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The Association of Airway Comorbidities With the Clinical Phenotypes and Outcomes of Patients With Antineutrophil Cytoplasmic Autoantibody–associated Vasculitis

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ABSTRACT. ***Objective***. We investigated the association of airway comorbidities with the clinical phenotypes and outcomes of myeloperoxidase (MPO)–antineutrophil cytoplasmic antibodies (ANCA)–positive ANCA-associated vasculitis (AAV).

Methods. An AAV patient multicenter cohort trial was established in 13 hospitals in western Japan between 2012 and 2018. We examined 143 of the new-onset MPO-ANCA–positive AAV patients. Their clinical characteristics and comorbidities at disease onset were compared based on clinical phenotypes. Multivariate analysis was performed to identify factors predictive of remission and death.

Results. Twenty-seven cases with granulomatosis with polyangiitis (GPA), 10 with eosinophilic GPA (EGPA), 81 with microscopic polyangiitis (MPA), and 25 with unclassified AAV were identified. The average age of MPO-ANCA–positive patients was 71.4 years. Comorbidity (87.4%) and airway comorbidity (70.6%) were frequently observed in these patients. Examination of the clinical phenotypes revealed that the cases of GPA were frequently accompanied by infectious airway comorbidity (upper airway disease, bronchiectasis, pulmonary infections), and most of the cases of MPA and unclassified AAV were accompanied by fibrotic interstitial lung disease (fILD) or emphysema. Among MPO-ANCA–positive patients, infectious airway comorbidity was predictive of both remission (HR 1.58, $P = 0.03$) and mortality (HR 2.64, $P = 0.04$), and fILD was predictive of mortality (HR 7.55, $P = 0.008$). The combination of infectious airway comorbidities and fILD caused the worst survival outcomes in patients.

Conclusion. MPO-ANCA–positive AAV was frequently accompanied by airway comorbidities. In addition to fILD, infectious airway comorbidities were closely associated with those clinical phenotypes and outcomes.

Key Indexing Terms: ANCA, ANCA-associated vasculitis, MPO-ANCA, vasculitis, comorbidity

Antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitis (AAV) is a systemic small-vessel vasculitis that is characterized by ANCA positivity and affects various organs, such as the lungs, kidneys, skin, and nervous system[1]. Even though the standard immunosuppressive treatment regimens of AAV have been established based on several key studies, we have still experienced difficulties in treating these patients[2]. Some patients with AAV do not achieve remission because their immunosuppressive treatments are insufficient. Conversely, others show negative outcomes due to the side effects from excessive immunosuppressive treatment.

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One of the reasons for these disparate results is the diversity of patients with AAV. Based on clinical phenotypes and pathologies, cases of AAV are divided into 3 diseases: granulomatosis with polyangiitis (GPA), eosinophilic GPA (EGPA), and microscopic polyangiitis (MPA). Two ANCA subtypes, myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)–ANCA, also exist. Moreover, age, organ involvement, and disease severity vary widely among patients with AAV. Recently, researchers have attempted to develop more personalized treatment strategies in order to realize safe, precise, and effective treatments for a wide variety of patients[3]. In order to pursue precision medicine, an improved understanding of the disease mechanism underlying AAV will be essential.

With regard to the various subtypes, MPA and MPO-ANCA–positive patients are most common in Asian countries, whereas GPA and PR3-ANCA–positive patients are most common in Western countries[4,5]. Previous genome-wide association studies proved that MPO-ANCA– and PR3-ANCA–positive AAV are genetically different diseases[6]. However, some patients with GPA are also positive for MPO-ANCA, which is predominant in Asian countries[7,8]. It is still controversial whether the differentiation between GPA and MPA is necessary among MPO-ANCA–positive AAV[9]. The Chapel Hill Consensus Conference classification is the nomenclature system for vasculitis, and was established to define individual types of vasculitis. However, in the clinical setting these classifications have led to diagnostic overlaps in patients with AAV[10,11]. Moreover, some MPO-ANCA–positive patients with AAV cannot be classified properly, such as those with pulmonary-limited AAV[12]. Thus, we overviewed our entire populations of MPO-ANCA–positive patients with AAV by using the European Medicines Agency (EMA) classification, which is often used in epidemiological studies to avoid diagnostic overlap. In this way, by providing a summary of MPO-ANCA–positive patients with AAV, we hoped to improve our understanding of the pathophysiology of AAV, and to provide clues to the disease's classification.

