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Epidemiology Of Giant Cell Arteritis Related Hospital Admissions In The United States From 2007-2016

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EPIDEMIOLOGY OF GIANT CELL ARTERITIS RELATED HOSPITAL ADMISSIONS IN THE UNITED STATES FROM 2007-2016

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By

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Abstract

The primary objective of this retrospective cross-sectional study is to investigate the national and regional incidence, epidemiology, and clinical characteristics of Giant Cell Arteritis (GCA) related hospital admissions in the United States (US) from 2007 to 2016. The secondary objectives are to investigate the rate of systemic complications, ocular involvement, resource utilization, and predictors of mortality in GCA. The Nationwide Inpatient Sample was queried to identify all patients hospitalized with an ICD 9 or ICD 10 code for GCA between 2007-2016. Incidence was calculated using US Census data, and risk factors for in-hospital mortality were analyzed with logistic regression.

A weighted total of 200,533 GCA related hospital admissions were included. The overall national incidence of GCA related hospital admissions was 6.42 per 100,000 population and 19.81 per 100,000 population for those ≥50 years. The median age was 80 years. The incidence was 3 times higher in women than men (3.43 vs. 1.33 per 100,000 population) and 2 times higher in Caucasians than African Americans (7.52 vs. 3.75 per 100,000 population). The most common systemic comorbidity was hypertension (73.2%), followed by hyperlipidemia (42.0%), and diabetes mellitus (33.2%). Autoimmune disorders were common: 23% of patients had thyroid disease, 14.6% had polymyalgia rheumatica, and 5.2% had rheumatoid arthritis. 18% of GCA patients had ocular involvement, 8.6% had stroke or cerebral arteritis, and 2.87% had aortic dissection/aneurysm or myocarditis. The in-hospital mortality was 2.7%. Age ≥75 years (OR, 1.99; 95% CI, 1.85 – 2.13; p <0.001), stroke (OR, 1.83; 95% CI, 1.68 – 1.98; p <0.0001), and aortic compromise (OR, 1.76; 95% CI, 1.54 – 1.99; p <0.0001) were significant predictors of mortality. Notably, there was no increase in mortality in patients with ocular involvement or autoimmune disease. In the US, Giant Cell Arteritis preferentially affects older individuals, females, and Caucasians. Approximately one fifth of cases had ocular involvement during the same hospital admission. Stroke, aortic compromise, and increased age are associated with higher mortality risk.

Acknowledgements

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Contents

Introduction

Disease Presentation and Diagnosis

Giant Cell Arteritis (GCA), also known as temporal arteritis, cranial arteritis, and Horton disease, is the most common systemic vasculitis. It is a potentially devastating systemic inflammatory condition affecting medium- and large-sized arteries such as the aorta, carotid arteries, and their major branches – particularly the temporal artery, a branch of the external carotid artery. GCA is often called a "do-not-miss" diagnosis because of its severe complications, including blindness, stroke, and aortic compromise. However, GCA diagnosis is challenging, as patient presentation can often be non-specific, with up to 50% presenting with only constitutional symptoms of muscle pain, fever, weight loss, night sweats, and fatigue. [1,2] Other symptoms include new onset headache, jaw claudication, scalp and temporal artery tenderness, and visual problems. [1,2] Unfortunately, many elderly adults with headaches and muscle pain may go for weeks before being assessed for GCA by an ophthalmologist or rheumatologist.[1] It is thus important to have a high index of suspicion for GCA when treating populations most at risk to prevent disease progression and fatality.

GCA is a clinical diagnosis supported by data from lab tests and a temporal artery biopsy (TAB) as the defined gold standard, with a positive biopsy specificity of 100%. However, most patients suspected of GCA usually receive high-dose steroid therapy before confirmation of diagnosis in up to 60-86% of cases,[3] as the results from biopsy can take weeks. Unfortunately, due to its invasive nature, TAB does not come without complications and risks: unintended biopsies of nerves and veins, post-operative hematoma, scalp necrosis, wound infection, and facial nerve damage have all been reported.[4] TAB also has a false negative rate of 7%[5] due to early treatment and skip

lesions,[3] as biopsy specimens have a relatively short length of 1-1.5 cm and may not capture true diseased areas. In addition, up to 44% of patients with clinical symptoms and features typical of GCA have a negative TAB.[6] Bilateral temporal artery biopsies have been explored to improve sensitivity, with 5% of patients with an initial negative result having a positive biopsy on the contralateral side.[7] However, bilateral TAB is thought to carry additional risk for procedural complications and thus is not common practice.

New non-invasive imaging modalities for the detection of GCA are being used instead. The primary non-invasive imaging modalities used to augment GCA diagnosis accuracy include cranial/temporal artery duplex ultrasound, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET), contrast-enhanced high-resolution MRI of the superficial and extracranial arteries, and transdermal optical coherence tomography (OCT).[2] However, duplex ultrasound of the temporal artery (TA-US) with/without its axillary branches is often considered first-line in terms of imaging techniques because of its cost-effectiveness and relatively high sensitivity and specificity, however also requires training and expertise.[6]

In TA-US, operators look for compressibility of the temporal artery (suspicious for GCA when it is non-compressible/stiff) and/or the halo sign, which is a hypoechoic ring around the arterial lumen that represents edematous thickening of the arterial wall from inflammation.[8] When comparing TAB with TA-US, it appears that the two diagnostic methods have similar sensitivities (and in some studies, the sensitivity of TA-US was higher),[6] but TA-US has lower specificity. In a meta-analysis and systematic literature review of 32 studies published during the years of 1993-2017 that provided TAB results for patients satisfying the ACR criteria for GCA diagnosis, there was an

estimated pooled sensitivity of 77% for TAB. Meta-analyses of data from studies on TA-US (with a data pool of up to 20 individual studies) estimated the halo sign sensitivity for GCA to be from 55-77%,[9–12] but noted atherosclerosis as a significant cause of false-positives.[13] On the other hand, the specificity of a positive TAB result is 100% (as the defined gold-standard), whereas a systematic literature review of 20 studies on TA-US found the halo sign specificity to be 81% (95% CI: 75-86%) when compared to a positive TAB.[14]

In addition to imaging and TAB, laboratory markers of the acute phase response are used in diagnostic criteria, such as erythrocyte sedimentation rate by the Westergren method (ESR/WESR) or plasma viscosity (PV), and/or C-reactive protein (CRP). Previously, only ESR was used in diagnosis, however a combination of ESR and CRP gives the best sensitivity and specificity.[2] If available, PV should also be incorporated in diagnostic workup, as this marker is not influenced by time to analysis, age, gender, or hematocrit.[2] Interestingly, thrombocytosis (with an elevated platelet count $\geqslant 400 \times 10^3/\mu l$) was found to be more specific for GCA than WESR alone (91% vs 27%), and had higher positive and negative predictive values.[15] A combination of these tests with clinical features (such as ischemic vision loss, jaw claudication, and age) was found to be a strong predictor of positive diagnosis by TAB, and developed into a single diagnostic prediction model and calculator to help in the triage of patients suspected of GCA.[16]

As an early summary of the previously described diagnostic methods, the American College of Rheumatology (ACR) developed criteria in 1990 for the classification of GCA as listed in Supplemental Table 1 below (adapted from Davies et al).[3] For diagnosis of GCA, at least 3 out of 5 criteria must be met, yielding a sensitivity

of 93.5% and specificity of 91.2% for distinguishing GCA among other vasculitides. [5] However, many clinicians contest that the ACR 1990 classification criteria may need an update to include a wider phenotype of GCA, such as constitutional and PMR symptoms, and a combination of abnormal serologic markers with newer imaging techniques such as ultrasound, CT, MRI and ^{18}F-FDG-PET.[2]

Criteria	Description
Age at disease onset ≥50 years	Development of symptoms or findings beginning at age 50 years or older
New headache	New onset of or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
Elevated erythrocyte sedimentation rate	Erythrocyte sedimentation rate ⩾50 mm/h by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

Supplemental Table 1. ACR 1990 Criteria for Classification of Giant Cell Arteritis.[3]

GCA Initial and Maintenance Treatment

GCA is considered a medical emergency due to the threat of vision loss and thus treatment is initiated in suspects with high-dose pulse therapy of glucocorticoids. An example course is 0.5-1.0 g methylprednisolone for 3-5 days or a 3-day induction with IV methylprednisolone at 15 mg/kg/day, followed by oral prednisone maintenance therapy at an initial dose of 1 mg/kg/day. [2] Unfortunately, there is often significant delay in initiating treatment, with a mean diagnostic delay of 9 weeks for those with cranial

symptoms and 17.6 weeks for those without.[2] In response to this problem, fast track outpatient centers (FTC) have been established to provide widely advertised diagnostic evaluation and specialist assessment, such as with vascular ultrasound and immediate treatment with glucocorticoids. [2] For instance, one Norway FTC study showed promising results of reducing the risk of permanent vision loss by 88% when evaluated in the FTC (RR 0.12, 95% CI: 0.01-0.97, $p = 0.01$) in addition to decreased inpatient care, with conventionally evaluated patients having an average of 3 inpatient stay days vs 0.6 days when evaluated in the FTC ($p < 0.0005$).[17]

