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In-hospital mortality associated with granulomatosis with polyangiitis and microscopic polyangiitis complicated with respiratory failure

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ABSTRACT

Background and aim: Our study aimed to determine the in-hospital mortality rate among granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) hospitalizations complicated with acute respiratory failure (ARF) in the US and determine prognostic factors during hospitalization.

Method: We performed a retrospective cohort analysis utilizing the National In-patient Sample (NIS) database to identify hospitalizations of patients with GPA or MPA associated with ARF from 2016 to 2021. The outcomes included in-hospital mortality, requirement of invasive procedures, and hospital length of stay. Univariable and multivariable analysis were used to identify prognostic factors associated with in-hospital mortality.

Results: We identified 21,430 weighted (4,283 unweighted) hospitalizations with diagnosis of GPA or MPA associated with ARF in the United States from 2016 to 2021. 78.3% of those were diagnosed with GPA, 19.2% with MPA, and 2.5% with both ICD-10 codes. The mean age was 63.7 years, 53.6% were female, and 73.3% were White. The rate of hemodialysis was 21.5%, plasmapheresis 7.4%, and extracorporeal membrane oxygenation in 0.5% of hospitalizations. The overall in-hospital mortality was 15.4%, compared to 35.9% in the subgroup requiring invasive mechanical ventilation (IMV). Independent prognostic factors associated with increased in-hospital mortality were higher age, acute kidney injury (AKI), sepsis, requirement of non-invasive mechanical ventilation, interstitial lung disease (ILD), history of stroke, shock, and requirement of IMV.



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Conclusion: GPA or MPA hospitalizations complicated with ARF were found to be associated with a high in-hospital mortality rate. At hospital-level prognostication assessment, we found that higher age, AKI, sepsis, shock, history of ILD, history of stroke, and requirement of mechanical ventilation were independently associated with increased in-hospital mortality.

Key words: ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, national Inpatient Sample database, respiratory Failure

Introduction

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are rare small-to-medium-vessel vasculitides belonging to the group of vasculitis termed antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) (1). Histologically, GPA is characterized histologically by necrotizing granulomatous inflammation with vasculitis, whereas MPA presents with necrotizing vasculitis in the absence of granulomas (1,2). Although recognized as distinct diseases, GPA and MPA can often share overlapping clinical features, and many pivotal trials have traditionally enrolled patients with both conditions together (3). The epidemiology of GPA and MPA shows substantial variation between populations and regions. Earlier studies reported that global incidence ranges from 0.5 to 20 cases/million per year and prevalence estimates from 20–160 cases per million in general population (4). More recent population-based studies demonstrate higher prevalence, now approaching 300–421 cases per million, which likely reflects both improved survival and greater diagnostic recognition (5). Nevertheless, due to its rarity, most of the clinical experience published regarding hospitalized patients with AAVs is derived from small registers (6–9). When used properly, national databases can help fill gaps in the scientific literature on rare diseases by allowing for analysis of a significant number of cases. (10,11). Clinically, GPA and MPA can involve nearly any organ or tissue, but the respiratory tract and the kidneys are most commonly affected (1,12). Pulmonary involvement is of particular concern, as it can progress to acute respiratory failure (ARF), often due

to severe pulmonary inflammation and diffuse alveolar hemorrhage (DAH). ARF is a life-threatening complication in AAV and contributes significantly to ICU admissions and mortality (13). Patients with GPA or MPA complicated by ARF experience high short-term mortality, but available data are mainly derived from small cohorts or non-U.S. populations (6–9). Given these limitations, a study evaluating inpatient mortality and predictors of poor outcomes in patients with GPA or MPA presenting with ARF using nationally representative U.S. data is warranted. Our study, therefore, aimed to determine the in-hospital mortality rate and clinical outcomes of these patients, as well as to identify predictors of mortality.

Methods

Data source

The study analyzed data from the National Inpatient Sample (NIS) database from 2016 to 2021. The NIS is part of a family of databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP) (14). The NIS is the largest publicly available all-payer inpatient healthcare database designed to produce U.S. regional and national estimates of inpatient utilization, access, cost, quality, and outcomes. The NIS contains a random 20% stratified sample of patients discharged from participating hospitals. Unweighted, it contains data from around 7 million hospital stays each year. Weighted, it estimates approximately 35 million hospitalizations nationally. The self-weighting design of the NIS allows

precise national estimates to be derived. To produce unbiased national estimates of total hospitalizations, diagnoses, and procedures, results will be presented as weighted frequencies (15). Each observation contained in the NIS contains patient- and hospital-level information for each discharge. The only clinical information available is that which is amenable to coding by the International Classification of Diseases (ICD) and ICD for Procedure codes. The criteria (clinical, lab, or radiographic) used to diagnose each medical condition are not recorded in the database. Multiple admissions for the same patient are not linked because there is no unique patient identifier; therefore, readmissions and transfers, if they occur, are counted as new admissions. Institutional review board approval determination was not required, as the NIS contains only de-identified inpatient hospitalizations (16). Following NIS/HCUP policy, only outcomes or variables with 11 or more events will be reported to protect patient's privacy.

Study population

First, we included all adult hospitalizations (age \geq 18 years) with a diagnosis of GPA or MPA using the ICD 10th revision (ICD-10) codes (Table S1), admitted from 2016 through 2021. Case definitions of GPA or MPA were based exclusively on the presence of ICD-10 codes. Hospitalizations coded for both GPA and MPA were also included in the analysis, as they might represent a group of cases with undifferentiated presentation. Second, GPA and MPA populations were stratified into two groups GPA or MPA with and without ARF. Hospitalization with ARF were identified using ICD-10 codes (Table S1). Hospitalizations with missing information for age, sex, or mortality were excluded.

Co-variables included in the analysis

Descriptors included were patient demographics (age, sex, and race) and hospital characteristics (location, teaching status, and bed size) (Table S2). We also used ICD-10 codes (Table S1) to identify coexisting chronic clinical conditions (hypertension, dyslipidemia, diabetes mellitus, history of tobacco use, obesity, low body mass, heart failure, atrial fibrillation, history of stroke, depression, COPD, obstructive sleep

apnea (OSA), asthma, interstitial lung disease (ILD), pulmonary hypertension, long-term dependence on oxygen, gastroesophageal reflux disorder, and end-stage renal disease [ESRD]), and acute comorbidities (acute kidney injury [AKI], sepsis, pneumonia, shock, hemoptysis, coma, gastro-intestinal bleeding).

