Original Article

The association of airway comorbidities with the clinical phenotypes and outcomes of ANCA-associated vasculitis patients.

Objectives: We investigated the association of airway comorbidities with the clinical phenotypes and outcomes of myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibodies (ANCA)-positive ANCA-associated vasculitis (AAV).

Methods: An AAV patient multi-center 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 for remission and death.

Results: Ten cases with eosinophilic granulomatosis with polyangitis (EGPA), *27* with granulomatosis with polyangitis (GPA), *81* with microscopic polyangitis (MPA) and *25* with unclassified AAV were identified. The average age was *71.4* years old. 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=*0.027*) and mortality (HR *2.64*, p=*0.040*), and fILD was predictive of mortality (HR *7.55*, p=*0.0078*). The combination of infectious airway comorbidities and fILD caused the worst survival outcomes in those patients.

Conclusions: 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.

Nobuyuki Ono[1], Yasushi Inoue[2], Tomoya Miyamura[3], Naoyasu Ueda[4], Shuji Nagano[5], Hisako Inoue[6], Kensuke Oryoji[7], Shun-ichiro Ota[8], Takuya Sawabe[9], Seiji Yoshizawa[10], Yukiko Takeyama[1,11], Yuri Sadanaga[1], Ayako Takamori[12],

Yasutaka Kimoto[13], Katsuhisa Miyake[14], Takahiko Horiuchi[13], Hitoshi Nakashima[14], Hiroaki Niiro[15] and Yoshifumi Tada[1]

[1]Department of Rheumatology, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga, Japan 8498501

[2]Department of Rheumatology, Fukuoka Red Cross Hospital, Fukuoka, Japan

[3]Department of Rheumatology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

[4]Department of Internal Medicine, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan

[5]Department of Rheumatology, Iizuka Hospital Iizuka Hospital, Fukuoka, Japan

[6]Department of Rheumatology, Saiseikai Fukuoka Hospital, Fukuoka, Japan

[7]Department of Rheumatology, Matsuyama Red Cross Hospital, Matsuyama, Japan

[8]Department of Rheumatology, Shimonoseki City Hospital, Shimonoseki, Japan

[9]Department of Rheumatology, Hiroshima Red Cross Hospital, Hiroshima, Japan

[10]Department of Rheumatology, Hamanomachi Hospital, Fukuoka, Japan

[11]Department of Rheumatology, Saiseikai Karatsu Hospital, Karatsu, Japan

[12]Clinical Research Center, Saga University Hospital, Saga, Japan

[13]Department of Rheumatology, Kyushu University Beppu Hospital, Beppu, Japan

[14]Department of Rheumatology, Fukuoka University, Fukuoka, Japan

[15]Department of Rheumatology, Kyushu University, Fukuoka, Japan

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Key messages: MPO-ANCA-positive AAV patients frequently have airway comorbidities. Airway comorbidities are closely associated with the clinical phenotypes and outcomes of these patients.

Corresponding author: Dr. Nobuyuki Ono, Department of Rheumatology, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan.

Tel: +81-982-31-6511; Email: nono@cc.saga-u.ac.jp

Introduction

Anti-neutrophil 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 excellent 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 miserable outcomes due to the side effects from excessive immunosuppressive treatment.

One of the reasons for these disparate results is the diversity of AAV patients. Based on clinical phenotypes and pathologies, cases of AAV are divided into three diseases: eosinophilic granulomatosis with polyangitis (EGPA), granulomatosis with polyangitis (GPA) and microscopic polyangitis

(MPA). Two ANCA subtypes, myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA, also exist. Moreover, the age, organ involvements and disease severity vary widely among AAV patients. Recently, researchers have attempted to develop more personalized treatment strategies in order to realize safe, precise and effective treatments for the wide variety of patients (3). In order to pursue precision medicine, an improved understanding of the disease mechanism underlying AAV will be essential.

