Cardiovascular Disease and Risk Factors among Patients with Rheumatoid Arthritis in a Tertiary Government Hospital in the Philippines

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ABSTRACT

Background. Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement. Comorbidities are highly prevalent in patients with RA, in particular cardiovascular disease (CVD), which is responsible for over 50% of premature deaths. This study aimed to describe cardiovascular diseases and their risk factors among patients with rheumatoid arthritis in the Philippine General Hospital (PGH).

Objective. To describe cardiovascular (CV) diseases and their risk factors among patients with rheumatoid arthritis.

Methods. A retrospective descriptive cross-sectional study was done in the University of the Philippines – Philippine General Hospital (UP-PGH) inpatient and outpatient services. The study included patients 18 years old and above diagnosed with RA and fulfills the 1987 American College of Rheumatology or 2010 American College of Rheumatology-European League Against Rheumatism (ACR/EULAR) classification criteria with no overlap features with other autoimmune connective tissue diseases and with complete records of the information required for the study from January 2019-December 2022. The primary outcomes of interest were the prevalence of CV diseases and CV risk factors. Descriptive statistics were used to summarize the data.

Results. There were 123 patients in the study, 93.4% outpatients, and 95.1% females, with a mean age and disease duration of 51.3 and 9.8 years, respectively. Disease activity was moderate in 35% and high in 9.7%, based on disease activity score (DAS 28) or clinical disease activity index (CDAI) scores. Methotrexate (54%) was the most commonly used conventional synthetic disease-modifying antirheumatic drug (csDMARD). Glucocorticoid use was observed in 51.2%. None of the patients were receiving a biologic DMARD. There were 24 (19.5%) patients with CV diseases, namely myocardial infarction, heart failure, and stroke. There were 87 (70%) patients with at least one CV risk factor and 62 (50.4%) with multiple risk factors. The risk factors identified were: dyslipidemia (43.1%), hypertension (40.7%), elevated body mass index (35.7%), and diabetes mellitus (15.4%). There were five deaths in the hospitalized patients (4%), one due to a myocardial infarction.

Conclusion. The majority (70%) in our cohort had at least one CV risk factor, 19.5% had an identified CV disease, and one died from a myocardial infarction. Dyslipidemia was the most common CV risk factor. The high proportion of patients with CV disease and CV risk factors highlights the need to add the screening and management of CV diseases and risk factors as a priority among patients with rheumatoid arthritis.

Keywords: cardiovascular disease, rheumatoid arthritis, Filipino, Asian, traditional risk factor, disease activity

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement.[1] Comorbidities, cardiovascular disease (CVD) in particular, are highly prevalent and responsible for over 50% of premature deaths.[2,3] CVD lowers life expectancy by 3 to 10 years and increases the mortality rate compared to the general population.[4] This association seems to be due to the increased occurrence of classical cardiovascular disease risk factors and comorbidities like smoking, obesity, hypertension, diabetes, metabolic syndrome, and the inflammatory burden from rheumatoid arthritis itself.[5]

There is mounting evidence supporting the role of inflammation in atherothrombosis. Interleukin 1β (IL-1β), a pro-inflammatory cytokine, plays multiple roles in the development of atherosclerotic plaques, such as induction of procoagulant activity, promotion of monocyte and leukocyte adhesion, and growth of vascular smooth muscle cells.[6] Thus, aside from traditional risk factors, the excess inflammation present in rheumatoid arthritis has been hypothesized to be a determinant of the observed higher CVD risk in RA either directly or through its impact on CVD risk factors.[7]

A 2005 survey by the Philippine Heart Association, conducted among a hospital-based Filipino population, found that hypertension was the most common cardiovascular condition (38.6%), followed by stroke (30%), coronary artery disease (17.5%), and heart failure (10.4%).[8] Meanwhile, in the general population, the 2012 survey conducted by the Food and Nutrition Research Institute (FNRI) reported the national prevalence rates for coronary artery disease (1.1%), cerebrovascular disease (0.9%), and peripheral arterial disease (1.0%). Cardiovascular risk factors in the general Filipino population included dyslipidemia (72%), smoking (31%), obesity (4.9% based on BMI, abdominal obesity in 10.2% of men and 65.6% of women), and diabetes (3.9%).[9] These figures underscore the high prevalence of CVD and its risk factors in the Filipino general population.

