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Evaluation of Pulmonary Involvement and Prognosis in Vasculitis Associated with Anti-Neutrophil Cytoplasma Antibodies

Anti-Nötrofil Sitoplazma Antikorları İle İlişkili Vaskülitlerde Akciğer Tutulumunun Ve Prognozunun Değerlendirilmesi

Esra Aydın[1], Sevil Kamalı[2]

[1]Recep Tayyip Erdoğan University, Department of Medical Oncology, Rize, Turkey
[2]Gaziosmanpaşa Hospital, Department of Rheumatology, Istanbul, Turkey

ABSTRACT

Objective: No study has evaluated AAV's lung prognosis and the Vasculitis Damage Index (VDI). This study investigated lung involvement in AAV-associated disease activity, morbidity, and mortality rate.
Method: This retrospective analysis included 51 cases who were followed up in our institution's rheumatology outpatient clinic and diagnosed with AAV according to ARC and/or CHCC criteria. The patients were supposed to have lung (pulmonary) involvement at the beginning of the disease. Initial Birmingham Vasculitis Activity Scores (BVAS) and imaging findings were noted. Respiratory function test (PFT), 6-minute walk test (6MWT), thorax CT findings, and vasculitis damage index (VDI) scores were recorded.
Results: ANCA positivity was detected in 94% of patients with AAV (66% C-ANCA/anti-PR3, 34% p-ANCA/anti-MPO). The total follow-up period was recorded as 66.5±52 months. Initial total and BVAS were calculated as 22±7 and 4.6±2.8. BVAS findings were determined as 80% nodule/cavity, 56% infiltration, 24% AH/massive hemoptysis, 11% respiratory failure, 5% pleural effusion/pleurisy, and 3% endobronchial involvement. Radiological improvement was seen in 35%, regression in 12%, progression in 12%, and sequela changes in 30% of the patients. Cumulative VHI and lung VHI scores were calculated as 3.5±2.3 and 0.5±0.8. The frequency of VHI findings was 22% lung function disorder, 8% lung fibrosis, 6% chronic dyspnea, 4% chronic asthma, and 2% pulmonary hypertension. Serious pulmonary infections were seen in 44% (27% had >1 severe infection). VHI was higher in those with serious pulmonary infections (p=0.006).
Conclusion: Lung involvement with AAV causes high rates of lung damage and increased mortality in long-term follow-up.

Keywords: Interstitial Lung Disease (ILD), Alveolar Hemorrhage (AH), Vasculitis Damage Index (VDI), Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitides (AAV), Anti-Neutrophil Cytoplasmic Antibody (ANCA).