Outcomes

The primary outcome of our study was the in-hospital mortality rate among hospitalizations of patients with GPA or MPA complicated with ARF. As the NIS database is a de-identified database and readmissions of the same patient are counted as new cases (hospitalizations), the in-hospital mortality in our study was defined as the risk of dying during each hospitalization. We also extracted data on the requirement of inpatient procedures (invasive mechanical ventilation [IMV], non-invasive mechanical ventilation [NIMV], hemodialysis, plasmapheresis, bronchoscopy, and extracorporeal membrane oxygenation [ECMO]). We analyzed length of stay (LOS). Independent predictors associated with all-cause in-hospital mortality were also analyzed.

Statistical analysis

We queried the HCUP NIS database from 2016 to 2021 to capture the hospitalizations of interest. As the NIS is a large administrative database, investigators should interpret results based on clinical relevance and not merely statistical significance. To ensure the appropriate use of the NIS database, we followed the checklist of key elements recommended in the HCUP Data Use Agreement (10,15). We utilized descriptive statistics to characterize demographics, existing co-occurrences, and in-hospital complications. Weighted frequencies were calculated using cluster, stratum, and weight variables for each year in survey-specific procedures (17). The frequencies were weighted by DISCWT and appropriate strata and cluster variables (NIS_STRATUM and HOSP_NIS, respectively). Survey methods were utilized for statistical analysis, including the regression models performed. GPA and MPA hospitalizations with and without ARF were compared for significant differences using Rao-Scott chi-square tests and Mann-Whitney U tests. Potential

prognostic factors associated with in-hospital mortality were evaluated among pre-existing comorbidities, demographics, hospital characteristics, and post-admission clinical complications and procedures. Reduced models were developed via backward elimination using an alpha threshold of 0.05. Variables that shown significant association with in-hospital mortality in univariate analysis with $p < 0.05$ were added to the final multivariable analysis. Variables considered as clinically relevant at authors discretion (sex, race) were also included. Analyses were generated using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics and study population

A total of 21,430 weighted (4,283 unweighted) hospitalizations with discharge diagnosis of GPA or MPA associated with ARF were identified between 2016 and 2021 in the United States. Among those 16,775 (78.3%) had the combination of diagnoses GPA and ARF and 4,110 (19.2%) had the combination of diagnoses MPA and ARF. 530 (2.5%) hospitalizations were coded with both GPA and MPA ICD-10 codes for the same patient, which might represent cases with undifferentiated presentation. Overall, the mean age of the target population (GPA or MPA and ARF) was 63.7 years (standard deviation 0.25), 53.6% of patients were female, and 73.3% were White. Most patients were treated in large bed size hospitals (55.5%). Most significant comorbidities found were heart failure (39.8%), COPD (31.0%), ESRD (30.3%), OSA (12.8%), asthma (9.4%), and ILD (11.8%) as shown in Table 1. Refer to Table S3 for detailed information regarding racial distribution, primary expected payer and hospital teaching status. Hospitalizations of patients with MPA and ARF had higher mean age (67.8 versus 65.0 years, $P < 0.001$), and higher prevalence of ILD (22.5% versus 9.0%, $P < 0.001$) and ESRD (34.1% versus 29.0%, $P < 0.001$) when compared to hospitalizations of patients with GPA and ARF (Table 1). Patients hospitalized with GPA or MPA and ARF had an elevated rate of other acute organ

failure and systemic complications. AKI was found in 45.5%, pneumonia in 40.3%, sepsis in 31.0%, and shock in 16.5% of hospitalizations (Table 2).

Invasive procedures

In the overall population, invasive mechanical ventilation was required in 28.7% hospitalizations. Non-invasive mechanical ventilation was required in 15.3% of patients. Hemodialysis was performed in 21.5% of hospitalizations, plasmapheresis in 7.4%, and ECMO in 0.5% (115 weighted cases) (Table 2). Hospitalizations of patients with MPA and ARF were associated with higher rate of invasive procedures IMV (31.3% versus 27.9%, $P = 0.03$), hemodialysis (27.1% versus 19.8%, $P < 0.001$), bronchoscopy (13.4% versus 9.0%, $P < 0.001$), plasmapheresis (16.4% versus 6.1%, $P < 0.001$), when compared with those with GPA and ARF (Table 2).

In-hospital mortality

The overall in-hospital mortality rate among those with GPA or MPA complicated with ARF was 15.4%, which represents an estimative of 3,330 deaths in the United States from 2016 to 2021. This was thirteen times higher (15.4% versus 1.2%, $P < 0.001$) than the in-hospital mortality rate of those hospitalized with GPA or MPA ICD-10 codes but without ARF. Those hospitalizations associated with ICD-10 coding for IMV had an in-hospital mortality rate of 35.9%. Hospitalizations associated with MPA and ARF had a higher all-cause in-hospital mortality rate when compared to those with GPA only and ARF (17.3%, versus 14.7%, $P < 0.001$) (Table 2).

Independent prognostic factors associated with in-hospital mortality

Considering overall population (GPA or MPA associated with ARF), our preliminary univariate analysis identified twenty-three variables that showed a potential association with the all-cause in-hospital mortality outcome (Table S4) and were selected for the multivariate analysis. Sex and race were added to the multivariate analysis at the author's discretion. The final model included age, sex, race, hypertension, hyperlipidemia, smoking,

Table 1. Baseline clinical characteristics of hospitalizations of granulomatosis with polyangiitis or microscopic polyangiitis associated with acute respiratory failure.

