



Rheumatoid arthritis is associated with increased in-hospital mortality in asthma exacerbations: a nationwide study

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Abstract

The relationship between RA and asthma has been yielding conflicting results, with most recent studies showing a possible positive association. The study aims at the outcomes of adult patients hospitalized for asthma exacerbation in those with and without RA. We used data from the National Inpatient Sample (NIS) for the period of 2012–2014. ICD 9 code was used to identify the diagnosis. Our primary outcome was in-hospital mortality. Our secondary outcome was total asthma exacerbation hospitalizations, length of stay, and total hospital charges. Compared to those without RA, RA was associated with increased hospitalizations for asthma exacerbation (unadjusted OR 1.29, $p < 0.001$; adjusted OR 1.06, $p = 0.002$), more respiratory and systemic comorbidities, increased in-hospital mortality (unadjusted OR 1.89, $p = 0.001$; adjusted OR 1.60, $p = 0.020$), length of stay (4.5 vs 3.8; unadjusted $p < 0.001$, adjusted $p < 0.001$), and total hospital charges (30,149 vs 26,247; unadjusted $p < 0.001$, adjusted $p = 0.048$). Our study was the first to demonstrate that RA is associated with increased in-hospital mortality, length of stay, and cost using a national inpatient database. We hypothesize that in asthmatic patients with concurrent RA, their asthma may represent a distinctive subgroup that is more severe and carries a poorer prognosis, which deserves more attention and future investigation.

Keywords Asthma · Cross-sectional study · Mortality · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory disorder which primarily affects the joints but also associated with extra-articular involvement and systemic comorbidities [1]. RA imposes increased risk of morbidity and accelerated mortality compared to general

populations [1]. Pulmonary involvement may occur in as many as 67% and is the second leading cause of death in patients with RA [2].

Asthma is a chronic inflammatory disease of the airways which affects nearly 10% of the US population [3]. Asthma is featured by episodes of acute exacerbation, which is characterized as acute worsening of symptoms which can be life-threatening and require hospitalization [4]. The relationship between RA and asthma has been yielding conflicting results. While earlier studies show a negative association between these two conditions [5, 6], results from more recent research suggested otherwise [7, 8]. It should also be noted that previous studies focused mainly on the incidence or prevalence of the two diseases, while little is known regarding the outcomes of asthma exacerbation in RA patients compared to those without RA.

The study aims at the outcomes of adult patients hospitalized for asthma exacerbation in those with and without RA. To our best knowledge, this is the first nationwide study evaluating the relationship between RA and asthma exacerbation in hospital settings.

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Methods

Data source

We used data from the National Inpatient Sample (NIS), the largest publicly available inpatient database in the USA sponsored by Agency for Healthcare Research and Quality (AHRQ) and the Healthcare Cost and Utilization Project (HCUP), for the period of 2012–2014. It is designed to approximate a 20% stratified sample of US community hospitals. Diagnoses and comorbidities for each admission were identified using International Classification of Diseases 9th Revision (ICD-9) codes and AHRQ comorbidity measures. After weighting, the data reflects over 95% of all hospital discharges within the USA. Our study does not need Institutional Review Board (IRB) approval according to our institution policy because the study does not involve intervention or interaction with human subjects, and no identifiable information is involved in any part of the research process.

Data quality

HCUP data quality report for NIS database is publicly available for each year. Reports for the year 2012–2014 were reviewed, and missing data rates were consistently <0.5% for most data elements.

Data samples

We included hospital admissions for asthma exacerbation for patients aged 18 years or older from year 2012 to 2014. Admission for asthma exacerbation is defined as a principal diagnosis of asthma (ICD-9 code 493.xx) for hospitalization. Rheumatoid arthritis was identified using ICD 9 code 714.0. Inflammatory diseases including ankylosing spondylitis and psoriasis were excluded, due to their possible association with asthma [9, 10] and also concern for incorrect coding for RA. ICD 9 code and AHRQ comorbidity measures used for respiratory and systemic comorbidities were provided in Supplemental Material 1.

Outcome measures

Our primary outcome was in-hospital mortality. Our secondary outcome was total asthma exacerbation hospitalizations, length of stay, and total hospital charges.

