Trends of Cardiac Complications in Patients With Rheumatoid Arthritis: Analysis of the United States National Inpatient Sample; 2005-2014

Dhrubajyoti Bandyopadhyay, MBBS, MD,
Upasana Banerjee, MBBS, MPH,
Adrija Hajra, MBBS, MD,
Sandipan Chakraborty, MBBS, MD,
Birendra Amgai, MD, Raktim K. Ghosh, MBBS, MD,
Faris I. Haddadin, MD, Vivek A. Modi, MBBS,
Kaushik Sinha, PhD, Wilbert S. Aronow, MD,
Prakash Deedwania, MD, and Carl J. Lavie, MD

Abstract: ***Background*: Rheumatoid arthritis (RA) is a chronic inflammatory condition. Chronic inflammation is associated with atherosclerosis, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease. But sparse data are available regarding the trends of cardiovascular diseases and complications in RA. We conducted a National Inpatient Sample database analysis to demonstrate the trends of cardiac complications in patients with RA.** ***Methods*: We used National Inpatient Sample data from 2005 to 2014 to identify admissions with the diagnosis of RA and identified who had associated cardiovascular complications also. The International Classification of Diseases-9th Revision-Clinical Modification codes were**

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used for the diagnoses of RA; congestive heart failure (CHF), acute myocardial infarction (AMI), and atrial fibrillation (AF). *Results*: A statistically significant increasing trend of AMI, CHF, and AF was found. Independent predictors of mortality in RA patients with AMI were age (OR 1.03, CI 1.02-1.04; $P < 0.001$), COPD (OR 1.67, CI 1.40-2.00; $P < 0.001$), cerebrovascular disease (OR 2.207, CI 1.71-2.86; $P < 0.001$), renal disease (OR 1.42, CI 1.16-1.75; $P = 0.001$), and alcohol abuse (OR 2.73, CI 1.73-4.32; $P < 0.001$). Independent predictors of mortality in RA patients with CHF were age (odds ratio [OR] 1.02, confidence interval [CI] 1.017-1.024; $P < 0.001$]), COPD (OR 1.09, CI 1.01-1.18; $P = 0.023$), cerebrovascular disease (OR 1.67, CI 1.44-1.95; $P < 0.001$), renal disease (OR 1.16, CI 1.07-1.27; $P = 0.001$). Independent predictors of mortality in RA patients with AF were age (OR 1.02, CI 1.02-1.03; $P < 0.001$), race (OR 1.16, CI 1.02-1.31; $P = 0.022$), COPD (OR 1.56, CI 1.42-1.71; $P < 0.001$), peripheral arterial disease (OR 1.34, CI 1.16-1.53; $P < 0.001$), cerebrovascular disease (OR 2.27, CI 1.0-2.58; $P < 0.001$), renal disease (OR 1.60, CI 1.44-1.80; $P < 0.001$). The mortality trend has increased significantly in the CHF ($P = 0.025$) and AF ($P = 0.042$) groups during this study period. *Conclusions*: We have found a significant increase in trend of cardiovascular complications in RA patients. The proportion of patients, with cardiovascular comorbidities, have also been increased significantly. (Curr Probl Cardiol 2021;46:100455.)

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis of unknown etiology affecting 1% of the adult population.[1,2] RA is associated with higher overall and cardiovascular disease (CVD) mortality and morbidity as compared with the population without RA. Indeed, CVD has been recognized as the leading cause of death among RA patients with the risk of developing CVD estimated to be at least 50% greater than general population.[3] The Nurses' Health Study, a prospective cohort study involving 114,342 women found to have > 2-fold higher risk of myocardial infarction in women with RA compared to

those without RA, even after adjusting for cardiovascular risk factors.[4] In a meta-analysis, which included 24 observational studies with a total of 111758 RA patients, 22,927 CVD events were registered.[5] Increased CVD morbidity and mortality are mainly due to accelerated atherosclerosis, as increased prevalence of traditional CVD risk factors and chronic systemic inflammation in RA, contribute to the increased risk of CVD in RA. Optimal control of the RA disease activity by disease-modifying antirheumatic drugs might reduce the risks of CVD morbidity and mortality.[3] The European League Against Rheumatism recommends aggressive control of traditional risk factors along with managing RA disease activity to reduce CVD.[6] Continued subtle disease activity is associated with atherosclerosis and heart dysfunction. Higher disease activity score 28, erythrocyte sedimentation rate, rheumatoid factor immunoglobulin M concentration and bone erosions were associated with deterioration of CV parameters.[7] Another National Inpatient Sample study has shown that RA was associated with increased use of thrombolysis and percutaneous coronary intervention in acute myocardial infarction (AMI) patients.[8] The information regarding CVD comorbidities, mortality, and trend of complications in RA patients is limited in the literature. Therefore, in this present study, we used the NIS database to review the trends of CVD complications in RA patients from 2005 to 2014.

Methods

Data Sources

The NIS database is the largest all-payer inpatient database in the United States (US). The NIS database has been developed by the Agency for Healthcare Research and Quality (AHRQ) under the healthcare cost and utilization project. The database encompasses several deidentified patient information regarding demographics, comorbidities, length of stay (LOS), mortality, hospital location, and charges. The diagnostic codes were recorded using the International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM). We used the data from 2005 to 2014 to identify all RA hospitalizations who had CVD complications, such as AMI, congestive heart failure (CHF), and atrial fibrillation (AF).