ÖZET

Amaç: Amniotik membranın, epitelyal hücrelerde vaskularizasyonu engelleyerek, inflamasyonu azaltarak ve apoptozisi Amaç: Günümüzde hiçbir çalışma AAV'nin akciğer prognozunu ve Vaskülit Hasar İndeksini (VHİ) değerlendirmemiştir. Bu çalışma AAV ile ilişkili hastalık aktivitesi, morbidite ve mortalite oranında akciğer tutulumunu araştırmıştır.
Yöntem: Bu retrospektif analiz, kurumumuzun romatoloji polikliniğinde takip edilen ve ARC ve/veya CHCC kriterlerine göre AAV tanısı konulan 51 vakayı (40 GPA, 8 MPA, 3 e-GPA) içermektedir. Hastaların hastalığın başlangıcında akciğer (pulmoner) tutulumu olduğu varsayılmıştır. Başlangıçtaki Birmingham Vaskülit Aktivite Skorları (BVAS) ve görüntüleme bulguları not edilmiştir. Solunum fonksiyon testi (SFT), 6 dakikalık yürüme testi (6MWT), toraks BT bulguları ve vaskülit hasar indeksi (VHİ) skorları kaydedilmiştir.
Bulgular: AAV'li hastaların %94'ünde ANCA pozitifliği saptandı (%66 C-ANCA/anti-PR3, %34 p-ANCA/anti-MPO). Toplam takip süresi 66.5±52 ay olarak kaydedildi. Başlangıç toplam ve BVAS sırasıyla 22±7 ve 4.6±2.8 olarak hesaplandı. BVAS bulguları sırasıyla %80 nodül/kavite, %56 infiltrasyon, %24 AH/masif hemoptizi, %11 solunum yetmezliği, %5 plevral efüzyon/plörezi ve %3 endobronşiyal tutulum olarak belirlendi. Hastaların %35'inde radyolojik iyileşme, %12'sinde gerileme, %12'sinde progresyon ve %30'unda sekel değişiklikleri görüldü. Kümülatif VHI ve akciğer VHI skorları sırasıyla 3.5±2.3 ve 0.5±0.8 olarak hesaplandı. VHI bulgularının sıklığı %22 akciğer fonksiyon bozukluğu, %8 akciğer fibrozu, %6 kronik dispne, %4 kronik astım ve %2 pulmoner hipertansiyondu. Ciddi pulmoner enfeksiyonlar %44'ünde görüldü (%27'sinde >1 ciddi enfeksiyon vardı). Ciddi pulmoner enfeksiyonu olanlarda VHI daha yüksekti (p =0.006).
Sonuç: AAV ile akciğer tutulumu yüksek oranda akciğer hasarına ve uzun vadeli takipte artan mortaliteye neden olur.

Anahtar Kelimeler: İnterstisyel Akciğer Hastalığı (İAH), Alveolar Hemoraji (AH), Vaskülit Hasar İndeksi (VHİ), Anti-Nötrofil Sitoplazmik Antikor İlişkili Vaskülitler (AAV), Anti-Nötrofil Sitoplazmik Antikor (ANCA).

Corresponding Author: Esra Aydın, e-mail: esra.aydin@erdogan.edu.tr
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INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a heterogeneous group of diseases that result in tissue and organ damage after inflammatory cell infiltration, necrosis, thrombus formation, and occlusion of small and medium-sized blood vessel walls (arteries, arterioles, capillaries, venules) [1]. With the detection of ANCA antibodies against digestive enzymes such as proteinase 3 (PR3), myeloperoxidase (MPO) in the neutrophil cytoplasm, elastase, cathepsin-G, and lysozyme in patients with vasculitis, it was thought that these antibodies play essential roles in the pathogenesis of vasculitis [2]. Wegener granulomatosis (WG), Churg-Strauss Syndrome (CSS), and microscopic polyangiitis (MPA) have been grouped as AAV [3]. In addition to structural findings, AAV may cause clinical findings related to skin, joint, eye, upper and lower respiratory tract, lung, kidney, central and peripheral nervous system, and, less frequently, gastrointestinal, urogenital, and cardiovascular system involvement [1]. Lung involvement is commonly seen in AAV (55-85%) [4, 5]. Asymptomatic nodules or infiltrates may be encountered in one-third of patients [5].

Patchy or diffuse infiltrative lesions are common in AAV. The migratory nature of these lesions is distinctive in eosinophilic granuloma with polyangiitis (e-GPA). Cavitable nodular and intrabronchial obstructive lesions are expected only in granulomatous inflammatory granuloma with polyangiitis (GPA) and e-GPA. AAV-associated alveolar hemorrhage (AH) may cause subclinical, mild, or severe findings at the onset or during the disease [1, 5].

In E-GPA, asthma is a clinical picture that is present in almost all cases before the development of vasculitis. Interstitial lung disease (ILD) is a finding of lung involvement that can be seen especially with MPA and has a poor prognosis. Lung findings in AAV have the potential for recurrence, and their effect on prognosis varies [4].

Within the scope of this research, we aimed to elucidate the contribution of lung involvement to AAV-associated disease activity, morbidity, and mortality rate in a cohort of AAV patients with lung involvement who were followed up in regular outpatient clinics.