GCA maintenance therapy traditionally consists of long-term glucocorticoid treatment, with the majority of patients on treatment for 2 years, and most off glucocorticoids by 4 years.[2] However, up to 85% of patients experience steroid-related side effects with prolonged treatment [2] or do not tolerate steroids at all, leading to a need for steroid-sparing therapy. Currently, the only licensed adjunctive treatment is the IL-6 inhibitor (a recombinant humanized anti-IL-6 receptor antibody) Tocilizumab, which is approved for restricted use in GCA by the National Institute for Health and Care Excellence and NHS England.[2] Other potential treatments include methotrexate, aspirin, cyclophosphamide, mycophenolate, leflunomide, and anti-TNF therapy, however these agents have limited evidence of efficacy in the current literature. [2]

Theories on GCA Pathogenesis and Etiology

Various factors influencing the pathogenesis of GCA have been explored. With an observed pattern of GCA incidence peaks that cycle approximately every decade, many have theorized a potential link to infectious causes, seasonal conditions, or solar

patterns.[2] In studies from Sweden, UK, Scotland, and Israel, a seasonal distribution of peaks for biopsy-proven GCA incidence was observed, ranging from late winter and autumn to late spring and early summer in the different regions.[18] In contrast, in an Australian/New Zealand database analysis,[19] the authors explored the influence of seasons on GCA disease onset and found no statistically significant relationship. Furthermore, in a study conducted at the Wills Eye Institute in Pennsylvania, Poisson regression analysis did not find any significant trend in time or cyclic pattern related to year, season, or month.[20] However, a recent study on long-term trends[21] found high correlation with GCA incidence 0-1 years after an AL index minimum (auroral electrojet and geomagnetic activity maximum), both with a main peak at 10 years and a minor peak at 4-5 years. The authors theorized that the effects of geomagnetic disturbances may result in reduced melatonin (an anti-inflammatory agent) excretion and increased free radical formation, which may contribute to the inflammatory etiology of GCA.

In seeking a possible infectious etiology/trigger, several studies have found simultaneous fluctuations in the incidence of GCA and infectious epidemics, such as *Mycoplasma pneumoniae*, parvovirus B19, human parainfluenza virus type 1, and *Chlamydia pneumoniae*.[2,18,22–24] This pattern may suggest that previous infection predisposes a patient to the development of unregulated inflammation leading to GCA, or that patients with GCA are more likely to become infected with a pre-existing altered immune system.[2]

Although the true pathogenesis of GCA is unknown, there have been many theories about the molecular/genetic etiology of GCA. As GCA is strongly associated with polymyalgia rheumatica (PMR), thyroid disease, and rheumatoid arthritis, and is in

some cases, familial clustered, a genetic predisposition to the development of autoimmunity is theorized.[25] For instance, 40% to 60% of GCA patients have concurrent PMR signs and symptoms, such as shoulder, hip, and neck pain in addition to morning stiffness.[26] In patients diagnosed with PMR, up to 21% are also diagnosed with GCA.[25] Furthermore, the high prevalence of GCA in Scandinavian or Caucasian populations may be explained by the association with the HLA-DRB1*04 allele, which is more common in Northern Europeans.[2,25]

Interestingly, there may also be a metabolic factor in the pathogenesis of GCA, with studies from Sweden and Iceland have found a reduced risk of GCA in obese and overweight individuals, in addition to a negative association with fasting blood glucose.[25] This posited relationship between diabetes mellitus and GCA remains controversial, with some studies finding diabetes to be less common in GCA patients[27,28] while others describe a positive association.[24]

GCA Comorbidities and Complications

Several other disease processes both lead to and stem from the development of GCA. GCA is associated with many systemic and ocular complications, with the most feared being permanent vision loss due to ischemic optic neuropathy and aortic/large vessel compromise.[29] Other important complications include amaurosis fugax, stroke, acute myocarditis, glossitis, and glossodynia (tongue pain).[30,31] We distinguish these from GCA comorbidities, which in prior studies hypertension, diabetes mellitus, previous atheromatous disease, venous thromboembolic diseases, thyroid diseases, and severe infections were shown to have high relative risk or odds ratios.[23,24,32,33] In addition,

independent of age or sex, GCA patients had higher rates of osteoporosis, likely due to the main treatment with systemic glucocorticoids.[34] Furthermore, both prior and active smoking history was strongly associated with GCA, especially in women.[18,32,35]

Previous Epidemiology Research

In our study, we were specifically interested in the epidemiology of GCA to understand and provide a general heuristic or reference for clinical diagnosis. In prior research from multiple North American and European studies, GCA was found to be more common in older adults generally over 50 years of age, who are Caucasian (particularly those of Scandinavian descent) and female, ranging from two-thirds to three-quarters of all GCA patients identifying female.[20,26,36,37] In addition, in studies on populations that are not predominately Caucasian, such as from Saudi Arabia, Japan, Korea, and in Alaskan Natives, the incidence of GCA was found to be very low.[18,25,38,39] However, a recent study by Gruener et al. reported similar incidence of GCA in Caucasian and African American populations when matched for age and sex.[36] This study was conducted at a single tertiary care hospital in the United States and concerns remained that it may not have been representative of the United States population at large; interest in generalizing conclusions about GCA demographics led us to conduct this investigation.

There are many difficulties when performing an epidemiological study of GCA. For example, in case definition per ACR classification criteria from 1990, patients below age 50 with a large vessel vasculitis are often not considered to have GCA and do not get a temporal artery biopsy.[40] Another challenge is case capture; as GCA is a rare disease that primarily occurs in the elderly, a large elderly population is needed to determine

incidence and prevalence, which may not always be feasible. Furthermore, there are many inconsistencies in the existing GCA epidemiology literature. For example, some studies draw from a TAB-GCA positive only patient population, while others use GCA clinical diagnostic codes that include both biopsy-proven patients and those meeting the ACR criteria without necessary biopsy for GCA diagnosis. However, the TAB method of diagnosis may not capture all GCA cases, as skip lesions and inadequate specimen length may lead to a higher false negative rate.[40] Finally, in calculating incidence and prevalence, many prior studies only included patients over 50 years of age.

Study Purpose and Goals

To date, there has been no nationwide study conducted to investigate the incidence and epidemiology of GCA in the United States. As GCA is a rare disease, conducting such a study would require a large population sample that is demographically representative of the entire United States population, and hence would be costly and time consuming.[40] In our study, we use the Nationwide Inpatient Sample (NIS) as a national surveillance system for all GCA related hospital admissions in the United States to generate population level estimates. We aim to observe the trend of GCA incidence in different ethnicities, especially after the astonishing results from the Wilmer Eye Institute study.[36] Given prior conflicting studies about seasonal patterns, we will also take note of the highest incidence months. We are also interested in any patterns found in GCA incidence and prevalence in the different regions of the United States, in addition to age, gender and social-economic status. As noted in the study by Watts et al,[40] our large dataset provides power to assess incidence in less common subsets of GCA patients, such as those who are younger than 50 years, non-Caucasian, and male. We aim to explore the range of comorbidities and complications associated with GCA, such as those of

ophthalmic, metabolic, autoimmune, and inflammatory origins. Finally, we will assess for predictors of mortality, with emphasis on whether visual complications are a significant risk factor.

Hypothesis

We hypothesize that given the vast amount of data from prior European and US studies, and the unique ethnic makeup of the Baltimore area in the Wilmer Eye Institute study, [36] GCA in the US nationally will be predominantly in elderly, Caucasian, and female populations. In addition, given the rise in average age of the US population, we expect an upwards trend in GCA incidence. Furthermore, as medical costs of hospitalization increase generally, we expect the average charge for GCA-related hospitalizations to also increase.

Methods

Student Contributions

Karen Qiang and Dr. Tahreem Mir, MD jointly produced the study design and hypothesis. Karen Qiang performed the background research and literature search for the study, drafted the manuscript and created the figures and tables. Drs. Tahreem Mir and Ninani Kombo, MD, provided invaluable mentorship and helped edit the manuscript into its final version. Dr. Wei (Tony) Fang, PhD, extracted all data from the NIS database and performed all statistical analyses. This study was later presented at national conferences; Women in Ophthalmology and American Academy of Ophthalmology (2021), as podium presentations by Karen Qiang. Currently, a manuscript is being revised for submission to *Arthritis & Rheumatology*, published by the American College of Rheumatology.

