Original Research Article

Rheumatoid Arthritis: Prevalence, Patterns of Presentations and Associated Factors among Arthritis Patients in Military Hospital, Sana'a, Yemen 2019-2021

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Abstract

Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement.

Objective: This study aimed to portray the prevalence and associated factors of rheumatoid arthritis among arthritis patients in Military hospital, in Sana'a, Yemen.

Methods: It was a facility-based prospective cohort study. From a total of 650 diagnosed patients, one hundred patients with RA were selected and evaluated. Data was collected using a researcher-administered questionnaire and analyzed by SPSS to compare patterns of presentation of RA and its associations with socio-demographic and clinical characteristics.

Results: In the present study of 650 patients with arthritis, out of 200 diagnosed cases of RA, only 100 patients who completed a routine follow-up were eligible for inclusion. 89% were females and the most frequent age was 31-50 years with age mean of 40.5 ± 15.5 and 60% were from Sana'a. Only 5% of patients had a Family history of RA. The most associated comorbidities were HTN, DM and gout. RF and Anti-CCP were positive among 57% and 98%, respectively. 64% of patients had a normal echo exam, while the most diagnosed disease at echo exam was hypertensive heart disease followed by rheumatic heart disease. Male patients with RA had more than four odds to have another autoimmune disease (OR = 4.87; CI:1.29-18.32; *P* = 0.011). Most patients with exacerbations showed low Vit D deficiency (80%), UTI (40%), and hypocalcemia (30%).

Conclusion: It was concluded that RA is one of the most common autoimmune diseases among Yemeni arthritis patients and most affected females in the middle ages. Concurrence between RA with other autoimmune diseases was seen especially SLE and hypothyroidism, with most patients presenting with disease exacerbations. HHD and RHD were the most encountered on echo screening. The study recommended standardizing the management of RA cases based on the updated guidelines internationally to decrease exacerbations and raise awareness among doctors and patients about the major exacerbating factors for the disease.

Keywords: Rheumatoid Arthritis, presentations, exacerbations, Arthritis, Yemen.

Introduction
Background

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease associated with progressive joint damage and disability [1-3], characterised by synovitis of peripheral joints, with extra-articular manifestations. If untreated, unopposed inflammation leads to joint destruction, loss of function and disability, and RA is also associated with premature mortality secondary, at least in part to the effects of chronic inflammation on cardiovascular health [2, 3]. RA is thought to be triggered by environmental factors [4, 5], in patients with an underlying genetic susceptibility [5, 6], leading to dysfunction of innate and adaptive immunity, tipping the balance in preference of autoimmunity over tolerance [7]. Whilst smoking is well recognised as a strong environmental risk factor, other potential factors include vitamin D deficiency [8]. Like other autoimmune diseases, there is growing interest in the role of vitamin D deficiency in the aetio-pathogenesis of RA [8].

The prevalence of RA in Northern Europe and North America is estimated at 0.5–1% and is expected to increase as population's age and mortality decrease [1, 9, 10]. Despite this low prevalence, RA is ranked as the 42nd highest attributable disease to global disability [11], with two-fold higher morbidity among women compared to men [12]. Other determinants of RA disease include age, socioeconomic status (SES), and ethnicity [13-16]. In the Middle East and North Africa (MENA) regions, the epidemiology of RA remains poorly understood with a dearth of data on its prevalence and disease activity among Arab populations. A recent global burden study estimated RA prevalence in MENA regions as among the lowest at 0.16% [12]. Based on limited evidence from several MENA regional studies [17-21], RA disease severity and management appear to vary geographically in the regions [21]. Disease-modifying anti-rheumatic drugs (DMARDs) are the mainstay treatment for RA prescribed to relieve joint pain and swelling, and to reduce disease activity and disability [21, 22]. Newer biological agents are typically used in patients with the severe unresponsive disease to the classical DMARDs [23, 24]. Although effective, they are significantly expensive, imposing a high economic individual and social burden [25].

Statement of the Problem

One meta-analysis comprising 111,758 patients found a 50% increased risk of CVD death, with Ischemic Heart Disease (IHD) and Cerebral Vascular Accidents (CVA) accounting for 59% and 52% increased risks, respectively [26]. Another meta-analysis of 14 observational studies concluded a 48% increased risk of incident CVD in patients with RA, with the risk of Myocardial Infarction (MI) and CVA being increased by 68% and 41%, respectively, with a single study identifying the risk of Congestive Heart Failure (CHF) increased by 87% [27]. These statistics are supported by a recent prospective population-based cohort study of CVD end-points showing that RA patients had higher rates, via adjusted incidence ratio (IRR) of MI (IRR: 1.43), unheralded coronary death (1.60), heart failure (1.61), cardiac arrest (2.26), peripheral arterial disease (1.36) and lower rates of stable angina (hazard ratio: 0.83) [28]. Increased incidence of CV events in RA patients has been linked to that in diabetics, with a two-fold increase compared to the general population [29].