METHOD

This retrospective analysis included 51 cases (40 GPA, 8 MPA, three e-GPA) who were followed up in our institution's rheumatology outpatient clinic and diagnosed with AAV according to American College of Rheumatology (ACR) and/or Chapel Hill Consensus (CHCC) criteria. At the beginning of the disease, the patients were supposed to have lung (pulmonary) involvement.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Our institution has granted ethics committee approval with protocol number 14/465-18, and informed consent has been obtained from all participants.

Inclusion Criteria

Patients who were followed up with the diagnosis of GPA, MPA or e-GPA, who had lung involvement at the beginning of the disease, who gave their consent to participate in the study, and who came to regular outpatient clinic follow-ups were included in the study.

Exclusion Criteria

AAV cases who did not have pulmonary involvement at the beginning, did not consent to participate in the study, and did not come to regular outpatient clinic follow-ups were excluded.

The characteristics and course findings of 51 cases with high-resolution computed tomography (HRCT), in which lung involvement was recorded at the beginning of the disease. Age and gender of the cases, duration of follow-up from the onset of symptoms to diagnosis and total follow-up, smoking and environmental exposure history, clinical, laboratory and imaging features of tissue and organ

involvement at the beginning of the disease and histopathological findings, and dose and duration of immunosuppressive therapy were obtained from the outpatient clinic follow-up file. Missing data that could not be obtained from the file were questioned again at the study visit. Initial disease activity findings were recorded on the BVAS form, a standard systemic vasculitis activity assessment measure. Initial lung findings and BVAS were calculated.

AAV recurrences and the presence of lung involvement in recurrences were evaluated. The patients' records were recorded for severe lung infections requiring hospitalization, plasma exchange and mechanical ventilation requirements, and microbiological examination results. Cumulative doses of IC, age, diabetes, and renal failure factors were compared in the groups with and without infection. The new HRCT, pulmonary function, and 6-minute walking tests were requested. HRCT imaging was performed in the supine position with a Toshiba Aquilion 64-slice computed tomography device, by taking end-inspiratory scans. The imaging used a 0.5-second scanning time, 195 milliAmpereSec current, 120 KiloVolt voltage, 0.5 mm slice thickness, and 0.5 mm slice interval. The images were transferred to film with a window interval of 1600 HU and a window center of -600 HU. The number, location, and dimensions of lung nodules were recorded. As suggested in different studies performed on AAV lung involvement cases, nodules were classified according to those between 0-3 cm and those larger than 3 cm, defined as mass-like, and the presence of central cavitation. Increased lung opacity was classified as consolidation, in which vascular structures could not be observed, and ground-glass infiltration, in which they could be observed. Nodule, cavitated nodule, mass-like formation, ground-glass infiltration, consolidation, fibrosis, atelectasis, emphysema and bronchiectasis were compared in the initial and follow-up HRCTs. The cases were classified as those showing complete recovery, regression (more than 50% decrease in the size of the lesions), progression (increase in the size), and sequelae changes compared to the baseline. The characteristics of the changes in the control HRCTs of the different lung lesions detected at the baseline were recorded. Spirometric evaluation was performed in the sitting position with the ZAN® 740N device. The spirometry acceptability criteria of the American Thoracic Society (ATS) were taken as the basis. Forced expiratory volume (FEV1), forced vital capacity (FVC), and FEV1/FVC values were recorded in one second. FEV1/FVC >70% and FVC <80% were considered restrictive patterns. FEV1/FVC <70% was regarded as an obstructive pattern. FEV1 >80% was classified as mild, 50-80% moderate, and <50% severe obstruction. In the DLCO measurement, the 10-second single breath holding technique was used, and values corrected according to the hemoglobin value were considered. DLCO <80% in PFT was evaluated as a diffusion disorder.

The six-minute walking test was performed in accordance with the ATS 2002 Guide. Walking distance and whether there was desaturation were recorded. Those walking below 400 m and those desaturated with effort were determined.