In 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). Recent GWAS studies proved that MPO-ANCA-positive AAV and PR3-ANCA-positive AAV were genetically different diseases (6). However, some percentage of GPA patients are also positive for MPO-ANCA, which is dominant in Asian countries (7) (8). It is still controversial whether the differentiation into GPA and MPA is necessary among MPO-ANCA-positive AAV (9). *CHCC classification is the nomenclature system for vasculitis, which was established to*

define individual types of vasculitis. However, in the clinical setting these classifications led to diagnostic overlaps in AAV patients. (10) (11). Moreover, some percentage of MPO-ANCA positive AAV patients can not be classified properly, such as those with pulmonary-limited AAV (12). Thus, we overviewed our entire populations of MPO-ANCA-positive AAV patients by using EMA classification, which is often used in epidemiological studies to avoid diagnostic overlap. In this way, by providing an overview of MPO-ANCA positive AAV patients, we hoped to improve our understanding of the pathophysiology of AAV, and to provide clues to the disease classification.

In this 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 with 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 AAV patients. Thus, we hypothesized that airway comorbidities affected the development of AAV. In the present study, to realize adequate precision medicine for individual AAV patients, we aimed to investigate the association of airway comorbidities with the clinical phenotypes and outcomes of MPO-ANCA-positive AAV patients.

Patients and Methods

Patients

The Kyushu Vasculitis (KVAS) cohort is a multi-center cohort of AAV patients that was established in 2012 among 13 hospitals in the western area of Japan. *All patients were newly diagnosed as having AAV by experienced rheumatologists at each hospital. These diagnoses were then confirmed by the inclusion criteria of primary vasculitis of the European Medicines Agency (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 six 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 of the other local ethical committees also approved this study. Rheumatologists evaluated all of the vasculitis-affected organs in each patient based on the Birmingham Vasculitis Activity Score (BVAS) (20). *Most of the AAV patients were evaluated with computed tomographic scannings of the head (65.1%) and chest (95.9%). Disease activities were measured by the BVAS. MPO-ANCA assays were mainly executed with a Nipro Nephroscholar MPO ANCⅡ kit (Nipro) or MBL MPO-ANCA ELISA (MBL). PR3-ANCA assays were executed with a Nipro Nephroscholar PR3 ANC 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 greater than 10 were classified into the higher ANCA group. Each rheumatologist reported all of the baseline comorbidities, which were assessed by determining the conditions that had been present before the AAV symptoms. They were categorized into four groups: airway comorbidity, heart disease, atherosclerosis and others (*Supplementary Table 1*). *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 non-tuberculosis mycobacterium infections, fungal infections).* The diagnoses of f*ibrotic interstitial lung disease (fILD)*, bronchiectasis and pulmonary emphysema were made based on the patient history and chest CT scan images according to t*he official ATS(American Thoracic Society) /ERS(European Respiratory Society) /JRS(Japanese Respiratory Society) /ALAT(Latin American Thoracic Association) statement for the diagnosis of idiopathic pulmonary*

fibrosis (21). *With respect to comorbidities, only patients exhibiting the UIP pattern or NSIP pattern were categorized as having fILD because of their chronicity.* Patients were treated by a standardized protocol. In brief, patients with active vasculitis were treated mainly with corticosteroids. Depending on their age, disease severity and organ involvements, immunosuppressants and corticosteroid pulse therapy were added at the discretion of the clinician. As initial remission induction therapy, cyclophosphamide was used in *35.2%*, and rituximab was used in *12.7%* of MPO-ANCA-positive AAV patients. *Remission was defined as the absence of disease activity attributable to vasculitis manifestations for more than one month.*

