0	1	2	3
308	Get in and out of a bus, car, train, or airplane?	0	1	2	3

Annex 4. Annex III: Declaration

I, the undersigned, declare that this postgraduate thesis is my original work, has not been presented for a degree in this or any other university and that all sources of material used for the thesis has been duly acknowledged.

Postgraduate Candidate: Nathan Kefelegn (MD, Internal Medicine Resident)

Signature: …….

This thesis has been submitted with my approval as advisor.

Advisor: Dr Becky Abdissa (MD, consultant Internist, Rheumatologist)

Signature: …….

Date of Submission: February 17 /2024

Place: Addis Ababa, Ethiopia