Although the increasing risk of CVD in the general population and RA patients, in particular, has been known for decades, patients with RA receive poorer CVD preventive care than other high-risk patients. There is an unmet need for improved CVD screening and preventive measures for patients with RA.[10] This study aimed to describe cardiovascular diseases and their risk factors among patients with rheumatoid arthritis in the Philippine General Hospital (PGH). We hypothesized that patients with RA would have a higher prevalence of cardiovascular risk factors and established cardiovascular disease compared to the general Filipino population. Describing the risks among our patients will improve the awareness and efforts of both patients and physicians to bring them under control.

MATERIALS AND METHODS

Study Design, Setting, and Population

This retrospective descriptive cross-sectional study involved a medical records review of patients with rheumatoid arthritis at the Philippine General Hospital from January 2019 to December 2022. Ethical approval was obtained before the conduct of the study. The following patients were included: 1) age 18 years old and above, 2) diagnosed by a rheumatologist with RA, 3) classified as RA based on the 1987 American College of Rheumatology (ACR) or 2010 American College of Rheumatology-European League Against Rheumatism (ACR/EULAR) classification criteria, 4) no overlap features with other autoimmune connective tissue diseases, and 5) with complete information as required by the study. A total enumeration of patients in the Division of Rheumatology patient census who matched the inclusion criteria was performed.

Data Collection and Analysis

We collected sociodemographic (age, gender, employment, family history) and clinical data. The clinical data included smoking history, the rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) tests that were recorded on diagnosis, the total disease duration, disease activity, RA and other medications, comorbidities, presence of CVD, and CVD risk factors as recorded on the latest clinical encounter. Disease activity was assessed using either the DAS28 or the CDAI, depending on data availability. Disease remission was defined as DAS28 ≤2.6; low disease activity as >2.6–3.2; moderate disease activity as >3.2–5.1; and high disease activity as >5.1. Alternatively, using the CDAI, remission was defined as a score ≤2.8; low disease activity as >2.8–10; moderate disease activity as >10–22; and high disease activity as >22.

CVD was defined as a chart diagnosis of ischemic heart disease (IHD), angina pectoris, myocardial infarction, coronary artery disease, heart failure, or cerebrovascular disease (ischemic or hemorrhagic stroke). The risk factors of interest were smoking, hypertension, diabetes mellitus, dyslipidemia, and obesity. Hypertension was defined as a recorded clinical diagnosis or the use of antihypertensive medications. Diabetes mellitus diagnosis was based on the recorded clinical diagnosis, a history of fasting blood sugar elevation ≥126 mg/dL, and current or previous use of antidiabetic medications. Impaired fasting glucose was based on a physician-documented diagnosis or a recorded fasting blood sugar level of 100 to 125 mg/dL. Dyslipidemia was defined as a recorded clinical diagnosis or documentation of any of the following: LDL ≥130 mg/dL, HDL <40 mg/dL for men or <50 mg/dL for women, triglycerides ≥150 mg/dL, or current or previous use of lipid-lowering agents.

Descriptive statistics, such as mean and standard deviation, were used to present the continuous variables, and frequency and percentage were used for categorical

data. There were five patients without any of the defining features of diabetes mellitus who were labeled as unclassified as to the presence of this risk factor. Likewise, there were 18 patients with no defining features of dyslipidemia who were unclassified. These unclassified patients were excluded from the computation of the proportion of these risk factors. These unclassified patients were still included in the study, as the absence of such historical data and laboratory tests was a relevant observation. In the final reporting, only available and clearly documented data were counted and summarized. Imputation or any other statistical analysis was not done.