In our study, we focused on airway comorbidities. Bronchial asthma is not only a major airway comorbidity but also an allergic etiological factor of EGPA. It has also been shown that ANCA appears in the course of inflammatory diseases, such as silicosis and interstitial lung disease[13,14]. In contrast, previous studies have revealed a close association between GPA and staphylococcal airway infection[15,16]. Moreover, cases of MPA are frequently accompanied by fibrotic interstitial lung disease (fILD), which is known to be a predictive factor of mortality for these patients[17,18]. Because most airway comorbidities accompany inflammations, it is speculated that a close relationship exists between disease developments and airway comorbidities in patients with AAV. Thus, we hypothesized that airway comorbidities affected the development of AAV. In our present study, to actualize adequate precision medicine for individual patients with AAV, we aimed to investigate the association between airway comorbidities with the clinical phenotypes and outcomes of MPO-ANCA–positive patients with AAV.

MATERIALS AND METHODS

Patients. The Kyushu Vasculitis (KVAS) cohort is a multicenter cohort of patients with AAV that was established in 2012 among 13 hospitals in the western area of Japan. All patients were newly diagnosed with AAV by experienced rheumatologists at each hospital. These diagnoses were then confirmed by the inclusion criteria for primary vasculitis using the EMA classification. All patients were classified based on their organ involvements using the EMA algorithm[19,11]. ANCA-positive patients without surrogate markers of EGPA, GPA, and MPA were considered to have unclassified AAV (uAAV). Patients lost to follow-up within 6 months were excluded, except in the case of deceased patients. Written informed consent was obtained from each participant. The ethical committee of Saga University Hospital approved the cohorts and the databases for research purposes (approval no. 2014-12-08). All the other local ethical committees also approved our study. Rheumatologists evaluated all the vasculitis-affected organs in each patient based on the Birmingham Vasculitis Activity Score (BVAS)[20]. Most of the patients with AAV were evaluated with computed tomography (CT) scans of the head (65.1%) and chest (95.9%). Disease activity was measured by the BVAS. MPO-ANCA assays were mainly executed using a Nipro Nephroscholar MPO ANCA kit (Nipro) or MBL MPO-ANCA ELISA (MBL). PR3-ANCA assays were executed with a Nipro Nephroscholar PR3-ANCA kit (Nipro) or MBL PR3-ANCA ELISA (MBL). ANCA assays were executed using different generations of indirect ELISA kits depending on the hospitals and periods. Among the 15 double-ANCA–positive patients, the 10 patients with ANCA ratios > 10 were classified in the higher ANCA group. Each rheumatologist reported all the baseline comorbidities, which were assessed by determining the conditions that had been present before the AAV symptoms. They were categorized into 4 groups: airway comorbidity, heart disease, atherosclerosis, and others (Supplementary Table 1, available with the online version of this article). Some airway comorbidities were subcategorized into allergic airway comorbidity (bronchial asthma, allergic rhinitis), upper airway comorbidity (sinusitis/otitis media, history of sinus surgery, severe dental caries), or pulmonary infections (history of pulmonary tuberculosis, pulmonary nontuberculosis mycobacterium infections, fungal infections). The diagnoses of fILD, bronchiectasis, and pulmonary emphysema were made based on the patient history and chest CT scan images according to the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement for the diagnosis of idiopathic pulmonary fibrosis[21]. With respect to comorbidities, only patients exhibiting the usual interstitial pneumonia pattern or nonspecific interstitial pneumonia pattern were categorized as having fILD because of their chronicity. Patients were treated by a standardized protocol, and patients with active vasculitis were treated mainly with corticosteroids. Depending on patients' age, disease severity, and organ involvements, immunosuppressants and corticosteroid pulse therapy were added at the clinician's discretion. As initial remission induction therapy, cyclophosphamide (CYC) was used in 35.2% and rituximab (RTX) in 12.7% of MPO-ANCA–positive patients with AAV. Remission was defined as the absence of disease activity attributable to vasculitis manifestations for more than 1 month.

Statistical analysis. Fisher exact test or chi-square test were used to compare the prevalence of various clinical manifestations in each group. Continuous variables were nonparametrically compared using the Wilcoxon test or Kruskal-Wallis test, as appropriate. The time to remission and overall survival were calculated from the date of the diagnosis of AAV to the date of remission or death or the last follow-up. Cox proportional hazards regression method was used to estimate multivariate adjusted HR. Overall survival was calculated from the date of the patient's initial immunosuppressive treatment to the date of death or the last follow-up. Kaplan-Meier curves were generated for the time to overall survival. We compared the groups' survival by using the log-rank test. Statistical analyses were performed using JMP

Pro v. 13.1 software (SAS Institute). *P* values were 2-sided, and those < 0.05 were considered statistically significant.