Data Source & Study Population

The NIS was queried between 2007 to 2016, to identify all patients admitted with a primary or secondary diagnosis of GCA. The NIS is part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ) and is the largest all payer inpatient database in the US. The NIS sampling strata includes hospital characteristics (e.g. urban or rural locations, hospital size, and teaching status) and payer status, in addition to patient demographics (age, race, sex, and median household income per patient's ZIP code as outlined in the NIS data element descriptions[41–44]) and admission details. The data was weighted according to the NIS sampling frame to generate national estimates.[45]

Until 2012, the NIS database comprised of a 20% stratified systematic sample of all US community hospitals, with all discharges retained from those hospitals. In 2012, to improve national estimates, the database was redesigned to include a 20% stratified sample of discharges from all hospitals in the HCUP. The NIS contains data for approximately 7 million hospital discharges per year from 44 participating states, representing 98% of the hospitalized US population. The institutional review board at the West Virginia University School of Medicine granted this study exempt status, as all data are publicly available and do not include patient identifiers. This study was conducted in adherence to the Declaration of Helsinki and United States federal and state laws.

Patients with a diagnosis of GCA and associated systemic comorbidities and complications were identified using relevant International Classification of Diseases, Ninth and Tenth Revision-Clinical Modification (ICD-9 & ICD-10) codes. Both primary

diagnosis (ICD-9 or ICD-10 code listing GCA as the first diagnosis) and secondary diagnosis of GCA (any listing of GCA in subsequent diagnosis codes in the admission diagnosis list) were included in our study. Median charge per hospitalization and total charges per year were calculated and inflation-adjusted using the Consumer Price Index (CPI) for Hospital Services from the US Bureau of Labor Statistics,[46] using the CPI in January per year in comparison to the CPI in December 2020.

Statistical Analysis

Statistical analysis consisted of descriptive statistics and regression analysis. Descriptive statistics were presented as frequencies with percentages for categorical variables and mean with standard error of mean (SEM) for continuous variables. Annual incidence of GCA was calculated per 100,000 population using US census data; the total number of GCA hospital admissions were divided by the total US population in the same period. Univariate and multivariable logistic regression models were used to assess variables associated with mortality. Comparisons between groups were done with a Chi-square test for categorical variables and independent samples t-test and Wilcoxon rank sum tests for continuous variables. Statistically significant associations after controlling for variables were calculated with a Cochran-Mantel-Haenszel test. Significance of trends over time was conducted using simple linear regression analysis. Differences in incidence between gender and racial groups were conducted with Wilcoxon rank sum and Kruskal-Wallis tests respectively. All p-values were nominal and a value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary NC).

Results

Sociodemographic and Baseline Characteristics

Demographics and Baseline Characteristics are described in Table 1. There was an estimated weighted 200,533 GCA-related hospital admissions during the study period, where 13.14% admissions had GCA as the primary diagnosis. The median age of GCA patients was 80 years, and 74.2% were female. Most patients were Caucasian (73.6%), followed by African American (7.4%), Hispanic (4.5%), and Asian/Pacific Islander (1.2%). The majority of patients were insured through Medicare or Medicaid (87.8%), while approximately 10% had private insurance. There was an even distribution of socioeconomic status among all household median income quartiles. The highest percentage of GCA related hospitalizations were in the South (32.8%). Many GCA patients presented to urban teaching hospitals (49.7%) and hospitals classified as large, based on bed size (58.4%). Most GCA patients were treated in urban hospitals (87.05%) and discharged home with (19.47%) and without (46.73%) home health care. The months of admission were evenly distributed, without a seasonal trend in GCA incidence.

Demographic Characteristics	**Total Weighted Number of GCA-related Hospitalizations=200533, *n* (%)**
Age, years Mean ± SEM Median	 77.70±0.05 80
Age, years <50 50-59 60-69 70-79 80+	 2489 (1.24) 9022 (4.50) 27949 (13.94) 59969 (29.91) 101091 (50.42)
Gender	

Female	148734 (74.17)
Race	
White	147512 (73.56)
African American	14771 (7.37)
Hispanic	8950 (4.46)
Asian, Pacific Islander	2276 (1.13)
Others	4165 (2.08)
Unknown	22862 (11.40)
Expected Primary Payer	
Medicare and Medicaid	175876 (87.8)
Private insurance	20367 (10.17)
Self-pay	1712 (0.85)
No charge	208 (0.1)
Others	2104 (1.05)
Household Median Income Quartile	
0-25th	43532 (21.71)
26th- 50th	50014 (24.94)
51st -75th	50854 (25.36)
76th-100th	52940 (26.4)
Unknown	3195 (1.59)
Region	
Northeast	48545 (24.21)
Midwest	49899 (24.88)
South	65670 (32.75)
West	36420 (18.16)
Bed Size of Hospital	
Small	32127 (16.07)
Medium	51095 (25.57)
Large	116636 (58.36)
Location and Teaching Status of Hospital	
Rural	25883 (12.95)
Urban nonteaching	74614 (37.33)
Urban teaching	99361 (49.72)
Length of Hospital Stay, days	
Mean ± SEM	5.38 ± 0.03
Median	4
Month of Admission	

January	16878 (8.85)
February	15700 (8.23)
March	16729 (8.77)
April	16014 (8.4)
May	16455 (8.63)
June	15726 (8.25)
July	15801 (8.29)
August	16645 (8.73)
September	14897 (7.81)
October	15828 (8.3)
November	14547 (7.63)
December	15488 (8.12)
Disposition of Patient	
Home or self-care	93690 (46.73)
Transfer to short-term hospital	4814 (2.4)
Skilled nursing or intermediate care facility	56674 (28.27)
Home health care	39030 (19.47)
Against medical advice	714 (0.36)
Unknown	138 (0.06)

Table 1. **Sociodemographic and Baseline Characteristics.** Data extracted from NIS database from 2007-2016; total GCA-related hospitalizations per category and corresponding percentage of total *n* in parentheses.

National and Regional Incidence of GCA-related Hospital Admissions

The national and regional incidence of GCA-related hospital admissions is presented in Figure 1A and 1B. The national incidence of GCA related hospital admissions was 6.42 per 100,000 population and 19.81 per 100,000 population in those >50 years of age during the study period (Figure 1A). After adjusting for region population, incidence was highest in the Northeast (8.7 per 100,000 population), followed by Midwest (7.42 per 100,000 population), South (5.63 per 100,000 population), and West (4.98 per 100,000 population) (Figure 1B). The average annual incidence rate for women was 9.49 per 100,000 population and for men 3.42 per 100,000 population

(Figure 1C). Incidence rate stratified by race showed the highest incidence for Caucasians (7.52 per 100,000 population), followed by African Americans (3.75 per 100,000 population), Hispanics (1.76 per 100,000 population) and Asian/Pacific Islanders (1.42 per 100,000 population) (Figure 1D). Of note, in the years 2007 – 2009, there was no available US census number of Pacific Islander individuals in the US and thus an average annual Pacific Islander population estimate from years 2010 – 2016 was used in substitute. This number was significantly smaller (541,567) than the average annual Asian population (16.2 million) estimate.

After controlling for age and gender, a statistically significant association between race and GCA was found (p <0.0001). Quantifying the difference using a log-linear model, the expected frequency of African American patients with GCA was only 7.2% of the expected frequency for Caucasian patients (p <0.05, 95% CI: 6.9%-7.4%).

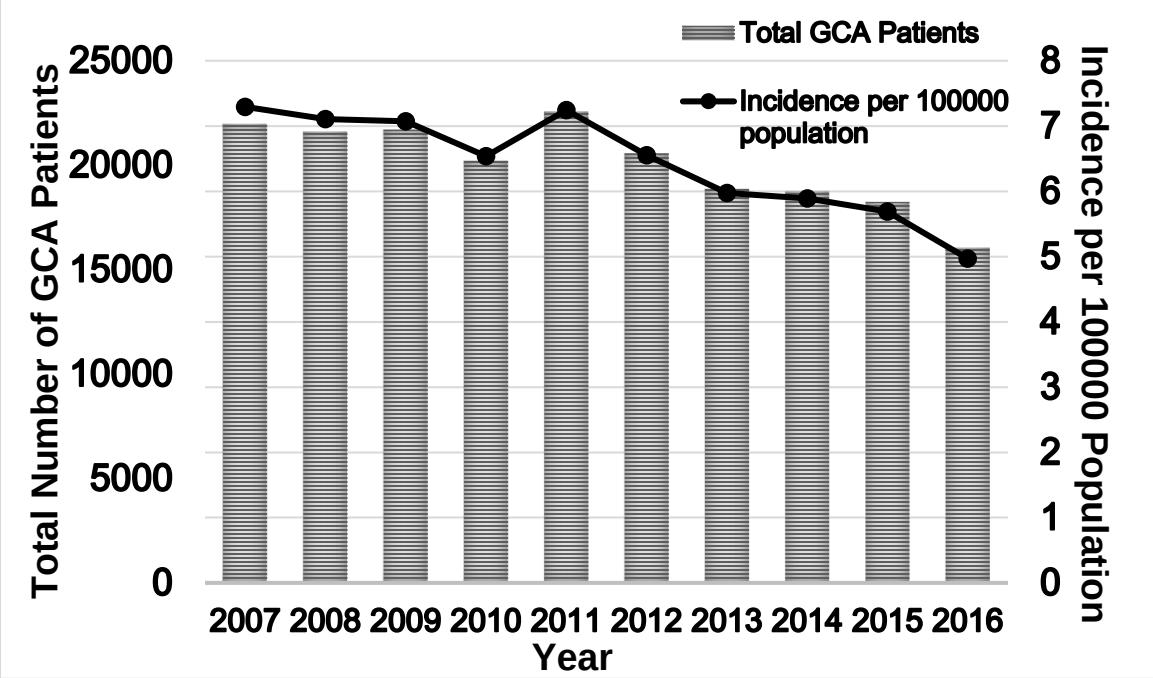

Figure 1A. National Incidence of GCA.