Study Population

Using the ICD-9-CM codes (714.0-4; 714.30-33) adult admissions (age $\geq$ 18 years) who had diagnosis of RA were identified from the NIS

database. Missing data on patient age, LOS, gender, mortality, total hospital charges, race (white vs nonwhite) and hospital location (urban vs rural) were excluded. Primary outcomes of interest were mortality, major CVD complications (AMI, CHF, AF), LOS, hospital charges (in US dollars), and hospital location (urban vs rural). The ICD-9-CM codes also helped to calculate the Charlson Comorbidity Index with Deyo Modifications.

Statistical Analysis

Descriptive statistics were used to summarize the continuous and categorical variables. The mean and standard deviation were used for continuous variables and the categorical variables were expressed as a percentage. The chi-squared test was used to compare the categorical variables, and the Kruskal-Wallis test was used to compare the continuous variables between the 3 groups of cardiac complications. Several variables were included in our analysis such as age ($\geq$18 years), gender (female vs male), race (white vs nonwhite), comorbid conditions (hypertension [HTN], diabetes mellitus [DM], peripheral arterial disease [PAD], cerebrovascular disease, renal disease, chronic obstructive pulmonary disease [COPD], and obesity), history of smoking, and alcohol abuse. Cochran Armitage test (p trend test) was used for categorical variables and Cuzich test (np trend test) was used for continuous variables to calculate trend across the years. Weighted data were used for all statistical analysis so that the outcomes can represent the entire US population. Multivariate logistic regression was performed to detect predictors for in-hospital mortality in RA patients with CVD complications. RA patients with CVD complications were divided into 3 groups: CHF, AMI, and AF, respectively. Common covariates included age, gender (female), race (nonwhite), HTN, DM, COPD, PAD, cerebrovascular disease, renal disease, obesity, smoking, and alcohol abuse. Covariate selection was based on previous knowledge related to heart diseases. The individual multivariate logistic regression model was created to identify mortality predictors across each group. Statistical significance was set at the *P* value of less than 0.05. All statistical analysis was performed using STATA/IC 15 (StataCorp, College Station, TX).

RESULTS

A total of 774,808 (unweighted) RA hospitalizations were identified in the NIS database between years 2005 and 2014 after excluding missing values. This data represents 3,831,006 (weighted sample size) RA hospitalizations in the US. Baseline demographics of all RA admissions are

TABLE 1. Demographic and clinical characteristics with in-hospital clinical outcomes of patients with Rheumatoid arthritis from 2005 to 2014 (unweighted, n = 774,808; weighted, n = 3,831,006).

Variables	Values
Age (y), mean ± SD	66.77 ± 14.86
Female gender, %	75.5
Race, %	
White	76.6
Nonwhite	23.4
Urban hospitals, %	80.4
Medical comorbidity, %	
Hypertension	62.9
Diabetes mellitus	26.9
COPD	20.8
Peripheral artery disease	6.0
Cerebrovascular disease	4.0
Renal disease	12.5
Obesity	4.8
Smoking	11.8
Alcohol abuse	2.0
Charlson Comorbidity Index, mean ± SD	2.40 ± 1.62
In-hospital mortality, %	2.3
Cardiac complications, %	
CHF	17.3
AMI	3.0
AF	14.6
LOS (d), mean ± SD	5.18 ± 5.65
Hospital charges × (10,000 USD), mean ± SD	4.03 ± 5.38

AF, atrial fibrillation; AMI, acute myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LOS, length of stay in hospital; SD, standard deviation.

presented in Table 1. Most of the patients were female and belonged to the white race and urban hospitals comprised most of the population. Table 2 demonstrates trends in patient demographics, comorbid conditions, LOS, mortality, CVD complications, age, and race. Between the year 2005 and 2014, the trends of CVD complications, such as AMI, CHF, and AF were found to be statistically significant ($P < 0.05$) (Fig 1).

Table 3 provides a comparison of demographics, comorbid conditions, LOS, etc between the 3 groups. Patients exclusively with AMI, CHF, and AF were included in the analysis to compare between the 3 groups. Patients who had more than 1 CVD complication were excluded from the comparison. There was a significant difference in age, LOS, Charlson Comorbidity Index, hospital charges, gender, race, mortality, and comorbidities between the 3 groups ($P < 0.001$).

TABLE 2. Trends of demographics, comorbid conditions, LOS, mortality, CVD complications, age, and race from 2005 to 2014 in patients with RA.