RESULTS

Patient backgrounds and comorbidities. We defined AAV as patients with ANCA who satisfied the inclusion criteria of primary vasculitis based on the EMA classification. From 2012 to 2018, 225 patients with small- and medium-vessel vasculitis were enrolled in the KVAS cohort. Among them, the outcomes of 195 patients with AAV were available (Table 1; Supplementary Table 2, available with the online version of this article). The average age was 69.2 years, and females accounted for 57.6% of the total cohort. There were 24 patients with EGPA, 51 patients with GPA, 89 patients with MPA, and 31 patients with uAAV. Pathological proof of vasculitis was available in 33% of patients. Although none of the patients in the uAAV group had pathological proof of vasculitis, we were able to confirm that there was no change in diagnosis at the last follow-up for any of the patients in this group. To study the overall picture of MPO-ANCA–positive patients with AAV, patients with uAAV were recruited into our study. The comparison of vasculitis organ involvement among all our MPO-ANCA–positive patients with AAV confirmed that our modified EMA classification grouped them appropriately (Supplementary Tables 2 and 3, available with the online version of this article). We conducted a comparison of comorbidities based on the reported disease histories and the radiographic findings of chest CT scans. In this cohort, most of the patients with AAV (88.2%) had comorbidities, and the number of comorbidities was 1.9/patient (Table 1). Airway comorbidities were the most common (68.7%), and fILD was the most common of the airway comorbidities (34.3%).

Next, we compared 28 ANCA-negative patients with AAV, 143 MPO-ANCA–positive patients with AAV, and 19 PR3-ANCA–positive patients with AAV. The demographic comparison among the 3 groups is shown in Table 1. The average ages were 58.4, 71.4, and 69.7, respectively. ANCA-negative patients were the youngest and most commonly presented with EGPA. PR3-ANCA–positive patients predominantly had GPA, while most of the MPO-ANCA–positive patients had MPA. However, we found that 18.9% of MPO-ANCA–positive patients had the GPA phenotype, and another 17.5% showed a uAAV phenotype. Next, we compared the distributions of comorbidities by ANCA type (Table 1). The ANCA-negative group had a higher rate of allergic airway comorbidity and lower rate of fILD and atherosclerosis. Compared to the PR3 group, the MPO group had a higher percentage of patients with airway comorbidity (70.6%), such as fILD (44.1%) and bronchiectasis (18.8%). The number of airway comorbidities in the MPO group (mean 1.2 ± SD 1.1) was also higher than that of the PR3 group (0.7 ± 1.0). The PR3 group had a higher rate of heart disease (21.0%).

Table 1. Demographics and comorbidities of patients with AAV at diagnosis.

Cases, n	All AAV 195	ANCA– 28	MPO 143	PR3 19	*P*, All	*P*, MPO vs ANCA–	*P*, MPO vs PR3
Sex, female	57.6	50.0	58.7	63.2	> 0.1	> 0.1	> 0.1
Age, yrs, mean ± SD	69.2 ±12.2	58.4 ± 14.2	71.4 ± 10.7	69.7 ± 10.7	**< 0.0001**	**0.0002**	> 0.1
Pathological proof of vasculitis	33.3	57.1	30.8	21.1	**0.02**	**0.045**	> 0.1
EGPA[a]	12.3 (33.3)	46.4 (30.0)	7.0 (30.0)	5.3 (0.0)	**< 0.0001**	**< 0.0001**	> 0.1
GPA[a]	26.2 (31.4)	21.4 (100)	18.9 (22.2)	79.0 (20.0)	**< 0.0001**	> 0.1	**< 0.0001**
MPA[a]	45.6 (46.1)	21.4 (83.3)	56.6 (43.2)	10.5 (50.0)	**< 0.0001**	**0.0003**	**< 0.0001**
uAAV[a]	15.9 (0.0)	17.5 (0.0)	17.5 (0.0)	5.3 (0.0)	> 0.1	> 0.1	0.10
Smoking	35.7	32.2	32.2	36.8	> 0.1	> 0.1	> 0.1
Comorbidity	88.2	96.4	87.4	78.9	> 0.1	> 0.1	> 0.1
n, mean ± SD	1.9 ± 1.4	1.6 ± 1.0	2.0 ± 1.5	1.7 ± 1.3	> 0.1	> 0.1	> 0.1
Airway comorbidity	68.7	75.0	70.6	47.4	> 0.1	> 0.1	**0.049**
n, mean ± SD	1.1 ± 1.0	1.1 ± 0.8	1.2 ± 1.1	0.7 ± 1.0	> 0.1	> 0.1	**0.04**
Allergic airway	15.3	50.0	9.8	10.5	**< 0.0001**	**< 0.0001**	> 0.1
Upper airway	13.8	10.7	13.3	26.3	> 0.1	> 0.1	> 0.1
Bronchiectasis	15.4	10.7	18.8	0	**0.02**	> 0.1	**0.008**
Pulmonary infections	7.7	7.1	7.0	10.5	> 0.1	> 0.1	> 0.1
Emphysema	1.8	7.1	21.0	10.5	> 0.1	> 0.1	> 0.1
fILD	34.3	7.1	44.1	10.5	**< 0.0001**	**0.0002**	**0.002**
Heart disease	8.2	7.1	6.3	21.0	> 0.1	> 0.1	0.05
Atherosclerotic disease	43.1	17.9	46.8	42.1	**0.01**	**0.01**	> 0.1
Malignancy	9.7	3.6	11.1	10.5	> 0.1	> 0.1	> 0.1
Use of CYC, 6m	34.7	33.3	35.2	26.3	> 0.1	> 0.1	> 0.1
Use of RTX, 6m	11.9	3.7	12.7	21.1	> 0.1	> 0.1	> 0.1