Cohort	Hospitalizations with GPA or MPA and ARF (weighted frequency) N= 21,430	Hospitalizations with GPA and ARF (weighted frequency) N =16,775 (78.3%)	Hospitalizations with MPA and ARF (weighted frequency) N = 4,110 (19.2%)	Hospitalizations with GPA and MPA and ARF (weighted frequency) N = 530 (2.5%)	P value
Characteristic					
Age, mean (SE)	63.7 (0.25)	65.0	67.8	69.7	<0.001
Sex (%)					<0.001
Female	53.5	52.1	60.1	50	
Income by Zip-code (percentile) (%)					0.83
0-25 th	26.8	27.1	26.1	22.3	
26-50 th	26.9	26.8	26.4	33.0	
51-75 th	25.3	25.2	25.9	24.3	
76-100 th	21.0	20.9	21.6	20.4	
Bed size of Hospital (%)					0.22
Small	16.7	17.0	14.7	20.8	
Medium	27.8	28.0	26.8	30.2	
Large	55.5	55.0	55.5	49.0	
Comorbidities					
Hypertension (%)	76.0	74.7	81.0	77.4	<0.001
Diabetes (%)	28.9	28.7	30.9	20.8	0.08
History of tobacco use (%)	32.8	33.1	32.0	26.4	0.31
Dyslipidemia (%)	35.6	35.3	37.0	34.9	0.65
Dependence on long-term oxygen (%)	12.0	*	*	*	N/A
Low body mass (%)	4.0	*	*	*	
Obesity (%)	17.7	18.3	15.9	12.3	0.10
Heart failure (%)	39.8	38.7	44.5	40.6	0.010
Atrial fibrillation (%)	26.7	26.2	28.1	32.1	0.25
Depression (%)	12.9	13.5	9.9	17.0	0.008
History or stroke (%)	4.3	*	*	*	N/A
COPD (%)	31.0	32.0	27.1	31.1	0.031
Obstructive sleep apnea (%)	12.8	*	*	*	N/A
Asthma (%)	9.4	*	*	*	N/A
Pulmonary hypertension (%)	9.2	*	*	*	N/A
Interstitial lung disease (%)	11.8	9.0	22.5	16.0	<0.001
Bronchiectasis (%)	4.3	*	*	*	N/A

Cohort	Hospitalizations with GPA or MPA and ARF (weighted frequency) N= 21,430	Hospitalizations with GPA and ARF (weighted frequency) N =16,775 (78.3%)	Hospitalizations with MPA and ARF (weighted frequency) N = 4,110 (19.2%)	Hospitalizations with GPA and MPA and ARF (weighted frequency) N = 530 (2.5%)	P value
Pulmonary embolism (%)	3.34	*	*	*	N/A
End stage renal disease (%)	30.3	29.0	34.1	41.5	<0.001
Gastrointestinal reflux disease (%)	23.4	23.6	22.4	22.6	0.75
Alcohol use disorder (%)	1.5	*	*	*	N/A

* Unweighted frequency ≤ 10 are not reportable following NIS database privacy policy. *Abbreviations:* ARF Acute respiratory failure; GPA Granulomatosis with polyangiitis; MPA Microscopic polyangiitis

Table 2. In-hospital outcomes and invasive procedures rate among hospitalizations of patients with GPA or MPA associated with ARF.

Cohort	Hospitalizations with GPA or MPA with ARF (weighted frequency) N= 21,430 (100%)	Hospitalizations with GPA and ARF (weighted frequency) N = 16,775 (78.3%)	Hospitalizations with MPA and ARF (weighted frequency) N = 4,110 (19.2%)	Hospitalizations with GPA and MPA and ARF (weighted frequency) N = 530 (2.5%)	P value
Characteristic					
All-cause in-hospital mortality (%)	15.4	14.7	17.3	21.7	0.036
Hospital length of stay, days (median, IQR)	7.5 (3.7 – 14.9)	7.0 (3.5 – 14.2)	9.5 (4.6 -16.9)	10.8 (6.2 -18.2)	<0.001
In-hospital complications (%)					
Acute kidney injury	45.5	42.3	56.9	59.4	<0.001
Pneumonia	40.3	40.4	39.7	43.4	0.75
Sepsis or septic shock	31.0	32.2	26.6	28.3	0.007
Shock	16.5	16.5	16.3	16.0	0.99
Hemoptysis	20.0	17.3	29.3	36.8	<0.001
Coma	0.6	*	*	*	N/A
Gastrointestinal bleeding	4.6	*	*	*	N/A
In-hospital procedures (%)					
Invasive mechanical ventilation	28.7	27.9	31.3	36.8	0.030

Cohort	Hospitalizations with GPA or MPA with ARF (weighted frequency) N= 21,430 (100%)	Hospitalizations with GPA and ARF (weighted frequency) N = 16,775 (78.3%)	Hospitalizations with MPA and ARF (weighted frequency) N = 4,110 (19.2%)	Hospitalizations with GPA and MPA and ARF (weighted frequency) N = 530 (2.5%)	P value
Non-invasive mechanical ventilation	15.3	14.9	17.5	10.4	0.06
Hemodialysis	21.5	19.8	27.1	31.1	<0.001
Plasmapheresis	7.4	6.1	16.4	13.2	<0.001
Bronchoscopy	9.9	9.0	13.4	12.3	<0.001
ECMO	0.5	*	*	*	N/A

* Unweighted frequency ≤ 10 are not reportable following NIS database privacy policy. *Abbreviations:* GPA Granulomatosis with polyangiitis; MPA Microscopic polyangiitis; ARF Acute respiratory failure; ECMO: extracorporeal membrane oxygenation

history of ILD, long-term oxygen dependence, OSA, asthma, atrial fibrillation, obesity, depression, stroke, gastro-esophageal reflux disease, AKI, sepsis, shock, coma, gastrointestinal bleeding, IMV, NIMV, plasmapheresis, bronchoscopy, and hospital teaching status. After adjustment for all covariates, the independent prognostic factors associated with increased risk of all-cause in-hospital mortality (Table 3) were higher age odds ratio (OR) 1.04 (CI 95% 1.03 – 1.04, $P < 0.001$); requirement of IMV (OR 5.04, CI 95% 4.05 – 6.27, $P < 0.001$), shock (OR 2.96, CI 95% 2.31 – 3.78, $P < 0.001$), history of stroke (OR 1.95, CI 95% 1.27 – 3.00, $P=0.002$), history of ILD (OR 1.72, CI 95% 1.30 – 2.27, $P<0.001$), requirement of NIMV (OR, 1.52, CI 95% 1.17 – 1.99, $P = 0.002$), AKI (OR, 1.43, CI 95% 1.17 – 1.75, $P < 0.001$), and sepsis (OR, 1.51, CI 95% 1.21 – 1.88, $P < 0.001$). Three co-variables were associated with lower likelihood of in-hospital mortality obesity (OR 0.67, CI 95% 0.50 – 0.89, $P = 0.005$), dyslipidemia (OR 0.70, CI 95% 0.57 – 0.87, $P < 0.001$), and history of tobacco use (OR 0.75, CI 95% 0.60 – 0.94, $P = 0.001$).