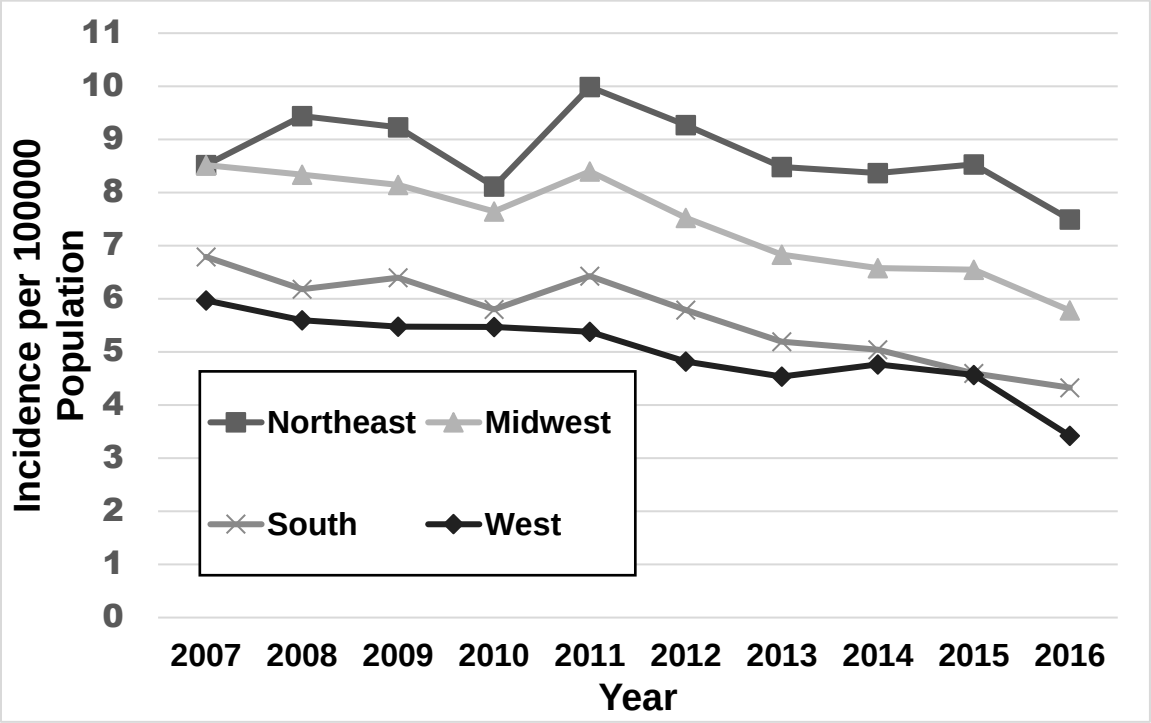

Figure 1B. Incidence Stratified by Region.

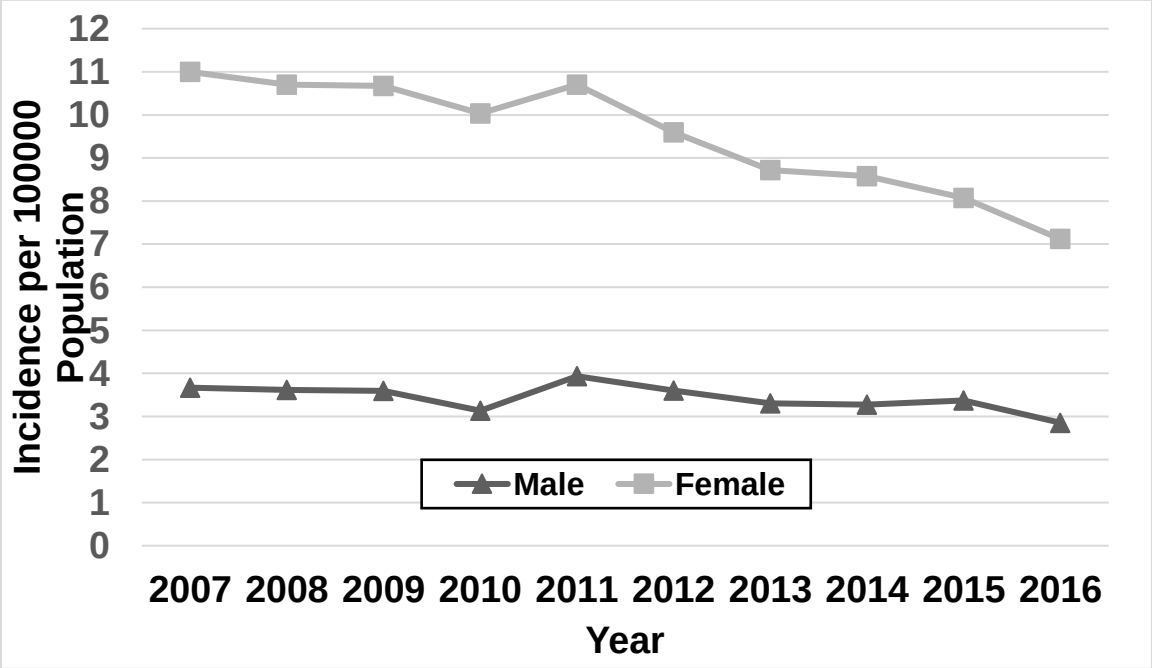

Figure 1C. Incidence Stratified by Gender.

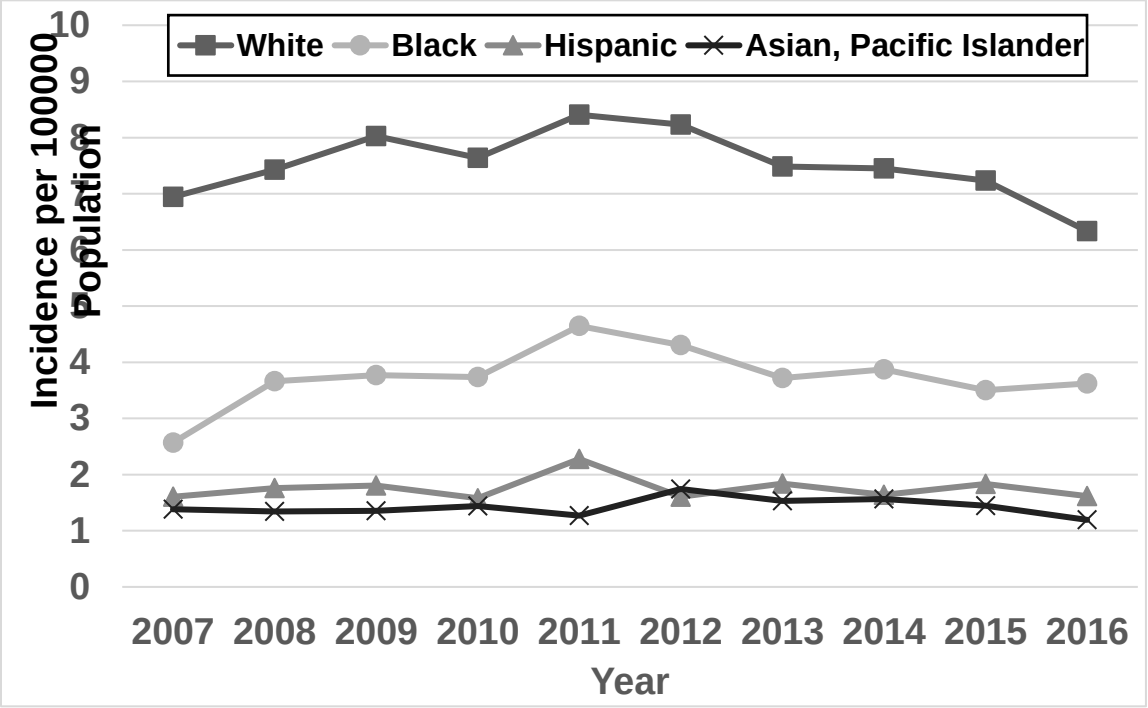

Figure 1D. Incidence Stratified by Race.

Systemic Comorbidities

The most common systemic comorbidity was hypertension (73.2%), followed by hyperlipidemia (42.0%), diabetes mellitus (33.2%), coronary artery disease (32.2%), thyroid disease (22.98%), polymyalgia rheumatica (14.56%), peripheral vascular disease (10.0%), obesity (8.7%) and rheumatoid arthritis (5.2%). 5.51% of our sample were active smokers, however prior smoking history was unable to be assessed. Common systemic comorbidities associated with GCA are presented in Table 2.

