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Increased hospitalization rates following heart failure diagnosis in rheumatoid arthritis as compared to the general population

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Abstract

Objective—To compare the frequency of and trends in hospitalizations after heart failure (HF) diagnosis in patients with and without rheumatoid arthritis (RA) during 1987–2015.

Methods—The study included a retrospectively identified population-based cohort of patients with incident HF and prior RA (age 18 years, 1987 ACR criteria) and a cohort of incident HF patients without RA matched 3:1 on age, sex, and year of HF diagnosis. Hospitalizations at the time of HF diagnosis were excluded. All subjects were followed until death, migration, or 12/31/2015.

Results—The study included 212 patients with RA (mean age at HF diagnosis 78.3 years; 68% female) and 636 non-RA patients (mean age at HF diagnosis 78.6 years; 68% female). The hospitalization rate after HF diagnosis was higher in RA vs non-RA (rate ratio [RR] 1.17; 95% CI 1.08–1.26). Hospitalization rates in both groups have been declining since 2005 and the difference between patients with and without RA may be decreasing after 2010. The magnitude of the increase was similar in both sexes and across all ages. Patients with RA were more likely to be hospitalized for noncardiovascular causes (RR 1.26; 95% CI 1.14–1.39), but not for HF or other cardiovascular causes compared to non-RA patients.

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Conclusions—The hospitalization rate following HF diagnosis was higher in RA versus non-RA patients regardless of sex and age. Increased hospitalization risk in patients with RA was driven by increased rates of non-cardiovascular hospitalization.

Keywords

Rheumatoid arthritis; heart failure; hospitalizations

INTRODUCTION

Comorbidity burden in patients with rheumatoid arthritis (RA) is substantial and is associated with increased healthcare utilization [1]. About 80% of patients with RA have one additional chronic condition, and studies have reported a 21% increase in the prevalence of comorbidity (primarily cardiovascular conditions) in RA over the past 20 years [2, 3]. Heart failure (HF) is one of the most common cardiovascular comorbidities in patients with RA. Our prior studies showed a 2-fold increased risk of HF in RA compared to the general population, and suggested a significant contribution of HF to the excess mortality in RA [4, 5]. A recent nationwide cohort study from Denmark reported 30%-increased risk of hospitalization with incident HF in RA [6].

Population-based studies of patients with HF both from the USA and Europe have reported frequent hospitalizations following HF diagnosis, increased readmission rates [7] and high out-of-hospital mortality rates, resulting in substantial clinical and economic burden associated with HF diagnosis [8]. More recent data suggest that from 2001 to 2014 there has been a decline in hospitalization rates for HF in the United States [9].

In view of the increased occurrence of HF in patients with RA, understanding the trends in hospitalization rates following HF diagnosis in RA as compared to the general population is important for healthcare planning, resource utilization and optimization of management. However, studies reporting hospitalization rates after the diagnosis of HF in patients with RA as compared to the general population are lacking.

To address this gap, we aimed to compare the frequency of and trends in hospitalizations for any cause after HF diagnosis in patients with and without RA during 1987–2015 and to assess risk factors for hospitalizations following HF in RA.

PATIENTS AND METHODS

A retrospectively identified population-based cohort of patients with incident HF in 1987–2012 and prior RA (age 18 years, 1987 ACR criteria) was assembled using the resources of the Rochester Epidemiology Project (REP). The REP is a unique population-based medical records linkage system that ensures ready access to the complete (in-patient and out-patient) medical records from all community medical providers in Olmsted County, MN [10]. For each patient, the earliest date of fulfillment of 4 1987 ACR criteria for RA was considered the RA incidence date. A comparison cohort of incident HF patients without RA matched 3:1 on age, sex, and year of HF diagnosis was assembled from the same underlying population.

