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Seasonal variation in incidence and relapse of granulomatosis with polyangiitis: A retrospective cohort study from Central Anatolia

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Abstract. *Background and Aim:* The etiology of granulomatosis with polyangiitis (GPA) remains under discussion. This study aims to explore patterns of organ involvement, ANCA antibody profiles, seasonal attack rates, and their interrelationship among patients diagnosed with ANCA-associated vasculitis (AAV) in Central Anatolia, shedding light on its multifactorial etiology involving drugs, genetics and environmental factors. *Methods:* We conducted a retrospective study involving patients aged 18 to 65 diagnosed with GPA and receiving care at Ankara Bilkent City Hospital Rheumatology Clinic. Diagnosis criteria followed the 2012 Chapel Hill Consensus Conference guidelines and the 2022 American College of Rheumatology/European Association of Rheumatology Societies classification for AAV. Patient data included demographics, antibody test results, seasons of diagnosis and flare, affected organs, and Birmingham Vasculitis Activity Score (BVAS). Organ involvement was determined based on biopsy findings or established criteria. *Results:* Our study included 75 patients, with the majority exhibiting cANCA-IFA positivity (94.7%) and PR3-ANCA ELISA positivity (98.3%). During follow-up, 70.7% experienced their first flare, with 37.7% experiencing a second flare. Lung involvement was most common at diagnosis and during flares, followed by ear-nose-throat and renal involvement. Seasonal analysis revealed peaks in disease onset in March, November, and April, with flares more common in September, May, October, and November. Autumn was the most common season for the first flare. *Conclusions:* This study provides novel insights into ANCA-associated vasculitis epidemiology in Central Anatolia. Our findings underscore the intricate seasonal variation and infectious triggers of GPA exacerbations, highlighting the importance of tailored management strategies to mitigate disease flares.

Key words: granulomatosis with polyangiitis, ANCA-associated vasculitis, environmental exposure, disease flares

Abbreviations

ACR: American College of Rheumatology
ANCA: Anti-neutrophil cytoplasmic antibody
AAV: ANCA-associated vasculitis
SARDs: Systemic autoimmune rheumatic diseases
PR3: Proteinase-3
MPO: Myeloperoxidase
Ig: Immunoglobulin
CHCC: Chapel Hill Consensus Conference
EMEA: European Medicines Agency
DCVAS: Diagnostic and Classification of the Systemic Vasculitis
GPA: Granulomatosis with polyangiitis

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EGPA: Eosinophilic granulomatosis with polyangiitis
MPA: Microscopic polyangiitis
RU/mL: Relative Units per milliliter
BVAS: Birmingham Vasculitis Activity Score
IFA: Indirect immunofluorescence assay
ELISA: Enzyme-linked immunosorbent assay
SPSS: Statistical Package for the Social Sciences