Condition	**Number of Patients, n (%)**
Hypertension	146782 (73.2)
Diabetes Mellitus	66498 (33.16)
Obesity	17762 (8.86)
Hyperlipidemia	84186 (41.98)
Coronary Artery Disease	64527 (32.18)
Peripheral Vascular Disease	20050 (10)

Autoimmune	
Rheumatoid Arthritis	10379 (5.18)
Polymyalgia Rheumatica	29203 (14.56)
Thyroid disease (autoimmune thyroiditis, hypothyroidism, hyperthyroidism, unspecified)	46081 (22.98)
Smoking	11053 (5.51)

Table 2. Systemic Comorbidities in Patients with Giant Cell Arteritis

Ocular and Systemic Complications

Approximately 17.8% of patients had associated ocular involvement. The most common ocular sequala was the occurrence of visual symptoms in 9.84% of patients, followed by vision loss at 5.09%. For some possible causes of vision loss, patients were diagnosed with ischemic optic neuropathy (0.7%), central retinal artery occlusion (0.39%), and branch retinal artery/cilioretinal artery occlusion (0.04%). A few had amaurosis fugax (0.51%), diplopia (0.72%) and/or visual field defects (0.54%).

Cerebrovascular complications (stroke or cerebral arteritis) occurred in 17.8% of patients and 2.9% of patients had cardiovascular complications (aortic aneurysms/dissections, acute myocarditis). A small percentage had cerebral arteritis (0.25%), acute myocarditis (0.03%), and/or HEENT symptoms such as jaw pain (0.11%), glossodynia (0.01%) and glossitis (0.05%). The in-hospital mortality was 2.7%. These results are reported in Table 3.

Complication	**Number of Patients, n (%)**
Ocular Involvement (total)	35777 (17.83)
Amaurosis fugax	1029 (0.51)
Ischemic optic neuropathy, anterior or posterior (AION/PION)	1401(0.7)
Central Retinal Artery Occlusions (CRAO)	784 (0.39)
Branch Retinal Artery, Cilioretinal Artery Occlusions (BRAO)	90 (0.04)
Diplopia	1450 (0.72)
Vision loss	10209 (5.09)

Visual field defects Visual symptoms	1083 (0.54) 19731(9.84)
Cerebrovascular (stroke, cerebral arteritis)	17308 (8.63)
Cardiovascular (aortic aneurysms/dissections, acute myocarditis)	5760 (2.87)
In-hospital Mortality	5428 (2.71)

Table 3. Ocular and Systemic Complications in Patients with Giant Cell Arteritis.

Predictors of Mortality in Patients with GCA

In univariate regression analyses, factors predictive of mortality included age >75 years (OR, 2.03; 95% CI, 1.89 - 2.18; p <0.0001), coronary artery disease (OR, 1.241; 95% CI, 1.173–1.312; p <0.0001), aortic pathology (OR, 1.835; 95% CI, 1.62–2.08; p <0.0001), stroke (OR, 1.75; 95% CI, 1.62–1.90, p <0.0001), and being of Asian/Pacific Islander descent (OR, 1.286; 95% CI, 1.00–1.63; p =0.04). Factors associated with lower mortality included female gender (OR, 0.831; 95% CI, 0.78– 0.88; p <0.0001), African American race (OR, 0.55; 95% CI, 0.47–0.64; p <0.0001), hypertension (OR, 0.66; 95% CI: 0.63–0.70; p <0.0001), and smoking (OR, 0.622; 95% CI, 0.54– 0.72; p <0.0001).

In the multivariable regression analysis, factors predictive of mortality included age>75 years (OR, 1.99; 95% CI, 1.85–2.13; p <0.001), stroke (OR, 1.83; 95% CI, 1.68–1.98; p <0.0001), aortic pathology (OR, 1.76; 95% CI, 1.54–1.99; p <0.0001), and Asian/Pacific Islander descent (OR, 1.44; 95% CI, 1.12–1.83; p <0.003). Factors associated with decreased mortality were female gender (OR, 0.88; 95% CI, 0.83–0.94; p <0.0001), African American race (OR, 0.68; 95% CI, 0.59–0.81; p <0.0001), hypertension (OR, 0.63; 95% CI, 0.60-0.67; p <0.0001), and smoking (OR, 0.73; 95% CI, 0.63–0.84; p <0.0001). Notably, neither ocular involvement (OR, 0.79; 95% CI, 0.72–0.87; p <0.0001), nor autoimmune diseases (OR, 0.787; 95% CI, 0.74–0.83, p values<0.0001) increased risk of mortality. These results are reported in Table 4.

	Odds Ratio	95% Confidence Interval (CI)	*p* value
Univariate Regression Analysis			
Age ⩾75	2.033	1.899 - 2.179	<0.0001
Female	0.831	0.783 - 0.882	<0.0001
Race			
White	1.077	0.989 - 1.175	0.0918
Black	0.548	0.468 - 0.64	<0.0001
Hispanic	0.976	0.835 - 1.136	0.7534
Asian, Pacific Islander	1.286	1.003 - 1.626	0.0411
Others	0.910	0.731 - 1.121	0.3847
Hypertension	0.662	0.626 - 0.701	<0.0001
Diabetes mellitus	0.908	0.857 - 0.962	0.0012
Atherosclerosis/Peripheral vascular disease	1.076	0.985 - 1.173	0.1012
Coronary artery disease	1.241	1.173 - 1.312	<0.0001
Aortic, large vessel artery pathology	1.835	1.616 - 2.075	<0.0001
Stroke	1.752	1.617 - 1.895	<0.0001
Smoking	0.622	0.536 - 0.717	<0.0001
Ocular Involvement	0.810	0.737 - 0.889	<0.0001
Autoimmune disease	0.802	0.757 - 0.850	<0.0001
Multivariable Logistic Regression Analysis			
Age ⩾75	1.985	1.850 - 2.132	<0.0001
Female	0.884	0.832 - 0.940	<0.0001
Race			
White	1.098	1.008 - 1.199	0.0339
Black	0.697	0.593 - 0.814	<0.0001
Hispanic	1.148	0.981 - 1.338	0.0813
Asian, Pacific Islander	1.442	1.123 - 1.826	0.0031
Others	0.973	0.781 - 1.200	0.8049
Hypertension	0.633	0.598 - 0.671	<0.0001
Diabetes mellitus	1.011	0.952 - 1.074	0.7099
Atherosclerosis/Peripheral vascular disease	1.030	0.941 - 1.124	0.5200
Coronary artery disease	1.189	1.122 - 1.259	<0.0001
Aortic, large vessel artery pathology	1.757	1.544 - 1.989	<0.0001
Stroke	1.826	1.684 - 1.977	<0.0001
Smoking	0.726	0.624 - 0.839	<0.0001
Ocular Involvement	0.788	0.716 - 0.865	<0.0001
Autoimmune disease	0.787	0.742 - 0.834	<0.0001

Table 4. Predictors of Mortality in Patients with Giant Cell Arteritis.

Healthcare Resource Utilization

The median length of hospital stay was four days. The median inflation adjusted charge per GCA-related hospital admission was $24,324. Over the study period, there was an increasing trend in the median inflation adjusted charge per admission; in 2007 the median charge was $24,173, and in 2016 the median charge was $35,208 (69% increase). The total inflation-adjusted charges for all GCA-related hospital admissions was 824.8 million in 2007, and 878.3 million in 2016 (Figure 2).