Statistical analysis

Weights were applied to each hospitalization per NIS database sets to represent the national hospitalization data. For univariate analyses, Student's *t* tests were performed for continuous variables and χ^2 analysis was performed for categorical

variables. Multivariate logistic and linear regression analysis was performed for categorical and continuous variables, respectively. Variables for adjustment include age, gender, race, socioeconomic status (including primary payer and median household income quartile for patient's ZIP code), active tobacco use, obesity, acute respiratory infection, respiratory comorbidities, and systemic comorbidities. Respiratory comorbidities included chronic obstructive pulmonary disease (COPD), bronchiectasis, obstructive sleep apnea (OSA), congestive heart failure (CHF), selected interstitial lung diseases (ILDs) and pulmonary hypertension. Selected ILDs were RA-associated ILD (RA-ILD) and idiopathic interstitial pneumonia, including all eight histological subtypes and pulmonary fibrosis. And systemic comorbidities included hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), cerebrovascular disease, chronic kidney disease (CKD), chronic liver disease, and cancer. Stata software was used for statistical analyses.

Results

Between 2012 and 2014, there was a total of 721,870 admissions for asthma exacerbation, among which 15,840 admissions had a concurrent diagnosis of RA. The characteristics of admissions for asthma exacerbation with and without RA were shown in Table 1. For the demographic information, compared those without RA, asthma exacerbation admissions with RA were older (mean age 63 vs 56, $p < 0.0001$), more female (89 vs 71%, $p < 0.0001$), more Caucasian (58 vs 52%, $p < 0.0001$) and less African American (23 vs 27%, $p < 0.0001$), more Medicare (62 vs 44%, $p < 0.0001$) and less Medicaid (14 vs 22%, $p < 0.0001$), and less ZIP code with median household income in the 0–25th percentile (33 vs 37%, $p < 0.0001$).

For comorbidities, asthma exacerbation admissions with RA were also associated with less active tobacco use (20 vs 25%, $p < 0.0001$), and more obesity (30 vs 26%, $p < 0.0001$), acute respiratory infections (25 vs 22%, $p < 0.0001$), major respiratory comorbidities, including COPD (10 vs 8%, $p < 0.0001$), bronchiectasis (1.7 vs 1.0%, $p = 0.0001$), OSA (19 vs 14%, $p < 0.0001$), CHF (19 vs 14%, $p < 0.0001$), selected ILDs (5.3 vs 1.6%, $p < 0.0001$), and pulmonary hypertension (6.1 vs 3.9%, $p < 0.0001$); and some major systemic comorbidities including HTN (57 vs 49%, $p < 0.0001$), DM (34 vs 29%, $p < 0.0001$), CAD (22 vs 16%, $p < 0.0001$), and CKD (11 vs 8%, $p < 0.0001$), but not for cerebrovascular disease (2.1 vs 1.8%, $p = 0.1264$), chronic liver disease (3.3 vs 3.0%, $p = 0.3250$) and cancer (1.9 vs 2.1%, $p = 0.5388$).

For primary outcome, RA was associated with increased in-hospital mortality (unadjusted OR 1.89, $p = 0.001$; adjusted OR 1.60, $p = 0.020$) in asthma exacerbation hospitalizations. Adjusted OR and *p* value for each variable in the multivariable

Table 1 Demographic and clinical characteristics of hospital admissions for asthma exacerbation with and without RA

