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ORIGINAL ARTICLE

Comorbidities in Black South Africans with established rheumatoid arthritis

Vikash Lala[1] | Mohammed Tikly[2] | Eustasius Musenge[3] | Nimmisha Govind[2]

[1]Department of Internal Medicine, University of the Witwatersrand, Johannesburg, South Africa

[2]Division of Rheumatology, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa

[3]School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

Correspondence
Nimmisha Govind, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa.
Email: nimmisha.govind@gmail.com

Abstract

Objective: Comorbidities contribute both to morbidity and mortality in rheumatoid arthritis (RA). The aim of the current study was to investigate the prevalence and spectrum of comorbidities in South Africans with established RA.

Methods: A retrospective, consecutive case record review of 500 Black South African patients with established disease of ≥5 years attending a tertiary rheumatology service was performed. Common comorbidities including those listed in the Charlson Comorbidity Score (CCS) were documented.

Results: Most patients, 463 known alive (AG) and 37 known deceased (DG), were female (87%). Mean (SD) age and disease duration were 60 (11.1) and 10.7 (5.0) years respectively, and 98% had ≥1 comorbidities. Median CCS was 2, significantly higher in DG than AG (4 vs 2, $P < .0001$). Despite hypertension (70%) and hypercholesterolemia (47%) being the commonest comorbidities overall and type 2 diabetes (T2D) occurring in 15.4%, clinical cardiovascular events were rare (0.6%). Peptic ulcer disease (odds ratio [OR] = 8.67), congestive cardiac failure (OR = 7.09), serious infections (OR = 7.02) and tuberculosis (OR = 2.56) were significantly more common in DG than AG. Multivariate analysis showed that American College of Rheumatology functional class 3/4 was associated with increased risk for serious infections (OR = 3.84) and tuberculosis (OR = 2.10).

Conclusion: Despite the high burden of cardiometabolic comorbidities in South Africans with established RA, cardiovascular events were rare. Serious infections and tuberculosis, both associated with severe functional disability, are a major cause of morbidity and mortality.

KEYWORDS
Africa, cardiometabolic disorders, comorbidities, infection, rheumatoid arthritis, tuberculosis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of varying severity. Its prevalence is influenced by geographical location and ethnicity. Initially thought to be less common and less severe in sub-Saharan Africa,[1] recent estimates based on medical schemes data suggest a prevalence of RA in South Africa of 0.5%.[2] The disease appears to be more common in urban than rural

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communities. Several recent studies also indicate that RA is often associated with profound disability in South Africans, mainly related to long delays in initiating disease-modifying antirheumatic drug (DMARD) therapy.[3]

With advances in therapy for RA and better control of disease activity, recognition and management of comorbidities have become an important component of improving overall health-related quality of life and mortality.[4-6] In industrialized Western countries, at least 1 comorbidity is present at disease onset in a 3rd of RA patients and 80% of patients during long-term follow-up have, on average, 2 comorbidities.[4,7] Reduced life expectancy in both women and men with RA is related to comorbid cardiorespiratory diseases, infections, hematologic and gastrointestinal diseases.[7] The cross-sectional multicenter COMORA study of RA patients from 17 European, North African, Asian and South American countries showed high rates of ischemic heart disease (IHD), solid tumors, chronic obstructive pulmonary disease and depression,[8] but with significant geographic variation in prevalence and patterns of comorbidities.

The Charlson Comorbidity Score (CCS) and index (CCI) have been widely used to generally assess the burden of comorbidities and predict short to medium term survival rates in a variety of chronic diseases.[9] The CCS is significantly higher in RA patients compared to the general population.[10] Other RA studies using the CCI show that comorbidities lead to increased disability[5] and that the CCI is an independent predictor of mortality in both RA and osteoarthritis.[11]

To date little is known on the prevalence and spectrum of comorbidities associated with RA in sub-Saharan Africa. We therefore undertook a retrospective study of the burden and spectrum of comorbidities in Black urban patients with long-standing established RA attending a tertiary care facility in South Africa. The study was approved by the Human Research Ethics Committee, University of the Witwatersrand (M140882).

2 | METHODS

A retrospective review of 500 consecutive case records of Black RA patients attending a tertiary rheumatology service in Gauteng, South Africa between 1988 and 2014 was performed. Case records of Black patients (defined as self-identification of all 4 grandparents as Black South Africans), fulfilling the 1987 American College of Rheumatology (ACR) classification criteria for RA,[12] ≥18 years at disease diagnosis and follow-up of ≥5 years from diagnosis were selected. The alive/deceased status was based on the status as at end August 2014. The deceased status was further confirmed by the hospital records.