Introduction

Systemic vasculitis, is categorized into large, medium, and small vessel vasculitis, based on the size of the affected blood vessels (1). Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) predominantly affects small vessels, leading to granulomatous or necrotizing inflammation across various organ systems, including the lungs, kidneys, skin, eyes, upper respiratory tract, and sino-nasal area. ANCAs, mainly of the immunoglobulin (Ig) G type, are often directed against myeloperoxidase (MPO) or proteinase-3 (PR3) and can frequently be detected in affected patients (2). Initial classification criteria developed by the American College of Rheumatology (ACR) in 1990 (3) were followed by the Chapel Hill Consensus Conference (CHCC) criteria in 1994, which focused on histological findings and were revised in 2012 to include ANCA as a key serological marker (4). Furthermore, the European Medicines Agency (EMEA) developed a consensus-based algorithm to incorporate these criteria for practical clinical use (5). Most notably, the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study has contributed to the development of the 2022 classification criteria established by the American College of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR), which represent a comprehensive, structured framework for classifying vasculitis (6). These updated criteria are intended to harmonize definitions, improve diagnostic accuracy, and enable consistent grouping of patients for clinical research. AAV encompasses three main subtypes with distinct clinical and pathological features: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA). The etiology of GPA is yet to be fully clarified, but complex mechanisms involving drugs, genetic, and environmental factors including airborne particles, especially silica dust, and infectious agents have been suggested as risk factors (7,8). In recent years, increasing research evidence has emphasized that environmental factors are involved in the occurrence and development of GPA. Many environmental factors, including silica exposure, season, latitude, and microbial infection, have been reported to be associated with GPA occurrence. Several studies have demonstrated that sustained exposure to silica in an occupational setting results in a 3.4–7-fold increased risk of positive ANCA presence (9,10). Additionally, season and latitude have different effects on the incidence of different subtypes of AAV. Generally, AAV tends to occur during winter (11,12). Epidemiological studies focusing on rare diseases like GPA are crucial for enhancing our understanding of etiological mechanisms and for guiding the planning and allocation of healthcare resources. Building upon existing research, our study aims to investigate the patterns of organ involvement, ANCA antibody profiles, seasonal attack rates, and their interrelationship among patients diagnosed with ANCA-related vasculitis from a tertiary center in central Anatolia. By elucidating these aspects, we seek to contribute valuable insights into the epidemiology of GPA in our population, which can inform clinical practice, resource allocation, and future research endeavours.

Materials and Methods

Our retrospective study included patients aged 18 to 65 who were diagnosed with granulomatosis with polyangiitis (GPA) and received regular follow-up at Ankara Bilkent City Hospital Rheumatology Clinic. Patients were included based on diagnoses of GPA according to the 2012 Chapel Hill Consensus Conference criteria. Furthermore, inclusion criteria adhered to the classification criteria established by the 2022 American College of Rheumatology/European Association of Rheumatology Societies for ANCA-associated vasculitis (AAV) (13). Patient demographic characteristics, antibody test results (including ANCA detected by indirect immunofluorescence assay [IFA], anti-proteinase-3 [PR3] enzyme-linked immunosorbent assay [ELISA], and anti-myeloperoxidase [MPO] ELISA), season of diagnosis and disease flare, affected organ systems, and the Birmingham Vasculitis Activity Score (BVAS) were systematically recorded. The determination of organ system involvement was based on biopsy results or established diagnostic criteria as

outlined in prior studies (14,15). For this study, a PR3-ANCA cut-off value of 200 RU/mL was utilized. This threshold was selected based on the upper detection limit of the PR3-ANCA assay used at our institution. The decision was also informed by previous literature, such as the study by Merindol et al., which proposed alternative cut-off values, including 65 RU/mL, for differentiating ANCA-associated vasculitis (AAV) from other mimicking conditions (16). It is important to note that PR3-ANCA thresholds can vary depending on assay protocols, clinical contexts, and the characteristics of the patient population being studied. Remission was defined as the absence of typical signs, symptoms, or other features of active AAV, with or without immunosuppressive therapy, following the criteria outlined by Hellmich et al. (17,18). A flare was defined as the recurrence of active AAV following a period of remission, as per the same criteria (17,18). Patients with potential infectious etiologies or other plausible causes such as drug reactions and malignancies were excluded. Only patients deemed to have experienced a flare after excluding these alternative explanations were included in our study.

Treatment and vaccination considerations

While we recognize that treatment regimens and prophylactic measures such as vaccination may significantly impact flare patterns and disease course, no separate analysis based on specific treatment types was conducted. Additionally, detailed data on Trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis in high-risk patients and vaccination status prior to immunosuppressive therapy were not available in the dataset used in this study. However, it is important to note that in our clinical setting, there is a consistent protocol to ensure patients receive necessary vaccinations and prophylactic treatments prior to starting immunosuppressive therapy. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0 software (IBM SPSS Corp.; Armonk, NY, USA). Normality of continuous variables was evaluated with Shapiro-Wilk test and with plots and histograms visually. Continuous variables were presented either with median (minimum-maximum or interquartile range (IQR)) or mean ± standard deviation, according to normality). Categorical variables are presented with numbers and percentages. The Mann–Whitney U-test or Student's t-test was used for comparison of continuous variables, according to normality of distribution. For the evaluation of categorical variables, the Pearson's Chi-Squared test was used. P values <.05 were considered statistically significant.