At the study visit, VHI was calculated by recording the findings related to the damage in the form. The groups with and without lung damage detected with cumulative VHI were compared according to demographic characteristics, exposure, smoking, tissue-organ involvement at the beginning of the disease, initial total and lung BVAS, cumulative VHI scores, IS doses, and ANCA subtype. Patients who died during the follow-up period and their causes of death were recorded.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the “Independent Sample T-test” was used for two groups, and the “Pearson Chi-Square Test” was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Lung involvement was revealed by HRCT in 100% of the cases, by bronchoscopy in 25%, and by histopathology in 17%. In 94% of the cases, 9 (11%) of the 77 histopathological examinations (transthoracic, transbronchial, and open lung biopsy) were lung-related. Histopathology revealed necrotizing granulomatous vasculitis in two cases and non-specific chronic inflammation findings in the other cases.

The doses and durations of IC treatment were elaborated, and it was found that TMP-SMX prophylaxis was used in 70% of the cases during the follow-up period. Pneumococcal and influenza vaccines were administered to one-fourth of the cases during the follow-up.

The initial total BVAS was calculated as 22±7 (range: 4 – 38), and the lung BVAS as 4.6 ±2.8 (range: 3 – 6). The distribution of initial BVAS findings is shown in Table 1. Plasma exchange was applied to 25% of the cases due to pulmonary-renal syndrome, and six cases (11%) were used with respiratory failure.

Table 1. Distribution of Initial Lung Imaging Findings of 51 Patients with AAV Lung Involvement According to BVAS

BVAS Subtypes	Frequency (%)
Nodule /cavity Nodule Cavitary nodule	80 54 26
Infiltration	56
Massive hemoptysis/alveolar hemorrhage	24
Respiratory failure	11
Pleural effusion/pleurisy	5
Endobronchial involvement	3
Wheezing	3

A total of 29 recurrences were recorded in 15 cases (30%) with lung involvement in AAV. Recurrence of lung findings was observed in 13 (44%). Concurrent lung infection accompanied 53% (n=7) of lung recurrences. A total of 87 serious infections requiring hospitalization developed in 25 cases (49%), and 44% (n=38) of the total infections were lung-related Table 2. There was no significant difference in cumulative doses of OS drugs, age, renal failure, and diabetes mellitus (DM) between the groups with and without severe lung infection. More than one lung infection was recorded in 27% of the cases. The main clinical and imaging features of these cases are shown in Table 3. The classification of the change detected in control HRCTs compared to the baseline showed that 80% of the cases in which progression was detected compared to the baseline with HRCT had ≥1 recurrence. IAH was detected in 4 cases (7%), 3 with MPA and 1 with GPA. In two instances, IAH was diagnosed 1 and 6 years before the AAV diagnosis. One patient with IAH was lost in the other three patients, during an average follow-up period of 120 months (28 – 180 months), one developed respiratory failure, and two patients had deterioration in respiratory function tests, but no respiratory failure developed.

Table 2. Major Clinical and Imaging Features of Patients with Multiple Lung Infections in a Cohort of Patients with AAV Lung Involvement

Cases	Lung Infections (n)	AAV Subgroup	Age	VDI	Lung VDI	HRCT	Prognosis	Mortality
1	4	GPA	52	6	1	10 N, 3 CN, Infiltration	Death	Infection
2	4	GPA	54	6	1	14 N, 1 CN, Infiltration	Death	Vasculitis
3	2	MPA	28	6	1	Pleural thickening	Following	Infection
4	2	GPA	42	2	0	5 N, Infiltration	Following	-
5	2	MPA	67	7	2	Infiltration, honeycomb	Death	-
6	8	GPA	66	4	2	12 N, 5 CN, Emphysema	Death	Vasculitis
7	3	GPA	53	7	2	Atelektazi, 1N, Sol bronşta ani sonlanma	Death	infection

N: Nodule, CN: Cavitary Nodule.