Data extracted from clinical records were demographics, 1991 ACR functional class (FC),[13] extra-articular manifestations, autoantibodies, comorbidities and drug therapy. Anemia, nodulosis, scleritis, cutaneous vasculitis and interstitial lung disease (ILD) diagnosed by high-resolution computed tomography, were recorded as extra-articular manifestations. Autoantibodies included rheumatoid factor (RF) and anti-citrullinated peptide antibodies. Comorbidities included in the CCS were documented.[9] Additional comorbidities that were documented were hypertension, hypercholesterolemia, serious infections, tuberculosis (TB), osteoporosis and history of fragility fractures. Serious infections, excluding TB, were defined as infections necessitating hospital admission and/or parental antibiotics and recorded as a binary, ie, one or more infections per patient. Osteoporosis was defined as a dual-energy X-ray absorptiometry (DEXA) bone scan T score of ≤ −2.5.[14] Gastroscopies and DEXA scans were generally performed only where clinically indicated. Presence of IHD, specifically, myocardial infarction, was based on a documented history in the clinical records. Medical treatment with low-dose oral prednisone (≤7.5 mg), nonsteroidal anti-inflammatory drugs (NSAIDs), traditional DMARDs and biological therapy was documented.

2.1 | Statistical analysis

Data were collected using REDCap electronic data capture tools[15,16] (hosted at University of the Witwatersrand) and exported into Microsoft Excel. Pearson's Chi-square test, and where appropriate the two-tailed Fisher's exact test, were applied to compare differences in frequencies of categorical variables between groups. For continuous variables, the unpaired Student's *T* test or Mann-Whitney test was used, depending on whether data were distributed normally or skewed, respectively. Multivariable logistic analysis was used to determine independent predictors/associations of common comorbidities and mortality. A P value $< .05$ was considered significant. Statistical analyses were done using MedCalc Statistical Software (version 20.008 MedCalc Software Ltd; https://www.medcalc.org.2021).

3 | RESULTS

Clinical and demographic characteristics of the 463 known alive patient group (AG) and 37 known deceased patient group (DG) are shown in Table 1. Most patients were middle-aged women, mean follow-up from diagnosis of 10.7 years, 20% having a smoking history, and 91% RF positive. Anemia was the commonest extra-articular manifestation occurring in almost 80% of patients during follow-up and almost a third had subcutaneous nodules. Anemia, nodulosis and ILD were more common in DG than AG.

Approximately 70% had severe disability (ACR FC 3/4). Most patients were treated with NSAIDs (98.8%), methotrexate (MTX) (95.4%), other DMARDs including sulfasalazine, leflunomide, chloroquine (93.0%) and low-dose oral prednisone (85.8%). A minority of patients were treated with biologics (3.6%). Eighteen percent of patients had rheumatic-based surgery, significantly higher in the DG than AG (odds ratio [OR] = 3.53) and especially for arthroplasty (OR = 3.16).

There were 98% of patients who had at least 1 comorbidity. As shown in Table 2, median CCS was 2 overall and when corrected for

TABLE 1 Demographic and cumulative clinical features and drug therapy in 500 South Africans with established rheumatoid arthritis

