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Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Active Kidney Involvement in the United States: 2016–2020

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Keywords
Antineutrophil cytoplasmic antibody · Vasculitis · Kidney · National Inpatient Sample · Epidemiology

Abstract
Introduction: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and its subtypes, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA), frequently present with acute kidney injury and can often lead to kidney failure, even with successful induction therapy. Few contemporary, nationally representative studies have described hospital complications of AAV. ***Methods:*** Using data from the 2016–2020 National Inpatient Sample, a nationally representative database, we identified hospitalizations from adults with a new diagnosis of AAV (subtype or unspecified) and an inpatient kidney biopsy during the index hospitalization. We described baseline characteristics, associated inpatient procedures and complications, and compared lengths of stay and costs by geographic region, hospital characteristics, and AAV subtype. ***Results:*** We identified an average of 1,329 cases of hospitalized AAV with a concurrent kidney biopsy per year over the 5-year period. More than 50% were not designated as having a specific subtype, likely owing to delays in documentation of histopathology. Kidney involvement was severe as the majority of patients developed acute kidney injury, and the proportion of patients who required inpatient dialysis was approximately 24%. Approximately 20% of patients developed hypoxia. Inpatient plasmapheresis was delivered to 20.4% and 20.6% of patients with GPA and MPA, respectively. There were no clinically meaningful or statistically significant differences in adjusted length of stay or inpatient costs among AAV subtypes. Admission in the Midwest region was associated with shorter hospital stays and lower costs than that in the Northeast, South, or West regions of the USA (adjusted p = 0.007 and <0.001, respectively). ***Conclusion:*** AAV with acute kidney involvement remains a challenging, high-risk condition. Maintaining a high index of suspicion and a low threshold for kidney biopsy should help ameliorate short- and long-term complications.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of multisystemic autoimmune diseases characterized by inflammation of small vessels with or without necrosis. AAV encompasses three clinical diseases: granulomatosis with polyangiitis

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Table 1. Number of patients with diagnosis of AAV with inpatient native kidney biopsy, 2016–2020

	2016		2017		2018		2019		2020		Total	
Total admissions	35,675,421		35,798,453		35,527,481		35,419,023		32,355,827		174,776,205	
Non-AAV related	35,646,116		35,769,638		35,499,231		35,390,063		32,328,887		174,633,935	
AAV related	29,305		28,815		28,250		28,960		26,940		142,270	
	Received inpatient kidney biopsy											
	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes
EGPA	1,705	25	1,890	15	1,855	25	1,770	15	1,390	25	8,610	105
MPA	1,705	230	1,755	290	2,030	240	2,270	275	2,125	325	9,885	1,360
GPA	3,720	355	3,840	340	3,590	315	3,320	300	3,055	330	17,525	1,640
Vasculitis	20,945	620	19,990	695	19,480	715	20,245	765	18,945	745	99,605	3,540
Total	28,075	1,230	27,475	1,340	26,955	1,295	27,605	1,355	25,515	1,425	135,625	6,645

Counts reflect national estimates. ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic GPA; vasculitis, subtype unspecified vasculitis.

(GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA) [1]. Kidney involvement is the most important determinant of mortality and morbidity in AAV. Thirty to 50% of patients with kidney involvement will progress to kidney failure within 5 years [2].

AAV is a rare disease with geographic variation in its incidence and prevalence. The worldwide annual incidence ranges from 1.2 to 3.3 cases per 100,000 individuals, while the prevalence ranges from 4.6 to 42.1 cases per 100,000 individuals [3]. MPA is associated with kidney involvement in about 80% of cases, whereas GPA and EGPA exhibit kidney involvement in about 60% and 25% of cases, respectively [4]. Clinically, AAV commonly manifests as rapidly progressive glomerulonephritis. Patients present with a constellation of acute kidney injury (AKI), proteinuria, hematuria, and hypertension within a few days to a few months [5]. The urgency and severity of clinical presentation prompt a sizeable fraction of patients to be hospitalized and to require urgent inpatient kidney biopsy for a confirmatory diagnosis and timely initiation of life- and kidney-saving treatment.

There is a lack of literature describing the economic and societal burden of systemic vasculitis [6]. Over the past decade, several studies analyzed national-level administrative datasets, aiming to describe the clinical and economic implications of AAV. However, gaps in our knowledge still exist. One major challenge is ambiguity in diagnosis codes in the International Classification of Diseases (ICD)-9 system for the corresponding AAV subtype. Moreover, previously published studies failed to distinguish patients with new-onset kidney involvement; patients might have retained the diagnosis from remote inpatient or outpatient encounters, related or perhaps unrelated to the AAV diagnosis.

In this study, we describe the profile of patients with AAV and active kidney involvement in the United States (USA) population, restricting review of hospitalizations to those during which patients underwent a concurrent native kidney biopsy. We also explore variations in associated lengths of stay, inpatient costs, and disposition by AAV subtype, region, and hospital characteristics.