Justification

Rheumatoid arthritis (RA) is a chronic auto-immune disease with no cure. However, early diagnosis and treatment with disease-modifying antirheumatic drugs (DMARDs) can help modulate the erosive nature of RA by reducing joint damage and deformity and decreasing the number of flares (periods of high RA disease activity or symptoms).

Based on limited evidence from several MENA regional studies [17-21], RA disease severity and management appear to vary geographically in the region. RA is one of the most frequent autoimmune diseases (ADs) among Yemeni patients with a steady rise in the frequency of ADs over the period 2014-2017 in Sana'a city [30]. Population-based studies for the assessment of the incidence/prevalence of RA and the trending increase in the prevalence in Yemen are considered issues for more studies, especially in light of the protracted war since 2015, which caused the worst catastrophic humanitarian crisis in the Middle East region.

Diagnosis and treatment: The categories of the 2010 ACR/EULAR criteria are grouped into four classifications, with point scores for each: joint symptoms; serology (including RF and/or ACPA); symptom duration, whether <6 weeks or >6 weeks; and acute-phase reactants (CRP and/or ESR) Pharmacologic and nonpharmacologic therapies. Many nonpharmacologic treatments are available for this disease, including exercise, diet, massage, counselling, stress reduction, and physical therapy, Medication-based therapies comprise several classes of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs), immunosuppressant, and corticosteroids and surgery [17-21].

Objectives

General objective: Portraying the prevalence and associated factors of rheumatoid arthritis among patients in Military Hospital, Sana'a, Yemen.

Specific objectives:

1- To determine the age and sex-specific point prevalence of RA.

2- To evaluate the echo result of patients with RA for incident cardiac disease.

3- To identify the associated chronic and autoimmune diseases with RA.

4- To determine the associated exacerbation factors for RA.

Methodology

Study design

This was a prospective, descriptive cohort study.

Study period

The study was conducted during the period July 2019- August 2021 over a period of 26 months.

Study Area

The study was conducted in the Military Hospital, internal medicine OPD, in Sana'a city, Sana'a city the capital of Yemen with a total population of more than four million (2020 Projection from national census 2004).

Study Population

The study population included all patients who were diagnosed with arthritis depending on The 2010 American College of Rheumatology/European League Against Rheumatism Classification criteria for Rheumatoid Arthritis [2]. All arthritis Patients were tested for diagnosis of RA, and from those with a positive diagnosis of RA random samples were taken until completing the sample size.

Inclusion criteria

The patients who were diagnosed with arthritis attended the Military Hospital during the study period either for diagnosis or follow-up.

Exclusion criteria

1- Age less than 15 years old.

2-If evidence concerning a diagnosis of RA was insufficient.

3- A loss to follow-up

4- Incomplete patient records

Sample size

Any patient who was diagnosed with arthritis when attend the centre during the study period either for diagnosis or follow-up and agreed to participate. From the pool of this arthritis patients, 100 RA patients were chosen according to the following:

The sample size was calculated using Epi Info software version 7.2.4.0 and according to the following equation: $n= P(1-P) (Z/E)^2$. Where n is the sample size, P is the assumed proportion (set at 0.5), Z is the value at CI 95% (equals 1.96) and E is the error margin (set at 5%), With the expected power to be 80%. $n= 0.5(1- 0.5) (1.96/0.10)^2 =96$.

The sample size was calculated to be 96 cases and increased to 100 to compensate for errors and missed data. Samples were drawn by simple random sampling of the total number of RA diagnosed samples among arthritis patients. Hence the design effect = 1.

Data collection

For each patient, demographic data were collected, including age, sex and residency places. In addition, clinical data were obtained, including the associated diseases as hypertension, SLE, DM, and hypothyroidism. Exacerbating factors were also included in the research and echo results.

The result of the rheumatoid factor (RF) test, erythrocyte sedimentation rate (ESR) and anti-cyclic citrullinated peptides (ACCP) were included in the analysis. Data was collected by the researchers or well-trained assistant using a structured questionnaire (Annex 1) filled through reviewing the study individual's records, containing relevant socio-demographic and clinical data, echo results and lab findings with the final diagnosis.