Variable	All patients (500) n (%)	Alive group (463) n (%)	Deceased group (37) n (%)	OR (95% CI)	*P* value
Age in y, mean (SD)	60.0 (11.1)	59.7 (11.1)	64.0 (10.7)	-	.02
Female	435 (87)	406(87.7)	29 (78.4)	0.51 (0.02, 1.17)	.12
Follow-up duration in y, mean (SD)	10.7 (5.0)	10.6 (4.9)	12.3 (5.6)	-	.05
Smokers (%)	82/395 (20.8)	73/367 (19.9)	9/28 (32.1)	1.91 (0.83, 4.39)	.15
American College of Rheumatology functional class 3/4	348 (69.6)	312 (67.4)	36 (97.3)	17.42 (2.37, 128.29)	.0001
Extra-articular disease					
Anemia	391 (78.2)	357 (77.0)	34 (91.9)	3.37 (1.01, 11.18)	.04
Nodulosis	155 (31.0)	137 (29.6)	18 (48.6)	2.25 (1.15, 4.43)	.02
Scleritis	17 (3.4)	17 (3.7)	0 (0.0)	0.67 (0.09, 5.16)	1.00
Interstitial lung disease	16 (3.2)	11 (2.4)	5 (13.5)	6.42 (2.10, 19.61)	.004
Systemic vasculitis	7 (1.4)	5 (1.1)	2 (5.4)	5.23 (0.98, 27.96)	.10
Autoantibodies, n positive/n tested (%)					
Rheumatoid factor	455/500 (91.0)	421/463 (90.9)	34 (91.9)	1.13 (0.33, 3.84)	1.00
Anti-citrullinated peptide antibodies	305/376 (81.1)	298/366 (81.4)	7/10 (70.0)	0.53 (0.13, 2.11)	.41
Drug therapy, ever					
NSAIDs	494 (98.8)	457 (98.7)	37 (100.0)	1.76 (0.21, 14.73)	.99
Methotrexate	477 (95.4)	441 (95.2)	36 (97.3)	1.80 (0.24, 13.71)	.72
Other synthetic DMARDs	465 (93.0)	428 (92.4)	37 (100.0)	0.33 (0.44, 2.48)	.35
Prednisone	429 (85.8)	394 (85.1)	35 (94.6)	3.07 (0.72, 13.04)	.14
Cyclophosphamide	11(2.2)	9 (1.9)	2 (5.4)	2.88 (0.60, 13.86)	.19
Biologics					
Tumor necrosis factor inhibitors	5 (1.0)	5 (1.1)	0 (0.0)	0.48 (0.60, 4.13)	.99
Rituximab	13 (2.6)	13 (2.8)	0 (0.0)	1.15 (0.15, 9.00)	1.00
Rheumatic surgery, any	90 (18)	75 (16.2)	15 (40.5)	3.53 (1.75, 7.11)	.0002
Soft-tissue procedures/arthrodectomy	23 (4.6)	19 (4.1)	4 (10.8)	2.83 (0.91, 8.81)	.08
Arthroplasty	73 (14.6)	61 (13.2)	12 (32.4)	3.16 (1.51, 6.62)	.001

Abbreviations: CI, confidence interval; DMARDs, disease-modifying anti-inflammatory drugs; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

age, was significantly higher in DG than AG (median [interquartile range], 4 [3, 6] vs 2 [1, 3], $P < .0001$, respectively). Hypertension (70%), hypercholesterolemia (47.4%) and type 2 diabetes (T2D) (15.4%) were the most common comorbidities. Peptic ulcer disease (PUD), congestive cardiac failure (CCF), peripheral vascular disease, liver disease, serious infections and TB were significantly more common in DG than AG. None of the TB cases had prior exposure to tumor necrosis factor inhibitors. Despite the high prevalence of hypertension, hypercholesteremia and T2D, myocardial infarction was documented in only 3 patients (0.6%), none resulting in death. Malignancies were rare: 3 patients each with cervical and breast carcinoma and 1 patient each with prostate carcinoma, renal cell carcinoma and multiple myeloma. There were no cases of lymphoma.

Documented causes of death were available in only 17 of 37 cases: severe sepsis (n = 4), ILD (n = 3), chronic obstructive pulmonary disease with cor-pulmonale (n = 2), CCF (n = 2), pulmonary TB with sepsis (n = 1), pulmonary embolus with sepsis (n = 1), anti-TB drug-induced liver injury (n = 1), post-TB bronchiectasis with cor-pulmonale (n = 1), colonic perforation (n = 1) and cervical cancer (n = 1).

Table 3 shows multivariate logistic regression analysis. Serious infections and TB were independently associated with each other. Other predictors of serious infections were severe functional disability, history of rheumatic surgery (soft-tissue and/or arthroplasty), and vasculitis. Age and diabetes were associated with hypertension. TB was independently associated with ILD and severe functional disability; CCF was independently associated with increasing age and ILD.

Compared to the known AG, patients who died had a significantly higher CCS (OR = 1.68 [1.29, 2.20]), more likely to have severe functional disability (OR = 4. 21 [1.73, 10.28]), nodulosis (OR = 2.28 [1.00, 5.17]) and prednisone use (OR = 3.76 [1.59, 8.88]). CCF

TABLE 2 Comorbidities in 500 South Africans with established rheumatoid arthritis