Methods

Data Source and Study Population

We performed an analysis of the National Inpatient Sample (NIS) database between 2016 and 2020. The NIS was developed for the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ) [7] and is the largest publicly available all-payer inpatient healthcare dataset in the USA. The NIS contains discharge-level data from about 20% of all admissions in US hospitals, excluding long-term acute care centers and rehabilitation hospitals. The NIS is designed to produce US regional and national estimates of inpatient utilization, access, cost, quality, and outcomes. It captures up to 40 medical diagnoses and 25 procedure codes using the International Classification of Diseases Clinical Modification, 9th (ICD-9-CM) and 10th revisions (ICD-10-CM/procedures [PCS]) based on the year of the dataset.

Beginning from October of 2015, NIS data coding transitioned from the International Classification of Diseases (ICD) version 9 (ICD-9) to ICD-10. In order to provide consistent results over the course of several years, we restricted our analytic sample to hospitalizations from year 2016 to year 2020 (year 2020 data are the most contemporary dataset available to the public as of early 2023). In ICD-10, there are unique codes for MPA, GPA, and EGPA (M317, M3131, and M301), respectively, correcting one of the major challenges facing health services researchers studying patients with AAV and its subtypes. The administrative codes for MPA, GPA, and EGPA were validated recently with high reliability [8]. We required that each hospitalization meet the following

Table 2. Baseline characteristics of patients with AAV and inpatient native kidney biopsy, year 2016–2020

Patient characteristics	EGPA (*N* = 105)	Vasculitis (*N* = 3,540)	GPA (*N* = 1,640)	MPA (*N* = 1,360)	All (*N* = 6,645)
Age, years	60.5 (54.5, 69.6)	63.6 (52.3, 72.7)	63.8 (52.3, 71.7)	68.7 (60.0, 76.5)	65.0 (53.3,73.5)
Female sex, *n* (%)	50 (47.6)	1,865 (52.7)	790 (48.2)	785 (57.7)	3,490 (52.5)
Designated race, *n* (%)					
White	60 (57.1)	2,345 (66.2)	1,215 (74.1)	815 (59.9)	4,435 (66.7)
Black	15 (14.3)	325 (9.2)	110 (6.7)	155 (11.4)	605 (9.1)
Hispanic	10 (9.5)	510 (14.4)	190 (11.6)	245 (18.0)	955 (14.4)
Others	15 (14.3)	255 (7.2)	90 (5.5)	115 (8.5)	475 (7.2)
Missing	5 (4.8)	105 (3.0)	35 (2.1)	30 (2.2)	175 (2.6)
Payer, *n* (%)					
Medicare/Medicaid	45 (42.9)	2,330 (65.8)	995 (60.7)	975 (71.7)	4,345 (65.4)
Private	45 (42.9)	960 (27.1)	535 (32.6)	285 (21.0)	1,825 (27.5)
Others	15 (14.3)	250 (7.1)	110 (6.7)	100 (7.4)	475 (7.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hospital region, *n* (%)					
Northeast	20 (19.1)	595 (16.8)	250 (15.2)	240 (17.7)	1,105 (16.6)
Midwest	10 (9.5)	855 (24.2)	455 (27.7)	345 (25.4)	1,665 (25.1)
South	50 (47.6)	1,270 (35.9)	600 (36.6)	445 (32.7)	2,365 (35.6)
West	25 (23.8)	820 (23.2)	335 (20.4)	330 (24.3)	1,510 (22.7)
Hospital teaching status, *n* (%)					
Rural	0 (0.00)	95 (2.7)	50 (3.1)	15 (1.1)	160 (2.4)
Urban nonteaching	25 (23.8)	615 (17.4)	250 (15.2)	210 (15.4)	1,100 (16.6)
Urban teaching	80 (76.2)	2,830 (79.9)	1,340 (81.7)	1,135 (83.5)	5,385 (81.0)
Hospital bed size, *n* (%)					
Small	20 (19.1)	595 (16.8)	305 (18.6)	170 (12.5)	1,090 (16.4)
Medium	35 (33.3)	915 (25.9)	385 (23.5)	405 (29.8)	1,740 (26.2)
Large	50 (47.6)	2,030 (57.3)	950 (57.9)	785 (57.7)	3,815 (57.4)
Comorbidity, *n* (%)					
CKD					
No	85 (81.0)	2,420 (68.4)	1,200 (73.2)	915 (67.3)	4,620 (69.5)
CKD 1+2	5 (4.8)	60 (1.7)	60 (3.7)	30 (2.2)	155 (2.3)
CKD 3	10 (9.5)	630 (17.8)	235 (14.3)	235 (17.3)	1,110 (16.7)
CKD 4	5 (4.8)	320 (9.0)	125 (7.6)	135 (9.9)	585 (8.8)
CKD 5	0 (0.0)	110 (3.1)	20 (1.2)	45 (3.3)	175 (2.6)
Smoking	25 (23.8)	840 (23.7)	395 (24.1)	335 (24.6)	1,595 (24.0)
Coronary artery disease	15 (14.3)	615 (17.4)	270 (16.5)	285 (21.0)	1,185 (17.8)
Chronic pulmonary disease	60 (57.1)	715 (20.2)	370 (22.6)	320 (23.5)	1,465 (22.1)
Diabetes	30 (28.6)	815 (23.0)	320 (19.5)	395 (29.0)	1,560 (23.5)
Hypertension	55 (52.4)	1,160 (32.8)	600 (36.6)	490 (36.0)	2,305 (34.7)
Obesity	15 (14.3)	610 (17.2)	345 (21.0)	210 (15.4)	1,180 (17.8)
Peripheral vascular disease	10 (9.5)	240 (6.8)	85 (5.2)	95 (7.0)	430 (6.5)