Results

The demographic characteristics of our patients were presented in Table 1. 75 patients were included in the study. The number of patients with cANCA-IFA positivity at the time of diagnosis was 71 (94.7%), and pANCA-IFA positivity was 1 (1.3). The number of patients with PR3-ANCA elisa positivity was 73 (98.3%). There was no PR3-ANCA ELISA positivity in 2 patients. Among these patients, the number of patients with PR3-ANCA ELISA titers between 20-200 RU/mL was 23 (30.7%), while the number of patients with titers >200 RU/mL was 50 (66.7%) (Table 1).

During follow-up, 53 (70.7%) of 75 patients experienced their 1st flare and others were in remission. Of the 53 patients who experienced a flare during follow-up, 28 (37.7%) experienced a second flare. The remaining 25 patients were in remission. The most common organ involvement at the time of diagnosis (44 (58.7%)) and in the 1st (24 (45.3%)) and 2nd (13 (46.4%)) flares was the lung and while this was followed by ear-nose-throat at the time of

Table 1. Demographic characteristics and antibody titters of patients.

	N=75
Gender, male, n (%)	42 (56)
Active smokers, n (%)	25 (33.3)
Age at symptom onset, years ± SD	47.40 ± 14.31
Age at diagnosis, years ± SD	47.52 ± 14.28
Duration of follow up, years, median (min-max)	4.0 (1.0-25.0)
cANCA-IFA positivity, n (%)	71 (94.7)
pANCA-IFA positivity, n (%)	1 (1.3)
PR3-ELISA positivity, n (%)	73 (98.3)
Titer 20-200 RU/mL, n (%)	23 (30.7)
Titer >200 RU/mL, n (%)	50 (66.7)
MPO-ELISA positivity, n (%)	0 (0)

Abbreviations: cANCA: cytoplasmic anti-neutrophil cytoplasmic antibody, pANCA: peripheral anti-neutrophil cytoplasmic antibody, IFA: immunoflourescence assay, PR3: proteinase 3: MPO: myeloperoxidase, ELISA: enzyme linked immunosorbent assay

Table 2. Birmingham Vasculitis Activity Score, organ involvement and seasonal distribution of patients at diagnosis, 1st flare, and 2nd flare

		Diagnosis	1st flare	2nd flare
	Number of patients n (%)	75 (100)	53 (70.7)	28 (37.7)
	BVAS score ± SD	6.73 ± 1.97	4.79 ± 1.33	6.21±1.25
Organ system involvements n (%)	Constitutional symptoms	15 (20)	3 (5.7)	2 (7.1)
	Lung	44 (58.7)	24 (45.3)	13 (46.4)
	Renal	30 (40)	13 (24.5)	7 (25)
	Skin	9 (12)	1 (1.9)	0
	Neurologic	3 (4)	0	0
	Ear, nose, throat	34 (45.3)	9 (16.9)	8 (28.6)
	Eye	14 (18.7)	6 (11.3)	3 (10.7)
Season n (%)	Spring	27 (36.0)	8 (15.1)	9 (32.1)
	Summer	14 (18.7)	9 (17.0)	7 (25.0)
	Autumn	16 (21.3)	24 (45.3)	8 (28.6)
	Winter	18 (24.0)	12 (22.6)	4 (14.3)