Data processing and analysis

Data were coded and analyzed using the Statistical Package for Social Sciences (SPSS version 24). Categorical data were presented as frequencies and percentages. Continuous data were presented as mean and standard deviation (SD). The chi-square test was used to compare categorical data. Continuous data were compared using the t-test. Continuous data were grouped to analyze associated factor using risk ratio (RR). The magnitude of associations was presented as crude RRs with a 95% confidence interval. A p-value of 0.05 or below was considered statistically significant.

Ethical consideration

Informed consent from patients was taken. Patient confidentiality was secured using a unique ID, with the freedom to withdraw from the study at any time without any interference with any ongoing management. The study was ethically approved by the Yemeni council of medical specialties, the department of internal medicine, the authority of the military hospital, the governmental health administration, and health facilities.

Results

650 patients with complaints of arthritis were evaluated in the OPD. 200(31%) of them were diagnosed with RA, 46% with RHD and 14% with SLE (Table 1). In this study, 100 RA patients were selected for the descriptive analysis

Table 1: Distribution of Arthritis diagnosis in Military hospital, Sana'a, Yemen 2019-2021(n=650)

Diagnosis	Frequency	%
RA	200	30.76
RHD	300	46.15
SLE	80	12.31
Seronegative	66	10.16
Scleroderma	2	0.31
Polymyositis (PM)	2	0.31
Total	650	100

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Table 2 shows that 55% of the study cases were in middle ages (31 50 years).

Table 2: Distribution of Rheumatoid Arthritis patients by age group in Military hospital, Sana'a, Yemen 2019-2021(n=100)

Age group	Frequency	%	P value
≤ 30 years	22	22	
31-50 years	55	55	
51-60	18	18	< 0.05
> 60 years	5	11	
Total	100	100	
Age (mean ± SD)	40.5± 15.5	years	
Age (Median + range)	40 (20-70)		

Table (3) shows that most cases were females (89%), with female to male ratio of 8:1 which is statistically significant (P < 0.05)

Table 3: Distribution of Rheumatoid Arthritis patients by sex in Military Hospital, Sana'a, Yemen 2019-2021(n=100)

Sex	Frequency	%	P value
Female	89	89	
Male	11	11	< 0.05
Total	100	100	

Most Rheumatoid Arthritis patients in Military hospital where from Sana'a followed by Sa'adah (Table 4)

Table 4: Distribution of Rheumatoid Arthritis patients by residence in Military hospital, Sanaa, Yemen 2019-2021(n=100)

City	Frequency	%
Sana'a	60	60
Sa'adah	11	11
Ibb	6	6
Al Baidah	6	6
Amran	5	5
Dhamar	7	7
Raymah	3	3
Taiz	2	2
Total	**100**	**100**

Only 5% of patients had a Family history of RA (Table 5)

Table 5: Distribution of Rheumatoid Arthritis patients by family history of RA in Military hospital, Sana'a, Yemen 2019-2021(n=100)

Family history of RA	Frequency	%
Yes	5	5%
No	95	95%

Table (6) shows the distribution of lab results among Rheumatoid Arthritis patients in Military hospital, Sanaa, Yemen 2019-2021. Results in the present study show that the frequency of anti-CCP in RA patients was 98% (Table 6).

Table 6: Distribution of lab results among Rheumatoid Arthritis patients in Military hospital, Sanaa, Yemen 2019-2021(n=100)

Investigation	Frequency	%
RF	57	57%
Anti-CCP	98	98%
Elevated ESR	100	100%

The most associated comorbidities were HTN, DM and gout (Table 7).

Table 7: Distribution of comorbidities among Rheumatoid Arthritis patients in Military hospital, Sana'a, Yemen 2019-2021(n=100)

Comorbidity	Frequency	%
HTN	23	23
DM	11	11
Gout	5	5
SLE	3	3
Hypothyroidism	3	3
HBV	2	2
HCV	1	1
Psoriasis	1	1
Vitiligo	1	1
TB	1	1
B12 deficiency	1	1

About two thirds of patients had a normal echo exam, while the most diagnosed disease at echo exam was hypertensive heart disease (HHD) followed by rheumatic heart disease (Table 8).

Table 8: Distribution of echocardiographic results among Rheumatoid Arthritis patients in Military hospital, Sanaa, Yemen 2019-2021(n=100)

Diagnosis	Frequency	%
Normal	64	64
HHD	23	23
RHD	11	11
IHD	2	2

Table 9 shows that male patients with RA had more than four odds to have another autoimmune disease which is statistically significant (P = 0.011)

Table 9: association of other autoimmune diseases by sex among Rheumatoid Arthritis patients in Military hospital, Sana'a, Yemen 2019-2021(n=100)

Parameter	Autoimmune disease			OR%(CI)	P value*
	Yes	No	Total		
Male	5	6	11	4.87(1.29-18.32)	0.011
Female	13	76	89		