Statistical analysis

Fisher's exact test *or Chi-squared test* was used to compare the prevalence of various clinical manifestations in each group. Continuous variables were non-parametrically 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 and death or the last

follow-up. Cox's proportional hazards regression method was used to estimate multivariate-adjusted hazard ratios (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, Cary, NC). P values were two-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 of 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 AAV patients were available *(Table 1, Supplementary Table 2)*. The average age was *69.2* years old, and females

accounted for *57.6*% of the total cohort. There were *24* EGPA, *51* GPA, *89* MPA and *31* uAAV patients. *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 AAV patients, uAAV patients were recruited into our study. The comparisons of vasculitic organ involvements among all our MPO-ANCA-positive AAV patients confirmed that our modified EMA classification grouped them appropriately (Supplementary Table 2, 3).* 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 AAV patients (*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 AAV, 143 MPO-ANCA-positive AAV and 19 PR3-ANCA-positive AAV patients. The demographic comparison among

the three groups is shown in Table 1. The average ages were *58.4*, *71.4* and *69.7 years old*, respectively. ANCA-negative patients were the youngest, and dominated with EGPA. PR3-ANCA-positive patients had predominantly 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 an unclassified AAV (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 fibrotic ILD 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 numbers of airway comorbidities of the MPO group (mean 1.2±1.1) were also higher than those of the PR3 group (mean 0.7±1.0)*. The PR3 group had higher rates of heart disease (*21.0*%).

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 the *143* MPO-ANCA-positive AAV patients 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%, *56.0*%). These patients also had a higher incidence of pulmonary emphysema (25.9%, *20.0*%), but not significantly. Greater numbers of patients in the MPA and uAAV had a smoking history (*37.0%, 40.0%*) and atherosclerotic disease (*50.6%, 56.0%*), 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 three types: allergic airway comorbidity (asthma, allergic rhinitis), infectious airway comorbidity (upper airway disease, bronchiectasis, pulmonary infection) and non-infectious 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 comorbidity *($p<0.0001$)*, whereas GPA frequently accompanied infectious airway comorbidity *($p=0.0021$)*, and MPA and uAAV accompanied non-infectious 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 patients with MPO-ANCA-positive AAVs.

Factors predictive of remission or death

To address the association of comorbidity with the outcomes of

MPO-ANCA-positive AAV patients, we studied the factors predictive of remission or death in MPO-ANCA-positive patients. *The rates of CY and RTX use during the initial six months in MPO-ANCA positive AAV patients are shown in Table 2. CY usage was not different among the three groups, while RTX was used most often in GPA patients, though the difference was not significant.* One hundred and *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, organ involvements of vasculitis and cyclophosphamide use (Table 3, model 1). Bronchiectasis was extracted as a predictive factor for remission by multivariate analysis (*HR 1.83, p = 0.0127*). Age (increased by 1 year; HR 1.10, p = 0.0057) and fILD were extracted as predictive factors for death by multivariate analysis (*HR 7.32, p = 0.0087*). *Interestingly, we found that bronchiectasis, which predicted fair remission outcomes, had the trend for death (HR 2.68, p = 0.0695)*. To confirm our results, we compared the survivals of

MPO-ANCA-positive AAV patients based on the existence of bronchiectasis and fILD. We divided the MPO-ANCA-positive patients into four 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 four groups (mean±SD: *16.0±7.8, 17.0±6.9, 14.6±6.4, 18.3±6.6*). In support of the results regarding the factors predictive for 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 three 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 cyclophosphamide use—for their ability to predict remission or death (Table 4, model 2). Only one independent factor, the existence of infectious airway comorbidity (*HR 1.58, p = 0.027*), was extracted as a predictive factor for remission by multivariate analysis. In addition to age (increased by 1 year; *HR 1.10, p = 0.010*), BVAS score (increased by 1 point; *HR 1.10, p = 0.040*) and heart disease (*HR 3.36, p=0.034*), fILD (*HR 7.55, p = 0.0078*) and infectious airway comorbidity (*HR 2.64, p = 0.040*) were extracted as predictive factors for death by multivariate analysis. Next, we compared the survivals of MPO-ANCA-positive AAV patients based on the existence of infectious airway comorbidities with or without fILD. For this purpose, we divided the MPO-ANCA-positive patients into four 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 four groups were comparable (mean±SD: *16.4±8.2, 15.4±6.2, 14.6±6.7, 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 three groups (Figure 2B). Thus, we found that the existence of infectious airway comorbidities also significantly worsened the survival of patients with MPO-ANCA-positive AAV and fILD.

