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Original article

The association of gout with incident giant cell arteritis in older adults

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ABSTRACT

Objectives: To assess whether gout is associated with a higher or lower risk of a new diagnosis of giant cell arteritis (GCA) in older adults, adjusting for known risk factors of GCA.
Methods: We used the 5% Medicare claims to conduct a multivariable Cox regression analyses to assess the association of gout with incident GCA in adults 65 years or older adjusting for age, gender, race (known risk factors for GCA) and Charlson–Romano comorbidity score, the use of medications for cardiovascular diseases (statins, beta-blockers, diuretics, ACE-inhibitors) and gout (allopurinol, febuxostat). Hazard ratios (HR) and 95% confidence intervals (CI) were calculated.
Results: There were 3004 incident cases (new diagnosis) of GCA with crude incidence rates of GCA of 28.0/100,000 person-years in patients without gout and 63.8/100,000 person-years in patients with gout. Multivariable-adjusted analyses showed that preexisting gout was associated with a higher risk of incident/new GCA diagnosis with a hazard ratio of 2.05 (95% CI: 1.76, 2.40), confirmed in sensitivity analyses that substituted continuous Charlson–Romano comorbidity score with categorized score or individual comorbidities (plus hypertension, hyperlipidemia, and coronary artery disease). Older age, female gender, white race and higher comorbidity index, were also associated with a higher hazard of GCA. Subgroup analyses did not show any significant variation of the association of preexisting gout with incident GCA by age, race or sex.
Conclusions: Gout was associated with more than 2-fold higher risk of incident GCA in older adults, independent of known risk factors of GCA. Future studies should explore the underlying mechanisms for this association.
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1. Introduction

Giant cell arteritis (GCA) is an autoimmune inflammatory vasculitis that affects large and medium sized arteries in people 50 years or older [1]. GCA is the most common primary vasculitis [1]. In a century since its first description, the only well-described risk factors for GCA are older age, female gender and being Caucasian [1]. Polymyalgia rheumatica (PMR) is the most closely associated condition with GCA [2]; herpes zoster may also be associated [3,4], although a recent study indicated that this association may be not specific to herpes zoster infection only [5]. Significant advances in our understanding of pathogenetic mechanisms of GCA have occurred in the last two decades [6–9].

On the other hand, it is challenging to study the epidemiology of GCA in population-based cohort studies. A prime example of difficulty in studying the risk factors of GCA is that in an epidemiological study that examined 50-years of data by a trained nurse who reviewed the medical records, only 173 cases of GCA could be examined [3]. Large tertiary-center cohorts are not representative and do not allow epidemiological evaluations. Therefore, studies using administrative databases might offer an imperfect solution to this problem. Database studies can uncover novel associations that can then be confirmed or dismissed using other data sources and study designs (i.e., cohort studies).

Gout, the most common inflammatory arthritis in adults, is characterized by the formation of monosodium urate crystals, which result in the activation of inflammasome and an increased production of pro-inflammatory cytokines, such as IL-1 beta (IL-1β), IL-6, IL-18 and others [10], which also play a central role in GCA [11]. Gout also increases in prevalence with age [12], similar to GCA. The sharing of inflammatory pathways and similar age of onset

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and increasing prevalence with age [3,12] suggests a possibility of an association of gout and GCA. Polymyalgia rheumatica (PMR), a disease considered to be variant of the same disease process as GCA and strongly associated with it [2], can evolve in to rheumatoid arthritis (RA) especially in the elderly [13]; gout rarely coexists with rheumatoid arthritis (RA), although a recent study highlights the clinical scenarios where gout may mimic RA [14]. The gender distribution differs between gout and GCA. This would indicate that the two conditions would likely not be associated.

The elderly population is rapidly growing in the US – adults 65 years or older will increase from 34.4 million in 2000 to more than 70 million in 2030 [15]. Given the knowledge gap regarding risk factors for GCA, studies of novel risk factors of GCA in the elderly are of interest. We aimed to assess whether gout was associated with a lower or higher risk of a new diagnosis of GCA in the elderly, and whether this association varied by age, gender or race/ethnicity in subgroup analyses.

2. Methods

2.1. Data sources and study cohort

We used the 5% Medicare claims sample from 2006–2012 for this cohort study. Study eligibility criteria were:

- Medicare beneficiaries enrolled in Medicare fee-for-service (Parts A, B), and not enrolled in Medicare Advantage Plan (due to incomplete claims data);
- people who lived in the US from 2006–2012.