Variables	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	*P* trend
Total number of RA cases (unweighted)	**54,363**	**57,538**	**54,652**	**68,429**	**75,804**	**81,352**	**96,714**	**94,085**	**94,449**	**97,422**	**0.004**
Total number of RA cases (weighted)	**265,488**	**280,968**	**265,079**	**334,635**	**382,953**	**406,946**	**465,156**	**470,425**	**472,245**	**487,110**	**0.004**
Age (y), mean ± SD	66.95 ± 14.91	66.91 ± 14.90	66.52 ± 15.07	66.78 ± 14.88	66.85 ± 14.91	66.46 ± 15.09	66.92 ± 14.85	66.81 ± 14.74	66.74 ± 14.73	66.79 ± 14.67	0.351
Female gender, %	75.85	75.96	75.91	75.36	75.96	75.66	75.76	75.1	75.28	74.6	<0.001
Race, %: white	80.19	78.02	76.46	78.42	77.08	75.69	75.59	75.87	75.64	75.54	<0.001
Race, %: nonwhite	19.81	21.98	23.54	21.58	22.92	24.31	24.41	24.13	24.36	24.46	<0.001
Urban hospitals, %	81.38	80.44	80.32	79.04	80.83	79.05	80.51	79.97	80.24	82.09	0.005
Medical comorbidity, %: HTN	53.88	56.76	58.46	59.27	62.56	63.05	65.21	65.92	66.47	67.53	<0.001
Medical comorbidity, %: DM	20.29	22.24	23.73	24.51	26.89	27.17	28.88	28.89	29.21	30.17	<0.001
Medical comorbidity, %: PAD	4.78	4.95	5.079	5.35	6.32	5.97	6.49	6.42	6.59	6.88	<0.001
Medical comorbidity, %: CVD	3.87	3.74	3.9	3.97	4.08	4.06	4.21	4.24	4.37	4.39	<0.001
Medical comorbidity, %: COPD	18.81	18.96	19.07	19.33	20.97	20.39	21.47	22.03	21.9	22.21	<0.001
Medical comorbidity, %: renal disease	2.23	5.31	8.87	9.78	12.75	12.97	14.92	15.38	15.86	17.22	<0.001
Medical comorbidity, %: obesity	2.42	2.73	2.97	3.55	4.46	4.76	5.48	5.74	6.16	6.91	<0.001

(*continued on next page*)

TABLE 2. (*continued*)

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Medical comorbidity, %: smoking	8.45	9.32	9.54	10.7	11.46	12.16	12.47	13.16	13.02	13.57	<0.001
Medical comorbidity, %: alcohol	0	0	2	1.81	2.18	2.29	2.4	2.66	2.66	2.89	<0.001
CCI, mean ± SD	2.04 ± 1.35	2.13 ± 1.41	2.24 ± 1.51	2.26 ± 1.52	2.40 ± 1.62	2.40 ± 1.64	2.49 ± 1.66	2.53 ± 1.69	2.54 ± 1.69	2.62 ± 1.74	0.003
In-hospital mortality, %	2.19	2.19	1.96	2.16	2.43	2.22	2.25	2.28	2.29	2.31	0.001
Cardiac complications, %: CHF	15.55	16.05	15.37	15.19	17.37	16.71	17.93	18.25	18.32	19.42	<0.001
Cardiac complications, %: AMI	2.79	2.94	2.8	2.84	2.96	2.83	2.92	3.13	3.07	3.18	<0.001
Cardiac complications, %: AF	11.82	12.33	12.58	12.52	14.05	13.81	15.37	16.03	16.64	16.97	<0.001
LOS (d), mean ± SD	5.33 ± 6.07	5.24 ± 5.54	5.19 ± 5.85	5.15 ± 5.56	5.25 ± 5.97	5.25 ± 5.69	5.23 ± 5.94	5.05 ± 5.40	5.06 ± 5.40	5.13 ± 5.33	0.04
Hospital charges × (10,000 USD), mean ± SD	2.68 ± 3.48	2.83 ± 3.45	3.19 ± 3.94	3.47 ± 4.19	3.82 ± 5.03	4.09 ± 5.28	4.42 ± 5.89	4.40 ± 5.75	4.73 ± 6.23	4.99 ± 6.60	0.003