Discussion

In this study, we examined the association of comorbidities with the disease onsets and on the outcomes of MPO-ANCA-positive AAV patients using a cohort database of AAV patients. We discovered the following. First, most of the MPO-ANCA-positive AAV patients 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. And third, the airway comorbidities of these patients also influenced their rates of remission and death. The co-existence of 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.

We found that most AAV patients had comorbidities, and those related to airway inflammations were particularly common. Several studies have shown that neutrophil extracellular traps (NETs) are the most important source of auto-antigens against ANCAs (25). In rheumatoid arthritis (RA), which is also a sero-positive autoimmune disease, several lines of evidence support the idea that anti-citrullinated peptide antibodies are generated on airway surfaces through the interaction with NETs (26) (27). The high frequency of airway comorbidities in MPO-ANCA-positive AAV patients 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 up-regulation of the systemic inflammatory response (29). The high

prevalence of airway comorbidities in MPO-ANCA-positive AAV patients may be partially explained by their advanced ages. Supporting the idea that GPA is correlated with airway infections, we found that the patients with MPO-ANCA-positive GPA also frequently had infectious airway comorbidities. Interestingly, another study reported that there were two clustering patterns of lung abnormalities among their MPA patients. One pattern was characterized by ILD, and the other pattern was characterized by airway and pleural lesions (30). In our study, we examined all of 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 AAV patients, we occasionally encountered patients with both GPA and MPA clinical phenotypes. Thus, infectious airway comorbidities complicate the clear differentiation between GPA and MPA among patients with MPO-ANCA-positive AAV.

Previous studies reported that ANCA against bactericidal/permeability-increasing protein (BPI) occurs in patients with

Gram-negative bacterial colonizations such as those in cystic fibrosis, diffuse pan-bronchiolitis 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 NETs formation was recently reported (34). These studies also support the notion of a relationship between chronic airway infections and ANCAs.

In contrast, MPA and uAAV had similar distributions of demographics, organ involvements, smoking history and comorbidities, except for their renal involvements. 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. Recent evidences have shown that NETs were observed in the sputum of COPD patients, and that nicotine drove NETs 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 co-existence of infectious airway comorbidities with ILD caused the worst survival outcomes. Most cohort studies have shown that infections were the major causes of mortality in AAV patients (37) (38). Supporting our results, a recent paper showed that bronchiectasis and endobronchial involvement were risk factors for severe respiratory infections following rituximab treatment in AAV. Interestingly, sulfamethoxazole-trimethoprim prophylaxis prevents severe infections (39). These results suggest that excessive immunosuppressive therapy leads to poor prognosis in AAV patients, 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 exacerbation of vasculitis. Thus, an initial evaluation of the whole airways is essential not only for their classification but for their precise management of AAV patients.

There were some limitations in this research. One was that there were 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 serial AAV cases during the observation period. There is no report in which comorbidities were examined in relation to clinical phenotypes on the same ANCA backgrounds. Another limitation is that this cohort study was executed mainly by rheumatologists. Thus there may 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 AAV patients, 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.

Conflict of Interest

The authors declare no conflicts of interest.

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Figure legends

Figure 1 Airway-comorbidity types determine the clinical phenotype of MPO-ANCA-positive AAV patients. Comparison of the types of airway comorbidity among MPO-ANCA-positive AAV patients by the clinical

phenotypes: EGPA (n=10), GPA (n=27), MPA (n=81) and uAAV (n=25).