Medicare is a federal health insurance program that covers 59 million Americans currently. Medicare beneficiaries are typically senior citizens aged 65 and older, although adults with qualifying permanent disabilities or certain approved medical conditions (such as end-stage renal disease or Lou Gehrig's disease) are also eligible for Medicare benefits, which include payment for a variety of health care expenses, inpatient and outpatient. The University of Alabama at Birmingham's Institutional Review Board approved this study and waived the requirement for informed consent (#120207004).

2.2. Study outcome

The study outcome was incident GCA, defined as the presence of at least two claims for GCA at least 4 weeks apart, identified with International Classification of Diseases, ninth revision, common modification (ICD-9-CM) code of 446.5, with an absence of GCA diagnosis in the baseline period of 365 days (1/1/2005 to 12/31/2005). The ICD-9-CM code-based approach is valid for identifying patients with vasculitis codes (that includes GCA, the most common vasculitis) with sensitivity of 94% and specificity of 95% [16]. To confirm that the GCA diagnoses in Medicare claims reflected true disease rather than misdiagnosis, we compared our GCA incidence rates to those reported for a similar age-group in population-based studies from Minnesota, Norway and Sweden [3,17,18].

2.3. Predictor of interest, covariates and confounders

The main predictor of interest was gout, identified by the presence of two claims for gout at least 4 weeks apart, based on the ICD-9-CM diagnostic code, 274.xx. The date of the second diagnostic code for gout was considered the date a patient met the diagnosis of gout. This ICD-9-CM code algorithm for gout has high accuracy with sensitivity of 90% and specificity of 100% [19]. The gout diagnosis had to always occur prior to the GCA diagnosis for study inclusion.

We obtained data on potential confounders and important covariates in our study. These included patient demographics (age, gender, and race/ethnicity; from Medicare denominator file and the beneficiary summary file), medical comorbidities (from the inpatient and outpatient Medicare claim files) during the baseline period. Medical comorbidity was assessed using a validated weighted comorbidity index, the Charlson–Romano comorbidity index. Additionally, the use of common cardiovascular medications and gout medications (Medicare part D prescription claims) was tracked throughout the observation period as a time-varying covariate, similar to patient age. We assessed the use of common cardiovascular drugs [statins, beta-blockers, diuretics, and angiotensin converting enzyme (ACE)-inhibitors], and gout drugs (allopurinol, febuxostat), to potentially reduce confounding bias as indicators of mild or suspected disease in the absence of a diagnostic code, markers for higher disease severity when present along with a diagnostic code, and/or their independent effects on inflammation.

2.4. Statistical analyses

Characteristics of patients with vs. without incident GCA were compared, and the respective crude incidence rates of GCA were calculated. We used a multivariable-adjusted Cox proportional hazard regression model to assess the association of gout with incident GCA. Our main multivariable-adjusted model included age, gender and race (known risk factors for GCA), Charlson–Romano comorbidity index score, and medications for cardiovascular diseases and gout. Sensitivity analyses were done by replacing the continuous Charlson–Romano score with: (1) categorical variable (Charlson-Romano score of 0, 1 or ≥ 2; model 2); and (2) individual Charlson–Romano comorbidities (model 3; also included hypertension, hyperlipidemia, and coronary artery disease). We calculated hazard ratio (HR) and 95% confidence intervals. Subgroup analyses by race, gender and age were done to assess whether the association of gout with GCA varied by these key patient characteristics.

2.5. Role of the funding source

The funding body did not play any role in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

3. Results

3.1. Study cohort characteristics and crude incidence rate of GCA

Among 1,737,027 eligible people in the study cohort, there were 3004 cases of incident GCA during the follow-up; 2,808 in people without gout and 196 in people with gout. People with incident GCA had a mean duration of gout of 2.2 years prior to the GCA diagnosis (SD: 1.7; median: 1.8; IQR: 0.5, 3.5 years). The crude incidence rate of GCA was 28.0 per 100,000 person-years in people without gout and 63.7 per 100,000 person-years in people with gout. The GCA incidence rate of 28/100,000 in our non-gout population mirrored the incidence rate of 19 to 29/100,000 noted in 50+ year-olds in the three largest population-based studies of GCA.

Compared to people who did not develop GCA, people who developed GCA were more likely to be older, female (58% vs. 75%), Caucasian (86% vs. 91%) and have a Charlson–Romano comorbidity score ≥ 2 (37% vs. 44%; Table 1). A higher prevalence of several comorbidities was noted in people with GCA compared to those

Table 1
Demographic and clinical characteristics of people with or without new giant cell arteritis (GCA).