Abbreviations: BVAS: Birmingham Vasculitis Activity Score

diagnosis (34 (45.3%)) and in those who experienced the 2nd flare (8 (28.6%)), we detected it as renal organ involvement in those who experienced the 1st flare (13 (24.5%)) (Table 2). The Sankey diagram in Figure 1 illustrates the distribution and transitions between seasons (Summer, Spring, Winter, and Autumn) and the "No Flare" category across three stages: Diagnosis, First Flare, and Second Flare. A significant proportion of individuals remained in the same seasonal category across all stages. For instance, many individuals initially diagnosed in "Winter" continued to exhibit flares in the "Winter" category during both the First and Second Flare stages. The diagram shows transitions between seasonal categories, with notable flows from one season to another. For example, individuals diagnosed in "Autumn" often transitioned to "Spring" or "Summer" in subsequent stages (Figure 1).

Disease onset peaks in March, followed by November and April. Flares were more common in September followed by May, October, and November. The 1st flare was the most common in autumn (24 (45.3%)). While this was followed by the winter season in those who were diagnosed (18 (24.0%)) and experienced the 1st flare (12 (22.6%)), it was followed by the autumn season in those who experienced the 2nd flare (8 (28.6%)) (Table 2).

When we compared patients according to PR3-ANCA ELISA titer at disease onset, (PR3-ANCA ELISA 20-200 RU/mL vs PR3-ANCA ELISA >200 RU/mL), we did not find a statistically significant difference between BVAS score and flare frequency. However, when compared in terms of systemic involvement, there was a significant difference in eye involvement ($p<0.05$). There was no significant difference in terms of other organ involvement ($p>0.05$) (Table 3).

Discussion

The etiology of granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, remains multifaceted, involving a complex interplay of genetic, epigenetic, and environmental factors. In our study, we aimed to delve into the intricate relationship between organ involvement, seasonal attack rates, and potential triggers of exacerbation in GPA. To the best of our knowledge, this study is the first from our region and country regarding this issue. Seasonality in the onset and relapse of GPA has been a subject of considerable investigation, yet findings across studies have been inconsistent. Mahr et al. (19) suggested that the incidence of AAV is significantly higher during summer, particularly in August. In studying the factors related to AAV relapse, Kemna et al. (20) showed that AAV is prone to relapse during autumn, accompanied by increased titers of ANCA-related immune markers.