RESULTS

Patient Characteristics

There were 159 patient charts reviewed, but 36 did not meet the inclusion criteria. The study included 123 patients (Table 1), who were predominantly outpatients (93.4%),

Table 1. Characteristics of RA Study Population (n = 123)

Characteristics	Total population, N = 123	With CVD, N = 24	Without CVD, N = 99
	Mean ± SD or frequency (%)		
Current age, in years	51.31 ± 13.40	59.2 ± 6.8	51.5 ± 13.40
Age at RA diagnosis, in years	42.21 ± 13.1	42.8 ± 9.23	40.1 ± 12.9
RA disease duration (years)	9.78 ± 9.4	10 ± 9.2	9.3 ± 9.7
Female	117 (95.1%)	23 (95.8%)	94 (94.9%)
Employment			
Never	25 (20.3%)	1 (4.1%)	24 (24.2%)
Previously employed	78 (63.4%)	22 (91.6%)	56 (56.5%)
Currently employed	20 (16.3%)	1 (4.1%)	19 (19.1%)
Family history			
Hypertension	78 (63.4%)	15 (62.5%)	63 (63.6%)
Cardiovascular disease	19 (15.4%)	10 (52.6%)	9 (9.0%)
Diabetes mellitus	33 (26.8%)	16 (66.6%)	17 (17.1%)
Rheumatoid arthritis	10 (8.1%)	1 (4.1%)	9 (9.0%)
Current disease activity scores			
DAS 28 (n=111)	3.53 ± 0.95	3.2 ± 1.03	3.4 ± 0.98
CDAI (n=12)	10.93 ± 6.04	8.66 ± 5.13	10.1 ± 6.23
Level of disease activity			
Remission	17 (13.8%)	3 (12.5%)	14 (14.1%)
Low	51 (41.5%)	14 (58.3%)	37 (37.3%)
Moderate	43 (35%)	4 (16.6%)	39 (39.3%)
High	12 (9.7%)	3 (12.5%)	9 (9.0%)
Autoantibody tests			
RF positive (n=120)	100 (81.3%)	22 (91.6%)	78 (78.7%)
ACPA positive (n=52)	17 (13.8%)	4 (16.6%)	13 (13.1%)
RF and ACPA negative	13 (10.5%)	2 (8.3%)	11 (11.1%)
Other comorbidities of patients			
Osteoarthritis	40 (32.5%)	11 (45.8%)	29 (29.2%)
Tuberculosis	20 (16.2%)	4 (16.6%)	16 (16.1%)
Malignancy	12 (9.7%)	1 (4.1%)	11 (11.1%)
Symptomatic treatment			
NSAIDs	24 (19.5%)	3 (12.5%)	21 (21.2%)
Paracetamol	19 (15.4%)	1 (4.1%)	18 (18.1%)
Opiates	13 (10.6%)	0 (0%)	13 (13.1%)
Steroids	63 (51.2%)	10 (41.6%)	53 (53.5%)
Disease-modifying drugs			
Methotrexate	67 (54%)	12 (50%)	55 (55.5%)
Hydroxychloroquine	18 (14.6%)	5 (20.8%)	13 (13.1%)
Combination (MTX + HCQ)	32 (26%)	4 (16.6%)	28 (28.2%)
None	6 (4%)	3 (12.5%)	3 (3.0%)
Prior use of other csDMARD (leflunomide, sulfasalazine)	2 (1.6%)	0 (0%)	2 (2.0%)
Prior use of tsDMARD or bDMARD therapy	20 (16.3%)	2 (8.3%)	18 (18.1%)

RA – rheumatoid arthritis, DAS – disease activity score, CDAI – clinical disease activity index, RF – rheumatoid factor, ACPA – anti-citrullinated peptide antibody, csDMARDs – conventional synthetic disease-modifying antirheumatic drugs, tsDMARD – targeted synthetic disease-modifying antirheumatic drugs, bDMARD – biologic disease-modifying antirheumatic drugs

female (95%), middle-aged (mean age 51.3 years), and unemployed (83.7%). Most patients have had a long duration of RA, and nearly half (45%) had moderate to high disease activity. Ninety percent were seropositive, and most of them were RF positive. Most patients (63.4%) had a family history of hypertension, and a few (8.1%) had rheumatoid arthritis.