	Study cohort	GCA during the follow-up	
		No	Yes
Total, *n*	1,737,027[a]	1,734,023	3004
Age, mean (SD)	75.3 (7.6)	75.3 (7.6)	76.1 (6.5)
Gender, *n* (%)			
Male	736,730 (42.4%)	735,977 (42.4%)	753 (25.1%)
Female	1,000,297 (57.6%)	998,046 (57.6%)	2251 (74.9%)
Race/ethnicity, *n* (%)			
White	1,496,380 (86.1%)	1,493,658 (86.1%)	2722 (90.6%)
Black	142,611 (8.2%)	142,431 (8.2%)	180 (6.0%)
Other/unknown	98,036 (5.6%)	97,934 (5.6%)	102 (3.4%)
Charlson–Romano comorbidity score, mean (SD)	1.61 (2.39)	1.61 (2.39)	1.76 (2.22)
Charlson–Romano score			
0	913,122 (52.6%)	911,831 (52.6%)	1291 (43.0%)
1	174,805 (10.1%)	174,420 (10.1%)	385 (12.8%)
≥2	649,100 (37.4%)	647,772 (37.4%)	1328 (44.2%)
Charlson–Romano comorbidities			
Myocardial infarction	69,150 (4.0%)	69,011 (4.0%)	139 (4.6%)
Heart failure	204,397 (11.8%)	204,035 (11.8%)	362 (12.1%)
Peripheral vascular disease	170,001 (9.8%)	169,634 (9.8%)	367 (12.2%)
Cerebrovascular disease	169,791 (9.8%)	169,356 (9.8%)	435 (14.5%)
Dementia	78,394 (4.5%)	78,337 (4.5%)	57 (1.9%)
Chronic pulmonary disease	271,909 (15.7%)	271,276 (15.6%)	633 (21.1%)
Connective tissue disease	47,979 (2.8%)	47,671 (2.7%)	308 (10.3%)
Peptic ulcer disease	32,976 (1.9%)	32,916 (1.9%)	60 (2.0%)
Mild liver disease	8568 (0.49%)	8549 (0.49%)	19 (0.63%)
Diabetes	321,602 (18.5%)	321,051 (18.5%)	551 (18.3%)
Diabetes with end organ damage	95,074 (5.5%)	94,900 (5.5%)	174 (5.8%)
Hemiplegia	14,430 (0.83%)	14,405 (0.83%)	25 (0.83%)
Renal failure/disease	59,890 (3.4%)	59,763 (3.4%)	127 (4.2%)
Any tumor, leukemia or lymphoma	175,225 (10.1%)	174,865 (10.1%)	360 (12.0%)
Moderate or severe liver disease	2009 (0.12%)	2006 (0.12%)	3 (0.10%)
Metastatic cancer	18,049 (1.0%)	18,029 (1.0%)	20 (0.67%)
AIDS	554 (0.03%)	554 (0.03%)	0 (0.00%)
Hypertension	840,033 (48.4%)	838,163 (48.3%)	1870 (62.3%)
Hyperlipidemia	605,197 (34.8%)	603,731 (34.8%)	1466 (48.8%)
Coronary artery disease	305,989 (17.6%)	305,328 (17.6%)	661 (22.0%)

[a] For incident GCA, a baseline period of 365 days was needed without a diagnosis.

without, in particular cerebrovascular disease, chronic pulmonary disease and connective tissue disease (Table 1).

3.2. Multivariable-adjusted estimates for hazards of incident GCA with gout

In the main multivariate model, gout was associated with an increased risk of incident GCA, HR was 2.05 (95% CI: 1.82, 2.54; Table 2). Women were 2.2-times more likely to have incident GCA compared to men, older age was associated with a higher HR of GCA and having 2 or more comorbidities was associated with a 1.7-times HR of incident GCA. Compared to white, black or other race were each associated with 0.6–0.7 times HR of incident GCA (Table 2).

Subgroup analyses of the association of gout with GCA by age, race, and gender showed no statistically significant differences by race or gender, likely due to wide confidence intervals (Table 3).

4. Discussion

In this study of elderly Medicare recipients, gout was independently associated with a 2-fold higher risk of incident GCA, and there were roughly 33 more GCA cases per 100,000 person-years in gout vs. non-gout populations. A GCA incidence rate of 28/100,000 in our non-gout population mirrored the GCA incidence rate of 19 to 29/100,000 noted in 50+ year-olds in the general population in three largest population-based studies of GCA from Minnesota, USA, Norway and Sweden [3,17,18], which are most widely-cited for GCA epidemiology. This finding provided a strong support to the accuracy of the ICD-9-CM codes used for GCA in our study and the validity of our study findings. Although the highly significant *P*-value is related to the large sample size (a desirable study characteristic), the 2-fold increase in the risk of incident GCA cannot be ignored. To our knowledge, these findings are novel and surprising.