Variables are described using medians and 25th and 75th or counts and percentages. Medians, counts, and percentages reflect national estimates. ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic GPA; vasculitis, subtype unspecified vasculitis.

criteria: (1) admission age ≥18 (adult); (2) having an inpatient procedure for native kidney biopsy; and (3) discharge diagnosis code with MPA, GPA, vasculitis, or EGPA. In clinical practice, it is common for clinicians (or coders) to designate the discharge diagnosis as "ANCA-associated vasculitis" when further specification is not available. There is an ICD-10 code (I7782) designated for AAV, effective October 2022. In the current study, for patients without a subcategorization of MPA, GPA, or EGPA, we also considered hospitalizations during which a kidney biopsy was performed and the ICD-10 code I776 ("arteritis unspecified") was selected. Using ICD-10 codes, we excluded hospitalizations of patients with kidney failure preceding hospitalization (including patients receiving maintenance dialysis as well as kidney transplant recipients). We aimed to include patients with an initial presentation of kidney disease and an eventual diagnosis within the spectrum of AAV. Ethical approval and consent were not required as this study was based on publicly available data.

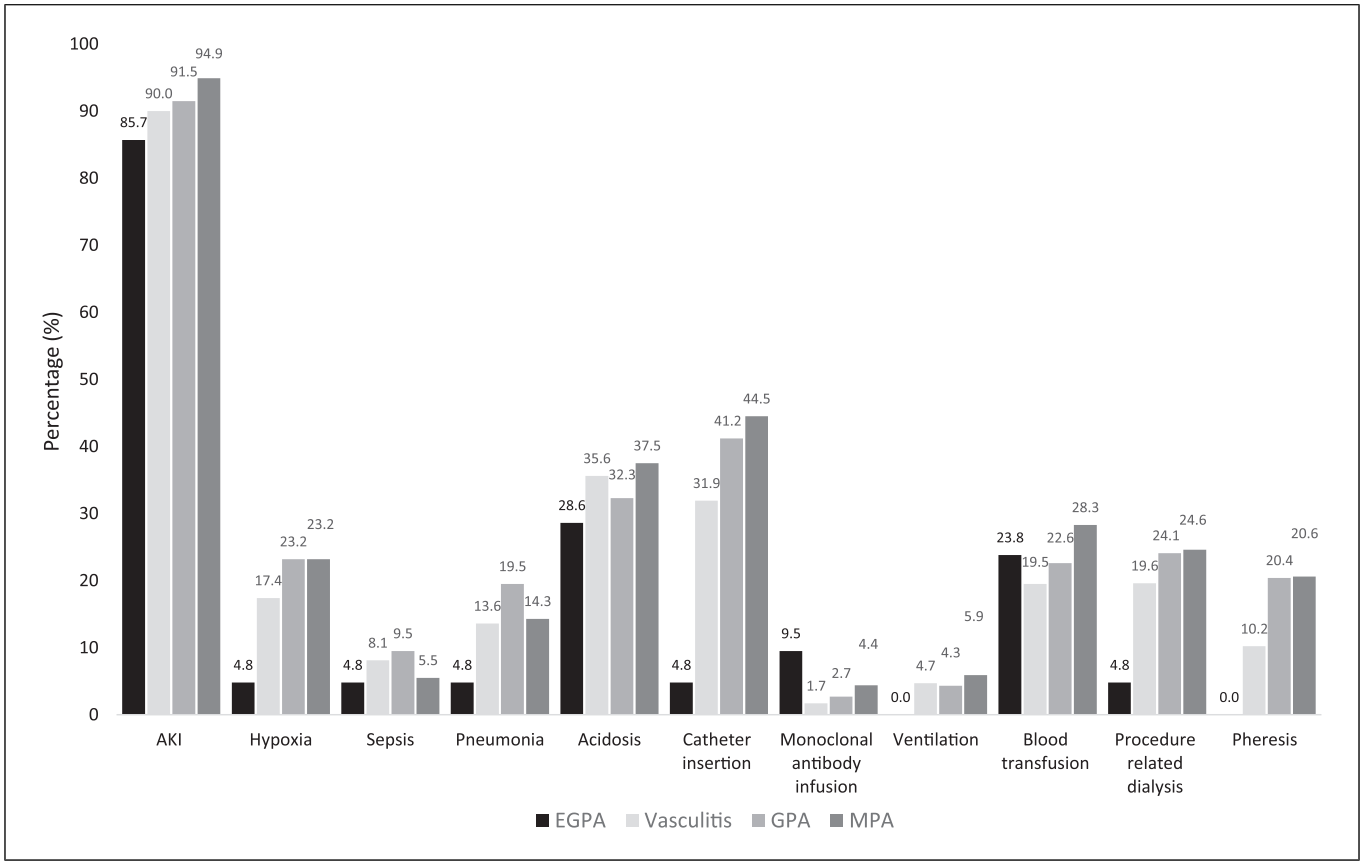

Fig. 1. Comorbid conditions and clinical events for patients hospitalized with AAV and inpatient kidney biopsy, 2016–2020.