Table 3. Cylinder Rod Ice Cube Lock Bottle

Findings		Frequency (%)
Nodule (0-3 cm)	Solid	31 (n=16)
	Cavitary	12 (n=6)
Mass-like Appearance (>3 cm)	Solid	2 (n=1)
	Cavitary	4 (n=2)
Increased Opacity in the Lungs	Consolidation	8 (n=4)
	Frosted Glass Infiltration	6 (n=3)
Bronchiectasis		10(n=5)
Atelectasis		16 (n=8)
Emphysema		8 (n=4)
Pleural Thickening		6 (n=3)
Pleural Effusion		2 (n=1)
Fibrotic Bands & Sequelae Changes		30 (n=17)

PFT and 6MWT were performed in 49 cases without physical disabilities and who could cooperate. PFT was normal in 69% of the cohort, and 6MWT was normal in 90%. Abnormal findings detected with PFT and 6MWT in the cases are shown in Table 4. 8 Of the 14 patients with obstructive PFT findings were smokers. Silica exposure and concurrent occupational lung disease were known in a total of 2 cases with GPA and MPA in whom restrictive PFT was detected.

Table 4. Distribution of Abnormal Findings in PFT and 6MWT in 51 Patients with Lung Involvement due to AAV

RFT Disorder (n=49)	GPA n (%)	MPA n (%)	e-GPA n(%)
Obstruction	10 (20)	2 (4)	2 (4)
Mild	6(12)	-	-
Moderate	2(4)	2(4)	-
Severe	2(4)	-	2(4)
Restriction	1 (2)	1 (2)	-
Diffusion disorder	6 (12)	4 (8)	2 (4)
Desaturation (n=40)	2 (4)	1 (2)	1 (2)
6MWT < 400 m (n=40)	1 (2)	1(2)	2(4)

Table 5. Comparison of Lung Injury and Non-Lung Injury Groups in Terms of Lung Infection, Extrapulmonary Infection, Relapse, Recurrence of Lung Findings, and Vaccination in a Cohort of Patients with Lung Involvement Due to AAV

		VDI=0			Lung VDI≥1			
		Mean±SD (n)	%	Median (Lower-Upper Limit)	Mean±SD (n)	%	Median (Lower-Upper Limit)	p-value
Lung Infection	(+)	7	20		10	59		***0,006***
	(-)	27	80		7	41		
Number of Pulmonary Infections		1,1 ±	0,4	1 (1 - 2)	2,7 ±	2,2	2 (1 - 8)	***0,007***
Extrapulmonary Infection	(+)	7	20		10	59		***0,006***
	(-)	27	80		7	41		
Number of Extrapulmonary Infection		2,9 ±	2,9	2 (1 - 9)	2,9 ±	2,7	2 (1 - 9)	NS
Recurrence of Pulmonary findings	(+)	4	12		4	24		NS
	(-)	30	88		13	76		
Recurrence	(+)	9	26		5	30		NS
	(-)	25	74		12	70		
Influenza vaccine	(+)	8	24		6	35		NS
	(-)	26	76		11	65		
Pneumococcal vaccine	(+)	8	24		6	35		NS
	(-)	26	76		11	65		

NS: Not significant.

The VHI calculated at the study visit of the cohort was 3.5±2.3 (range: 0 – 9), and the lung VHI was 0.5±0.8 (range: 0 – 4). In 34% (n=17) of the cases, lung VHI ≥ 1 was detected. (VHI=1 in 10 cases, VHI=2 in 6 cases, VHI=4 in 1 case). No significant difference was found in the groups with and without lung damage in terms of demographic characteristics, exposure, smoking, BVAS, and ANCA subtype. Cumulative VHIs were higher in the group with lung damage (p =0.001). When the initial findings of the disease were compared in the groups with and without lung injury, upper respiratory tract

involvement was more common in the group without lung injury; gastrointestinal and peripheral nervous system involvement was significantly more common in the group with lung injury ($p<0.05$). Pulmonary and extrapulmonary infections and the number of pulmonary infections were significantly higher in the group with lung injury than in the group without lung injury (Table 5). The recurrence rate of pulmonary findings, influenza, and pneumococcal vaccination rates did not differ significantly in the groups with and without lung injury. There was no significant difference in terms of OS drug exposure in the groups with and without lung VHI≥1. Five patients (4 GPA, 1 MPA) (10%) died at the 11th, 19th, 60th, 96th, and 130th months of follow-up. One patient died due to malignancy, two patients died due to uncontrolled disease activation and serious infection, and two patients died due to serious infection.