HF was defined using the Framingham criteria [11, 12]. HF diagnosis requires 2 of the major criteria [i.e., paroxysmal nocturnal dyspnea or orthopnea, neck vein distention, rales, radiographic cardiomegaly (i.e., increasing heart size on chest radiograph), acute pulmonary edema, S3 gallop, increased central venous pressure 16 cm of water at the right atrium, circulation time 25 seconds, hepatojugular reflux, weight loss > 4.5 kg in 5 days in response to treatment of congestive HF)], or the presence of 1 major criterion and 2 minor criteria (i.e., bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by 33% from maximal value recorded, and tachycardia rate 120 beats/min). Minor criteria were counted only if they could not be attributed to another medical condition. Data on hospitalizations (i.e., admission dates, discharge dates, and admission and discharge diagnoses by International Classification of Diseases Ninth Edition [ICD-9] coding) were retrieved electronically from billing data of Olmsted County medical providers including Mayo Clinic and Olmsted Medical Center and their affiliated hospitals.

All subjects were followed until death, migration, or December 31, 2015. Hospitalizations at the time of HF diagnosis were excluded from analyses. Readmission was defined as a hospital admission date within 30 days of a prior discharge date. Data on primary discharge diagnosis were available since 1995. For analyses using discharge diagnosis, additional cases and comparators who died or emigrated from Olmsted County prior to 1995 were excluded, and follow-up began with the latter of the HF diagnosis date or January 1, 1995.

Information on the following risk factors for hospitalization for any cause following HF diagnosis was collected by retrospective medical records review in all patients with RA: smoking status (current or former smoker), body mass index, hypertension, diabetes mellitus, myocardial infarction (MI), Charlson comorbidity index, and RA disease characteristics (i.e., RA disease duration, rheumatoid factor [RF] and/ or anti-citrullinated protein antibody [ACPA] positivity, and severe extra-articular manifestations [ExRA]). Hypertension was defined according to the criteria of the Joint National Committee on Detection, Evaluation and treatment of High Blood Pressure as 2 ambulatory blood pressure readings 140 mm Hg systolic and/or 90 mm Hg diastolic obtained during a 1year period, physician diagnosis or documented use of antihypertensive medications. Diabetes mellitus was defined as at least 2 measurements of fasting plasma glucose 126 mg/dl or a 2-hour plasma glucose 200 mg/dl, physician diagnosis or documented use of insulin and/or oral hypoglycemic agents. MI was defined according to standardized criteria [13]. Rheumatologic disease was removed from the calculation of the Charlson Comorbidity Index. Severe ExRA was defined as the presence of pericarditis, pleuritis, Felty's syndrome, glomerulonephritis, cutaneous vasculitis, peripheral neuropathy, scleritis, episcleritis or retinal vasculitis [14]. The institutional review boards of the Mayo Clinic and the Olmsted Medical Center approved this study. This manuscript follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting guidelines for observational studies [15].

Statistical analysis

Descriptive statistics (mean, percentages, etc.) were used to summarize the data. Rank sum and chi-square tests were used to compare characteristics between the HF patients with and without RA. Data were analyzed using person-year methods. Comparisons of person-year rates were performed using Poisson methods. Poisson regression models with smoothing splines were used to examine trends over time while allowing for non-linear effects. Comparisons of length of stay for HF patients with and without RA were performed using generalized linear models adjusted for age, sex, and calendar year with random effects to account for multiple hospitalizations in the same patient. Readmission rates were calculated as the number of readmissions divided by the number of subsequent hospitalizations excluding the first hospitalization for each patient, as this could not be a readmission by definition. Conditional frailty models were used to analyze risk factors for hospitalizations for any cause following HF diagnosis adjusting for age, sex and calendar year of HF diagnosis [16]. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria.