Study Variables and Study Outcomes

We ascertained basic demographic variables including age, sex, designated race, payer, and disposition information through the NIS Core file, and hospital characteristics including hospital region, teaching status, and bed size through the NIS Hospital file. Coding for race in NIS combines designated race and ethnicity into one data element. If both designated race and ethnicity were available, ethnicity was prioritized over race in setting the HCUP value for race [9]. We utilized Elixhauser comorbidity software refined for ICD-10-CM codes and reported comorbidities based on relevance with AAV, including chronic kidney disease (CKD) and CKD stages, history of hypertension, diabetes, obesity, coronary artery disease, peripheral arterial disease, smoking, and chronic obstructive pulmonary disease [10, 11]. We identified the most frequent associated diagnosis codes including AKI, hypoxia, sepsis, pneumonia, and acidosis. We also identified the most frequent procedure codes including intravenous catheter insertion, monoclonal antibody infusion, mechanical ventilation, blood transfusion, procedure-related dialysis, and pheresis. We collected length of stay from the NIS Core file. We estimated costs from the total charge for each hospitalization by applying hospital-specific charge-to-cost ratios. We accounted for severity of illness with the base APR-DRG, the severity of illness subclass, and the risk of mortality subclass within each base APR-DRG from NIS Severity file.

Statistical Analysis

All analyses considered the complex survey design, and the final results are weighted estimates that reflect national estimates. We pooled data from 2016 to 2020 and summarized baseline characteristics by AAV subtype as well as unspecified vasculitis. We report medians and 25%, 75% percentiles for continuous variables and counts and proportions for categorical variables. In addition to describing characteristics of the patient population – as a whole and by AAV subtypes – we determined median lengths of stay and hospital costs and explored whether these varied by region and hospital characteristics. We also report disposition (to home or to a rehabilitation or skilled nursing facility) and rates of inpatient mortality.

We used generalized linear models to determine whether geographic region, hospital characteristics, or AAV subtype were associated with differences in lengths of stay or inpatient costs. We adjusted all models for age, sex, designated race/ethnicity, and severity of illness. We observed missing data in fewer than 5% of hospitalizations for each variable. We assumed the data to be missing completely at random and performed a complete case analysis. We conducted the analysis using SAS software (SAS Institute Inc., Cary, NC, USA) and Stata, version 18 (Stata Corp LP, College Station, TX, USA).

Table 3. Lengths of stay, inpatient costs, and disposition of patients with AAV and inpatient native kidney biopsies, 2016–2020

	EGPA (*N* = 105)	Vasculitis (*N* = 3,540)	GPA (*N* = 1,640)	MPA (*N* = 1,360)	All (*N* = 6,645)
Length of stay, days	7.3 (4.3, 13.5)	9.1 (5.3, 14.9)	11.2 (6.7, 16.3)	11.4 (7.4, 17.3)	10.1 (6.0, 15.8)
Cost (US dollars)	23,889 (14,542, 32,475)	23,137 (12,740, 38,862)	29,120 (17,253, 48,008)	30,598 (19,090, 52,594)	26,695 (14,907, 43,820)
Missing, *n* (%)	0 (0)	5 (0.7)	4 (1.2)	3 (1.1)	12 (0.9)
Disposition, *n* (%)					
Home	85 (81.0)	2,210 (62.4)	1,020 (62.2)	840 (61.8)	4,155 (62.5)
Transfer to rehabilitation facility	20 (19.1)	1,220 (34.5)	580 (35.4)	450 (33.1)	2,270 (34.2)
AMA	0 (0.0)	80 (2.3)	35 (2.1)	65 (4.8)	180 (2.7)
Death	0 (0.0)	30 (0.9)	5 (0.3)	5 (0.4)	40 (0.6)

Variables are described using medians and 25th and 75th or counts and percentages. Medians, counts, and percentages reflect national estimates. ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic GPA; vasculitis, subtype unspecified vasculitis; AMA, against medical advice.