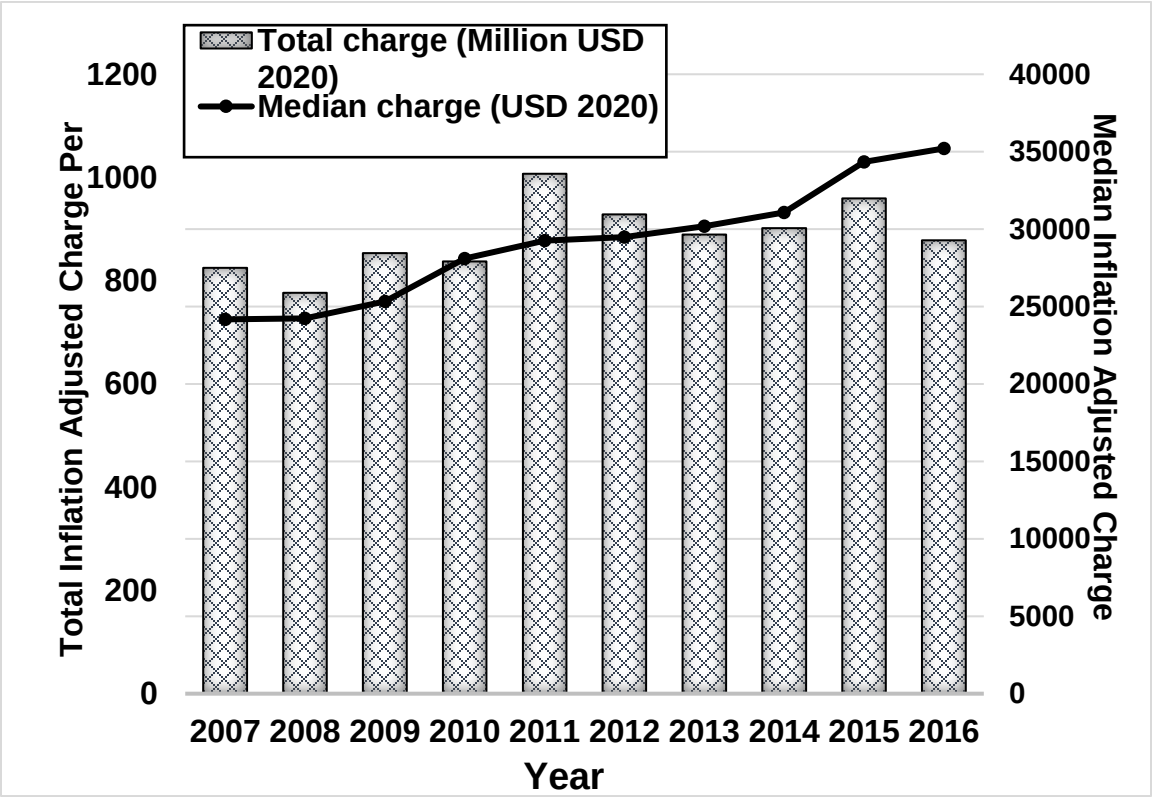

Figure 2. Median and total charge per hospitalization.

Discussion

Giant cell arteritis demonstrates a high societal burden both in substantial systemic and ocular morbidity and mortality and in increasing healthcare costs associated with GCA-related hospitalization. To our knowledge, we present the first nationwide study to investigate the incidence and epidemiology of GCA related hospital admissions, associated systemic complications, rate of ocular involvement, predictors of mortality and associated healthcare resource utilization in the United States.

The national incidence of GCA-related admissions was 6.42 per 100,000 population, with a downward trend between 2007 (7.29 per 100,000) to 2016 (4.96 per 100,000) that was shown to be statistically significant ($p = 0.0002$). This interesting result does not follow the current increasing trends in overall hospital admissions and a growing elderly population in the United States, as studied per year from 1946-2019.[47] However, a population-based study of Olmsted County, Minnesota also reported a declining hospitalization rate for GCA between the years of 1987-2012.[48] These results may reflect an increased awareness of GCA in the primary care setting, leading to higher rates of outpatient treatment with earlier diagnosis/treatment and thus prevention of severe complications that require hospitalization, such as vision loss, aortic compromise, and stroke.

The incidence for individuals ⩾50 years was 19.81 per 100,000 population which is consistent with what has been previously reported.[49–51] Chandran et al.[49] reported an incidence of 19.8 per 100,000 population in individuals >50 years over a 60-year study period (1950-2009) in Olmsted County, Minnesota. Barra et al.[51] reported an incidence of 25 per 100,000 population in the Canadian population, while the incidence in a European

population is estimated to be between 7-43 per 100,000 population.[25] The regional incidence was higher in the Midwest (7.42 per 100,000 population) and Northeast, (8.74 per 100,000 population) and lower in the South (5.63 per 100,000 population) and West (4.98 per 100,000 population). This may be partially related to a higher proportion of Caucasian individuals in the Midwest (79%) and Northeast (69.8%) and lower percentage in the South (60.2%) and West (53.9%), according to 2011 US Census Bureau data. [52]

A cyclic pattern of incidence has been reported in previous studies on GCA however, our data did not show a seasonal trend in GCA-related hospital admissions. In our study, there was a similar number of patients admitted each calendar month (Table 1). Our study only spanned across 10 years, we were therefore unable to describe any long-term cyclic patterns over decades as observed in some studies.[21,50]

The average incidence of GCA-related hospitalizations in women was nearly three times higher than in men (9.49 vs. 3.42 per 100,000 population), a statistically significant difference (p value < 0.0001). Prior studies have shown similar female preponderance with the reported incidence being 1.9 to 7.7 fold higher in females in comparison to men.[26,36,53–55] The incidence was also two times higher in Caucasians (7.51 per 100,000 population) in comparison to African Americans (3.74 per 100,000 population). This difference between Caucasian and African American incidence rates, in addition to the four racial groups studied (Caucasian, African American, Hispanic, and Asian/Pacific Islander) was statistically significant (p value < 0.0001). This is consistent with what has been previously reported in the literature,[53–55] with the exception of a recent study conducted in Baltimore which reported similar rates of GCA in Caucasian

and African Americans.[36] This study was conducted at a single tertiary care center and may not be representative of the United States population.

Previous literature has shown a strong association of GCA with polymyalgia rheumatica (PMR) [56,57] and thyroid disease. [25,58–60] Approximately 40-60% of GCA patients have been reported to have concurrent polymyalgia rheumatica.[26] In patients diagnosed with PMR, up to 21% are also diagnosed with GCA.[50] In our study, 23% (46,081 out of 200,533) of hospitalized patients with GCA had thyroid disease and 14% (29,203 out of 200,533) had a diagnosis of polymyalgia rheumatica. This may be due to a higher prevalence of thyroid disease in general when compared to PMR. Diab et al.[61] found the prevalence of thyroid dysfunction in older adults aged $\geqslant$65 was nearly 25%.

Interestingly, our data shows few GCA patients diagnosed with obesity (8.9%), in contrast to the nationwide obesity rate of 42.5% in the general American population,[62] potentially supporting the hypothesized role of metabolic factors in the pathogenesis of the disease. Studies from Sweden and Iceland have similarly found a reduced risk of GCA in obese and overweight individuals, in addition to a negative association with fasting blood glucose. [25] Amidst ongoing controversy regarding the relationship between diabetes mellitus and GCA, we also note a high percentage of GCA patients with concurrent diabetes (33%) in this expansive sample. This is greater than the national average of 10.2% overall, and 21.4% in individuals aged $\geqslant$65.[63]

Giant cell arteritis is associated with significant ocular and systemic complications. Ocular manifestations include anterior and posterior ischemic optic neuropathy, retinal arterial occlusions, amaurosis fugax, ocular ischemic syndrome,

cotton-wool spots, and diplopia. Approximately 18% of our inpatient GCA sample had ocular involvement. In comparison, older US studies conducted at tertiary referral centers found 24-50% of GCA patients have visual symptoms.[64–66]

Systemic complications include aortic/large vessel compromise,[29] stroke, and acute myocarditis.[31] Of these, stroke appears to be the most common systemic complication in our sample at 8.4%, followed by aortic aneurysms or dissection at 2.8%. Previously reported prevalence of stroke in GCA was 3-7%,[67,68] but aortic involvement in GCA had been inconclusive, ranging from 0-27%.[67] These complications greatly increased the risk for mortality, with odds ratios of 1.83 and 1.75 respectively. This corresponds with previous reports of an increased mortality ratio in GCA patients with aortic involvement (2.63).[69] Ocular complications did not increase the rate of mortality, with an odds ratio of 0.79. This may reflect the higher likelihood of rapid diagnosis or earlier presentation in patients with ocular symptoms compared to a general presentation.

We distinguish these complications from GCA comorbidities, which prior studies posit to include hypertension, previous atheromatous disease, venous thromboembolic diseases, thyroid disease, diabetes, and severe infections. [23,24,32,33] Our study suggests that prior atheromatous disease may only be present in a minority of GCA patients; we see minority prevalence of peripheral vascular disease (10%), coronary artery disease (32%), and hyperlipidemia (42%) in our dataset. By contrast, hypertension was found in 73% of the noted GCA population. Given epidemiological studies showing US prevalence of hypertension at only 29% overall and 33.2% in the elderly population age 60 years and older,[70] hypertension may prove to be a more substantial driver of pathogenesis.

Interestingly, we did not find a positive correlation of GCA incidence with smoking, as this systemic comorbidity was only observed in 5% of GCA patients (Table 2) and was negatively associated with mortality (Table 4). This directly contradicts prior research [18,32,35] and vascular theories of GCA pathogenesis. However, it is possible that smoking status and drug use were not commonly recorded as ICD 9-10 codes, and instead written in electronic notes as only part of patient history, if noted at all with an incomplete social history. In addition, ICD 9 and 10 codes only describe current active smoking, and not a prior history of smoking or tobacco use.