Gout and GCA are both characterized by chronic inflammation and are common in the elderly. The pathologic lesion in arteries consists of macrophages and T cells, often organized into granulomas [11]. IL-1β, IL-6 and IL-18 are the main cytokines responsible for severe inflammation in gout [10,20], which also play a central role in the pathogenesis of GCA [11]. In addition to a higher production of IL-1β and interferon gamma (IFN-γ) by temporal arterial vessel walls in GCA [21], studies demonstrated a key role for IL-1β and IL-6 in the acute phase response in GCA [22–24]. Case reports of refractory GCA responding to IL-1 blockade with anakinra, an IL-1 receptor antagonist, further support the hypothesis that IL-1β may be one of key cytokines in the pathogenesis of GCA [25]. Activation and increased production of pro-inflammatory cytokines, including IL-1ß, IL-6 and IL-18 in gout may potentially explain the increased risk of GCA in people with gout. A recent GCA epidemiological study concluded that "long-standing alterations of the immune system are associated with susceptibility to GCA" [5], similar to our hypothesis. Our findings and these hypotheses need to be tested in future studies and examined in other datasets, and findings need confirmation in population-based cohorts.

A practical implication of our study finding is that physicians providing care to gout patients should target optimal control of gout with urate-lowering and anti-inflammatory therapy. Our study was not designed to investigate whether improving gout control could have potential benefits of reducing the risk of GCA, an impor-

Table 2
Association of gout and other risk factors with incident GCA.

	Multivariable-adjusted(Model 1)[a]		Multivariable-adjusted(Model 2)[a]		Multivariable-adjusted (Model 3)[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (in years)						
65–< 75	Ref		Ref		Ref	
75–< 85	**1.70 (1.57, 1.83)**	**< 0.0001**	**1.66 (1.54, 1.80)**	**< 0.0001**	**1.62 (1.50, 1.75)**	**< 0.0001**
≥ 85	**1.27 (1.11, 1.44)**	**0.0003**	**1.24 (1.09, 1.41)**	**0.001**	**1.30 (1.14, 1.48)**	**< 0.0001**
Gender						
Male	Ref		Ref		Ref	
Female	**2.19 (2.02, 2.38)**	**< 0.0001**	**2.20 (2.02, 2.39)**	**< 0.0001**	**2.10 (1.93, 2.29)**	**< 0.0001**
Race						
White	Ref		Ref		Ref	
Black	**0.67 (0.58, 0.78)**	**< 0.0001**	**0.67 (0.58, 0.78)**	**< 0.0001**	**0.72 (0.62, 0.83)**	**< 0.0001**
Other	**0.56 (0.46, 0.68)**	**< 0.0001**	**0.56 (0.46, 0.69)**	**< 0.0001**	**0.60 (0.49, 0.73)**	**< 0.0001**
Charlson–Romano score, per unit change	**1.09 (1.07, 1.10)**	**< 0.0001**				
Charlson–Romano score						
0	N/A		Ref		N/A	
1			**1.56 (1.39, 1.75)**	**< 0.0001**		
≥ 2			**1.71 (1.58, 1.85)**	**< 0.0001**		
Gout	**2.05 (1.76, 2.40)**	**< 0.0001**	**2.02 (1.73, 2.35)**	**< 0.0001**	**1.81 (1.55, 2.12)**	**< 0.0001**

GCA: giant cell arteritis; N/A: not applicable; HR: hazard ratio; CI: confidence interval; Ref: referent category.
Bold represents statistical significance, with a *P*-value < 0.05.

[a] Model 1 included Charlson–Romano score as a continuous variable; model 2 replaced it with categorized Charlson–Romano score; and model 3 replaced it with each of the 17 Charlson–Romano comorbidities (plus hypertension, hyperlipidemia, coronary artery disease); all models were adjusted for medications for cardiovascular diseases (statins, beta-blockers, diuretics, ACE-inhibitors) and urate-lowering therapy for gout (allopurinol, febuxostat).

tant but difficult question that subsequent studies need to address. Since GCA can lead to irreversible vision loss and is associated with increased mortality [1,2,26], its risk reduction is highly desirable, despite rare incidence. Due to the low incidence of GCA, regular screening for GCA in gout patients is unlikely to yield meaningful improvement in the clinical detection rate of GCA.