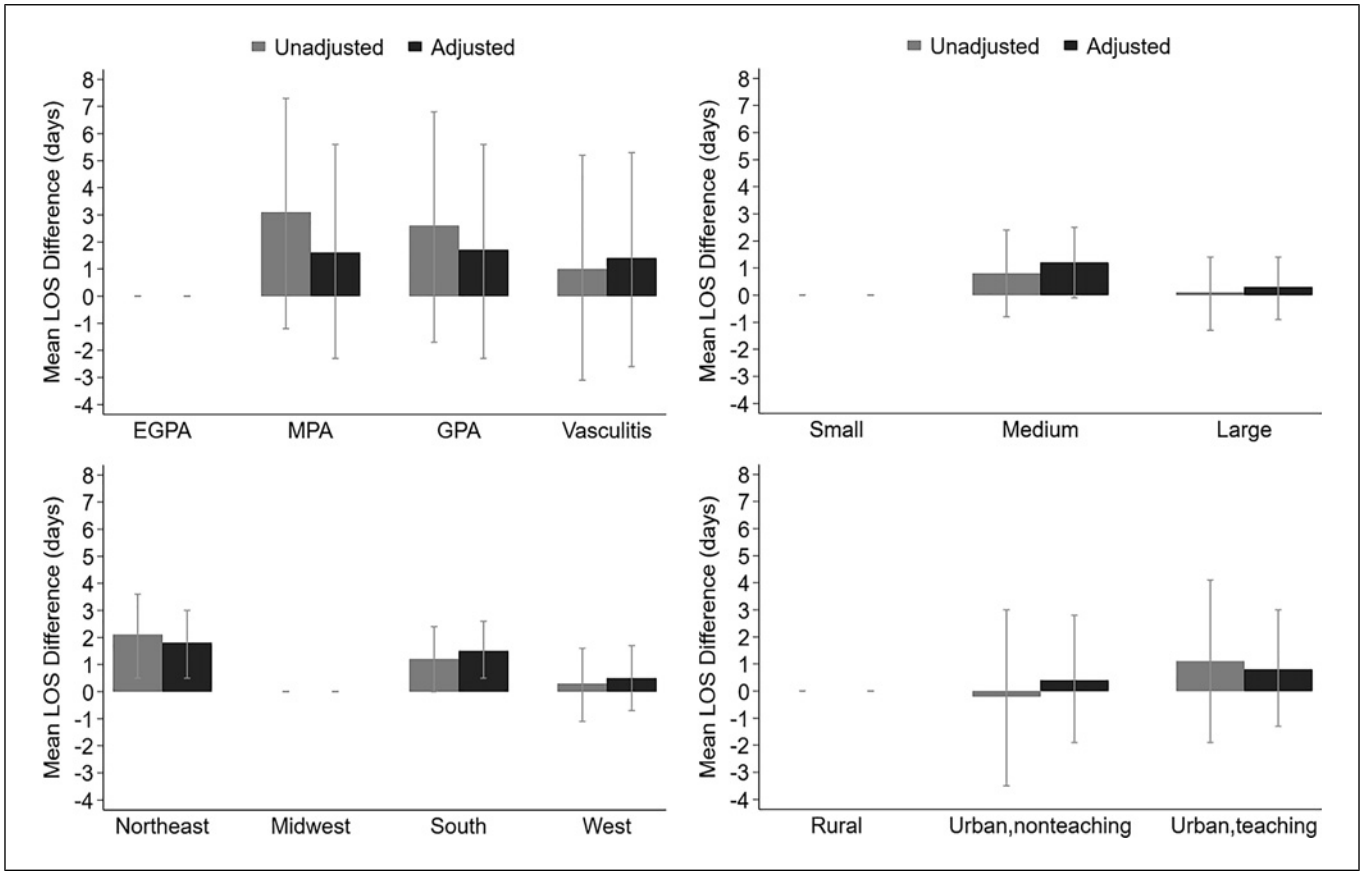

Fig. 2. Length of stay (unadjusted and adjusted), mean (95% CIs) by AAV subtype, hospital size and type, and region. Adjusted for age, sex, designated race, and severity of illness. ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic GPA; vasculitis, subtype unspecified vasculitis. Referent groups: EGPA, small hospitals, Midwest region, and rural hospitals.