Values are presented as % unless otherwise stated. Values in bold are significant. [a] The ratio of patients with pathological proof of vasculitis. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; CYC: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; fILD: fibrotic interstitial lung disease; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; RTX: rituximab; uAAV: unclassified AAV.

Distribution of comorbidities by clinical phenotypes among MPO-ANCA–positive patients. To address the association with clinical phenotypes, the distributions of comorbidities were compared only among MPO-ANCA–positive patients (Table 2). We recruited 143 MPO-ANCA–positive patients with AAV for further analysis; this group consisted of 10 cases of EGPA, 27 cases of GPA, 81 cases of MPA, and 25 cases of uAAV. The EGPA patients were the youngest, and the uAAV patients were the oldest. Airway comorbidities were frequently observed in all clinical phenotypes. All EGPA patients had allergic airway comorbidity (100%). Among GPA patients, upper airway comorbidity was observed most frequently (40.7%). GPA patients also had more bronchiectasis (29.6%) and pulmonary infection (18.5%), but not significantly more. Among the patients with MPA and uAAV, fILD was observed significantly more frequently (54.3% and 56.0%, respectively). These patients also had a higher incidence of pulmonary emphysema (25.9% and 20.0%, respectively), but not significantly. Greater numbers of patients in the MPA and uAAV had a smoking history (37.0% and 40.0%, respectively) and atherosclerotic disease (50.6% and 56.0%, respectively), but these differences were not significant.

The types of airway disease determine the clinical phenotypes of MPO-ANCA–positive AAV. The etiology of EGPA is directly associated with allergic disease, while GPA is thought to be associated with infectious disease[22]. We divided the airway comorbidities into 3 types: allergic airway comorbidity (asthma, allergic rhinitis), infectious airway comorbidity (upper airway disease, bronchiectasis, pulmonary infection), and noninfectious airway comorbidity (fILD, pulmonary emphysema). Because it is known that the main etiologies of upper airway comorbidities and bronchiectasis are chronic infections, they are grouped into infectious airway comorbidities[23,24]. As expected, most of our patients with EGPA had allergic airway comorbidities ($P < 0.0001$), whereas GPA frequently accompanied infectious airway comorbidity ($P = 0.0021$) and MPA and uAAV accompanied noninfectious airway comorbidity ($P < 0.0001$; Figure 1). In this way, we determined that the classification of clinical phenotypes is clarified by the type of airway comorbidities in MPO-ANCA–positive patients with AAV.

Factors predictive of remission or death. To address the association between comorbidities and the outcomes of MPO-ANCA–positive patients with AAV, we studied the factors predictive of remission or death in MPO-ANCA–positive patients. The rates of CYC and RTX use during the initial 6 months in MPO-ANCA–positive patients with AAV are shown in Table 2. CYC usage was not different among the 3 groups, while RTX was used most often in patients with GPA, though the difference was not significant. One hundred ten cases of remission (76.9%), 33 relapses (23.1%), and 21 deaths (14.7%) were observed during the course of the average observation period of 726 ± 543 days. First, we examined various factors for their ability to predict remission or death, including patient backgrounds, comorbidities, vasculitis organ involvements, and CYC use (Table 3). Bronchiectasis was extracted as a predictive factor for remission by multivariate analysis (HR 1.83, $P = 0.01$). Age (increased by 1 yr; HR 1.10, $P = 0.006$) and fILD (HR 7.32,

Table 2. Accompanying comorbidities before the diagnosis of MPO-ANCA–positive patients with AAV.