* X^2 test; P value significant below 0.05

Discussion

Rheumatoid arthritis (RA) is the most common type of autoimmune arthritis. In spite of the low prevalence of RA, the high disability and morbidity with the wide complications that accompanythe disease put it high on the list of autoimmune diseases burden. The present cross-sectional study cohort comprised 650 adults with a history of chronic arthritis

complaints who attended the Military Hospital for management,

where the prevalence of RA was 31%, coming next after RHD (Table 1), but first among those above 50 years old. A similar result was reported by a previous study in Yemen which found that RA is one of the most frequent autoimmune diseases (ADs) among Yemeni patients with a steady rise in the frequency of ADs over the period 2014-2017 in Sana'a city [30]. Regional and global variations in the incidence and prevalence of RA were reported but mostly with increasingly trend patterns [10, 25, 31-34].

Regarding sex variation, in the MENA regions, many studies reported higher female prevalence of ADs, including RA, with F: M prevalence ratio ranging from 1.3:1 to 12.5:1[32-35]. Similarly, this study discovered a higher proportion of females (91%) with RA compared to male (11%) with the ratio of 8:1 (Table 3), which was higher than what was reported previously among RA patients in Yemen (4:1) [30] and suggesting notable differences from the global average of 2:1 [31].

More than half of the cases were in middle ages (31-50 years) (Table 2), which is consistent with what was reported through literature [9, 18, 30, 32, 33]. The age of early diagnosis of RA is varied between developing and developed countries, mainly due to differences in health services access, availability of diagnostics, and awareness among patients. Ethnicity also plays role in the progression and modality of age presentation among patients [15].

Most cases of RA in this study were from urban areas (Table 4), which is in consistent with what was reported in Yemen [30], regionally [32, 33], and globally [10, 25, 31, 34, 35]. This may be due to better access and higher awareness for those from urban area

The most associated comorbidities were HTN, DM and gout. Similarly, a study in

SA reported hypertension (26.7%) and diabetes mellitus (18.7%) as the most encountered comorbidities [36]. Another study implicated increased cardiovascular events among RA patients [37].

A previous study in Yemen showed the coexistence of ADs in Yemeni patients, with the most frequent concurrence between ADs was between SLE and RA (55.6%), as well as AIH and AIG (16.7%) [30]. Similarly, SLE and Hypothyroidism were the most frequent autoimmune diseases that coexist among this study patient (Table 7). These diseases share a similar mechanism of disturbed human autoimmunity by the presence of circulating autoantibodies, increasing concentration, and range of inflammatory mediators [38].

Autoantibodies were seen among the present study patients, with 98% and 57%. of patients showing Anti-CCP and RF, respectively. ESR was elevated among all patients (Table 6).

A province study found that disease activity and RF positivity play an important risk factor for ischemic heart disease in RA [39], while another study found no significant independent associations between characteristics of RA disease and ventricular function, although echocardiographic screening may have clinical value in identifying subclinical ventricular dysfunction, especially in older RA patients [40]. In the present study, echocardiographic screening showed that about a third of RA patients had cardiac disease manifestations. The most common findings were for HHD (23%) and RHD (11%) (Table 8), with no significant associations with RA, which may be due to association with older ages of patients and other comorbidities seen among them as HTN, DM and RHD.Patients who flared had significantly worse outcomes [41].

Over-use of joints was identified as the most common cause of a flare [41, 42].

In this study, most patients presented with disease exacerbations of RA, and among them, 80% had vitamin D deficiency (Table 9). Previous work found that a low Vit D level was not identified to be a risk factor for RA severity or flare ups; although not statistically significant, Vit D treatment might be clinically effective [43] Furthermore, among those with exacerbations, 40% had infections (mainly UTI) and 30% had hypocalcemia. Stopping medications was associated with disease flares in 18% of patients.

Conclusion

● RA is one of the common ADs in Yemen.
● The disease is mostly affecting females in middle age.
● Concurrence between RA with other ADs was seen especially SLE (overlap syndrome) and hypothyroidism.
● Most patients with exacerbations showed low Vit D and calcium levels.
● Echocardiographic screening showed associated cardiac disease manifestations of HHD and RHD with IHD evidence, which most attributed to the comorbidities of HTN and DM.

Recommendations

● Standardizing management of RA cases according to the updated guidelines internationally to decrease severity and complications and to obtain remission of disease [20,21].
● Raising awareness among doctors and patients about good follow up and treatment for the major exacerbation factors for the disease.
● Further population-based studies for the assessment of the incidence and prevalence of RA and the environmental factors associated with the trending increase in prevalence in Yemen are recommended.

Conflict of Interest

The authors declare that they have no competing interests

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