Overall, those with CVD seemed to be slightly older when they were diagnosed with RA. They were less frequently employed but more commonly previously employed, and had a higher proportion of family history of CVD and diabetes mellitus. They also had a higher proportion of seropositive disease on diagnosis, but with a lower proportion of patients in moderate and high disease activity during the latest disease assessment.

Treatment for Rheumatoid Arthritis

Several forms of pharmacologic symptomatic therapies were given, mostly steroids (51.2%). However, fewer patients with CVD were on steroids. Disease-modifying anti-rheumatic drug (DMARD) treatment given as methotrexate monotherapy was observed in 67 patients (54%), and combination methotrexate-hydroxychloroquine in 32 (26%). None of the patients were on other conventional DMARDs, such as leflunomide or sulfasalazine, or targeted DMARDs at the time of data collection. Two (1.6%) patients previously took leflunomide, while 20 (16.3%) patients previously used targeted synthetic DMARD (tsDMARD), namely baricitinib or tofacitinib, or biologic DMARD (bDMARD), namely etanercept, abatacept, infliximab, tocilizumab, and golimumab. These drugs were accessed during participation in clinical trials or through government subsidies. Thirteen (10.5%) patients had an adverse reaction to methotrexate, ten (8.1%) of which had transaminitis, and three (2.4%) had cytopenia. Six patients (4.9%) developed Cushing's syndrome, and one patient (0.8%) developed avascular necrosis (AVN) attributed to steroid use. There were no reported adverse events to other RA drugs.

Cardiovascular Disease, Risk Factors, and Treatment

Twenty-four patients (19.5%) had documented cardiovascular disease, which included ischemic heart disease, myocardial infarction, angina, stroke, and heart failure. (Table 2) Patients with CVD were older (mean age 59.2 ± 6.8 vs. 51.5 ± 13.4 years) and had more cardiovascular risk factors than those without. Seventy percent of patients had at least one traditional CVD risk factor, and 48.8% had two or more.

Dyslipidemia was the most prevalent risk factor, present in 43% (53/105) of patients, excluding 18 patients who could not be classified for this risk factor (Table 2).

Table 2. Cardiovascular Disease and Traditional Risk Factors (n=123)

Cardiovascular Disease	Frequency	Percentage
No CV disease	99	80.5
With CV disease	24	19.5
Angina	9	7.3
Myocardial infarction	6	4.9
Heart failure	8	6.5
Stroke	1	0.8
Risk Factors	**With CVD, n = 24 (19.5%)**	**Without CVD, n = 99 (80.5%)**
Dyslipidemia, (n=105)	14 (58.3%)	39 (39.3%)
Hypercholesterolemia	12 (50.0%)	26 (26.2%)
High LDL	10 (41.6%)	16 (16.1%)
Hypertriglyceridemia	3 (12.5%)	15 (15.1%)
Hypertension	17 (70%)	34 (34.3%)
Dysglycemia, (n=118)		
Impaired fasting glucose	4 (16.6%)	8 (8.0%)
Diabetes mellitus	6 (25%)	13 (19.1%)
Smoking	6 (25%)	4 (4.0%)
High BMI		
Overweight	4 (16.6%)	22 (22.2%)
Obese	6 (25%)	12 (12.1%)
Moderate to high disease activity	7 (29.1%)	48 (48.4%)
One traditional risk factor*	1 (4.1%)	14 (14.1%)
Two or more traditional risk factors*	13 (54.1%)	20 (20.2%)
One traditional risk factor* and moderate to high disease activity	2 (8.3%)	8 (8.0%)
Two or more traditional risk factors* and moderate to high disease activity	8 (33.3%)	21 (21.2%)

**Traditional risk factors are dyslipidemia, hypertension, dysglycemia, smoking, and high BMI.*

All the traditional risk factors (dyslipidemia, hypertension, dysglycemia, high BMI, and smoking) were more common in patients with CVD. There were more frequent patients with CVD who had two or more of these traditional risk factors (54.1% versus 20.2%).