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 four 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 four 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=24); those with only fILD (Inf (-) fILD (+), n=45); and those with both conditions (Inf (+) fILD (+), n=18).

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

	all AAV	ANCA(-)	MPO	PR3	p value (all)	p value MPO vs ANCA(-)	p value MPO vs PR3)
cases	195	28	143	19			
female	57.6%	50.0%	58.7%	63.2%	>0.1	>0.1	>0.1
age (y.o. 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%	**0.0146**	**0.0453**	>0.1
EGPA (*)	12.3% (33.3%)	46.4% (30.0%)	7.0% (30.0%)	5.3% (0.0%)	**<0.0001**	**<0.0001**	>0.1
GPA (*)	26.2% (31.4%)	21.4% (100%)	18.9% (22.2%)	79.0% (20.0%)	**<0.0001**	>0.1	**<0.0001**
MPA (*)	45.6% (46.1%)	21.4% (83.3%)	56.6% (43.2%)	10.5% (50.0%)	**<0.0001**	**0.0003**	**<0.0001**
uAAV (*)	10.7% (0.0%)	17.5% (0.0%)	17.5% (0.0%)	5.3% (0.0%)	>0.1	>0.1	0.0996
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
number	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	**0.0487**
number	1.1±1.0	1.1±0.8	1.2±1.1	0.7±1.0	>0.1	>0.1	**0.0362**
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%	**0.0215**	>0.1	**0.0076**
pulm. 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**	**0.0024**
heart diseases	8.2%	7.1%	6.3%	21.0%	>0.1	>0.1	0.0526
atherosclerotic dis.	43.1%	17.9%	46.8%	42.1%	**0.0121**	**0.0118**	>0.1
malignancy	9.7%	3.6%	11.1%	10.5%	>0.1	>0.1	>0.1
usage of CY (6m)	34.7%	33.3%	35.2%	26.3%	>0.1	>0.1	>0.1
usage of RTX (6m)	11.9%	3.7%	12.7%	21.1%	>0.1	>0.1	>0.1

uAAV: unclassified AAV; fILD: fibrotic interstitial lung disease

* The ratio of patients with pathological proof of vasculitis

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

	EGPA	GPA	MPA	UAAV	p value
cases	10	27	81	25	
female	50.0%	66.7%	55.6%	64.0%	>0.1
age (mean±SD)	62.0±14.0	70.0±8.9	71.7±10.8	76.0±8.1	**0.0054**
BVAS	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%	0.0877
comorbidity	100%	81.5%	86.4%	92.0%	>0.1
number	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%	0.0510
number	1.9±1.0	1.4±1.3	1.1±1.0	0.9±0.8	0.0986
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
pulm. infections	10.0%	18.5%	4.9%	0.0%	**0.0412**
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%	37.04%	50.6%	56.0%	>0.1
malignancy	10.0%	14.8%	7.4%	20.0%	>0.1
use of CY (6m)	22.2%	24.0%	39.2%	25.0%	>0.1
use of RTX (6m)	0.0%	24.0%	14.9%	4.2%	0.0822

Table 3. Predictors of remission and death in MPO-ANCA-positive AAV patients 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, years	0.99	0.61	0.99	0.79	**1.11**	**0.0097**	**1.10**	**0.0057**
male	0.88	0.61	0.92	0.67	1.17	0.83	1.56	0.37
BVAS, point	1.01	0.65	-	-	1.11	0.0681	1.09	0.065
eGFR, ml/min	0.99	0.82	-	-	0.98	0.146	0.08	0.091
ENT (BVAS)	1.17	0.62	-	-	0.32	0.21	-	-
pulmonary hemorrhage (BVAS)	0.81	0.71	-	-	6.22	0.20	6.26	0.160
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**	**0.0127**	2.59	0.12	2.68	0.0695
pulmonary infection	1.19	0.72	-	-	3.01	0.34	-	-
fILD	0.88	0.59	-	-	**5.84**	**0.0240**	**7.32**	**0.0087**
emphysema	1.62	0.12	-	-	1.28	0.72	-	-
heart disease	0.38	0.12	0.37	0.0563	2.45	0.36	2.73	0.0980
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 CY	1.06	0.83	-	-	0.87	0.83	-	-