Length of stay

The median LOS among overall population of patients with GPA or MPA and ARF was 7.5 days (IQR 3.7 – 14.9). Hospitalizations associated with

MPA and ARF had longer LOS (9.5 versus 7.0 days, $P<0.001$) than those hospitalizations with GPA and ARF (Table 2).

Discussion

Despite being relatively rare, we identified 4,283 hospitalizations associated with the diagnosis of GPA or MPA complicated with ARF. Invasive mechanical ventilation support was used in more than one quarter of these cases. This large retrospective study confirmed previous evidence showing the deadly association between GPA or MPA and ARF. One-third of the cases that required IMV died. We identified eleven independent prognostic factors associated with in-hospital mortality, eight of which were associated with increased mortality, and three with decreased mortality. GPA and MPA are rare AAVs in the US, but these conditions are associated with high in-hospital mortality when complicated by ARF. Overall, the in-hospital mortality rate found in our study was high (15.4%), and even higher among those patients requiring IMV (35.9%). In a retrospective study of 121 intensive care unit (ICU) patients with small vessel vasculitis, 90-day mortality was higher in immune-related ARF cases (32%) than in non-immune causes (15%) (7). Overall, in previous

Table 3. Multivariable analysis for prognostic factors of all-cause in-hospital mortality among hospitalization with GPA or MPA and acute respiratory failure (n = 4,283).

Characteristics	OR	95% IC	P value
Factors associated with increased in-hospital mortality			
Higher age	1.04	1.03 – 1.04	< 0.001
Acute kidney injury	1.43	1.17 – 1.75	<0.001
Sepsis	1.51	1.21 – 1.88	<0.001
Non-invasive mechanical ventilation	1.52	1.17 – 1.99	0.002
Interstitial lung disease	1.72	1.30 – 2.27	<0.001
History of stroke	1.95	1.27 – 3.00	0.002
Shock	2.96	2.31 – 3.78	< 0.001
Invasive mechanical ventilation	5.04	4.05 – 6.27	< 0.001
Factors associated with lower in-hospital mortality			
Obesity	0.67	0.50 – 0.89	0.005
Dyslipidemia	0.70	0.57 – 0.87	< 0.001
Tobacco use	0.75	0.60 – 0.94	0.001

Abbreviations: GPA Granulomatosis with polyangiitis; MPA Microscopic polyangiitis

retrospective studies of patients with AAVs admitted to ICU, the mortality rate ranges from 11 to 53% (6–9,18,19). Comparing our mortality rates to those in prior studies is challenging due to some aspects. First, as the NIS database studies, readmissions of the same patient are counted as new hospitalizations. Therefore, the denominator number of the mortality equation is increased, and ultimately leading to lower mortality rate in a determined period. Second, our study considered hospitalizations in all hospital units, including regular floor and ICU beds. In contrast, most previous studies assessed only ICU patients, who are expected to have a higher mortality rate. Our findings validate previous evidence that patients with GPA or MPA complicated with ARF, especially those requiring ICU or IMV, are associated with a high in-hospital mortality rate, even when assessing a large number of hospital admissions. We also found that hospitalizations associated with MPA and ARF had higher in-hospital mortality rate compared with those associated with GPA and ARF. In our study, patients hospitalized with MPA appeared to be sicker and had longer LOS. MPA patients were older, and required more invasive procedures such as mechanical ventilation, hemodialysis, bronchoscopy

and plasmapheresis compared to those with GPA. Similar findings have been shown in previous studies (22, 23). The poorer prognosis associated with MPA might be related to the higher incidence of renal disease and ILD when compared to patients with GPA (24). Identification of the predictors of mortality is vital for risk assessment and prognostication. Previous publications have addressed this issue by studying patients with AAVs in different settings including outpatient clinics (20–23), general hospital (24), and ICU only (9,18,25). Following univariable and multivariable analysis, we identified eight independent prognostic factors associated with higher risk of in-hospital mortality, and three associated with lower risk. The requirement of both non-invasive and invasive mechanical ventilation was identified as independent prognostic factor of higher in-hospital mortality risk. Previous studies have found similar results. Holguin et al studied medical records of 65 patients hospitalized (in the ward or ICU) with AAV and pulmonary complications in one medical center in Atlanta, Georgia (24). Respiratory failure and mechanical ventilation were also independent predictors of mortality in studies that addressed ICU and outpatient population with AAVs, in China (9) and Italy (20)

respectively. Our findings not only support the previous evidence that patients who require IMV have a higher in-hospital mortality risk, but the risk of dying is five times higher if compared with those who did not require IMV. AKI also emerged as an independent prognostic factor of in-hospital mortality in our study. Renal involvement is a hallmark of AAV and has long been recognized as a determinant of long-term outcomes. In ICU-based studies, AKI, particularly when dialysis was required, was associated with higher mortality rates (9,26). Similar to our findings, a multicenter French ICU study of AAV patients found that AKI had a higher risk of death (27). Our findings strengthen the evidence that AKI remains a key prognostic marker in the acute phase of GPA or MPA with respiratory failure. Sepsis was another independent prognostic factor associated with higher mortality. Infections are a leading cause of death in AAV, particularly during hospitalizations and among immunosuppressed patients (28,29). In our population, the coexistence of sepsis likely reflects severe immunologic and infectious complications during hospitalization, emphasizing the need for vigilant infection prevention and early management in this group. Previous studies have suggested that ILD is a major prognostic factor in AAV patients (30–32). ILD has been reported in about 23% of GPA patients and up to 45% in MPA patients, but only 11.8% of patients hospitalized with GPA or MPA and ARF were also identified with ILD in our study. It is possible that the prevalence of ILD in our study is underestimated due to under coding. Nevertheless, being coded for ILD along with GPA or MPA and ARF was identified as an independent prognostic factor associated with in-hospital mortality with an increased OR of 1.72 compared to those without ILD. Our findings align with what Zhou et al found in their meta-analysis assessing the impact of ILD on mortality in AAV patients (33). Our analysis showed an increased relative risk of death among those with AAV associated with ILD by almost three times. Although there is no specific treatment for patients with ILD and AAV, this association supports the use of ILD as a major prognostic factor among those with GPA or MPA and ARF. Surprisingly, we found three variables associated with a reduced risk of in-hospital mortality history of tobacco use, obesity, and dyslipidemia. The paradoxical association of smoking with reduced