RESULTS

The study included 212 patients with RA and 636 patients without RA who were similar in age, sex, Charlson comorbidity index and Framingham criteria fulfillment for HF (Table 1). Table 2 shows hospitalization rates after HF diagnosis overall and subdivided according to age, sex, calendar year, HF disease duration and categories of primary discharge diagnosis among patients with and without RA. The hospitalization rate after HF diagnosis was higher in RA at 100.2 hospitalizations/100 person years, with 857 hospitalizations over 854.9 person years of follow up as compared to non-RA at 86.0 hospitalizations/100 person years, with 3047 hospitalizations over 3541.5 person years of follow up, rate ratio [RR] 1.17; 95% confidence interval [CI] 1.08–1.26; Table 2). Hospitalization rates in both groups have been declining since 2005 and the difference between patients with and without RA may be decreasing after 2010 (Figure 1, Panel A). The magnitude of the increased risk was similar in both sexes, across all ages, and throughout the duration of HF. Following HF diagnosis, patients with RA experienced a higher rate of hospitalizations for non-cardiovascular causes (RR 1.26; 95% CI 1.14–1.39), but not for HF (RR 0.96; 95% CI 0.75–1.20) or other cardiovascular causes (RR 0.99; 95% CI 0.81-1.20) compared to the patients without RA, using data on primary discharge diagnosis which were available starting 1995. The leading non-CV cause of hospitalization was respiratory disease in both cohorts.

Readmission rates were similar among the patients with RA (206 readmissions; 30% of 693 subsequent hospitalizations) compared to the patients without RA (667 readmissions; 27% of 2488 subsequent hospitalizations; p=0.13). There was no overall difference in hospital length of stay in patients with and without RA (mean of 5.6 vs 5.3 days, respectively, p=0.31). Length of stay was higher in earlier years in RA than non-RA and declined faster in RA than non-RA over time, with similar length of stay in both groups in recent years (interaction p=0.019, Figure 1, Panel B).

Among patients with RA, 112 (53%) were positive for RF/ACPA antibody and 19 (9%) had severe ExRA prior to HF diagnosis. Mean RA disease duration at the time of HF diagnosis

was 13.6 (10.5) years. Smoking (current or former) (Hazard Ratio [HR] 1.33, 95%CI 1.06–1.68), prior MI (HR 1.37, 95%CI 1.03–1.82) and higher Charlson comorbidity index values (HR 1.10, 95%CI 1.06–1.14), but not other traditional cardiovascular risk factors and RA disease characteristics, were associated with increased risk for hospitalization (Table 3).

DISCUSSION

Healthcare utilization in patients with chronic conditions is one of the drivers of the healthcare crisis in the US [17, 18]. Hospitalizations of patients with HF account for a large part of healthcare costs related to HF thus presenting a major public health problem. This large population-based study is one of the first to report trends in hospitalizations following HF diagnosis in patients with RA compared to the general population. A recent large nation-wide cohort study by Khalid et al reported a 30%-increased risk of hospitalization for incident HF in RA vs the general population [6]. Our study extends these findings by showing increased rates of hospitalization subsequent to HF diagnosis in patients with versus without RA, suggesting increased healthcare use and associated economic costs in patients with RA who have HF as compared to the general population. There is a potential improving trend in HF hospitalizations in RA after 2010, which mirrors the decline in HF hospitalizations in the general population that has occurred since implementation of the 2005 ACC/AHA HF management guidelines [9].

Similar to the findings from the earlier studies of HF hospitalizations in the general population of the Olmsted County, non-cardiovascular causes were the most common reasons for hospital admission in the our RA cohort [7, 19]. Respiratory disease was one of the leading causes for hospitalization in this RA cohort, which is consistent with earlier reports of the major effect of pulmonary disease on healthcare use and mortality in RA [1].

Smoking, prior MI and higher Charlson comorbidity index values were associated with increased risk of hospitalization. This finding is concordant with the results from a prospectively followed cohort of the German register RABBIT where smoking and older age were among the risk factors for the outcome event (hospitalization or death) in patients with RA and HF [20]. A high number of comorbid conditions (> 6 comorbidities) in patients with HF who developed the outcome event was also noted in this study. Taken together, these findings suggest that common risk factors and comorbidity burden have a major effect on healthcare use and hospitalizations in RA for which an improved approach for comorbidity management should be sought.