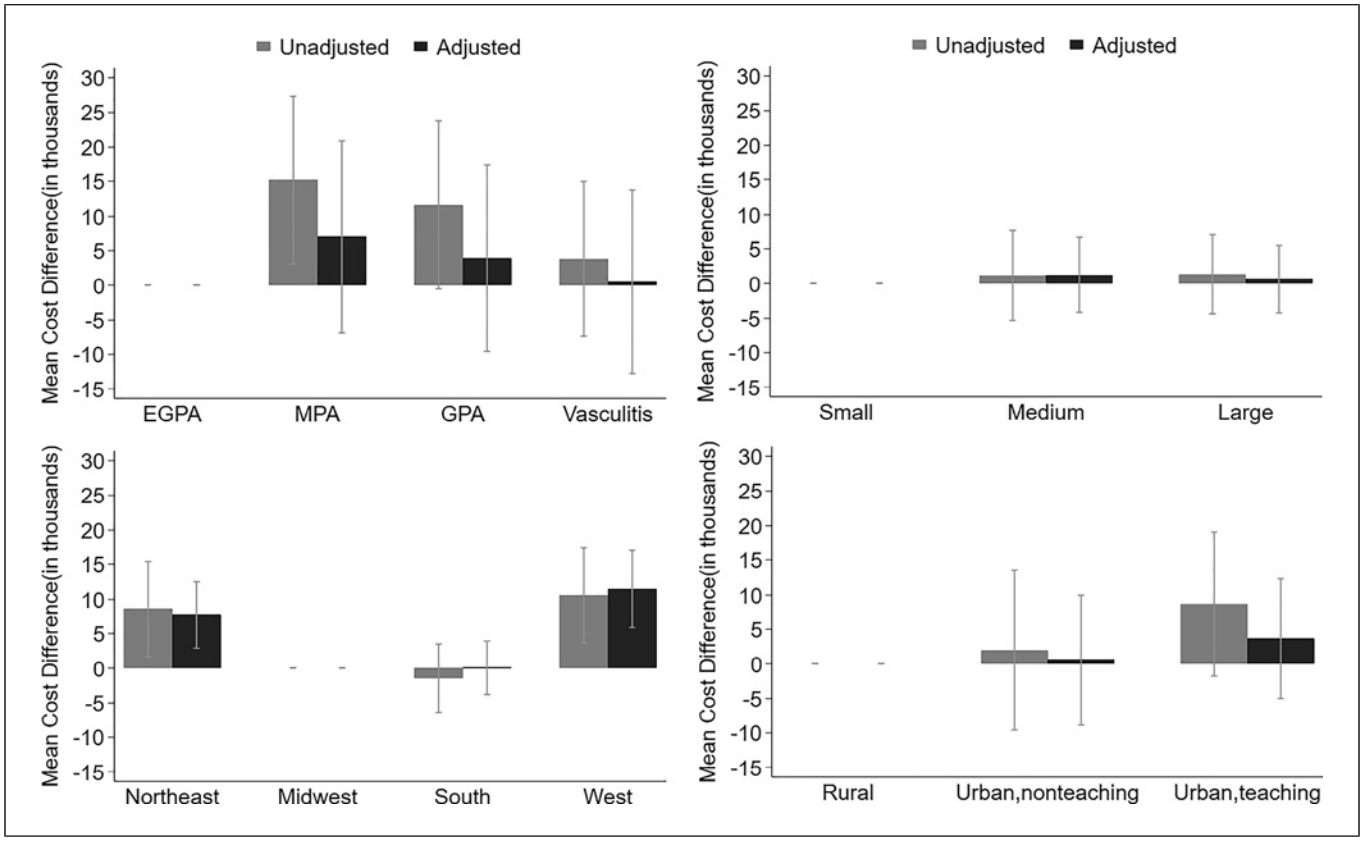

Fig. 3. Total costs (unadjusted and adjusted), mean (95% CIs) by AAV subtype, hospital size and type, and region. Adjusted for age, sex, designated race, and severity of illness. ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic GPA; vasculitis: subtype unspecified vasculitis. Referent groups: EGPA, small hospitals, Midwest region, and rural hospitals.

Results

Sample

We identified 1,329 records of adults hospitalized with AAV, a concurrent kidney biopsy, and no kidney failure prior to admission between January 1, 2016, and December 31, 2020. After applying complex survey analysis methods, these records represent 6,645 hospitalizations nationwide (Table 1).

Population Characteristics and Clinical Events

Over the 5-year period, there were between 26,940 and 29,305 annual admissions for patients with a discharge diagnosis of AAV or unspecified vasculitis. About 4.6% received concurrent inpatient kidney biopsy (Table 1). Table 2 describes demographic characteristics and comorbidities of the study population by AAV subtypes. Figure 1 shows commonly observed comorbid conditions and clinical events during hospitalization, also stratified by AAV subtypes.

EGPA is a much less common subtype of AAV relative to GPA or MPA. While there were only 105 hospitalizations including kidney biopsy over 5 years, due to its distinct clinical features [12], we separately described eGPA alongside GPA and MPA. Compared to patients with GPA or MPA, patients with EGPA were younger. More patients with EGPA carried a diagnosis of chronic pulmonary disease (57.1%), compared with 22.6% and 23.5% in patients with GPA and MPA, respectively (Table 2). Patients with EGPA had the lowest proportion with sepsis (4.8%), pneumonia (4.8%), acidosis (28.6%), catheter insertion (4.8%), and provision of dialysis (4.8%) during hospitalization. No patients with EGPA received pheresis or mechanical ventilation during hospitalization, but patients with EGPA were more likely to receive monoclonal antibody infusion (9.5%) (Fig. 1).

The mean age of patients with MPA was slightly older than patients with GPA (68.7 vs. 63.8 years), female predominant (57.7% vs. 48.2%), and more likely to be non-white (40.1% vs. 25.9%). Regarding payer and hospital region, teaching status, and bed size, there was a similar pattern in distribution among the three remaining groups (GPA, MPA, and unspecified vasculitis). Some key observations include: 60.7–71.7% were insured by Medicare/Medicaid; 32.7–36.6% were treated in the South region, followed by the West and Midwest regions, each accounting for 20.4–27.7% of patients. The Northeast region had the lowest proportion of patients, ranging 15.2–17.7%. Seventy-nine point nine to 83.5% of patients were admitted to urban teaching hospitals. Fifty-seven point three to 57.9% of patients were admitted to hospitals categorized as large in terms of bed size (Table 2).

CKD was more common in patients with MPA relative to those with GPA (32.7% vs. 26.8%), as was diabetes (29.0% vs. 19.5%). Obesity was more common in patients with GPA relative to MPA (21.0% vs. 15.4%) (Table 2).

AKI was prevalent in more than 85.7% of patients across all groups, with the highest prevalence in the MPA group (94.9%). Among GPA, MPA, and unspecified vasculitis groups, 19.6–24.6% required inpatient dialysis, 10.2–20.6% received pheresis, 17.4–23.2% experienced hypoxia, 5.5–9.5% were diagnosed with sepsis, and 4.3–5.9% required mechanical ventilation (Fig. 1).