in-hospital mortality has already been described in the literature among patients with acute ischemic stroke, acute coronary syndrome, and heart failure exacerbation (34–36). Ali et al. found that smokers admitted with acute ischemic stroke had 36% lower in-hospital mortality odds compared to never smokers (34). This apparent smoker's paradox should not be interpreted as a benefit of cigarette smoking because the hazardous effects of smoking are well established, negatively affecting almost all body organs. Tolulope et al found that both current and former smoking statuses were associated with an increased mortality risk in adults hospitalized with COPD exacerbations (37). It is not completely clear why the history of smoking was associated with a lower in-hospital mortality rate among patients with GPA or MPA and ARF. It is possible that our model was unable to completely control confounders such as the burden of smoking, active versus former smoking, age of onset and duration of GPA and MPA. Our study found an "obesity paradox," where obese patients (body mass index [BMI] > 30) had lower in-hospital mortality than non-obese patients. This aligns with recent research showing better survival in obese individuals with pulmonary embolism and cardiovascular diseases (38,39). Conversely, in our study low body mass (BMI < 18.5) did not seem to have association with in-hospital mortality in univariable analysis [OR 1.31 (CI 95% 0.89 – 1.93; P= 0.20)]. Some speculate that increased nutritional reserves could serve as protective mechanisms to support the enhanced survival among obese critically ill patients (40). The obesity paradox is not completely understood and warrants further investigation. Similar to obesity, dyslipidemia has been found to be an independent factor related to lower in-hospital mortality. Although numerous studies have confirmed that low-density lipoprotein cholesterol (LDL-C) levels is a major risk factor for cardiovascular disease, the relationship between LDL-C level and mortality risk in different populations remains controversial. Li et al found a J-shaped association between cholesterol level and all-cause mortality in critically ill patients, with lower LDL-C concentration was associated with a higher risk of all-cause mortality (41). Low cholesterol levels have also been associated with higher mortality risk in patients with ILD. Chen et al assessed a retrospective cohort of patients with ILD and even after

adjusting for sex, age, smoking history, body mass index and the use of antifibrotic and lipid-lowering drug, lower total cholesterol levels were identified as an independent risk factor for mortality (42). The impact of cholesterol level in-hospital mortality seems to be complex and our findings suggest that the history of dyslipidemia might have an inverse association with in-hospital mortality. Further research is needed to fully understand this relationship in diverse patient populations and clinical settings. It is also possible that even with statistical adjustments with the multivariable analysis, other unknown or unmeasured confounders can still distort results leading to the paradoxical findings described above. Medical literature has strong evidence that smoking, dyslipidemia, and obesity are risk factors associated with long-term reduced overall survival. The paradox association found in our study should not be interpreted as protective factor. Our paradox findings are likely associated with unknown or unmeasured confounders that are still distorting the results. Limitations of this study include its administrative and retrospective nature in which variables related to comorbidities and procedures rely on the quality of documentation and the billing process. Clinical research in vasculitis using the NIS database is a powerful tool for generating valid, large-scale, population-level insights into hospitalizations, however the lack of clinical granularity warrants careful interpretation of the findings. We did not have access to complete chart data to better characterize which diagnostic criteria were used to label a patient with GPA or MPA. It is possible that some of the cases coded as GPA or MPA do not fulfill all the guideline-based criteria diagnosis (12,43,44). However, using a pragmatic definition of GPA and MPA cases, our study may better reflect the real-world outcomes of patients hospitalized with ARF who were diagnosed and treated as GPA and MPA based on the discretion of bedside-physicians in the US (45). Another limitation of our study is that we could not distinguish the cause (immune versus non-immune) of ARF in our population. The NIS database provides outcome data only regarding the same hospitalization, therefore all conclusions should be read as prognostication associated with hospitalization-level risk only, not as patient-level prognostication. However, to the best of our knowledge, our data highlights the largest real-world cohort of hospitalizations for GPA or MPA

complicated with ARF, comprising more than 1,000 unweighted hospitalizations of patients with GPA or MPA on invasive mechanical ventilation. Our large cohort allowed the team of investigators to draw statistically robust findings regarding independent prognostic factors associated with all-cause in-hospital risk of death. This information can help physicians at the bedside to better advise family members and patients about the prognosis during the hospital course. In this nationwide representative retrospective study, GPA or MPA hospitalizations complicated with ARF were found to be associated with a high in-hospital mortality rate. More than one third of those requiring IMV died. At hospital-level prognostication assessment, we found that higher age, AKI, sepsis, shock, history of ILD, history of stroke, and requirement of mechanical ventilation were independently associated with increased in-hospital mortality.

Ethics Approval and Consent to Participate: The study was exempted from going through Institutional Review Board because it used a deidentified database.

Availability of Data and Material: The datasets analyzed for this study are available from the corresponding author Dr. Costa Filho (francisco.costafilho@corewellhealth.org) upon reasonable request.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Authors' contributions: FF: Conceptualization, Methodology, Investigation, Supervision; FF, AB: Data curation, Formal analysis; FF, PK, PJK: Validation; FF, VM, AB, PK, PJK: Visualization, Writing – review and editing; FF, VM, AF: Writing – original draft; AF, AB: Formal analysis, Writing – review and editing. FF takes responsibility for the content of the manuscript, including the data and analysis.

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ANNEX

Table S1. Data on various medical comorbidities and procedures were obtained using International Classification of Diseases (ICD) diagnosis and procedural codes. We used ICD Tenth Revision.