Strengths of this study include its population-based design, availability of information on all hospitalizations in the community, long and complete follow up and the availability of a comparison cohort from the same underlying population.

Potential limitations include lack of information on anti-rheumatic medications. Lack of increase in HF hospitalizations in users of tumor necrosis factor antagonists vs users of nonbiologic disease-modifying anti-rheumatic drugs has been previously reported in a large nation-wide study [21]. Due to the observational nature of this study and the inherent likelihood of confounding by indication, it is unlikely that the availability of information on

Data on primary discharge diagnosis were not available prior to 1995. As such, we cannot estimate what conditions accounted for increased risk of hospitalization following HF in earlier years and whether hospitalizations due to cardiovascular causes were more prominent contributor than after 1995. Data on hospitalizations outside the community were not available; however, these are likely rare due to the relatively isolated location of Olmsted County. Olmsted County, MN population is predominantly white, thus the findings of this study may not be readily generalizable to more ethnically diverse populations.

In summary, hospitalization rate following HF diagnosis was higher in RA than in non-RA patients regardless of age and sex. This difference was particularly apparent between 1990 and 2010. The increased hospitalization risk in patients with RA was due to an increased rate of non-cardiovascular hospitalization. Smoking, prior MI and Charlson comorbidity index were associated with increased risk of hospitalization, suggesting that increased management complexity among patients with comorbid RA may play a role in more frequent hospitalizations in patients with RA and HF.

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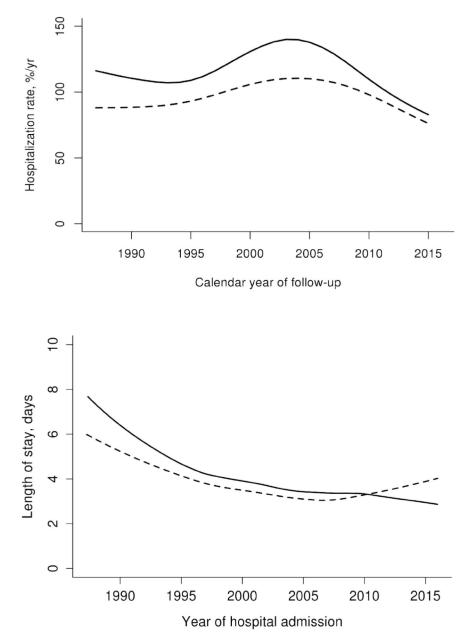


Figure 1.

Calendar year trends in hospitalization rates following heart failure diagnosis (Panel A) and trends in hospital length of stay (Panel B) in patients with rheumatoid arthritis (solid line) and non-RA subjects (dashed line)

Table 1:

Characteristics of patients with heart failure with and without rheumatoid arthritis

Characteristic	RA (n=212)	Non-RA (n=636)
Age at HF diagnosis	78.3 (±9.8)	78.6 (±9.7)
Sex, female	144 (68%)	432 (68%)
Follow up, years	4.0 (±4.2)	5.6 (±4.8)
Charlson Comorbidity index	3.9 (±2.9)	3.8 (±3.2)
Framingham criteria fulfillment for HF		
2 Major	182 (86%)	545 (86%)
1 Major and 2 Minor	23 (11%)	83 (13%)

Abbreviations: RA= rheumatoid arthritis; HF= heart failure

Values in the table are mean ($\pm standard$ deviation) or N (%), as indicated.

Table 2.