DISCUSSION

This study examined the course of lung involvement and its contribution to disease severity and lethality in a selected AAV cohort. Lung involvement in AAV is one of the common internal organ involvements mostly responsive to immunosuppressive treatments. Still, recovery may result in damage, and functional capacity and survival may be negatively affected. Few studies examine the effect of lung involvement on lung and general disease prognosis in AAV. The vast majority of the AAV cohort consisted of patients with GPA. The initial findings of lung involvement overlapped with the frequencies reported in different studies. In our cohort, initial lung involvement findings were evaluated for the first time with BVAS, a standard vasculitis activity assessment tool. BVAS lung involvement indicators consist of seven findings: nodule/cavity, infiltration, pleural effusion/pleurisy, massive hemoptysis/alveolar hemorrhage, respiratory failure, endobronchial involvement, and wheezing. In our cohort, high rates of nodule/cavity (80%) and infiltration (56%) were detected in CT images. These findings were followed by massive hemoptysis/alveolar hemorrhage (24%) and pleural effusion (5%). In previous literature with conventional radiographic imaging and/or CT, different frequencies of nodules (70-90%), cavitary nodules (15-49%), infiltration/consolidation (23-53%), mass-like formations (20-60%) and pleural effusion (12-20%) were reported [6]. The frequency of endobronchial involvement was considerably lower (3%) in our cohort than that reported in two different cohorts of 30 and 74 patients (30% and 55%). In these cohorts, it was observed that not only mass lesions but also all tracheobronchial lesions, such as infiltration, ulcers, and stenosis were recorded as findings of endobronchial involvement [7]. In AAV, "respiratory failure" often develops based on AH associated with lung involvement. The frequency of AH in different AAV cohorts, including patients with AH, was 8-36% and 24% in our cohort [8]. Respiratory failure during AH was reported as 11% in our cohort, 27% in a review of 90 patients examining different studies, and 13% in a survey of 80 AAV patients [9]. Comparing factors that can trigger respiratory failure other than AH in these studies is difficult. The frequency of wheeze, a finding of obstructive lung disease in AAV, could not be obtained from other studies. Our cohort detected "wheeze" associated with endobronchial involvement at a low frequency (3%). The different frequencies of clinical and imaging findings reported in AAV cohorts may generally reflect the severity of disease and the variety of diagnostic methods.

During the mean follow-up period of 5 years in the AAV cohort, the prognosis of the lung findings was examined using the criteria for radiological recovery and lung damage findings in the VHI, considering the exposure to treatment, relapses, and the presence of serious infections. When the HRCTs obtained at the baseline and the study visit were compared, 35% complete recovery, 30% sequelae, and 12% regression in the initial findings were observed. In comparison, 12% of the patients showed progression in the findings. In 80% of the cases with progression, lung findings recurred. Recovery without sequelae was observed at a higher rate in infiltrates (52%), and 25-30% in nodular, cavitary, and mass-like lesions. In AAV cohorts reported from different countries, after a mean follow-up period of 2 years, 25-50% complete recovery, 40-60% partial recovery, and 10-15% increase in lesion size were observed in radiological lesions [6, 10]. In a French study examining patients with GPA, it was reported that after a mean follow-up of 2 years, ground-glass infiltrates, nodules, and consolidations disappeared in 100%, 69%, and 44%, respectively. All mass-like lesions healed with scarring [11]. In another study, ground-glass infiltrates and cavitary nodules completely disappeared in all patients after treatment, and