Variables	ICD-10 CM/PCS codes
Target population	
Granulomatosis with polyangiitis	M31.3; M31.30; M31.31
Microscopic polyangiitis	M31.7
Acute respiratory failure	J80; J96.0; J96.00; J96.01; J96.02; J96.2; J96.20; J96.21; J96.22; J96.90; J96.91; J96.92; R06.03
Comorbidities	
Chronic obstructive pulmonary disease	J41, J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J98.2, J98.3, J44, J44.0, J44.1, J44.8, J44.9
Hypertension	I10; I110; I119; I120; I129; I130; I1310; I1311; I132; I150; I151; I152; I158; I159; I160; I161; I169
Diabetes Mellitus	E08.00; E08.01; E08.10; E08.11; E08.21; E08.22; E08.29; E08.4x; E08.5x; E08.6x; E08.8; E08.9; E10.x; E11.x; E13; E14.x;
Dyslipidemia	E78; E78.0; E78.41; E78.49; E78.00; E78.01; E78.1; E78.2; E78.3; E78.4; E78.5; E78.89; E78.9
History of tobacco use	Z72.0; Z87.891; F17.200; F17.2xx; F17.2xx; T65.2xxx
Dependence on long-term oxygen	Z99.81
Heart failure	I09.81; I11.0; I13.0; I13.2; I50.20; I50.21; I50.22; I50.23; I50.30; I50.31; I50.32; I50.33; I50.40; I50.41; I50.42; I50.43; I50.9; I97.130; I97.131; I50.1; I97.110; I97.111; I25.5; I42.0; I42.1; I42.2; I42.5; I42.6; I42.7; I42.8; I42.9; I50.810; I50.811; I50.812; I50.813; I50.814; I50.82; I50.83; I50.84; I50.89
Depression	
Obesity	E66.01; E66.2; Z68.30; Z68.31; Z68.32; Z68.33; Z68.34; Z68.35; Z68.36; Z68.37; Z68.38; Z68.39; Z68.41; Z68.42; Z68.43; Z68.44; Z68.45
Low body mass	Z68.1
Atrial fibrillation	I48.0; I48.1; I48.2; I48.3; I48.4; I48.91; I48.92; I48.11; I48.19; I48.20; I48.21
Stroke	I60.xx; I61.xx; I63.xxx; I69.xxx; G46.x
Acute kidney injury	N17; N17.0; N17.1; N17.2; N17.8; N17.9
ESRD on dialysis or chronic kidney disease stage V	N18.6; I12.0; I13.11; I13.2; N18.5; Z99.2; R88.0; I95.3
Depression	F32; F32.0; F32.1; F32.2; F32.3; F32.4; F32.5; F32.89; F32.9; F33.0; F33.1; F33.2; F33.3; F33.40; F33.41; F33.42; F33.8; F33.9; F34.81; F34.89; F34.9; F39.; F06.31; F06.32; F06.33; F06.34

Variables	ICD-10 CM/PCS codes
Pulmonary disorders: COPD	J41.0; J41.1; J41.8; J42; J43.0; J43.1; J43.2; J43.8; J43.9; J44.0; J44.1; J44.9; J98.2; J98.3; J98.4
Obstructive sleep apnea	G47.33
Asthma	J45; J45.20; J45.21; J45.22; J45.30; J45.31; J45.32; J45.40; J45.41; J45.42; J45.50; J45.51; J45.52; J45.901; J45.902; J45.909; J45.990; J45.991; J45.998
Pulmonary disorders: Pulmonary hypertension	I27.0; I27.20; I27.21; I27.22; I27.23; I27.24; I27.29; I27.81; I27.83; I27.89; I27.9
Pulmonary disorders: Interstitial lung disease (do not include pneumoconiosis)	J70.2; J70.3; J70.4; J82; J84.01; J84.10; J84.111; J84.112; J84.113; J84.114; J84.115; J84.116; J84.117; J84.17; J84.2; J84.81; J84.82; J84.89; J84.9
Pulmonary disorders: Bronchiectasis	J47.0; J47.1; J47.9
Pulmonary embolism	I27.82; I26; I26.9; I26.02; I26.03; I26.04; I26.09; I26.92; I26.93; I26.94; I26.95; I26.96; I26.99
Gastroesophageal reflux disease	K21.0; K21.9
Frailty	R54
Alcohol use disorder	E24.4; F10.10; F10.120; F10.121; F10.129; F10.14; F10.150; F10.151; F10.159; F10.180; F10.181; F10.182; F10.188; F10.19; F10.20; F10.21; F10.220; F10.221; F10.229; F10.230; F10.231; F10.232; F10.239; F10.24; F10.250; F10.251; F10.259; F10.26; F10.27; F10.280; F10.281; F10.282; F10.288; F10.29; F10.920; F10.921; F10.929; F10.94; F10.950; F10.951; F10.959; F10.96; F10.97; F10.980; F10.981; F10.982; F10.988; F10.99; G31.2; G62.1; G72.1; I42.6; K29.20; K29.21; K70.0; K70.10; K70.11; K70.2; K70.30; K70.31; K70.40; K70.41; K70.9; K85.20; K85.21; K85.22; K86.0; O35.4XX0; O35.4XX1; O35.4XX2; O35.4XX3; O35.4XX4; O35.4XX5; O35.4XX9; O99.310; O99.311; O99.312; O99.313; O99.314; O99.315; Z71.41
Pneumonia	J13; J14; J15.0; J15.1; J15.20; J15.211; J15.212; J15.3; J15.4; J15.5; J15.61; J15.69; J15.7; J15.8; J15.9; J16.0; J16.8; J17; J18.0; J18.1; J18.2; J18.8; J18.9; J22; J20.0; J20.1; J20.2; J85.0; J85.1; J85.2
Sepsis or septic shock	A40; A40.0; A40.1; A40.3; A40.8; A40.9; A41; A41.1; A41.01; A41.02; A41.1; A41.2; A41.3; A41.4; A41.5; A41.50; A41.51; A41.52; A41.53; A41.54; A41.59; A41.8; A41.81; A41.89; A41.9; R65.20; R65.21
Hemoptysis	R04.2; R04.89; R04.9; R04.8
Coma	R40.0; R40.1; R40.2; R40.20; R40.2A; R40.2420; R40.2421; R40.2422; R40.2423; R40.2424; R40.2430; R40.2431; R40.2432; R40.2433; R40.2434; R40.2440; R40.2441; R40.2442; R40.2443; R40.2444
Shock or vasopressors	R65.21; R57.0; R57.1; R57.8; R57.9; R57; 3E030XZ; 3E033XZ; 3E040XZ; 3E043XZ
Gastrointestinal bleeding	K92.0; K92.1; K92.2