The strengths of this study include its timespan, large sample size and nationwide estimates, representative of the entire United States population. This study has several limitations including the potential for misdiagnosis based on ICD codes; it is particularly relevant as there was a change from ICD-9 to ICD-10 in 2015; however, the large sample size may mitigate, or render negligible the risk of such misclassifications. In addition, our study did not capture the majority of the GCA cases that were diagnosed and treated in the outpatient setting. A population-based study from the Mayo Clinic found the average hospitalization rate for GCA patients to be 39.5% between the years of 2007 – 2012.[48] Furthermore, it is possible that the patients who were hospitalized with a diagnosis of GCA had higher rates of ocular and systemic complications in comparison to those who were treated in the outpatient setting.[71]

It is also important to consider potential impacts stemming from racial disparities in medicine. Hospitalizations for ambulatory care sensitive conditions (ACSH), conditions for which timely and appropriate outpatient care could reduce risks of hospitalization, is recommended as a proxy for primary care access by the US Institute of

Medicine.[72] Rates of ACSH are relatively higher in African American and Hispanic populations, suggesting disproportionate health care access leading to more severe disease and need for admission. [73,74] However, it is unclear whether increased primary care opportunities truly lead to decreased hospitalizations for GCA, as the decision to admit for intravenous steroid treatment and temporal artery biopsy is influenced by both the clinician's confidence in GCA diagnosis and the severity of symptoms and complications in the patient. On the other hand, for many life-threatening conditions, African Americans and ethnic minorities are denied admission for appropriate care, as manifested by decreased rates of cardiac catherization and more advanced stages of cancer at diagnosis when compared with Caucasians.[75] It could be argued that with more timely office visits and higher clinical suspicion for GCA diagnosis, Caucasian patients are more likely to be hospitalized and promptly treated. Despite this disadvantage, we found a lower risk of mortality for hospitalized African American individuals with GCA.

In conclusion, this study is the first to provide nationwide estimates on the incidence and epidemiology of GCA related hospitalization in the United States over a 10-year study period. With this updated epidemiological information, we aim to provide clinicians an accurate reference for pattern recognition in GCA diagnosis and treatment. With the high median cost ($24,324) for a GCA-related hospital stay, a physician's clinical decision on admission for temporal artery biopsy must be accurate. We confirm that GCA preferentially affects women, elderly, and Caucasian individuals. Approximately one-fifth of hospitalized GCA patients have ocular complications. Patients who are older (>75 years) or those who develop associated stroke or aortic aneurysm/dissection have significantly worse mortality. Notably, our study is inherently

limited by reliability of ICD 9 and 10 diagnosis codes in an inpatient database, and future studies on nationwide epidemiology may be able to take advantage of the Medicare database, which includes data from patients over 65 years of age from both outpatient and inpatient settings. Finally, optimal diagnosis of GCA undoubtedly requires a combination of clinical judgment, laboratory results, imaging studies, and temporal artery biopsy results.

Bibliography

1. Ness T, Bley TA, Schmidt WA, Lamprecht P. The diagnosis and treatment of giant cell arteritis. Deutsches Arzteblatt International 2013;110(21):376–84.

2. Lyons HS, Quick V, Sinclair AJ, Nagaraju S, Mollan SP. A new era for giant cell arteritis. Eye (Basingstoke) [Internet] 2020;34(6):1013–26. Available from: http://dx.doi.org/10.1038/s41433-019-0608-7

3. Davies CG, May DJ. The role of temporal artery biopsies in giant cell arteritis. Annals of the Royal College of Surgeons of England [Internet] 2011;93(1):4–5. Available from: https://pubmed.ncbi.nlm.nih.gov/21418754

4. Guffey Johnson J, Grossniklaus HE, Margo CE, Foulis P. Frequency of unintended vein and peripheral nerve biopsy with temporal artery biopsy. Archives of ophthalmology (Chicago, Ill : 1960) 2009;127(5):703.

5. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis and rheumatism 1990;33(8):1122–8.

6. Luqmani R, Lee E, Singh S, et al. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): A diagnostic accuracy and cost-effectiveness study. Health Technology Assessment 2016;20(90):1–270.

7. Pless M, Rizzo JF 3rd, Lamkin JC, Lessell S. Concordance of bilateral temporal artery biopsy in giant cell arteritis. Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society 2000;20(3):216–8.

8. Schäfer VS, Chrysidis S, Dejaco C, et al. Assessing Vasculitis in Giant Cell Arteritis by Ultrasound: Results of OMERACT Patient-based Reliability Exercises. The Journal of rheumatology 2018;45(9):1289–95.

9. Karassa FB, Matsagas MI, Schmidt WA, Ioannidis JPA. Meta-Analysis: Test Performance of Ultrasonography for Giant-Cell Arteritis. Annals of Internal Medicine [Internet] 2005;142(5):359–69. Available from: https://www.acpjournals.org/doi/abs/10.7326/0003-4819-142-5-200503010-00011

10. Arida A, Kyprianou M, Kanakis M, Sfikakis PP. The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis. BMC musculoskeletal disorders 2010;11:44.

11. Ball EL, Walsh SR, Tang TY, Gohil R, Clarke JMF. Role of ultrasonography in the diagnosis of temporal arteritis. The British journal of surgery 2010;97(12):1765–71.

12. Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt WA, Ramiro S. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. RMD Open

[Internet] 2018;4(1):e000612. Available from: http://rmdopen.bmj.com/content/4/1/e000612.abstract

13. de Miguel E, Beltran LM, Monjo I, Deodati F, Schmidt WA, Garcia-Puig J. Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis. Rheumatology [Internet] 2018;57(2):318–21. Available from: https://doi.org/10.1093/rheumatology/kex381

14. Rinagel M, Chatelus E, Jousse-Joulin S, et al. Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature. Autoimmunity Reviews [Internet] 2019;18(1):56–61. Available from: https://www.sciencedirect.com/science/article/pii/S1568997218302611

15. Foroozan R, Danesh-Meyer H, Savino PJ, Gamble G, Mekari-Sabbagh ON, Sergott RC. Thrombocytosis in patients with biopsy-proven giant cell arteritis. Ophthalmology 2002;109(7):1267–71.

16. Ing EB, Lahaie Luna G, Toren A, et al. Multivariable prediction model for suspected giant cell arteritis: development and validation. Clinical ophthalmology (Auckland, NZ) 2017;11:2031–42.

17. Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: Towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatology (United Kingdom) 2016;55(1):66–70.

18. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Care and Research 2009;61(10):1454–61.

19. de Smit E, Clarke L, Sanfilippo PG, et al. Geo-epidemiology of temporal artery biopsy-positive giant cell arteritis in Australia and New Zealand: is there a seasonal influence? RMD Open 2017;3(2):e000531.

20. Kisza K, Murchison AP, Dai Y, et al. Giant cell arteritis incidence: Analysis by season and year in mid-Atlantic United States. Clinical and Experimental Ophthalmology 2013;41(6):577–81.

21. Wing S, Rider LG, Johnson JR, et al. Do solar cycles influence giant cell arteritis and rheumatoid arthritis incidence? BMJ Open 2015;5(5):1–9.

22. Rhee RL, Grayson PC, Merkel PA, Tomasson G. Infections and the risk of incident giant cell arteritis: A population-based, case-control study. Annals of the Rheumatic Diseases 2017;76(6):1031–5.

23. Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: Data-driven analysis of comorbidities. Arthritis Care and Research 2015;67(3):390–5.

24. Mohammad AJ, Englund M, Turesson C, Tomasson G, Merkel PA. Rate of comorbidities in giant cell arteritis: A population-based study. Journal of Rheumatology 2017;44(1):84–90.

25. Sharma A, Mohammad A, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: A systematic literature review. Seminars in Arthritis and Rheumatism 2020;50(5):1040–8.

26. Crowson CS, Matteson EL. Contemporary prevalence estimates for giant cell arteritis and polymyalgia rheumatica, 2015. Seminars in Arthritis and Rheumatism [Internet] 2017;47(2):253–6. Available from: http://dx.doi.org/10.1016/j.semarthrit.2017.04.001

27. Udayakumar PD, Chandran AK, Crowson CS, Warrington KJ, Matteson EL. Cardiovascular risk and acute coronary syndrome in giant cell arteritis: a population-based retrospective cohort study. Arthritis care & research [Internet] 2015;67(3):396–402. Available from: https://pubmed.ncbi.nlm.nih.gov/25074472

28. Ungprasert P, Upala S, Sanguankeo A, Warrington KJ. Patients with giant cell arteritis have a lower prevalence of diabetes mellitus: A systematic review and meta-analysis. Modern Rheumatology 2016;26(3):410–4.

29. Koster MJ, Matteson EL, Warrington KJ. Large-vessel giant cell arteritis: Diagnosis, monitoring and management. Rheumatology (United Kingdom) 2018;57:ii32–42.

30. Kumarasinghe AP, Hepburn A, Reuther WJ, Pratt C. Temporal arteritis presenting with tongue necrosis. BMJ Case Reports 2012;(C):4–7.

31. Tracey G, Kevin S. Investigation and management of giant cell arteritis. Prescriber 2020;31(2):28–32.

32. Duhaut P, Pinede L, Demolombe-Rague S, et al. Giant cell arteritis and cardiovascular risk factors: A multicenter, prospective case-control study. Arthritis and Rheumatism 1998;41(11):1960–5.

33. Yavne Y, Tiosano S, Watad A, et al. Association between giant cell arteritis and thyroid dysfunction in a “real life” population. Endocrine [Internet] 2017;57(2):241–6. Available from: http://dx.doi.org/10.1007/s12020-017-1347-9

34. Mahr A, Belhassen M, Paccalin M, et al. Characteristics and management of giant cell arteritis in France: A study based on national health insurance claims data. Rheumatology (United Kingdom) 2020;59(1):120–8.