nodular/mass-like formations in 47% [10]. Since information on lung recurrences and therapy could not be obtained in these studies, explaining the different recovery rates was impossible. In a review examining lung fibrosis in AAV, it was reported that lung fibrosis may precede AAV (54%), coincide (39%), or occur in the course of AAV (6%), with data obtained from different centers [12]. In our cohort, ILD was detected in 4 (7%) patients, 3 of whom were p-ANCA/anti-MPO positive MPA. ILD was present in 66% of patients diagnosed with MPA before diagnosis. It has been suggested that the MPO-ANCA subgroup in AAV plays a role in the pathogenesis of ILD. In a study of 510 patients diagnosed with AAV, lung fibrosis was detected in 3% of all patients and 7% of patients with MPA (n=194). In different studies, the mortality rate was found to be high in cases with ILD [13, 14]. One of the deaths recorded in our cohort (20%) was associated with ILD. However, it was observed that 50% of the patients with ILD continued their follow-up without severe lung damage, and 25% with respiratory failure. In our cohort, obstructive and diffusion disorders were detected in one-third of the patients with PFT, which is consistent with the literature. Approximately half of the patients with obstructive dysfunction were smokers. A study conducted in England on 30 patients with AAV reported that 15 patients with lung involvement had significantly lower carbon monoxide transfer and lung capillary blood volume than patients without involvement [15]. In another study conducted in Norway, PFT abnormalities were found in one-third of 41 patients with GPA. Alveolar diffusion disorder was the most common in this study. Lung involvement has been reported to be a risk factor for low DLCO and reduced FEV1 [16].

In the course of AAV, relapses are frequently seen concerning many factors. Different studies have been conducted on significant patient cohorts, indicating that lung involvement increases the frequency of relapses [17, 18]. A study examining new organ involvements in relapses reported that the most common new lung and peripheral nervous system involvements were detected in relapses [19]. Although relapses were seen in 29% of the patients in our cohort, the contribution of lung involvement to relapse could not be examined because all patients had lung involvement. It was determined that relapses of lung findings accompanied approximately half of the relapses. It was observed that relapses, whether related to the lung or not, were more common in the group with lung damage, but did not reach statistical significance.

Severe infections in AAV affect approximately one-third of the patients and play an important role in mortality. Many studies have shown that infections observed in the first year of AAV are the most important cause of death [20 – 22]. Among the serious infections requiring hospitalization in patients with GPA, lung infections are the most common (36-56%) [23]. Some studies have suggested that lung involvement increases the risk of lung infection [20, 24]. Our study observed that approximately half of the serious infections were of lung origin, consistent with the frequencies reported in the literature. Serious infection rates were significantly higher in the group with lung damage. Considering that organ damage in AAV reflects the severity of the disease, it should be expected that severe disease and a more severe IC treatment regimen may increase the general risk of infection. Recurrent lung infections were observed to be associated with a high rate of mortality (71%), similar to the literature. Although a traditional relationship has been defined between infection and age, renal functions, DM, and IC drug doses, this relationship shown in our study did not reach statistical significance. This situation is related to the comparison being made in a limited number of patient subgroups. In our study, the distribution frequency of infections during the follow-up period was examined; it was noted that it was seen most in the first year (51%), gradually decreased after the first year and disappeared completely, and showed a bimodal pattern by making a second peak after 60 months and reaching a frequency of 33%. Studies conducted in different cohorts also emphasized that infections were seen most frequently in the first year and continued to be a problem in the late period. These studies did not mention a bimodal pattern with peaks in the early and late periods [25]. It is thought that the late infection peak in AAV may be contributed to by the damage that gradually increases over time, parallel to the mortality that peaks in the early and late periods.