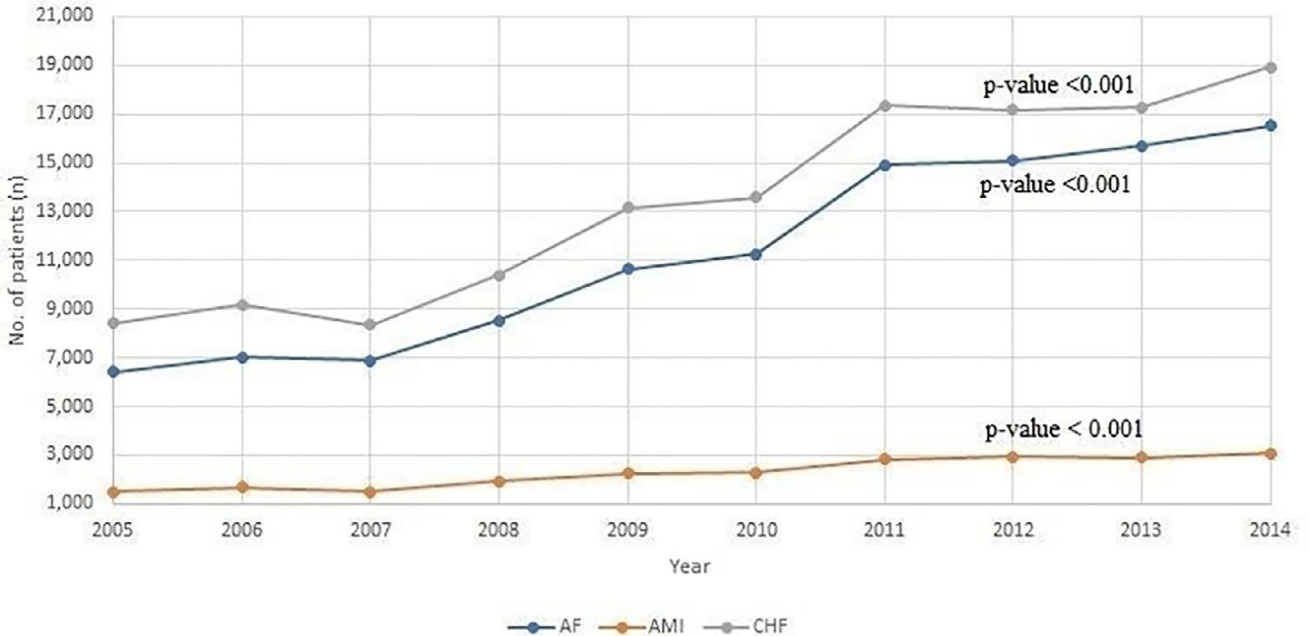

FIG 1. Trend of cardiac complications in rheumatoid arthritis.
AF, atrial fibrillation; AMI, acute myocardial infarction; CHF, congestive heart failure.

TABLE 3. Cardiac complications comparison.

Variables	AMI (uWT: n = 11,661) (WT: n = 57,673)	CHF (uWT: n = 81,322) (WT: n = 402,658)	AF (uWT: n = 64,379) (WT: n = 318,535)	*P* value
Age (y), mean ± SD	68.36 ± 12.30	71.69 ± 12.59	75.06 ± 10.25	<0.001
Female Gender, %	63.9	74.6	69.5	<0.001
Race, %				<0.001
White	79.9	71.8	87	
Nonwhite	20.1	28.3	13	
Urban hospitals, %	77	78.6	81.1	<0.001
Medical comorbidity, %				
Hypertension	70.9	72.8	70.4	<0.001
Diabetes	30.4	38.9	26.3	<0.001
COPD	19.4	35.5	23.4	<0.001
PAD	8.9	9.1	7.9	<0.001
Cerebrovascular disease	5.0	4.0	6.6	<0.001
Renal disease	12.6	27.4	14.3	<0.001
Obesity	3.2	7.8	3.6	<0.001
Smoking	20.0	9.9	6.0	<0.001
Alcohol	1.7	1.4	1.4	0.021
Charlson Comorbidity Index, mean ± SD	3.09 ± 1.34	3.76 ± 1.57	2.31 ± 1.52	<0.001
In-hospital mortality, %	6.7	3.8	3.6	<0.001
LOS (d), (mean ± SD)	4.89 ± 5.31	6.07 ± 6.83	5.74 ± 5.66	<0.001
Hospital charges × (10,000 USD), mean ± SD	6.12 ± 7.37	4.25 ± 5.96	4.45 ± 6.08	<0.001

AF, atrial fibrillation; AMI, acute myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LOS, length of stay in hospital; PAD, peripheral arterial disease; SD, standard deviation; uWT, unweighted; WT, weighted.

AMI

On multivariate analysis, independent predictors of mortality in patients of RA with concomitant AMI were age (OR 1.03, CI 1.02-1.04; $P < 0.001$), HTN (OR 0.60, CI 0.51-0.71; $P < 0.001$), COPD (OR 1.67, CI 1.4-2; $P < 0.001$), cerebrovascular disease (OR 2.21, CI 1.71-2.86; $P < 0.001$), renal disease (OR 1.42, CI 1.16-1.75; $P = 0.001$), smoking (OR 0.71, CI 0.55-0.90; $P = 0.005$), and alcohol abuse (OR 2.73, CI 1.73-4.32; $P < 0.001$) (Table 4).

Overall, the number of AMI complications in RA patients has significantly increased over the 10 years ($P < 0.001$) (Fig 1). However, the mortality in the AMI group did not follow a linear trend ($P = 0.586$) (Fig 2).

TABLE 4. Mortality outcome in acute myocardial infarction.

Variables	OR	LCI	UCI	*P* value
Age	1.03	1.02	1.04	<0.001
Gender (F vs M)	1.16	1.0	1.37	0.07
Race (NW vs W)	1.12	0.93	1.36	0.223
HTN	0.60	0.51	0.71	<0.001
DM	1.11	0.94	1.31	0.21
COPD	1.67	1.40	2.0	<0.001
PAD	1.06	0.82	1.35	0.67
Cerebrovascular disease	2.21	1.71	2.86	<0.001
Renal disease	1.42	1.16	1.75	0.001
Obesity	0.90	0.55	1.48	0.674
Smoking	0.71	0.55	0.90	0.005
Alcohol	2.73	1.73	4.32	<0.001

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes; F, female; HTN, hypertension; LCI, lower confidence interval; M, male; NW, nonwhite; OR, odds ratio; PAD, peripheral artery disease; UCI, upper confidence interval; W, white.