	EGPA	GPA	MPA	uAAV	*P*
Cases, n	10	27	81	25	
Sex, female	50.0	66.7	55.6	64.0	> 0.1
Age, yrs, mean ± SD	62.0 ± 14.0	70.0 ± 8.9	71.7 ± 10.8	76.0 ± 8.1	**0.005**
BVAS, mean ± SD	18.9 ± 5.5	17.9 ± 8.5	16.3 ± 6.4	10.3 ± 5.9	**0.0003**
eGFR mL/min, mean ± SD	98.8 ± 18.8	64.8 ± 29.9	52.4 ± 31.4	69.5 ± 25.5	**< 0.0001**
Smoking	20.0	14.8	37.0	40.0	0.09
Comorbidity	100	81.5	86.4	92.0	> 0.1
n, mean ± SD	2.3 ± 1.1	2.1 ± 1.6	2.0 ± 1.6	2.0 ± 1.2	> 0.1
Airway comorbidity	100.0	63.0	70.4	68.0	0.05
n, mean ± SD	1.9 ± 1.0	1.4 ± 1.3	1.1 ± 1.0	0.9 ± 0.8	0.10
Allergic airway comorbidity	100.0	0.0	4.9	0.0	**< 0.0001**
Upper airway comorbidity	10.0	40.7	8.6	0.0	**< 0.0001**
Bronchiectasis	20.0	29.6	14.8	16.0	> 0.1
Pulmonary infections	10.0	18.5	4.9	0.0	**0.04**
Emphysema	10.0	11.1	25.9	20.0	> 0.1
fILD	10.0	14.8	54.3	56.0	**0.0001**
Heart disease	0.0	3.7	7.4	8.0	> 0.1
Atherosclerotic disease	20.0	37.0	50.6	56.0	> 0.1
Malignancy	10.0	14.8	7.4	20.0	> 0.1
Use of CYC, 6m	22.2	24.0	39.2	25.0	> 0.1
Use of RTX, 6m	0.0	24.0	14.9	4.2	0.08

Values are presented as % unless otherwise stated. Values in boldface are significant. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; BVAS: Birmingham Vasculitis Activity Score; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; EGPA: eosinophilic granulomatosis with polyangiitis; fILD: fibrotic interstitial lung disease; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; RTX: rituximab; uAAV: unclassified AAV.

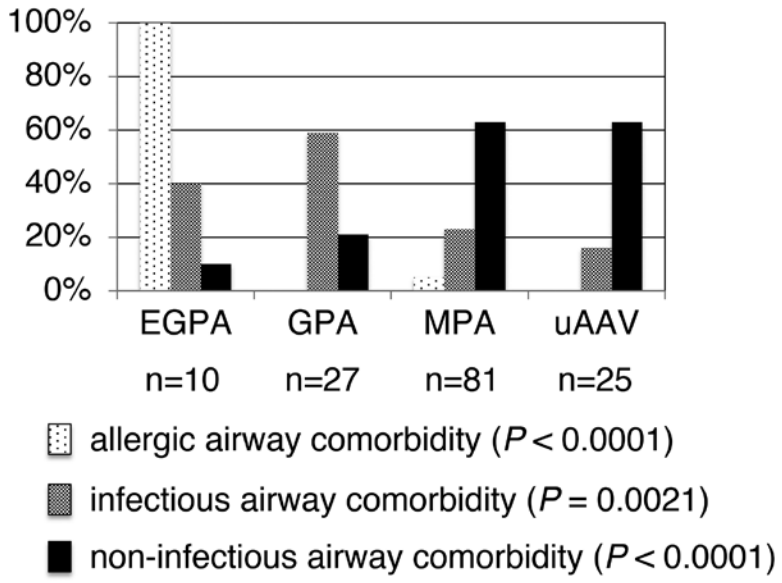

Figure 1. Airway comorbidity types determine the clinical phenotype of MPO-ANCA–positive patients with AAV. Comparison of the types of airway comorbidity among MPO-ANCA–positive patients AAV by the clinical phenotypes: EGPA (n = 10), GPA (n = 27), MPA (n = 81) and uAAV (n = 25). ANCA: antineutrophil cytoplasmic antibody; AAV: antineutrophil cytoplasmic antibody–associated vasculitis; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; uAAV: unclassified AAV.

Table 3. Predictors of remission and death in MPO-ANCA–positive patients with AAV by univariate analysis and multivariate analysis (model 1).

	Predictors of Remission				Predictors of Death			
	Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Age, yrs	0.99	0.61	0.99	0.79	**1.11**	**0.01**	**1.10**	**0.006**
Sex, male	0.88	0.61	0.92	0.67	1.17	0.83	1.56	0.37
BVAS	1.01	0.65	–	–	1.11	0.068	1.09	0.07
eGFR, mL/min	0.99	0.82	–	–	0.98	0.15	0.08	0.09
ENT (BVAS)	1.17	0.62	–	–	0.32	0.21	–	–
Pulmonary hemorrhage (BVAS)	0.81	0.71	–	–	6.22	0.20	6.26	0.16
Kidney (BVAS)	0.73	0.30	–	–	0.68	0.68	–	–
Allergic airway comorbidity	0.65	0.27	–	–	0.68	0.76	–	–
Upper airway comorbidity	0.66	0.26	–	–	1.64	0.56	–	–
Bronchiectasis	1.66	0.07	**1.83**	**0.01**	2.59	0.12	2.68	0.07
Pulmonary infection	1.19	0.72	–	–	3.01	0.34	–	–
fILD	0.88	0.59	–	–	**5.84**	**0.02**	**7.32**	**0.009**
Emphysema	1.62	0.12	–	–	1.28	0.72	–	–
Heart disease	0.38	0.12	0.37	0.06	2.45	0.36	2.73	0.10
Smoking	0.66	0.15	–	–	1.25	0.78	–	–
Atherosclerotic disease	0.84	0.43	–	–	1.00	0.99	–	–
Malignancy	0.66	0.25	–	–	0.93	0.94	–	–
Use of CYC, 6m	1.06	0.83	–	–	0.87	0.83	–	–