Characteristic	Asthma exacerbation with RA (<i>n</i> = 15,840)	Asthma exacerbation without RA (<i>n</i> = 721,870)	<i>p</i> value
Mean age	63	56	< 0.0001
Gender (female)	89%	71%	< 0.0001
Race			
White	58%	52%	< 0.0001
Black	23%	27%	< 0.0001
Hispanic	11%	12%	0.2036
Asian or Pacific Islander	1.3%	2.0%	0.0025
Native American	0.9%	0.6%	0.0362
Other	5.8%	6.4%	0.0701
Primary expected payer			
Medicare	62%	44%	< 0.0001
Medicaid	14%	22%	< 0.0001
Private insurance	18%	22%	< 0.0001
Self-pay	3.1%	8.7%	< 0.0001
No charge	0.16%	1.1%	< 0.0001
Other	2.4%	2.7%	0.4406
Median household income quartile for patient's ZIP code			
0–25th percentile	33%	37%	< 0.0001
25th–50th percentile	25%	25%	0.4585
51th–75th percentile	22%	20%	0.0226
75th–100th percentile	18%	15%	0.0001
Active tobacco use	20%	25%	< 0.0001
Obesity	30%	26%	< 0.0001
Acute respiratory infection	25%	22%	< 0.0001
Respiratory comorbidities			
Chronic obstructive pulmonary disease	10%	8%	< 0.0001
Bronchiectasis	1.7%	1.0%	0.0001
Obstructive sleep apnea	19%	14%	< 0.0001
Congestive heart failure	19%	14%	< 0.0001
Selected interstitial lung diseases*	5.3%	1.6%	< 0.0001
Pulmonary hypertension	6.1%	3.9%	< 0.0001
Systemic comorbidities			
Hypertension	57%	49%	< 0.0001
Diabetes mellitus	34%	29%	< 0.0001
Coronary artery disease	22%	16%	< 0.0001
Cerebrovascular disease	2.1%	1.8%	0.1264
Chronic kidney disease	11%	8%	< 0.0001
Chronic liver disease	3.3%	3.0%	0.3250
Cancer	1.9%	2.1%	0.5388

*Selected ILD were RA-associated ILD (RA-ILD) and idiopathic interstitial pneumonia, including all eight histological subtypes and pulmonary fibrosis

analysis are shown in Table 2. For secondary outcomes, RA was associated with a higher risk of admissions for asthma exacerbation (unadjusted OR 1.29, $p < 0.001$; adjusted OR 1.06, $p = 0.002$), increased length of stay (4.5 vs 3.8;

unadjusted $p < 0.001$, adjusted $p < 0.001$), and total hospital charges (30,149 vs 26,247; unadjusted $p < 0.001$, adjusted $p = 0.048$) than those without RA in asthma exacerbation hospitalizations.

Table 2 Adjusted odds ratio and *p* value for each variable in multivariable analysis

	Adjusted odds ratio	<i>p</i> value
Rheumatoid arthritis	1.60	0.020
Age	1.03	<0.001
Gender (female)	0.83	0.037
Race		
White	1.00 (reference)	–
Black	0.76	0.016
Hispanic	0.96	0.758
Asian or Pacific Islander	1.18	0.451
Native American	0.94	0.915
Other	1.03	0.899
Primary expected payer		
Medicare	1.00 (reference)	–
Medicaid	1.03	0.848
Private insurance	0.97	0.851
Self-pay	1.18	0.444
No charge	0.32	0.258
Other	1.52	0.114
Median household income quartile for patient's ZIP code		
0–25th percentile	1.00	–
25th–50th percentile	0.95	0.658
51th–75th percentile	0.88	0.253
75th–100th percentile	0.89	0.346
Active tobacco use	0.88	0.289
Obesity	0.82	0.062
Acute respiratory infection	2.31	<0.001
Respiratory comorbidities		
Chronic obstructive pulmonary disease	0.65	0.009
Bronchiectasis	0.47	0.088
Obstructive sleep apnea	0.77	0.054
Congestive heart failure	2.25	<0.001
Selected interstitial lung diseases*	2.00	<0.001
Pulmonary hypertension	1.88	<0.001
Systemic comorbidities		
Hypertension	0.74	0.002
Diabetes mellitus	0.82	0.027
Coronary artery disease	1.29	0.010
Cerebrovascular disease	2.26	<0.001
Chronic kidney disease	1.20	0.149
Chronic liver disease	1.32	0.226
Cancer	2.78	<0.001

*Selected ILD were RA-associated ILD (RA-ILD) and idiopathic interstitial pneumonia, including all eight histological subtypes and pulmonary fibrosis

Discussion

To the best of our knowledge, our study is the first to evaluate the outcomes of asthma exacerbation in adult patients with

RA in hospital settings. We restricted patient populations to adult because RA and juvenile idiopathic arthritis are recognized as two related but distinctive disorders. Our study showed that compared to those without RA, hospitalizations for asthma exacerbation in patients with RA were associated with more respiratory and systemic comorbidities, increased in-hospital mortality, length of stay, and total hospital charges. The increased in-hospital mortality remained significant after adjusting socioeconomic factors and major medical comorbidities. Since treatment of RA may involve systemic corticosteroid, one may argue that the increased in-hospital mortality may be caused by a decrease in hospitalizations of mild-to-moderate exacerbations due to steroid effects. However, this explanation was not likely because our study also showed that the RA was also associated with increased risk of hospitalizations for asthma exacerbation. It is well known that acute respiratory infections (ARI) are a common trigger for asthma exacerbation [11] and patients with RA are at higher risk of ARI due to their underlying dysregulated immune system and being treated with immunosuppressive medications [12], the positive association between our primary and secondary outcomes and RA remained statistically significant (except for total hospital charges) after adjusting ARI.