Treatment for CVD risk factors was as follows: antihypertensive agents (51, 41.5%), statins (33, 26.8%), hypoglycemic agents (19, 15.4%), and antiplatelet agents (7, 5.7%). Notably, 20 patients with dyslipidemia were not receiving statin therapy.

Among the eight hospitalized patients, five (4%) expired. The causes of death were as follows: septic shock secondary to bacterial infection in two patients (1.6%), critical COVID-19 pneumonia in one patient, underlying malignancy in one patient, and acute myocardial infarction in one patient. The remaining three patients were admitted due to infections that were resolved.

DISCUSSION

Our cohort of 123 patients with RA collected over four years in the Philippine General Hospital was predominantly female and with long-standing seropositive disease. Nearly half (44.7%) of patients had moderate to high RA disease activity. Around 20% had CVD, 70% had at least one traditional CVD risk factor, and 50.4% had two or more.

One notable finding is the low rate of employment (20%) in our patients. This reflects the impact of RA on work participation and is comparable to international studies showing that 44.3% of RA patients in Brazil and 41.7% in Korea remained employed.[11,12] A meta-analysis by Kirkeskov et al. reported lower employment rates in RA patients with longer disease duration and higher disease activity.[13] Health-related problems were the main reasons for non-employment.[11]

Unemployment is associated with an increased risk of cardiovascular disease, including coronary heart disease (CHD) and heart failure. This association is linked to various factors, including stress, unhealthy behaviors like increased smoking and alcohol consumption, and reduced access to healthcare.[14,15] Unemployment leads to isolation and financial difficulties that increase stress and unhealthy coping mechanisms, such as smoking and alcohol consumption, unhealthy diet, and reduced physical activity. These unhealthy behaviors, stress, anxiety, and depression are known risk factors for cardiovascular disease and death.[16] Longer periods of unemployment and multiple job losses have cumulative harmful effects over time.[14]

Almost all of our patients were treated with csDMARD, methotrexate, and/or hydroxychloroquine, combined with low-dose steroids in 50%. Some of our patients, most of them indigent, were intolerant or unresponsive to methotrexate or unable to steadily procure hydroxychloroquine, and they needed to maintain steroids to control joint pain and inflammation. However, this creates a problematic situation in the long term since steroid use, especially when prolonged, is known to predispose to hypertension, obesity, poor glycemic control, and infections, like tuberculosis (TB).[17,18] Physicians and patients must realize that while steroids are low in cost, their continued use may cause more harm than benefit. Rather, DMARDs must be optimized to achieve better health outcomes and minimize steroid use.

Methotrexate and hydroxychloroquine were the only csDMARDs readily available in the Philippines during the period of data collection. Similar to data published from the PGH RA Database and Registry (RADAR) in 2014[19], 10.5% of our patients were methotrexate intolerant, requiring lowering the dose, shifting to the subcutaneous form, or discontinuation. Gastrointestinal adverse effects (nausea, vomiting, abdominal pain, transaminase elevations) were the main reasons for intolerance. Transaminitis is possibly aggravated by coexistent non-alcoholic fatty liver disease (NAFLD) related to diabetes and dyslipidemia.[20]

Although 16% of our patients were able to use tsDMARD or bDMARD in the past while participating in clinical trials or special government subsidy programs, none of the patients were maintaining them. The advent of the pandemic led to the rechanneling of government funds for COVID-19 control and the loss of the RA treatment subsidy. Thus, although our patients with moderate to high disease activity needed second- and third-line targeted therapies, these were not accessible. The high cost and limited access to hydroxychloroquine and bDMARDs, and methotrexate intolerance contributed to the difficulty observed in controlling disease activity in our patients, 45% of whom remain with moderate or worse disease activity.