Variables	ICD-10 CM/PCS codes
Invasive mechanical ventilation	5A09B5K; 5A09C5K; 5A09D5K; 5A1935Z; 5A1945Z; 5A1955Z; 0BH17EZ; Z99
Non invasive ventilation	5A0920Z; 5A09357; 5A09358; 5A09359; 5A0935A; 5A0935B; 5A0935Z; 5A09457; 5A09458; 5A09459; 5A0945A; 5A0945B; 5A0945Z; 5A09557; 5A09558; 5A09559; 5A0955A; 5A0955B; 5A0955Z
Red blood cell Blood transfusion	30230N1
Plasmapheresis	6A550Z3; 6A551Z3
Hemodialysis	Z49.31; Z99.2; 5A1D00Z; 5A1D70Z; 5A1D80Z; 5A1D90Z
ECMO	5A1522F; 5A1522G; 5A1522H; 5A15A2F; 5A15A2G; 5A15A2H; Z92.81
Bronchoscopy	0BJ08ZZ; 0B9D8ZX; 0BBC8ZX; 0BJ08ZZ; 0BJ18ZZ; 0BJK8ZZ; 0BJL8ZZ; 0BBM8ZX; 0BBL8ZX; 0BBK8ZX; 0BBJ8ZX; 0BBH8ZX; 0BBG8ZX; 0BBF8ZX; 0BBD8ZX; 0BBC8ZX

Abbreviations: ICD 10 CM/ PCS codes – International Classification of Diseases Tenth Revision Clinical Modification/Procedure Coding System

Table S2. Hospital bed size categories used in the National Inpatient Database since 1998.

Bed size categories beginning in 1998 by number of available beds			
Location and Teaching status	Hospital Bedsizes		
	Small	Medium	Large
NORTHEAST REGION			
Rural	1-49	50-99	100+
Urban, nonteaching	1-124	125-199	200+
Urban, teaching	1-249	250-424	425+
MIDWEST REGION			
Rural	1-29	30-49	50+
Urban, nonteaching	1-74	75-174	175+
Urban, teaching	1-249	250-374	375+
SOUTHERN REGION			
Rural	1-39	40-74	75+
Urban, nonteaching	1-99	100-199	200+
Urban, teaching	1-249	250-449	450+
WESTERN REGION			
Rural	1-24	25-44	45+
Urban, nonteaching	1-99	100-174	175+
Urban, teaching	1-199	200-324	325+

Table S3. Baseline clinical characteristics of hospitalizations of granulomatosis with polyangiitis or microscopic polyangiitis with and without acute respiratory failure between 2016 and 2021.

Cohort	All hospitalizations with GPA or MPA (weighted frequency) N= 80,915	Hospitalizations with GPA or MPA and ARF (weighted frequency) N= 21,430 (26.5%)	Hospitalizations with GPA or MPA without ARF (weighted frequency) N= 59,485 (73.5%)	P value
Characteristic				
Age, mean (SE)	62.3 (0.15)	63.7 (0.25)	61.9 (0.18)	<0.001
Age group (%)				<0.001
18-39 (Ref)	11.8	9.0	12.8	
40-59	25.2	24.6	25.4	
60-79	49.3	52.2	48.4	
>= 80	13.6	14.2	13.4	
Sex (%)				0.08
Female	54.7	53.5	55.1	
Race (%)				0.39
White	74.0	73.3	74.2	
Black	7.8	8.1	7.7	
Hispanic	12.3	12.8	12.1	
Asian/Pacific Islander	1.1	2.2	2.2	
Native American	1.1	0.8	1.2	
Other	2.6	2.7	2.5	
Income by Zip-code (percentile) (%)				0.008
0-25 th	25.1	26.8	12.8	
26-50 th	26.5	26.9	25.4	
51-75 th	26.0	25.3	48.4	
76-100 th	22.4	21.0	13.5	
Bed size of Hospital (%)				0.32
Small	17.2	16.7	17.4	
Medium	27.0	27.8	26.7	
Large	55.8	55.6	56.0	
Hospital setting teaching status				0.15
Rural	6.3	5.7	6.5	
Urban non-teaching	17.5	17.4	17.5	
Urban teaching	76.2	76.9	76.0	
Payer				0.68
Medicare	62.1	62.8	61.9	
Medicaid	9.7	9.6	9.7	
Private	24.1	23.7	24.3	
Self-pay	2.0	1.8	2.1	

No charge	0.2	0.2	0.2	
Other	1.8	1.9	1.8	
Comorbidities				
Hypertension (%)	74.7	76.0	74.3	0.03
Diabetes (%)	26.8	28.9	26.1	<0.001
History of tobacco use (%)	34.6	32.8	35.3	0.003
Dyslipidemia (%)	37.3	35.6	37.9	0.007
Dependence on long-term oxygen (%)	6.6	12.0	4.6	<0.001
Low body mass (%)	3.4	4.0	3.2	0.018
Obesity (%)	15.3	17.7	14.4	<0.001
Heart failure (%)	28.0	39.8	23.8	<0.001
Atrial fibrillation (%)	21.8	26.7	20.0	<0.001
Depression (%)	13.6	12.9	13.9	0.09
History of stroke (%)	4.3	4.3	4.2	0.81
COPD (%)	22.7	31.0	19.7	<0.001
Obstructive sleep apnea (%)	10.8	12.8	10.1	<0.001
Asthma (%)	9.8	9.4	9.9	0.38
Pulmonary hypertension (%)	5.2	9.2	3.8	<0.001
Interstitial lung disease (%)	7.1	11.8	5.4	<0.001
Bronchiectasis (%)	2.8	4.3	2.2	<0.001
Pulmonary embolism (%)	2.1	3.34	1.6	<0.001
End stage renal disease (%)	27.3	30.3	26.3	<0.001
Gastrointestinal reflux disease (%)	26.4	23.4	27.5	<0.001
Frailty (%)	0.3	*	0.3	*
Alcohol use disorder (%)	1.8	1.5	1.9	0.09
HIV (%)	0.2	*	0.2	*

* Unweighted frequency ≤ 10 are not reportable following NIS database privacy policy. ** Chi-square tests cannot be computed because at least one table cell has 0 frequency. *Abbreviations:* GPA Granulomatosis with polyangiitis; MPA Microscopic polyangiitis; ARF Acute respiratory failure; SE Standard error; HIV Human immunodeficiency virus

Table S4. Unadjusted prognostic factors (univariable analysis) of all-cause in-hospital mortality among hospitalizations with GPA or MPA and acute respiratory failure.