Comorbidity	All patients (500) n (%)	Alive group (463) n (%)	Deceased group (37) n (%)	OR (95% CI)	*P* value
Charlson comorbidities					
Peptic ulcer disease	73/114 (64.0)	60/100 (60.0)	13/14 (92.9)	8.67 (1.09, 68.87)	.02
Liver disease: mild	11 (2.2)	8 (1.7)	3 (8.1)	5.02 (1.27, 19.79)	.04
Diabetes mellitus	77 (15.4)	71 (15.3)	5(13.5)	0.86 (0.33, 2.29)	.82
Congestive heart failure	33 (6.6)	23 (5.0)	10 (27.0)	7.09 (3.07, 16.38)	<.0001
Cerebrovascular disease	14 (2.8)	11 (2.4)	3 (8.1)	3.63 (0.97, 13.62)	.08
Hemiplegia	7 (1.4)	5 (1.1)	2 (5.4)	5.23 (0.98, 27.96)	.09
Peripheral vascular disease	3 (0.6)	1 (0.2)	2 (5.4)	26.40 (2.34, 298.37)	.02
Clinical cardiovascular events	3 (0.6)	3 (0.6)	0 (0.0)	0.30 (0.03, 2.73)	.31
COPD	7 (1.4)	5 (1.1)	2 (5.4)	5.23 (0.98, 27.96)	.09
HIV infection	44/472 (9.3)	41/446 (91.2)	3/26 (11.5)	1.29 (0.37, 4.48)	.72
Renal failure, moderate/severe	33 (6.6)	29 (6.3)	4 (10.8)	1.8 (0.60, 5.40)	.29
Malignancies	9 (1.8)	7 (1.5)	2 (5.4)	3.72 (0.75, 18.60)	.14
Charlson comorbidity score[a]	2 (1, 3)	2 (1, 3)	4 (3, 6)-	-	<.0001
Other comorbidities					
Hypertension	350 (70.0)	324 (70.0)	26 (70.3)	1.01 (0.49, 2.11)	1.00
Hypercholesterolemia	221/466 (47.4)	209/443 (47.2)	12/23 (52.2)	1.22 (0.53, 2.83)	.67
Osteoporosis	62/132 (47.0)	58/126 (46.0)	4/6 (66.7)	2.35 (0.40, 18.75)	.42
History of fractures	39 (7.8)	33 (7.1)	6 (16.2)	2.52 (0.98, 6.48)	.06
Serious infections	56 (11.2)	41 (8.9)	15 (40.5)	7.02 (3.38, 14.57)	<.0001
Tuberculosis	53 (10.6)	45 (9.7)	8 (21.6)	2.56 (1.11, 5.94)	.03

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; OR, odds ratio.
[a]Median (interquartile range) and corrected for age.

(OR = 4.73 [1.65, 13.62]) and serious infections (OR = 4.05 [1.65, 9.95]) were more common in the DG and in 2 and 6 patients were the immediate known causes of death, respectively.

4 | DISCUSSION

Like studies in other populations, comorbidities were common in this cohort of largely indigent Black South Africans with established RA. Almost all patients had at least 1 comorbidity. Hypertension was the commonest comorbidity in almost 3 quarters of patients and about 10% had TB and/or human immunodeficiency virus (HIV) infection.

A recent study of privately insured patients in South Africa, based on a medical claims database, showed hypertension, dyslipidemia, hypothyroidism and T2D to be the most common comorbidities.[2] Although not strictly comparable in terms of design and ascertainment of comorbidities, our findings are mostly similar with respect to the age of the patients and spectrum of comorbidities except that IHD, serious infections and HIV were not specifically documented in the previous study. Hypertension was significantly more common in the present cohort (70%) compared to a recent study in the general Soweto population (47.5%).[17] The profile of comorbidities observed in the present study is comparable to that of RA patients in the Philippines, a developing country like South Africa, in which the prevalence of hypertension (27%), TB (13.1%) and PUD (7.5%) were relatively common, but with low prevalence of IHD (1.6%).[18]

Over the last 2-3 decades there has been increasing public awareness and active screening for chronic diseases like hypertension and diabetes at primary healthcare clinics in South Africa. Hypertension has been identified as a major public health priority. Similar to our findings, community-based studies of cardiometabolic comorbidities showed that the prevalence of hypertension, hypercholesterolemia and T2D were 56%, 39% and 9%, respectively.[17,19,20] Like in the Heart of Soweto Study[17] where ischemic cardiomyopathy was uncommon and less frequent than idiopathic cardiomyopathy, IHD was rare in our study. The rarity of IHD in Black South Africans in spite of traditional cardiovascular risk factors, has previously been well documented. An interethnic study of RA showed that traditional and non-traditional cardiovascular risk factors are consistently and independently related to carotid artery atherosclerosis in White but not Black South Africans with RA.[21] These findings highlight global interethnic differences in the risk for IHD in patients with RA. Similarly, the prevalence of IHD