In general, a higher prevalence of CV risk factors has been observed in RA patients compared to the general population.[21] This was likewise seen in our study, dyslipidemia and hypertension in >40%, and diabetes mellitus and obesity in 14-15%. Nearly all patients received appropriate medications for their comorbid conditions. While our findings are generally aligned with existing literature, some differences were observed. A cross-sectional study in India reported diabetes mellitus and hypertension as the most prevalent CV risk factors[22], while a cohort from Pakistan, showed a higher proportion of dyslipidemia (53.5%)[23]. These differences may be attributed to variations in patient demographics, healthcare access, screening practices, or criteria used to define comorbidities across studies. Moreover, 14% of our patients did not have lipid determination, which may underestimate the true prevalence of dyslipidemia. However, even if we were to assume normal lipid values among those not tested, our cohort still showed a high proportion of dyslipidemia. The rheumatology clinic, therefore, needs to include the lipid profile as one of the priority tests to periodically monitor in our patients with RA.

The interplay between inflammation and cardiometabolic risk in RA is complex. Elevated levels of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), IL-6,

and IL-1, and acute-phase reactants such as CRP have been associated with insulin resistance, endothelial dysfunction, and changes in lipoprotein composition and function.[24] These changes may contribute to accelerated atherosclerosis, even in the presence of seemingly normal or low lipid levels—a phenomenon referred to as the lipid paradox.[24,25] In our study, disease activity was assessed using either the DAS28 or the CDAI, depending on the data available in each patient's medical record. Among those with a recorded DAS28, the majority of scores were calculated using erythrocyte sedimentation rate (ESR) rather than C-reactive protein (CRP). Only nine patients had CRP results available, which limited our ability to assess its association with disease activity and CV risk, an important limitation, given that CRP is a well-established marker of systemic inflammation and has been linked to increased CV risk in RA patients.[26] Future prospective studies with standardized and complete data collection could better evaluate these associations. Additionally, laboratory tests such as lipid profiles and fasting glucose were not always performed at the same time as disease activity assessments. This temporal mismatch may have limited our ability to explore associations between inflammation and cardiovascular risk factors in greater detail.

The presence of CV diseases in our cohort appears relatively high (20% overall, 7.3% angina, 6.5% heart failure, 4.9% myocardial infarction, 0.8% stroke). While direct comparisons should be made cautiously due to differences in study design, methodology, and healthcare settings, it is worth noting that the COMORA study, a large, multicenter, international cohort involving 17 countries, including Japan, Korea, and Taiwan, reported an overall CV event rate of 6%.[2] This is similar to the study by Blum et al., which showed a 1.5-2-fold higher occurrence of CV events in RA compared to the general population and CV events as the leading cause of death.[27] Compared with data from the FNRI, which report a prevalence of coronary artery disease at 1.1% and cerebrovascular disease at 0.9% in the general Philippine population,[9] the observed burden of CV disease in our RA cohort appears higher. This may be attributable to the well-documented association between RA and elevated CV risk, potentially driven by chronic systemic inflammation, the presence of conventional risk factors, and the contributory effects of certain medications such as corticosteroids.

Our findings underscore the importance of a three-prong approach in the management of RA: optimal control of cardiovascular risk factors, control of RA disease activity, and monitoring for the adverse effects of treatment. To achieve this, access to tsDMARDs and bDMARDs needs to improve, and screening and treatment for CV disease and risk factors must be consistent and prioritized.

As a retrospective study conducted at a tertiary government hospital, this work has inherent limitations. Selection bias is possible, as patients with more severe or complex disease may be overrepresented. Inconsistent documentation may also have introduced information bias, though efforts were made to use standardized definitions and extract only clearly recorded data. The lack of synchronized timing between disease activity measures and laboratory results further limits the strength of any associations that could be drawn. These constraints emphasize the need for more robust, prospective data in future research.

CONCLUSION

The majority (70%) in our cohort had at least one CV risk factor and 19.5% had an identified CV disease. Dyslipidemia was the most common CV risk factor. The high proportion of patients with CV disease and risk factors highlights the need to add the screening and management of CV diseases as a priority among patients with rheumatoid arthritis.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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