Our study showed that elderly women were 2.2-times more likely than men and African-Americans were 0.7-times as likely as whites to have incident GCA. The incidence of GCA increased after 65 years of age, as reported previously [3,4]. A novel study finding was the association of 2 or more comorbidities with a 1.7-times HR of incident GCA, which indicated increased susceptibility in people with higher comorbidity load, and the potential utility of assessing Charlson comorbidity index in older adults.

We found no significant difference in the risk of GCA associated with gout by age, gender or race, an important negative finding. However, HR of GCA with gout differed numerically in blacks vs. whites, 2.81 (95% CI: 1.73, 4.58) vs. 1.96 (95% CI: 1.65, 2.32), respectively.

Our study has several limitations. Our results may not be generalizable to younger people (< 65 years). Our study findings are at potential risk of confounding bias due to observational design, which we attempted to reduce by including several potential confounders in our study and performing sensitivity analyses. Findings are at the potential risk of misclassification bias, since we used diagnostic codes, which carry a possible risk of inaccuracy. We used validated algorithms for gout and GCA to reduce misclassification bias, and we expected this bias to be non-differential. A study that used gout classification criteria as gold standard reported lower accuracy for diagnostic codes [27], indicating potential misclassification bias, which would bias the findings towards null, making them conservative estimates. In addition, the GCA incidence rate in our study matched the reported incidence rate in 50+ year-olds from three widely-cited, largest-to-date population-based studies of GCA from Minnesota, Norway and Sweden [3,17,18], which should increase confidence in study findings. In our cohort, 5.4% people had a diagnosis of gout which is within the range of prevalence rates of 3.7% to 12.6% for US adults 50 years or older previously reported [12], further supporting the diagnostic accuracy. We considered limiting the cohort to biopsy-proven GCA, but decided against it, since not all patients with GCA get biopsies and people with GCA may have negative biopsies but still meet criteria for GCA [28,29], and Medicare claims do not provide results of tests. A potential diagnostic delay in GCA is sometimes seen in clinical practice which implies that in some cases the onset of GCA symptoms may have preceded gout onset even though the diagnosis of GCA occurred after the diagnosis of gout; however, the median time from gout to GCA diagnosis was 1.8 years, indicating that this may only have contributed a small measurement error, at worst. Surveillance bias is possible, if the health care providers were more likely to monitor or investigate patients with gout for the development of symptoms of GCA compared to people without gout. Given no

Table 3
Association of gout with incident GCA, in subgroup analyses by age, gender and race.

	Multivariable-adjusted (Model 1)		Multivariable-adjusted (Model 1)		Multivariable-adjusted (Model 1)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
	65–< 75 years		75–< 85 years		≥ 85 years	
Gout	**2.24 (1.60, 2.85)**	**< 0.0001**	**1.86 (1.49, 2.33)**	**< 0.0001**	**2.26 (1.40, 3.63)**	**0.0008**
	Female		Male			
Gout	**1.91 (1.55, 2.35)**	**< 0.0001**	**2.24 (1.77, 2.84)**	**< 0.0001**		
	Black		White		Other race	
Gout	**2.81 (1.73, 4.58)**	**< 0.0001**	**1.96 (1.65, 2.32)**	**< 0.0001**	**2.56 (1.30, 5.06)**	**0.007**

Interaction terms: Gout × age *P*-value = 0.18; Gender × gout *P*-value = 0.16; Gout × race *P*-value = 0.14.
GCA: giant cell arteritis; HR: hazard ratio; CI: confidence interval.
Bold represents statistical significance, i.e., *P*-value < 0.05.

known association of gout and GCA, this is unlikely to explain our findings. We recognize that any association noted in an observational study may be due to chance; therefore, reproduction of these findings is essential.

Our study included a large sample size, and a representative population of the US elderly. Our study findings were robust, replicated in several multivariable-adjusted models.

5. Conclusion

Gout was associated with an almost twice the risk of GCA in the elderly, independent of other factors. Older age and higher medical comorbidity was associated with a higher risk of GCA. Male gender and African-American race were associated with a lower risk of incident GCA. The risk of GCA associated with gout did not differ significantly by age, sex or race, although non-significant trends were noted by race. Future studies should explore the common disease mechanisms that underlie this association of gout with GCA, including a focus on the pro-inflammatory cytokines such as IL-1ß, IL-6, IL-18 and others.

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Author contributions

JAS designed the study, developed study protocol, reviewed analyses and wrote the first draft of the paper. DC performed the data abstraction and data analyses. All authors made revisions to the manuscript, read, and approved the final manuscript.

Consent to publish

No individual person's data were presented in any form in this study and therefore no consent to publish is required.

The corresponding author certifies that all authors approved the entirety of the submitted material and contributed actively to the study.

Disclosure of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2018.05.011.

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