CHF

On multivariate analysis, independent predictors of mortality in patients of RA with concomitant CHF were age (odds ratio [OR] 1.02, confidence interval [CI] 1.017-1.024; $P < 0.001$), gender (female vs male) (OR 0.89, CI 0.82-0.97; $P = 0.007$), HTN (OR 0.57, CI 0.53-0.62; $P < 0.001$), DM (OR 0.73, CI 0.68-0.80; $P < 0.001$), COPD (OR 1.09, CI 1.01-1.18; $P = 0.023$), cerebrovascular disease (OR 1.67, CI 1.44-1.95; $P < 0.001$), renal disease (OR 1.16, CI 1.07-1.27; $P = 0.001$), obesity (OR 0.74, CI 0.61-0.89; $P = 0.001$), and smoking (OR 0.61, CI 0.51-0.72; $P < 0.001$) (Table 5).

TABLE 5. Mortality outcome in congestive heart failure.

Variables	OR	LCI	UCI	*P* value
Age	1.02	1.017	1.024	<0.001
Gender (F vs M)	0.89	0.82	0.97	0.007
Race (NW vs W)	0.92	0.84	1.0	0.059
HTN	0.57	0.53	0.62	<0.001
DM	0.73	0.68	0.80	<0.001
COPD	1.09	1.01	1.18	0.023
PAD	1.02	0.90	1.16	0.73
Cerebrovascular disease	1.67	1.44	1.95	<0.001
Renal disease	1.16	1.07	1.27	0.001
Obesity	0.74	0.61	0.89	0.001
Smoking	0.61	0.51	0.72	<0.001
Alcohol	1.12	0.79	1.58	0.52

COPD, chronic obstructive pulmonary disease; DM, diabetes; F, female; HTN, hypertension; LCI, lower confidence interval; M, male; NW, nonwhite; OR, odds ratio; PAD, peripheral artery disease; UCI, upper confidence interval; W, white.

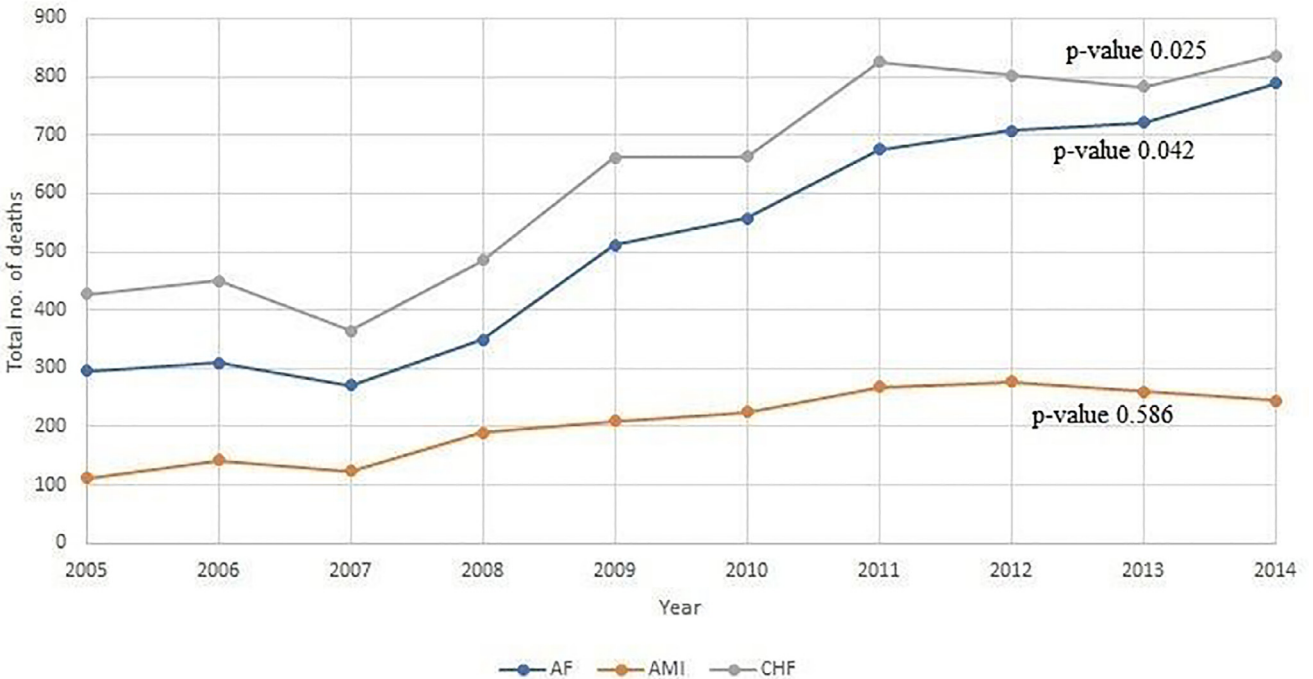

FIG. 2. Mortality trend of rheumatoid arthritis patients with cardiac complications.
AF, atrial fibrillation, AMI, acute myocardial infarction; CHF, congestive heart failure.

Overall, the number of CHF complications in RA patients has significantly increased over the 10 years ($P < 0.001$) (Fig 1). Moreover, the mortality trend also has risen significantly in the CHF group in 10 years period ($P = 0.025$) (Fig 2).