Values in bold are significant. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; fILD: fibrotic interstitial lung disease; MPO: myeloperoxidase.

P = 0.009) were extracted as predictive factors for death by multivariate analysis. Interestingly, we found that bronchiectasis, which predicted fair remission outcomes, had the trend for death (HR 2.68, *P* = 0.07). To confirm our results, we compared the survival of MPO-ANCA–positive patients with AAV based on the existence of bronchiectasis and fILD. We divided the MPO-ANCA–positive patients into 4 groups: those with neither bronchiectasis nor fILD (Br [–] fILD [–], n = 66);

those with only bronchiectasis (Br [+] fILD [–], n = 14); those with only fILD (Br [–] fILD [+], n = 51); and those with both fILD and bronchiectasis (Br [+] fILD [+], n = 12). The BVAS scores were comparable among the 4 groups (16.0 ± 7.8, 17.0 ± 6.9, 14.6 ± 6.4, and 18.3 ± 6.6, respectively). In support of the results regarding the factors predictive of remission, the group with only bronchiectasis showed better outcomes than the group with only fILD. Nonetheless, the group with both bronchiectasis and fILD showed a significantly worse outcome compared to the other 3 groups (Figure 2A).

We found that the progression of the other infectious airway comorbidities showed similar trends, generally ending in death (Table 3). To address the question of whether infectious airway comorbidity determined the outcomes of these patients, we further examined various factors, including patient backgrounds, allergic and infectious airway comorbidities, organ involvements of vasculitis, and CYC use, for their abilities to predict remission or death (Table 4). Only 1 independent factor, the existence of infectious airway comorbidity (HR 1.58, $P = 0.03$), was extracted as a predictive factor for remission by multivariate analysis. In addition to age (increased by 1 year; HR 1.10, $P = 0.01$), BVAS score (increased by 1 point; HR 1.10, $P = 0.04$), heart disease (HR 3.36, $P = 0.03$), fILD (HR 7.55, $P = 0.008$), and infectious airway comorbidity (HR 2.64, $P = 0.04$) were extracted as predictive factors for death by multivariate analysis. Next, we compared the survival of MPO-ANCA–positive patients with AAV based on the existence of infectious airway comorbidities with or without fILD. For this purpose, we divided the MPO-ANCA–positive patients into 4 groups: those with neither comorbidity (Inf [–] fILD [–], n = 55), those with only infectious airway comorbidity (Inf [+] fILD [–], n = 25), those with only fILD (Inf [–] fILD [+], n = 45), and those with both comorbidities (Inf [+] fILD [+], n = 18). The BVAS scores of the 4 groups were comparable (16.4 ± 8.2, 15.4 ± 6.2, 14.6 ± 6.7, and 16.8 ± 6.0, respectively). As expected, the group with only infectious airway comorbidity showed a milder outcome than the other groups. Nonetheless, the infectious comorbidities group with fILD showed a significantly worse outcome than the other 3 groups (Figure 2B). Thus, we found that the existence of infectious airway comorbidities also significantly worsened the survival of MPO-ANCA-positive patients with AAV and fILD.

DISCUSSION

In our study, we examined the association between comorbidities, and the disease onset and outcomes of MPO-ANCA–positive patients with AAV using a cohort database of patients with AAV. First, we discovered that most of the MPO-ANCA–positive patients with AAV had comorbidities, with airway comorbidities being the most common. Second, the types of airway comorbidities were closely associated with the clinical phenotypes of MPO-ANCA–positive AAV. Third, the airway comorbidities of these patients also influenced their rates of remission and death. The coexistence of the infectious airway comorbidity and fILD was associated with the worst survival outcomes in MPO-ANCA–positive patients. Our results should have important implications for AAV classification and treatment strategies.