Characteristics	Vital status as deceased at discharge among hospitalizations with GPA or MPA and ARF	Vital status as alive at discharge among hospitalizations with GPA or MPA and ARF	OR	95% IC	P value
Age, mean (SE)	68.1 (0.51)	62.9 (0.28)	-	-	<0.001
Age group (%)					<0.001
18-39 (Ref)	3.5	10.0	1	-	
40-59	18.5	25.7	2.2	1.3 – 3.7	
60-79	58.6	51.1	3.6	2.2 – 5.8	
>= 80	19.4	13.2	4.6	2.7 – 7.6	
Sex					0.15
Male	49.0	46.0	0.9	0.8 – 1.1	
Female (Ref)	51.0	54.0	1	-	
Race					0.08
White (Ref)	71.4	73.4	1	-	
Black	7.4	8.3	0.9	0.7 – 1.3	
Hispanic	12.7	12.8	1.0	0.8 – 1.3	
Asian/Pacific Islander	3.8	2.0	1.9	1.2 – 3.1	
Native American	1.1	1.0	1.5	0.6 – 3.4	
Other	3.6	2.5	1.5	1.0 – 2.4	
Income by Zip-code (percentile) (%)					0.89
0-25th (Ref)	25.7	27.0	1	-	
26-50th	27.7	26.7	0.7	0.6 – 1.0	
51-75th	25.7	25.2	0.7	0.6 – 0.9	
76-100th	20.9	21.1	1.0	0.6 – 1.5	
Comorbidities prior to hospitalization					
Hypertension	72.4	76.6	0.8	0.6 – 1.0	0.023
Diabetes	29.9	28.7	1.1	0.9 – 1.3	0.56
Tobacco use	22.1	34.7	0.5	0.4 – 0.7	<0.001
Dyslipidemia	30.3	36.5	0.8	0.6 – 0.9	0.002
Dependence on long-term oxygen	8.0	12.8	0.6	0.4 – 0.8	<0.001
Low body mass	5.0	3.9	1.3	0.9 – 1.9	0.21
Obesity	11.5	18.8	0.6	0.4 – 0.7	<0.001
Heart failure	42.0	39.5	1.1	0.9 – 1.3	0.22
Atrial fibrillation	37.4	24.8	1.8	1.5 – 2.1	<0.001
Depression	9.4	13.5	0.7	0.5 – 0.9	0.002
History or stroke	9.1	3.4	2.8	2.0 – 3.9	<0.001
COPD	28.8	31.4	0.9	0.7 – 1.1	0.17
Obstructive sleep apnea	9.9	13.4	0.7	0.5 – 0.9	0.006

Characteristics	Vital status as deceased at discharge among hospitalizations with GPA or MPA and ARF	Vital status as alive at discharge among hospitalizations with GPA or MPA and ARF	OR	95% IC	P value
Asthma	5.1	10.1	0.6	0.4 – 0.8	<0.001
Pulmonary hypertension	7.7	9.4	0.8	0.6 – 1.1	0.14
Interstitial lung disease	14.9	11.2	1.4	1.1 – 1.8	0.014
Bronchiectasis	4.4	4.3	1.0	0.7 – 1.5	0.94
Pulmonary embolism	4.6	3.1	1.5	1.0 – 2.2	0.10
End stage renal disease	31.5	30.1	1.1	0.9 – 1.3	0.47
Gastrointestinal reflux disease	17.0	24.5	0.6	0.5 – 0.8	<0.001
Frailty	*	*	*	*	*
Alcohol use disorder	*	*	*	*	*
HIV	*	*	*	*	*
In-hospital complications					
Acute kidney injury	65.0	41.9	2.6	2.2 – 3.1	<0.001
Pneumonia	41.7	40.1	1.1	0.9 – 1.3	0.45
Sepsis or septic shock	55.2	26.6	3.4	2.9 – 4.0	<0.001
Shock	47.9	10.8	7.6	6.3 – 9.2	<0.001
Hemoptysis	22.0	19.7	1.1	0.9 – 1.4	0.18
Coma	1.7	0.4	4.0	1.9 – 8.9	0.014
Gastrointestinal bleeding	8.5	3.9	2.3	1.7 – 3.2	<0.001
In-hospital procedures					
Invasive mechanical ventilation	67.0	21.8	5.4	4.3 – 6.8	<0.001
Non-invasive mechanical ventilation	19.3	14.6	1.4	1.1 – 1.7	0.005
Hemodialysis	20.3	21.7	0.9	0.7 – 1.1	0.41
Plasmapheresis	11.7	6.7	1.8	1.4 – 2.4	<0.001
Bronchoscopy	13.5	9.3	1.5	1.2 – 2.0	0.003
ECMO (extra corporal membrane oxygenation)	1.2	0.4	1.2	0.4 – 2.9	0.07
Bed size of Hospital					0.44
Small	16.5	16.7	0.9	0.7 – 1.2	
Medium	25.9	28.1	0.9	0.7 – 1.1	
Large (Ref)	57.6	55.2	1	-	
Hospital setting teaching status					0.036
Rural	4.2	6.0	0.7	0.5 – 1.0	
Urban non-teaching	15.6	17.7	0.7	1.1	
Urban teaching (Ref)	80.2	76.3	1	-	
Payer					0.07
Medicare (Ref)	67.1	62.0	1	-	

Characteristics	Vital status as deceased at discharge among hospitalizations with GPA or MPA and ARF	Vital status as alive at discharge among hospitalizations with GPA or MPA and ARF	OR	95% IC	P value
Medicaid	8.6	9.8	0.7	0.6 – 1.0	
Private	20.3	24.3	0.7	0.6 - 0.9	
Self-pay, No charge, other	4.0	3.9	1.0	0.6 - 1.5	

* Unweighted frequency ≤ 10 no reportable statistics. ** Chi-square tests cannot be computed because at least one table cell has 0 frequency. *Abbreviations:* GPA Granulomatosis with polyangiitis; MPA Microscopic polyangiitis; ARF Acute respiratory failure; SE Standard error; HIV Human immunodeficiency virus

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