AF

On multivariate analysis, independent predictors of mortality in patients of RA with concomitant AF were age (OR 1.02, CI 1.015-1.025; $P < 0.001$), race (nonwhite vs white) (OR 1.16, CI 1.02-1.31; $P = 0.022$), HTN (OR 0.62, CI 0.57-0.68; $P < 0.001$), DM (OR 0.90, CI 0.82-1.0; $P = 0.049$), COPD (OR 1.56, CI 1.42-1.71; $P < 0.001$), PAD (OR 1.34, CI 1.16-1.53; $P < 0.001$), cerebrovascular disease (OR 2.27, CI 2.0-2.58; $P < 0.001$), renal disease (OR 1.60, CI 1.44-1.79; $P < 0.001$), and smoking (OR 0.80, CI 0.66-0.98; $P = 0.034$) (Table 6).

Overall, the number of AF complications in RA patients has significantly increased over the 10 years ($P < 0.001$) (Fig 1). Moreover, the mortality trend also has risen significantly in the AF group over the 10-year period ($P = 0.042$) (Fig 2).

Discussion

We studied a total of 3,831,006 (weighted) hospitalizations related to RA (mean age 66.77 y; 75.5% females). We have demonstrated the following major findings: (1) a significant increase in the number of RA

TABLE 6. Mortality outcome in atrial fibrillation.

Variables	OR	LCI	UCI	*P* value
Age	1.02	1.015	1.025	<0.001
Gender (F vs M)	1.05	0.95	1.15	0.324
Race (NW vs W)	1.16	1.02	1.31	0.022
HTN	0.62	0.57	0.68	<0.001
DM	0.90	0.82	1.0	0.05
COPD	1.56	1.42	1.71	<0.001
PAD	1.34	1.16	1.53	<0.001
Cerebrovascular disease	2.27	2.0	1.58	<0.001
Renal disease	1.60	1.44	1.79	<0.001
Obesity	1.09	0.85	1.40	0.507
Smoking	0.80	0.66	0.98	0.034
Alcohol	0.92	0.62	1.39	0.70

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes; F, female; HTN, hypertension; LCI, lower confidence interval; M, male; NW, nonwhite; OR, odds ratio; PAD, peripheral artery disease; UCI, upper confidence interval; W, white.

patients during our study period; (2) the proportion of patients, with comorbidities, such as, HTN, DM, PAD, cerebrovascular disease, COPD, renal disease, obesity, smoking, and alcohol abuse have increased; and (3) CVD complications (CHF, AMI, AF) in RA patients have also been increased significantly from 2005 to 2014.

Patients with RA are at higher risk of CVD morbidity and mortality compared with the general population.[9] There is also evidence of increased CVD mortality in RA patients.[10] Extra-articular manifestations of RA, usually related to uncontrolled inflammation, increases the CVD morbidity as well as mortality. Evidences suggest that processes intrinsic to the RA pathogenesis play an important role in CV damage and its clinical consequences (Fig 3).[2]

We have found a very high percentage (62.9%) of RA patients with HTN. If we consider RA patients either with AMI, CHF, or AF, more than 70% patients in each group have also been found to have HTN. Previous studies have demonstrated the prevalence of HTN in RA ranging between 3.8% and 73%.[11-16] Many factors including arterial stiffness, side effects of medications, physical inactivity, high sensitivity C-reactive protein (hsCRP) had been implicated in developing HTN in RA.[10] In addition, 26.9% of patients with RA in our cohort also had DM. The highest percentage of DM patients (39%) was found in RA patients with CHF. We detected COPD in 20.8% our RA patients, with the highest percentage (35.5%) being in RA with CHF group. CVD comorbidities, including HTN, DM, COPD, can be found more frequently in RA patients.[17] Arterial stiffness is an important predictor of CVD and CVD mortality.[18,19] Long-term use of NSAIDs and steroid increases the CV risks including DM and HTN.[17,20] Use of antitumor necrosis factor (TNF) therapy is associated with higher BP, but DMARDs including hydroxychloroquine, methotrexate, TNFα antagonist, and interleukin-1β antagonists alter glucose metabolism in a favorable direction.[20,21] Chronic systemic inflammation in RA may predispose to development of the CVD morbidities, like DM and COPD.[20,22] Apart from inflammation, the presence of obesity, RF, and disease activity may play a role in insulin resistance and eventually in the development of DM.[20] A diagnosis of COPD significantly increased the risk of death in RA patients and affects more than 10% of patients with RA.[23] Smoking increases the risk of both COPD as well as RA.[24] There was the highest percentage of smokers in RA patients who had concomitant AMI (20%). The role of smoking in increasing the risk of RA may be explained by the oxidative stress, inflammation, autoantibody formation, and epigenetic changes.[25] The interaction between smoking and HLA-DRB1 shared epitope has attributed to the risk of