Outcomes

Table 3 shows lengths of stay, inpatient costs, and disposition among patients in all AAV subtypes. More than one-third of patients were discharged to a rehabilitation facility (including skilled nursing); inpatient mortality rates were relatively low. There were no material differences in lengths of stay or inpatient costs among different AAV subtypes, bed size, or teaching status ($p = 0.804$ and 0.052, $p = 0.134$ and 0.898, and $p = 0.647$ and 0.364, respectively) (Fig. 2, 3, respectively). There was regional variation in costs, with the highest costs in the West region and the lowest costs in the Midwest region ($p < 0.001$), while lengths of stay were longest in the Northeast and shortest in the Midwest ($p = 0.007$) (Fig. 2, 3, respectively).

Discussion

AAV is a rare disease. Disease complexity by multiorgan involvement, a typically chronic course often with a relapsing and remitting pattern, and disparate preferences for treatment strategies from different centers contribute to the heterogeneity of data observed from retrospective cohort studies [13–15]. Incidence and prevalence rates and survival associated with AAV subtypes vary geographically [16, 17]. During the past decade, utilization of national-level administrative data allowed authors to describe the broadly recognized clinical consequences and economic costs associated with these diseases. For example, Panupattanapong et al. [13] analyzed the 2006–2014 Truven Health Analytics MarketScan® Commercial Claims and Encounters Database. The dataset only captures an insured population below the age of 65 years. Therefore, the authors could only ascertain the incidence and the prevalence of GPA in pediatric and adult (<65 years) population in the USA. In general, the incidence of GPA increases with age, with a peak in the 60 to 70 years of age range, so that a sizeable fraction of patients was likely missed by this approach.

Another limitation of prior reports is the lack of individual codes for AAV subtypes in ICD-9-CM. When Ungprasert et al. [18] utilized the NIS database from 2005 to 2014, they were only able to specifically report on GPA and found higher in-hospital mortality and costs compared with patients without GPA. The NIS utilized the ICD-10-CM coding version from 2015 onward; ICD-10-CM uniquely captures the diagnosis of MPA and EGPA as well. Therefore, when Rivera et al. [19] explored the NIS database from 2016 to 2018, they were able to include patients with MPA when reporting reasons for admissions and inpatient mortality. However, this study, along with other past studies on AAV, included a mixed cohort of those presenting to the hospital with active kidney injury or admitted for other reasons concurrently with a remote diagnosis and little or no active kidney involvement. For example, when Idolor et al. [20] claimed that lengths of stay and inpatient costs were higher in GPA with renal involvement compared to those without, "maintenance hemodialysis" in "GPA without renal involvement" was reported as 12.33%.

We aimed to overcome these limitations by including only those patients with a diagnosis of AAV (with GPA, MPA, EGPA, and unspecified vasculitis subtypes) who underwent kidney biopsy during the index hospitalization. While it is possible that a small number of patients might have been admitted for a second kidney biopsy, our restriction should have resulted in a cohort of patients who were diagnosed with AAV during their index hospitalization. Since few patients undergo follow-up kidney biopsy for AAV, this restriction should mitigate the issue of multiple admissions per patient since NIS captures data on distinct hospitalization events rather than on individual patients.

Our study found that the number of admissions due to AAV or unspecified vasculitis with active kidney involvement in the USA was relatively steady from year 2016–2020. Consistent with current clinical knowledge, EGPA was the least common of the three designated subtypes. Patients with EGPA were younger and more frequently presented with a history of chronic obstructive pulmonary disease, which may have reflected misclassification of pulmonary disease associated with EGPA. Patients with EGPA generally had less severe manifestations of kidney disease and the most favorable clinical outcome. Compared with GPA, MPA demonstrated a somewhat more severe presentation vis-à-vis kidney involvement. The incidence of AKI (94.9% vs. 91.5%), acidosis (37.5% vs. 32.3%), catheter insertion (44.5% vs. 41.2%), blood transfusion (28.3% vs. 22.6%), and dialysis (24.6% vs. 24.1%) were higher in patients with MPA compared with patients with GPA. In contrast, patients with GPA demonstrated a somewhat more severe presentation vis-à-vis lung involvement with higher incidence of sepsis (9.5% vs. 5.5%) and pneumonia (19.5% vs. 14.3%). Both subtypes received similar levels of plasmapheresis. Patients with unspecified AAV had baseline characteristics similar to those with GPA and MPA. It is certainly possible (perhaps likely) that these patients were diagnosed with AAV by virtue of a positive ANCA, myeloperoxidase (MPO), or proteinase-3 (PR-3) antibody test but were discharged before the histopathological diagnosis was finalized. This may explain why infusion of monoclonal antibodies and the use of plasmapheresis were lower in this group, as they may have returned for treatment after their initial hospitalization.