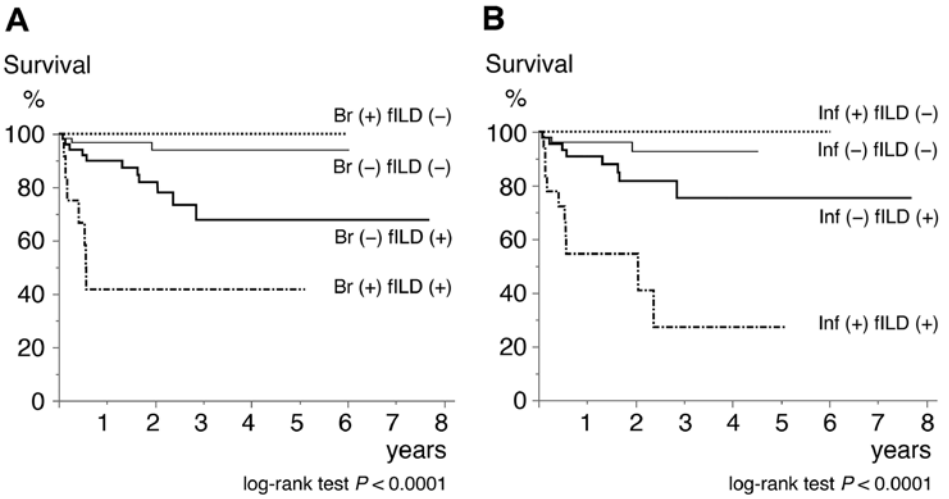

Figure 2. Comparison of survival outcomes of MPO-ANCA-positive AAV patients by the presence of infectious and non-infectious airway comorbidities. (A) Kaplan-Meier survival curves were compared based on the existence of bronchiectasis and ILD in 4 subgroups of MPO-ANCA–positive patients: those with neither bronchiectasis nor ILD (Br [–] fILD [–], n = 66); those with only bronchiectasis (Br [+] fILD [–], n = 14); those with only ILD (Br [–] fILD [+], n = 51); and those with both conditions (Br [+] fILD [+], n = 12). (B) Kaplan-Meier survival curves were compared based on the existence of infectious airway comorbidities with or without ILD in 4 subgroups of MPO-ANCA–positive patients: those with neither infectious airway comorbidities nor fILD (Inf [–] fILD [–], n = 55); those with only infectious airway comorbidity (Inf [+] fILD [–], n = 25); those with only fILD (Inf [–] fILD [+], n = 45); and those with both conditions (Inf [+] fILD [+], n = 18). AAV: antineutrophil cytoplasmic antibody–associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; Br: bronchiectasis; ILD: interstitial lung disease; Inf: infectious airway comorbidities; fILD: fibrotic interstitial lung disease; MPO: myeloperoxidase.

Table 4. Predictors of remission and death in MPO-ANCA–positive patients with AAV by univariate analysis and multivariate analysis (model 2).

	Predictors of Remission				Predictors of Death			
	Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Age, yrs	0.99	0.72	0.99	0.85	**1.10**	**0.01**	**1.10**	**0.01**
Sex, male	0.97	0.91	0.94	0.76	1.37	0.66	1.61	0.34
BVAS	1.01	0.48	–	–	1.10	0.07	**1.10**	**0.04**
eGFR, mL/min	0.99	0.68	–	–	0.99	0.17	0.99	0.38
ENT (BVAS)	0.88	0.65	–	–	0.38	0.22	–	–
Pulmonary hemorrhage (BVAS)	0.82	0.72	–	–	8.03	0.14	7.24	0.14
Kidney (BVAS)	0.68	0.20	–	–	0.78	0.79	–	–
Allergic airway comorbidity	0.64	0.25	–	–	0.63	0.69	–	–
Infectious airway comorbidity	1.44	0.15	**1.58**	**0.03**	**3.41**	**0.03**	**2.64**	**0.04**
fILD	0.89	0.62	–	–	**6.08**	**0.02**	**7.55**	**0.008**
Pulmonary emphysema	1.46	0.22	–	–	1.34	0.67	–	–
Heart disease	0.46	0.19	0.40	0.08	3.42	0.14	**3.36**	**0.03**
Smoking	0.64	0.12	–	–	1.17	0.85	–	–
Atherosclerotic disease	0.90	0.64	–	–	1.23	0.72	–	–
Malignancy	0.63	0.19	–	–	0.80	0.81	–	–
Use of CYC, 6m	1.11	0.67	–	–	0.84	0.80	–	–

Values in bold are significant. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; fILD: fibrotic interstitial lung disease; MPO: myeloperoxidase.

We found that most patients with AAV had comorbidities, and that those related to airway inflammations were particularly common. Several studies have shown that neutrophil extracellular traps (NET) are the most important source of autoantigens against ANCA[25]. In rheumatoid arthritis, which is also a seropositive autoimmune disease, several lines of evidence support the idea that anticitrullinated peptide antibodies are generated on airway surfaces through the interaction with NET[26,27]. The high frequency of airway comorbidities in MPO-ANCA–positive patients with AAV suggests that airway comorbidity plays an important role in the generation of MPO-ANCA by inflaming the airways.