The negative effect of high (VDI>5) damage scores calculated with VHI in AAV on survival has been demonstrated in many studies [26, 27]. This study evaluated lung damage with VHI criteria for the first

time. It was shown that the lung damage scores obtained with VHI correlated with total vasculitis damage scores. Although data indicate that initial disease activity may contribute to overall damage [26], its correlation with lung damage could not be demonstrated. However, lung damage was observed significantly more frequently in patients with peripheral nervous system and gastrointestinal system involvement. Although it is conceivable that this finding may reflect the initial disease severity, the relationship between the damage and total activity scores could not be demonstrated.

The fact that lung damage was significantly less common in patients with upper respiratory tract involvement was evaluated as a finding supporting that upper respiratory tract involvement is a good prognostic factor within the FFS, as revealed by FVCG. In our cohort, the most common damage detected by VHI was lung dysfunction (n=11, 22%). In a study evaluating early and late damage due to vasculitis at 6 months and an average of 7 years of follow-up, compiled from six randomized controlled clinical trials including 535 patients with AAV, it was reported that the most common early stage lung chronic dyspnea (6%) and late stage lung dysfunction (12%) were observed [28]. However, since data on the characteristics of initial lung involvement and relapses could not be obtained in this study, different frequencies could not be interpreted. In our study, 10% of the patients died during an average 5-year follow-up, and severe infection was found to be responsible for 80% of the deaths. All of the patients who died had more than one severe infection during their follow-up. AAV mortality has always been high compared to age- and gender-matched populations in different studies. In AAV studies, 10-year survival is around 75-88% [23, 27]. The most common causes of death were infections in the first year (48%), followed by active vasculitis (20%); after the first year, cardiovascular events (26%), malignancy (22%), and infections (20%) [28]. Luqmani et al. [29] reported that in 255 patients with GPA, during a mean follow-up of 6.4 years, the mortality rate increased 9-fold in the first year due to infection, vasculitis, and renal failure. Between 1 and 10 years, the risk decreased significantly compared to the healthy population, although it was higher than the baseline, and after 10 years, the mortality rate increased 4.4-fold with a second peak. The mortality rate was 11% in the first year of the disease and 20% during the follow-up period. In different studies, it has been reported that advanced age, high BVAS scores, severe renal involvement, high damage scores, and secondary infections increase the mortality [20, 22, 23]. In the study by Koldingness et al. [16], 10-year lung survival was 97%.

Studies conducted in China (n=398) and Germany (n=155) have shown that lung involvement increases the mortality [20, 23]. In a large AAV cohort (n=235), it was reported that lung involvement in 99 patients over 65 years of age was more widespread and severe than in younger patients, and the response to treatment and survival were poorer. Lung infections were observed to be more frequent in these patients and to increase the mortality. Studies also indicate lung involvement does not affect survival [30, 31]. In the prognosis study evaluating the data obtained from EUVAS clinical studies, the effect of lung involvement on survival was not reported [30, 32]. It was observed that AH, which can progress with severe lung involvement, increased the mortality rate by 8-fold in patients with MPA. In different AAV cohorts, it was reported that AH alone, without renal or respiratory failure, did not affect long-term survival. Although AH was frequently observed (24%) in our cohort, it was observed that it did not lead to death.

CONCLUSION

In a selected cohort of patients with lung involvement due to AAV, lung involvement was observed to cause a high rate of lung damage (34%) in long-term follow-up, but in a small number of patients, it caused chronic dyspnea. It was demonstrated that the high rate of serious infections during the disease peaked after the first and fifth years and followed a bimodal pattern. It was thought that this course could be related to vasculitis-related activity at the beginning of the disease and the damage caused by vasculitis in the long term. It has been shown that approximately half of the serious infections affect the lungs and that recurrent lung infections contribute significantly to the damage and mortality.

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Competing interests
The authors declare that they have no competing interests.

Consent for Publication
The original article is not under consideration by another publication, and its substance, tables, or figures have not been published previously and will only be published elsewhere.

Data Availability
The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical Declaration
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Our institution has granted ethics committee approval. As this was retrospective research, no informed consent was obtained from participants.

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