Table 4. Predictors of remission and death in MPO-ANCA-positive AAV patients 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, years	0.99	0.72	0.99	0.85	**1.10**	**0.013**	**1.10**	**0.010**
male	0.97	0.91	0.94	0.76	1.37	0.66	1.61	0.34
BVAS, point	1.01	0.48	-	-	1.10	0.072	**1.10**	**0.040**
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**	**0.027**	**3.41**	**0.026**	**2.64**	**0.040**
fILD	0.89	0.62	-	-	**6.08**	**0.022**	**7.55**	**0.0078**
pulmonary emphysema	1.46	0.22	-	-	1.34	0.67	-	-
heart disease	0.46	0.19	0.40	0.078	3.42	0.14	**3.36**	**0.034**
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 CY	1.11	0.67	-	-	0.84	0.80	-	-

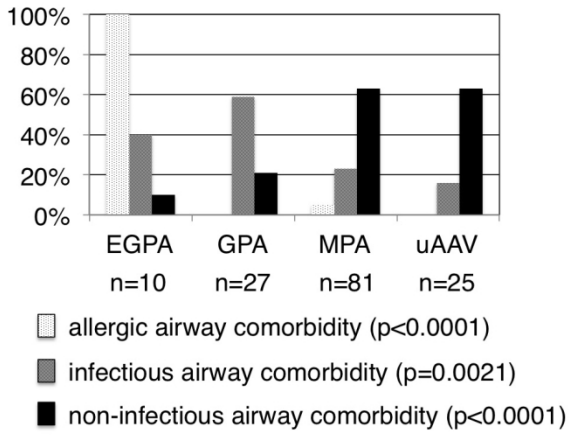

Figure 1 Airway-comorbidity types determine the clinical phenotype of MPO-ANCA-positive AAV patients.

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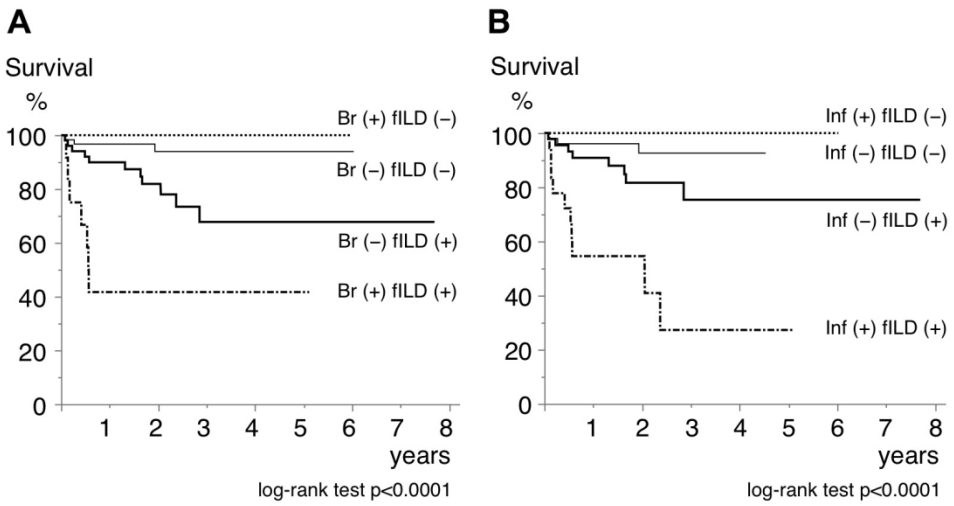

Figure 2 Comparison of survival outcomes of MPO-ANCA-positive AAV patients by the presence of infectious and non-infectious airway comorbidities.

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