TABLE 3 Independent predictors/associations of major comorbidities and death in 500 South Africans with established rheumatoid arthritis

Variable	OR (95% CI)	*P* value
Serious infections		
Tuberculosis	5.25 (2.57, 10.70)	<.0001
ACR functional class 3/4	3.84 (1.92, 7.69)	.0001
Rheumatic surgery, any	2.14 (1.06, 4.31)	.03
Vasculitis	6.19 (1.10, 34.70)	.04
Tuberculosis		
Serious infection	5.31 (2.60, 10.83)	<.0001
Interstitial lung disease	4.68 (1.43, 15.29)	.01
ACR functional class 3/4	2.10 (1.00, 4.41)	.049
Congestive cardiac failure		
Age	1.08 (1.04, 1.12)	.0001
Interstitial lung disease	4.88 (1.40, 16.99)	.01
Hypertension		
Age	1.06 (1.04, 1.09)	<.0001
Diabetes	2.31 (1.07, 5.01)	.03

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; OR, odds ratio.

in patients from the COMORA study which were mainly from developed countries was much higher (5%) compared to this study (0.6%).

In contrast, serious infections and TB were a major burden, with serious infections being an independent risk factor for mortality. Serious infections occurred more commonly in patients with TB, severe functional disability, vasculitis and those who underwent rheumatic surgery. The increased incidence of serious infections is well documented in RA[22,23] as is the association with premature death.[24,25] TB is a major public health challenge and South Africa currently globally ranks as one of the countries with the highest prevalence.[26,27,28] As in the case of serious infections, TB was associated with severe disability and ILD. The latter might have been the result of post-TB lung scarring rather than a predisposing factor.

Apart from ACR FC 3/4, a measure of severe disability, being associated with both serious infections and TB, it was the strongest single independent factor associated with mortality, consistent with several previous studies. Wolfe et al. found, for every grade increase in ACR FC, the risk of death increased 24.1% and similarly, Pincus et al.[29] showed that the 5-year survival rates for RA patients with a FC 4 were comparable to those with triple-vessel coronary artery disease and stage 4 Hodgkin disease.

While CCS were higher in patients who died, the Charlson instrument has limitations in the setting of RA in Africa since it does not include important and common comorbidities like TB and serious infections. South Africa, like many other countries in sub-Saharan Africa, has a huge burden of infectious diseases[30] in the general population. Moreover, corticosteroids and DMARDs are known to increase the risk of infections in RA patients who have inherently compromised immunity.

Prednisone use was associated with mortality, similar to a previous retrospective study of electronic medical records in which prednisone dose higher than 5 mg was associated with all-cause mortality in RA.[31] Corticosteroid use, apart from increasing the risk of IHD, hypertension, osteoporosis and infections, might be a surrogate of ongoing refractory RA necessitating its prolonged use to control disease activity.

There are several limitations to the study. The retrospective nature of this study is a major shortcoming with respect to missing data and inconsistences in documenting clinical problems in case records. Moreover, improvement in early detection of comorbidities like osteoporosis and PUD with the greater availability of DEXA and gastroscopies over time might have previously underestimated these comorbidities. Lack of more contemporary data is a further limitation. The small number of deceased patients and inability to ascertain the causes of death in more than half of the known deaths made it difficult to determine with certainty the relationship of comorbidities and death. Also, we were unable to quantify the cumulative prednisone dose and its relationship with comorbidities. Because of resource constraints, patients are not routinely screened for IHD and hence the actual prevalence might be higher.

Notwithstanding these limitations, our findings provide new insights into the spectrum and burden of comorbidities in Black indigent South Africans with established RA. Despite the high burden of cardiometabolic comorbidities, myocardial infarction was rare. On the other hand, serious infections and TB, both associated with severe functional disability, were a major cause of morbidity and mortality. There is a need for prospective longitudinal studies of incident RA cases to better define the total burden of comorbidities and overall cost of treating RA in sub-Saharan Africa.

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CONFLICT OF INTEREST

The authors declare no competing interest.

AUTHOR CONTRIBUTIONS

MT, VL, EM and NG contributed substantially to conception and design, acquisition of data, or analysis and interpretation of data, drafting of the article and the final approval of the version to be published. In addition, EM contributed substantially to the statistical analysis.

ORCID

Nimmisha Govind https://orcid.org/0000-0003-2900-1042

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