35. Mahr A, Aouba A, Richebé P, Gonzalez-Chiappe S. Épidémiologie et histoire naturelle de l’artérite à cellules géantes (Horton). Revue de Medecine Interne [Internet] 2017;38(10):663–9. Available from: http://dx.doi.org/10.1016/j.revmed.2017.03.007

36. Gruener AM, Poostchi A, Carey AR, et al. Association of Giant Cell Arteritis With Race. JAMA Ophthalmology [Internet] 2019;137(10):1175–9. Available from: https://doi.org/10.1001/jamaophthalmol.2019.2919

37. Bara L, Pope JE, Pequeno P, et al. Incidence and prevalence of giant cell arteritis in Ontario, Canada. Rheumatology 2020;1–9.

38. Gonzalez-Gay MA, Martinez-Dubois C, Agudo M, Pompei O, Blanco R, Llorca J. Giant cell arteritis: Epidemiology, diagnosis, and management. Current Rheumatology Reports 2010;12(6):436–42.

39. Chaudhry IA, Shamsi FA, Elzaridi E, Arat YO, Bosley TM, Riley FC. Epidemiology of giant-cell arteritis in an Arab population: A 22-year study. British Journal of Ophthalmology 2007;91(6):715–8.

40. Watts RA. 2. Epidemiology of giant cell arteritis: a critical review. Rheumatology [Internet] 2014;53(suppl_2):i1–2. Available from: https://doi.org/10.1093/rheumatology/keu183

41. HCUP NIS Description of Data Elements. Race. [Internet]. Agency for Healthcare Research and Quality, Rockville, MD. 2008;Available from: www.hcup-us.ahrq.gov/db/vars/race/nisnote.jsp

42. HCUP NIS Description of Data Elements. Region of hospital. [Internet]. Agency for Healthcare Research and Quality, Rockville, MD. 2008;Available from: www.hcup-us.ahrq.gov/db/vars/hosp_region/nisnote.jsp

43. HCUP NIS Description of Data Elements. Indicator of sex. [Internet]. Agency for Healthcare Research and Quality, Rockville, MD. 2008;Available from: www.hcup-us.ahrq.gov/db/vars/female/nisnote.jsp

44. HCUP NIS Description of Data Elements. Median household income for patient's ZIP code. [Internet]. Agency for Healthcare Research and Quality, Rockville, MD. 2008;Available from: www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp

45. Agency for Healthcare Research and Quality. HCUP NIS Database Documentation. Healthcare Cost and Utilization Project (HCUP) [Internet]. 2021 [cited 2021 Nov 5];Available from: https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp

46. US Bureau of Labor Statistics. Consumer Price Index for all urban consumers: hospital services [Internet]. [cited 2020 Nov 8];Available from: https://www.bls.gov/cpi/

47. Michas F. Total hospital admissions in the United States 1946-2019 [Internet]. 2021;Available from: https://www.statista.com/statistics/459718/total-hospital-admission-number-in-the-us/

48. Michet III CJ, Achenbach SJ, Crowson CS, Matteson EL. Hospitalization rates and utilization among patients with giant cell arteritis: A population-based study from 1987 to 2012. Seminars in Arthritis and Rheumatism [Internet] 2015;45(1):70–4. Available from: https://www.sciencedirect.com/science/article/pii/S0049017215000451

49. Chandran AK, Udayakumar PD, Crowson CS, Warrington KJ, Matteson EL. The incidence of giant cell arteritis in Olmsted County, Minnesota, over a 60-year period 1950-2009. Scandinavian journal of rheumatology [Internet] 2015;44(3):215–8. Available from: https://pubmed.ncbi.nlm.nih.gov/25606666

50. Sharma A, Mohammad AJ, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: A systematic literature review. Seminars in Arthritis and Rheumatism [Internet] 2020;50(5):1040–8. Available from: https://www.sciencedirect.com/science/article/pii/S0049017220302043

51. Barra L, Pope JE, Pequeno P, et al. Incidence and prevalence of giant cell arteritis in Ontario, Canada. Rheumatology [Internet] 2020;59(11):3250–8. Available from: https://doi.org/10.1093/rheumatology/keaa095

52. US Census Bureau. Race Data Tables: The Black Alone Population in the United States: 2011 [Internet]. Current Population Survey. 2011 [cited 2021 Jan 14];Available from: https://www.census.gov/data/tables/2011/demo/race/ppl-ba11.html

53. Huston KA, Hunder GG, Lie JT, Kennedy RH, Elveback LR. Temporal arteritis: a 25-year epidemiologic, clinical, and pathologic study. Annals of internal medicine 1978;88(2):162–7.

54. Smith CA, Fidler WJ, Pinals RS. The epidemiology of giant cell arteritis. Report of a ten-year study in Shelby County, Tennessee. Arthritis and rheumatism 1983;26(10):1214–9.

55. Liu NH, LaBree LD, Feldon SE, Rao NA. The epidemiology of giant cell arteritis: A 12-year retrospective study. Ophthalmology 2001;108(6):1145–9.

56. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota, 1970-1991. Arthritis and rheumatism 1995;38(3):369–73.

57. Kermani TA, Warrington KJ. Polymyalgia rheumatica. The Lancet [Internet] 2013;381(9860):63–72. Available from: http://dx.doi.org/10.1016/S0140-6736(12)60680-1

58. Nicholson GC, Gutterridge DH, Carroll WM, Armstrong BK. Autoimmune Thyroid Disease and Giant Cell Arteritis: a Review, Case Report and Epidemiological Study. Australian and New Zealand Journal of Medicine 1984;14(4):487–90.

59. Bowness P, Shotliff K, Middlemiss A, Myles AB. Prevalence of Hypothyroidism in Patients with Polymyalgia Rheumatica and Giant Cell Arteritis. Rheumatology [Internet] 1991;30(5):349–51. Available from: https://doi.org/10.1093/rheumatology/30.5.349

60. Mohammad AJ, Englund M, Turesson C, Tomasson G, Merkel PA. Rate of comorbidities in giant cell arteritis: A population-based study. Journal of Rheumatology 2017;44(1):84–90.

61. Diab N, Daya NR, Juraschek SP, et al. Prevalence and Risk Factors of Thyroid Dysfunction in Older Adults in the Community. Scientific Reports 2019;9(1):1–8.

62. Ogden CL, Fryar CD, Martin CB, et al. Trends in obesity prevalence by race and hispanic origin - 1999-2000 to 2017-2018. JAMA - Journal of the American Medical Association 2020;324(12):1208–10.

63. DHHS. National Diabetes Statistics Report, 2020. National Diabetes Statistics Report 2020;2.

64. Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. American journal of ophthalmology 1998;125(4):509–20.

65. Liu GT, Glaser JS, Schatz NJ, Smith JL. Visual Morbidity in Giant Cell Arteritis: Clinical Characteristics and Prognosis for Vision. Ophthalmology [Internet] 1994;101(11):1779–

85. Available from: https://www.sciencedirect.com/science/article/pii/S016164209431102X

66. Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. Ophthalmology 1993;100(4):550–5.

67. Lensen KDF, Voskuyl AE, Comans EFI, van der Laken CJ, Smulders YM. Extracranial giant cell arteritis: A narrative review. The Netherlands journal of medicine 2016;74(5):182–92.

68. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine 2009;88(4):227–35.

69. Koster MJ, Warrington KJ, Matteson EL. Morbidity and Mortality of Large-Vessel Vasculitides. 2020;

70. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension Prevalence and Control Among Adults: United States, 2015-2016. NCHS data brief 2017;(289):1–8.

71. van der Geest KSM, Sandovici M, Brouwer E, Mackie SL. Diagnostic Accuracy of Symptoms, Physical Signs, and Laboratory Tests for Giant Cell Arteritis: A Systematic Review and Meta-analysis. JAMA internal medicine 2020;180(10):1295–304.

72. Millman M. Access to health care in America. National Academies Press; 1993.

73. Laditka JN, Laditka SB, Mastanduno MP. Hospital utilization for ambulatory care sensitive conditions: health outcome disparities associated with race and ethnicity. Social Science & Medicine [Internet] 2003;57(8):1429–41. Available from: https://www.sciencedirect.com/science/article/pii/S0277953602005397

74. O'Neil SS, Lake T, Merrill A, Wilson A, Mann DA, Bartnyska LM. Racial Disparities in Hospitalizations for Ambulatory Care–Sensitive Conditions. American Journal of Preventive Medicine [Internet] 2010;38(4):381–8. Available from: https://www.sciencedirect.com/science/article/pii/S0749379710000061

75. Mayberry RM, Mili F, Ofili E. Racial and Ethnic Differences in Access to Medical Care. Medical Care Research and Review [Internet] 2000;57(1_suppl):108–45. Available from: https://doi.org/10.1177/1077558700057001S06