RA is classically associated with excessive proinflammatory response by T helper type 1 (T_H-1) lymphocytes, while asthma is characterized by airway inflammation primarily involved overactivity of T helper type 2 (T_H-2) lymphocytes [5]. Conventional theory suggests an inverse relationship between T_H-1 cells predominant diseases and T_H-2 cells predominant diseases through counter-regulatory mechanisms [5]. However, recent studies demonstrated that they could coexist [13], which is consistent with our findings. The association between RA and asthma may involve T_H-17 lymphocytes, natural killer group 2D (NKG2D), and shared genetic markers including CD86 and CD40L interaction and HLA-DRB1 [14]. In addition, there is one recent study which identified a subgroup of asthma with a gene expression of T_H-1 predominant inflammatory pathway including tumor necrosis factor α (TNF- α) [15].

Asthma is a heterogeneous disorder, and studies have been undertaken to identify different subgroups of asthma with distinctive biological and clinical features, including different response to treatment and prognosis [16]. Based on our result and previous studies, we hypothesize that in asthmatic patients with concurrent RA, their asthma represents a distinctive subgroup that is more severe and carries a poorer prognosis. Anti-TNF therapy has been a landscape-changing treatment for RA [17]; however, in asthma, results from randomized controlled trials were mixed [18–21]. One of the possible explanations for the conflicting results was that anti-TNF therapy may be effective only in a subgroup of asthmatic patients with enhanced TNF- α axis, though there is currently no proposed objective measurement for it. Since TNF- α pathway makes

a major contribution to the pathogenesis of RA [17], whether anti-TNF therapy will improve the outcome in this subgroup of asthmatic patients with concurrent RA deserves more investigations.

There are several limitations of our study. First, our retrospective cross-sectional design makes it possible for bias from unmeasured confounders. At the meantime, our study used ICD-9 code to identify diagnosis, which poses a risk for misclassification bias. In addition, because we used an inpatient database, there may be a documentation bias for conditions which are commonly encountered in outpatient settings, such as tobacco abuse. Although it would be interesting and clinically important to evaluate how different RA treatment affects asthma outcome, there is no medication data recorded with NIS database. Last but not the least, the study populations were predominantly females, which may limit generalizability of the study findings to male populations.

Conclusion

Our study demonstrated that compared to those without RA, asthma exacerbation requiring hospitalization in patients with RA was associated with more respiratory and systemic comorbidities and increased in-hospital mortality, length of stay, and cost. We hypothesize that in asthmatic patients with concurrent RA, their asthma may represent a distinctive subgroup that is more severe and carries a poorer prognosis.

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Compliance with ethical standards

Disclosures None.

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Supplement Material 1

CD 9 code and AHRQ comorbidity measures used to identify respiratory and systemic comorbidities

Obesity	AHRQ comorbidity measure: Obesity
Acute Respiratory Infection	460 - 466
Chronic Obstructive Pulmonary Disease	491.xx, 492.x, 496
Bronchiectasis	494.x
Obstructive Sleep Apnea	327.23
Congestive Heart Failure	428.xx
Selected Interstitial Lung Diseases*	516.3x, 714.81, 515
Pulmonary Hypertension	416.0, 416.8
Hypertension	401.x, 405.xx
Diabetes Mellitus	250.xx
Coronary Artery Disease	410 - 414
Cerebrovascular Disease	430 - 438
Chronic Kidney Disease	580 - 593, 585.x
Chronic Liver Disease	571.xx, 070.xx (excluding 070.0, 070.01, 070.20, 070.21, 070.30, 070.31, 070.41, 070.43, 070.51, 070.53)
Cancer	140.xx - 208.xx, 2090.xx - 2093.xx

* Selected ILD were RA associated ILD (RA-ILD), idiopathic interstitial pneumonia, including all eight histological subtypes and pulmonary fibrosis