In general, the mucociliary defense of airways plays an important role in the clearance of pathogens. It has been shown that elderly individuals exhibit reduced mucociliary clearance[28]. It is also suggested that the reduced mucosal function in elderly individuals changes the microbiome of the airways, leading to an upregulation of the systemic inflammatory response[29]. The high prevalence of airway comorbidities in MPO-ANCA–positive patients with AAV may be partially explained by their advanced ages. Supporting the idea that GPA is correlated with airway infections, we found that the MPO-ANCA–positive patients with GPA also frequently had infectious airway comorbidities. Interestingly, another study reported that there were 2 clustering patterns of lung abnormalities among their MPA patients. One pattern was characterized by interstitial lung disease (ILD), and the other pattern was characterized by airway and pleural lesions[30]. In our study, we examined all the cases of MPO-ANCA–positive AAV and found that the airway involvements in these patients were closely associated with GPA. Because infectious airway comorbidities were frequently observed in elderly MPO-ANCA–positive patients with AAV, we occasionally encountered patients with both GPA and MPA clinical phenotypes. Thus, infectious airway comorbidities complicate the clear differentiation between GPA and MPA among MPO-ANCA–positive patients with AAV.

Previous studies reported that ANCA against bactericidal/permeability-increasing protein (BPI) occurs in patients with gram-negative bacterial colonization, such as those found in cystic fibrosis, diffuse panbronchiolitis, and bronchiectasis[31,32,33]. BPI-ANCA has been closely associated with the lung severity and prognosis of cystic fibrosis patients[31]. In addition, a relationship between BPI-ANCA and NET formation was previously reported[34]. These studies also support the notion of a relationship between chronic airway infections and ANCA.

In contrast, MPA and uAAV had similar distributions of demographics, organ involvement, smoking history, and comorbidities, except for renal involvement. We found that both patients with MPA and those with uAAV frequently had alveolar airway comorbidities, ILD, and pulmonary emphysema. Although ILD is an autoimmune disease, pulmonary emphysema is recognized as an inflammatory airway disease that is mainly caused by smoking. Evidence has shown that NET were observed in the sputum of chronic obstructive pulmonary disease patients, and that nicotine drove NET formation and accelerated an autoimmune mouse model[35,36]. These results support the idea that both alveolar airway comorbidities also play a role in ANCA generation. Finally, our study also provided support for the idea that ILD appears in MPO-ANCA–positive cases, and is a poor prognostic factor[18]. However, whether ILD is induced by vasculitis remains a controversial question, because of the rare appearance of vasculitis in the ILD specimens. Further studies of the relationship between vasculitis and ILD will be needed.

It is quite important that infectious airway comorbidity was extracted as a contradictory factor that was associated with both remission and poor prognosis. Despite the fair outcomes

of the patients with only infectious airway comorbidity, the coexistence of infectious airway comorbidities with ILD caused the worst survival outcomes. Most cohort studies have shown that infections were the major cause of mortality in patients with AAV[37,38]. Supporting our results, a previous paper showed that bronchiectasis and endobronchial involvement were risk factors for severe respiratory infections following RTX treatment in AAV. Interestingly, sulfamethoxazole-trimethoprim prophylaxis prevents severe infections[39]. These results suggest that excessive immunosuppressive therapy leads to poor prognosis in patients with AAV, because infectious airway diseases run the risk of deteriorating their intrinsic infections by immunosuppressive treatments. In addition, it is important to control airway comorbidities, which contribute to both the induction of ANCA generation and the exacerbation of vasculitis. Thus, an initial evaluation of the whole airways is essential, not only for their classification but for their precise management of patients with AAV.

There were some limitations to our research. One was that there was only a small number of cases for each clinical disease type, and another is that the comorbidities were ambiguous. However, most of the facilities recruited patients with serial ANCA measurements during the observation period. There is no report on which comorbidities were examined in relation to clinical phenotypes on the same ANCA backgrounds. Another limitation is that our cohort study was executed mainly by rheumatologists; thus, there might have been a patient bias. Therefore, we need to further verify our results by collaborating with other specialists, such as nephrologists and pulmonologists. In addition, there is ambiguity as to whether upper airway inflammation or pulmonary lesions should be considered as comorbidities or as a lesion of vasculitis. In our present study, we permitted clinicians to perform such registration at their own discretion. Depending on the individuals, there might be less agreement even in the diagnosis of airway disease based on chest CT. However, our extensive collection of background factors from each AAV patient clarified their disease mechanisms. To pursue the best personalized medicine for various types of patients with AAV, it is important to collect the background factors, and to comprehend the role of each in disease progression.

In conclusion, we have shown that comorbidities with airway inflammation are closely associated with the onset of AAV, clinical disease type, and outcome. These findings should have important implications for the consideration of future AAV classification and treatment strategies.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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