Clearly, AAV is associated with substantial healthcare costs and incremental increases in cost among patients with kidney involvement, consistently reported by studies derived from different study populations [12, 18, 20, 21]. Cases with the most severe clinical presentation from active kidney involvement are generally admitted; during hospitalization, costs are frequently incurred for the ICU stay, kidney biopsy, mechanical ventilation, blood transfusion, dialysis, and plasmapheresis. Huang et al. [22] studied 2015–2016 Medicare Part A/B claims and found that Medicare beneficiaries with AAV had larger differences in hospital-based resource utilization relative to outpatient services when compared with Medicare beneficiaries without AAV.

We found little difference in lengths of stay and costs across the AAV subtypes with kidney involvement. We observed shorter lengths of stay and lower costs in the Midwest relative to the Northeast and higher costs in the West. Although we could not further examine the cause(s) for the discrepancy, we propose that these may be attributed to variations in disease severity, treatment strategies, or preferences across different regions.

The study on GPA and MPA conducted by Bataille et al. [10] in a large fraction of the French population was extremely informative. The authors analyzed data from the general health insurance scheme (covering 76% of the French population) from 2010 to 2017 and reported prevalence, incidence, portions of system/organ involvement, and mortality associated with GPA and MPA. They found that despite advances in the therapeutic management of patients [23, 24], mortality rates remained high. We found the inpatient mortality rate for AAV with active kidney involvement in the USA to be 0.6% on the average; we could not assess longer term mortality.

By leveraging the strengths of the NIS dataset, including data on hospital-based procedures, we were able to construct a "cleaner" cohort than most previously published reports, largely by restricting hospitalizations to those which were likely to represent the initial presentation of kidney disease. Owing to the scope of the data and by pooling multiple years, we were able to compare clinical characteristics and complications associated with the three major subtypes of AAV. This approach provided a condensed overview of the clinical logistics and accurately reflected common practices in the US. By way of example, we found that 1 in 5 patients with GPA and MPA received plasmapheresis, despite mixed evidence as to its safety and effectiveness [25, 26]. It is noteworthy that a higher proportion of patients received mechanical ventilation relative to plasmapheresis. Plasmapheresis is often initiated in patients because of diffuse alveolar hemorrhage. Whether diffuse alveolar hemorrhage contributed to the need for mechanical ventilation is unknown.

There are several limitations to our study. First, owing to the database we selected, we could not have captured patients with AAV with evidence of kidney disease not severe enough to require hospitalization and/or where kidney biopsy might have been performed in the outpatient setting. Second, we would not have captured patients with AAV in whom kidney biopsy was an absolute or relative contraindication due to heightened risks, including patients with a solitary kidney, severe hypertension, severe pulmonary compromise, the need for anticoagulation without the capacity for a short-term hold (e.g., patients with mechanical heart valves), the inability to lay prone due to morbid obesity or musculoskeletal disorders, or where patients refused or were unable to consent to kidney biopsy. Third, we were unable to rule out cases where AAV is seen in conjunction with other forms of glomerulonephritis, including anti-glomerular basement membrane disease and

membranous nephropathy [27, 28]. Fourth, the NIS has no patient identifiers, and the dataset cannot be linked to other post-hospitalization data sources, limiting our assessment of outcomes to those that occurred in hospital. Fifth, the NIS lacks detailed clinical data unrelated to claims, such as the serum creatinine or the ratio of partial pressure of oxygen to the fraction of inspired oxygen, which could shed light on the severity of end-organ involvement. Sixth, MPA and GPA are clinical syndromes with significant overlap. The ambiguity in clinical diagnosis can lead to misclassification by subtype in any AAV cohort. As such, we did not emphasize comparisons across the three subtypes and uncharacterized vasculitis. The different disease states may also be described by the presence or absence of antibodies to the MPO and/or PR-3 antigens. Finally, as with all observational studies, there is likely to be residual confounding for which we could not adjust.

In summary, we provide an updated description of clinical characteristics and in-hospital complications and outcomes for patients presenting with AAV and acute kidney involvement in the USA. Observational ("real-world") studies incorporating longer term outcomes (including pharmacoepidemiology) and prospective randomized clinical trials are needed to improve outcomes associated with these rare diseases.

Statement of Ethics

Ethical approval and consent were not required as this study was based on publicly available data.

Conflict of Interest Statement

Dr. Chertow has served on the Board of Directors of Satellite Healthcare, a nonprofit dialysis provider. He has served as Chair or Co-Chair of Trial Steering Committees with Akebia, AstraZeneca, CSL Behring, Sanifit, and Vertex. He has served as an Advisor to Applaud, CloudCath, DURECT, Eliaz Therapeutics, Miromatrix, Outset, Physiowave, Renibus, and Unicycive. He has served on Data Safety Monitoring Boards with Bayer, Mineralys, and Recor. The remaining authors have no disclosures to report.

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Author Contributions

Study design and data interpretation: J.T., S.L., M.M.-R., and G.M.C.; data analysis: J.T. and S.L.; drafting the manuscript: J.T. and G.M.C.; and revising manuscript content and approving final version of the manuscript: J.T., S.L., M.M.-R., V.C., and G.M.C. All authors take responsibility for the integrity of the data analysis.

Data Availability Statement

All data generated or analyzed during this study are included in this article, as possible. Further inquiries can be directed to the corresponding author.

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