Hospitalization rates following diagnosis of heart failure in patients with and without rheumatoid arthritis

	RA	RA					Rate Ratio (95% CI)
Group	Number of hospitalizat ions	Number of person- years	Rate (per 100 person- years)	Number of hospitaliz ations	Number of person- years	Rate (per 100 person- years)	(95% CI)
Overall	857	854.9	100.2	3047	3541.5	86.0	1.17 (1.08- 1.26)
Age group:							
- 40-64 years	70	98.2	71.3	174	280.9	62.0	1.16 (0.87- 1.52)
- 65–79 years	386	382.3	101.0	1238	1374.9	90.0	1.12 (1.00- 1.25)
- 80 years	401	374.4	107.1	1635	1885.7	86.7	1.24 (1.11- 1.38)
Sex:							
- Female	577	623.4	92.6	1976	2464.0	80.2	1.15 (1.05- 1.26)
- Male	280	231.6	120.9	1071	1077.6	99.4	1.22 (1.07- 1.39)
Calendar year of nospital admission							
- 1987–1990	36	36.0	100.0	108	124.6	86.7	1.16 (0.78- 1.66)
- 1991–1995	126	134.0	94.0	401	502.4	79.8	1.18 (0.96- 1.43)
- 1996–2000	180	168.8	106.6	692	751.2	92.1	1.16 (0.98- 1.36)
- 2001–2005	249	207.1	120.2	810	846.5	95.7	1.26 (1.09- 1.45)
- 2006–2010	161	160.5	100.3	672	767.5	87.6	1.15 (0.96- 1.36)
- 2011–2015	105	148.5	70.7	364	549.3	66.3	1.07 (0.86- 1.32)
HF Disease duration:	<u> </u>	<u> </u>		<u> </u>	<u>.</u> 	<u> </u>	<u> </u>
- 0-2 years	496	401.7	123.5	1517	1497.8	101.3	1.22 (1.10- 1.35)
- 3-4 years	144	167.8	85.8	501	682.3	73.4	1.17 (0.97- 1.40)
- 5–9 years	141	213.6	66.0	724	918.9	78.8	0.84 (0.70- 1.00)
- 10 years	76	71.9	105.7	305	442.5	68.9	1.54 (1.19- 1.96)
Primary discharge liagnosis ^{**}		 	 		<u> </u>	 	
Heart failure	87	714.2	12.2	387	3047.1	12.7	0.96 (0.75-1.20)

	RA			Non-RA			Rate Ratio (95% CI)
Group	Number of hospitalizat ions	Number of person- years	Rate (per 100 person- years)	Number of hospitaliz ations	Number of person- years	Rate (per 100 person- years)	
Other CV	122	714.2	17.1	525	3047.1	17.2	0.99 (0.81– 1.20)
Non-CV	506	714.2	70.9	1714	3047.1	56.3	1.26 (1.14– 1.39)

Abbreviations: RA= rheumatoid arthritis; CV=cardiovascular

** Available for hospitalization in 1995-present.

Table 3.

Risk factors for hospitalization for any cause following heart failure diagnosis in patients with rheumatoid arthritis

Characteristics at heart failure diagnosis**	Value*	Hazard Ratio (95% Confidence Interval)
Prior myocardial infarction	35 (17)	1.37 (1.03–1.82)
Ever smoker (current or former)	121 (58)	1.33 (1.06–1.68)
Hypertension	137 (65)	1.23 (0.97–1.55)
Sex, male	68 (32)	1.21 (0.95–1.53)
Diabetes mellitus	36 (17)	1.15 (0.87–1.52)
Charlson comorbidity index	3.9 (2.9)	1.10 (1.06–1.14)
RF and/or ACPA positive	112 (53)	1.05 (0.84–1.31)
Age (per 10 years)	78.3 (9.8)	1.04 (0.93, 1.17)
RA disease duration	13.6 (10.5)	1.01 (1.00–1.02)
Calendar year	1999 (7)	1.00 (0.99–1.02)
Body mass index 30 kg/m ²	63 (30)	0.88 (0.70-1.11)
Severe extra-articular manifestations of RA	19 (9)	0.82 (0.54–1.24)

Abbreviations: RA=rheumatoid arthritis; RF= rheumatoid factor; ACPA=anti-citrul inated protein antibodies

Values in the table are mean (\pm SD) for continuous characteristics and N (%) for discrete characteristics

** Data on risk factors were available on all patients except 2 patients without RF/ACPA testing and 4 with unknown smoking status.

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