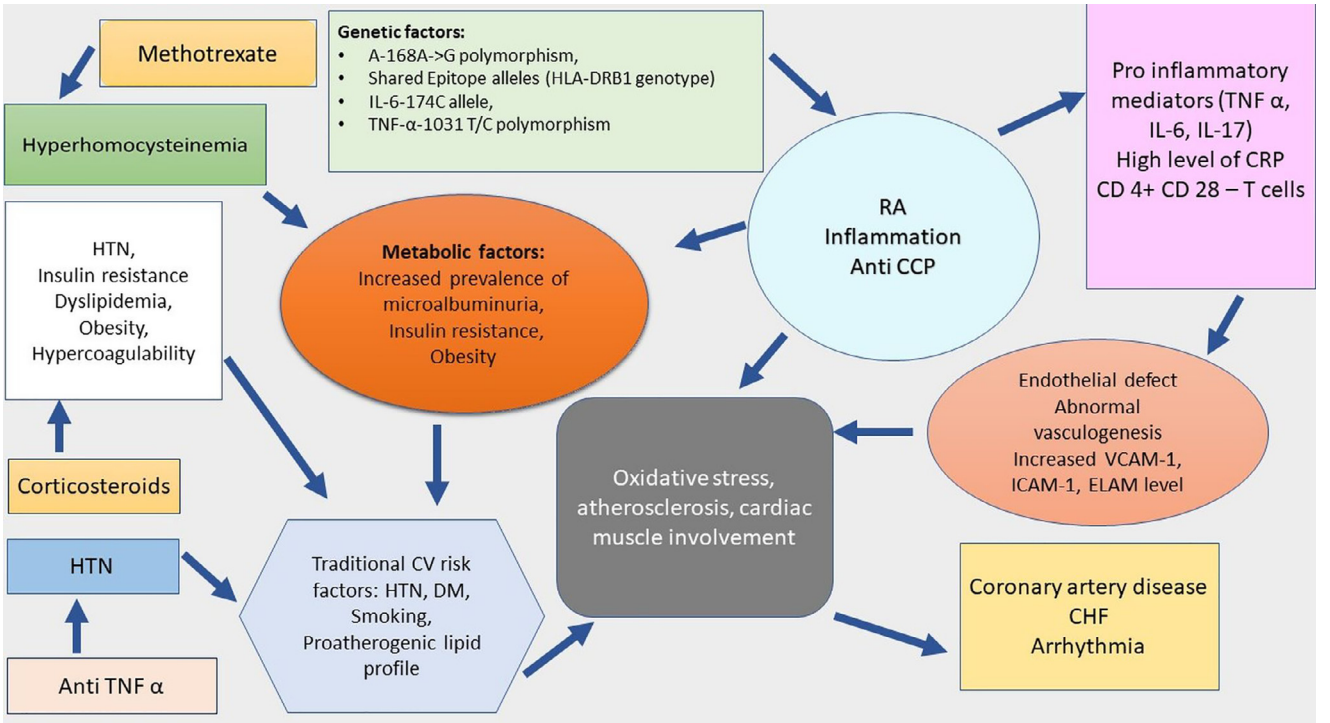

Fig. 3. Pathogenesis of CVD in RA.

developing RA with positive anticitrulline protein antibodies and RF.[26] Sustained smoking cessation in the early years of RA diagnosis may play an important role in reducing mortality risk.[27] Obesity and smoking both are important risk factors for CVD. In our study, 7.8% of RA patients were obese who had concomitant CHF. A cross-sectional analysis was performed utilizing the database of Clalit Health Services, Israel that showed a significant association of obesity with RA.[28] Studies have found obese patients to have worse Disease Activity Scores in RA.[29] The relation between intake of alcohol and RA is fascinating. Mild to moderate amount of alcohol intake is protective in RA patients.[30,31] In our analysis, less than 2% of patients with AMI, CHF, or AF have been detected to abuse alcohol. We have found 6% of patients with RA had PAD. Interestingly, patients with RA were found to have an independently higher risk of peripheral arterial occlusive disease.[32] We have demonstrated 4% of RA patients had cerebrovascular disease and 12.5% had renal disease. Chronic inflammation and atherosclerosis associated with RA are important risk factors for these diseases.[33-35] Carotid ultrasonography may be recommended to identify subclinical atherosclerosis in RA patients and prevent the complications including cerebrovascular disease.[36] RA patients have an increased risk for recurrent ischemic stroke which is enhanced by smoking.[37]

AMI

Atherosclerosis in RA is contributed by the underlying inflammatory process. Infiltration of macrophages and T cells in the atherosclerotic plaques plays an important role. The pathogenesis is supported by elevated levels of inflammatory cytokines such as TNF, interleukins-1, and -6 (IL-1, IL-6), and metalloproteases in RA individuals.[38,39] Interestingly, in RA patients, elevations of these cytokines and metalloproteases are potent predictors of future CVD events.[38,39] Atherosclerosis is a major predisposing factor for the development of coronary artery disease and AMI in RA patients who frequently experience silent AMI and sudden cardiac death.[39] Also, RA patients carry a higher plaque burden compared to general population.[10] The role of inflammation in atherosclerosis has been studied extensively. In Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial involving 10,061 stable post-MI patients with hsCRP levels $\geq$ 2 mg/L showed that the use of canakinumab (anti-IL-1b) was responsible for 31% reduction in CVD mortality.[40] On the contrary, another randomized, double-blind, placebo-controlled trial (the Cardiovascular Inflammation Reduction Trial) demonstrated that

low-dose methotrexate did not reduce levels of IL-1b, IL-6, or hsCRP. Low dose methotrexate also failed to show fewer CVD events than placebo among patients with atherosclerosis.[41] Several facts may explain the difference in these 2 trials. In CANTOS trial the inhibition of IL-1b−IL-6 signaling, causes the reduction of CVD events. The anti-inflammatory mechanism of methotrexate is likely adenosine mediated. The difference between the targeted pathway may result in different outcomes in these studies. Moreover, the reduction of CRP by methotrexate is limited to clinical situations in which level of inflammation is high. The CANTOS included patients with residual inflammatory risk and persistently elevated hs CRP levels (median baseline level was 4.2 mg/L). By contrast, the Cardiovascular Inflammation Reduction Trial included patients with a lower median hs CRP level (1.6 mg/L).[41]

In our analysis, 3% of the patients were found to have AMI in our study. The independent predictors of mortality in RA with AMI were increasing age, HTN, the presence of COPD, cerebrovascular disease, renal disease, smoking, and alcohol abuse.

CHF

RA patients have a 2-fold increased risk for the development of CHF compared to the general population[42]; 17.3% of RA patients in our study were detected to have CHF. The correlation between RA and CHF can be explained by the increased risk of developing ischemic heart disease secondary to accelerated atherosclerosis caused by systemic inflammation. Focal or diffuse inflammatory infiltration of the pericardium and myocardium may play a role in the pathogenesis of CHF.[43] High TNFα level in RA is associated with CHF and left ventricular dysfunction. Recent studies have shown a pivotal role of T cells in CHF, as T-cell infiltration in the left ventricle predisposes cardiac fibrosis.[44] Increased left ventricular mass, independently related to disease duration with preserved systolic function, is a typical finding in RA patients with CHF.[2] Advancing age, HTN, DM, COPD, PAD, cerebrovascular disease, renal disease, and smoking were the independent predictors of mortality in patients who had RA with CHF.

AF

A population-based study by Bacani et al in Minnesota showed an increased risk for AF in RA patients. Chronic inflammation in RA has been implicated in the development of AF. Patients with RA are known

to have an increased prevalence of diastolic dysfunction, and this can be associated with the occurrence of AF. Other potential risk factors for the development of AF in RA patients include severe extra-articular RA, use of cox-2 inhibitors, and increased atherosclerosis.[45] A meta-analysis involving 39,912 patients of RA supports the increased risk of AF in RA individuals.[46] In our study, we found 14.6% of patients with the diagnosis of AF. In patients of RA with AF, independent predictors of mortality were advancing age, HTN, DM, COPD, PAD, cerebrovascular disease, renal disease, and smoking.

An interesting finding of our analysis is that HTN, DM, obesity, and smoking have been surprisingly associated with less CVD complications with an odds ratio of <1. The following facts can potentially explain this apparent surprising protective role of these factors: (A) The NIS database is based on the discharge diagnoses, and in patients who are sicker and have multiple other severe comorbidities, there is less likelihood of coding HTN, smoking, and DM at the time of discharge. On the other hand, in patients with few comorbidities, there could be a higher probability of coding these chronic comorbidities. Thus, the discharge diagnosis often misses these chronic comorbid conditions in relatively sicker individuals. (B) The patients with multiple comorbidities often receive multiple treatments. As they are on more protective medications, there is possibly better outcome in these patients. (C) Previous studies have shown that obesity can show favorable outcome in CVD patients. The "obesity paradox" has been found in several CVD conditions including AMI, CHF, and AF. The result can be explained by the fact that obese patients may present at a younger age with a smaller number of comorbidities.[47] (D) The baseline cardiorespiratory fitness of the patients and associated confounding factors can also alter the study results.[48] (E) Similar to the "obesity paradox," several studies have also noted a "smoking paradox" where smoking was a protective factor for patients with the acute coronary syndrome/AMI.[49,50]

Sedentary lifestyle due to the nature of the disease, side effects of drugs used in RA, and newer diagnostic tools to detect cardiac complications at earlier stages may explain the increasing trend of CVD morbidities and complications in the past 10 years. The development of newer therapies prolonging the disease duration might also have contributed to the increasing prevalence of RA.

Limitations

Though our NIS study highlighted several important CV aspects of RA patients, it is not without limitations. Being a retrospective study using

NIS administrative database has some pitfalls, including coding errors and wrong entries. It also does not provide patient level information, including disease duration of individual patients, medications, echocardiographic characteristics, and lab values. These administrative codes, however, have been used in numerous published manuscripts and the quality of coding data has been assessed to be appropriate. The NIS database provides information only about the initial hospitalization and not follow-up data, therefore preventing the assessment of long-term clinical outcomes. Also, it only includes hospitalizations, so 1 patient can have multiple entries. It is also difficult to assess whether a diagnosis was present before hospitalization or resulted from the event during the hospitalization. It is well-established fact that the duration of RA has significant impact on mortality and morbidity.

Conclusion

To the best of our knowledge, this is the first study evaluating CVD complications in RA patients from the NIS database between the years 2005 and 2014. Since we are using a national database, the results of our analysis can be extrapolated to represent a broad spectrum of hospitals throughout the US. Further prospective studies are needed to ascertain this association and implement a better management plan for CVD in RA patients.

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Role of Individual Authors

DB: participated in formulation of plan and data processing and analysis and writing; UB, SC, BA: participated in data processing and analysis and writing; AH, RKG, FH, VAM, KS: concept design and writing; WSA, PD, CJL: supervision and concept design and presentation of the project.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2019.100455.

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