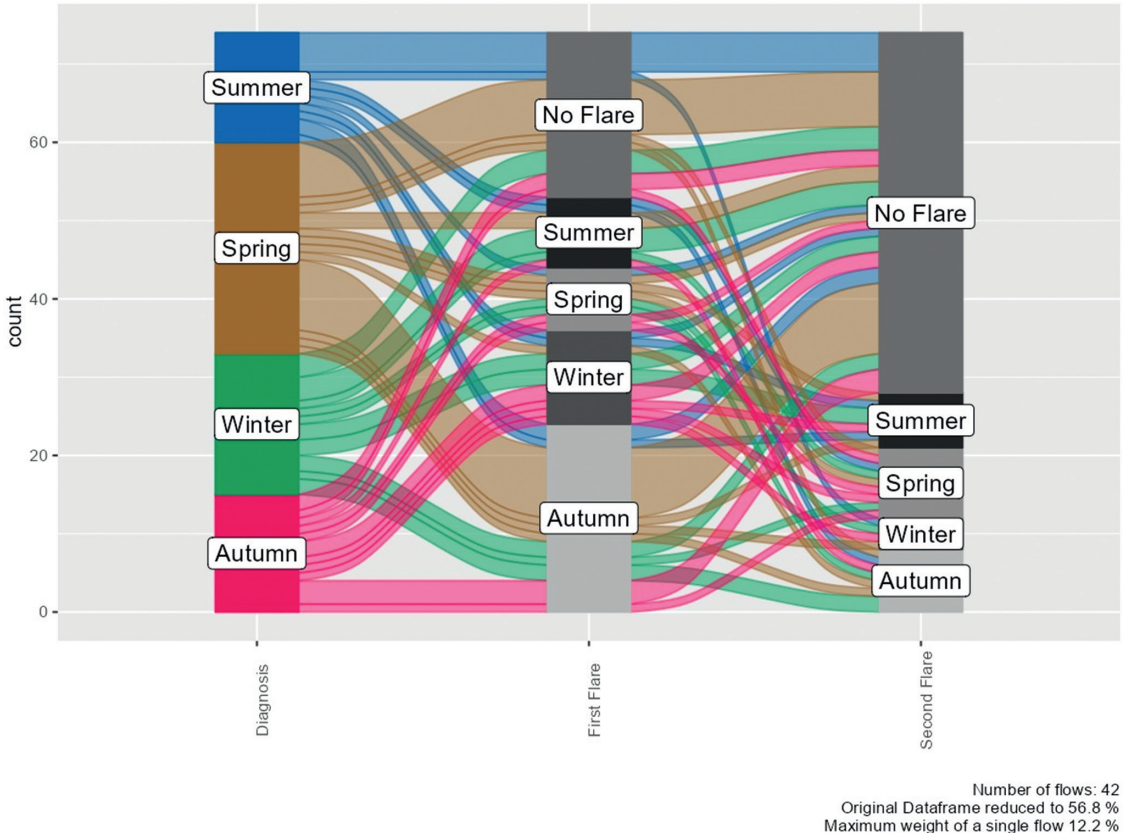

Figure 1. The Sankey diagram illustrates seasonal transitions across the stages of "Diagnosis," "First Flare" and "Second Flare." **Summer**: Blue, **Spring**: Brown, **Winter**: Green, **Autumn**: Pink, **No Flare**: Gray. The flow lines represent the transitions of individuals between seasons at each stage. The thickness of the lines indicates the number of individuals in the respective group. For example, some individuals diagnosed in the "Winter" category transitioned to "Spring" or "No Flare," while others remained in the "Winter" category. The diagram provides a detailed visualization of seasonal changes and the distribution of the "No Flare" condition.

Table 3. Birmingham Vasculitis Activity Score, season at diagnosis and flares, and flare frequency of patients with PR3-ANCA ELISA 20-200 RU/mL and PR3 ANCA ELISA>200 RU/mL

	PR3-ELISA 20-200 RU/mL (n:25)	**PR3-ELISA>200 RU/mL (n:50)**	**P**
BVAS score ± SD	3.72±2.11	3.82±1.68	0.825
Constitutional symptoms, n (%)	4 (16)	11 (22)	0.761
Lung, n (%)	16 (64)	28 (56)	0.507
Renal,n (%)	9 (36)	21 (42)	0.617
Skin,n (%)	5 (20)	4 (8)	0.132
Neurologic,n (%)	2 (8)	1 (2)	0.256
Ear, nose, throat, n (%)	11 (44)	23 (46)	0.870
Eye, n (%)	8 (32)	6 (12)	0.036
Spring, n (%) **Summer, n (%)** **Autumn, n (%)** **Winter, n (%)**	11 (47.8) 3 (13) 5 (21.7) 4 (17.4)	13 (28.9) 10 (22.2) 10 (22.2) 12 (26.7)	0.428
1st flare, n (%) **2nd flare, n (%)**	16 (64) 9 (36)	31 (62) 19 (38)	0.866

Abbreviations: BVAS: Birmingham Vasculitis Activity Score, PR3-ELISA: polymerase 3 enzyme linked immunosorbent assay

Although the majority of hospital (21–23) and population-based studies (11,12) report a peak onset in winter. These studies report a statistically higher symptom onset in winter (December-February, 30.2% - 43%, expected: 25%), and lower than expected symptom onset in summer (June-August, 11%). Paradoxically, a French study reported a summer peak, particularly in August (19), while an increased incidence during autumn (March-May) was noted in New Zealand. In contrast, there studies were unable to find any consistent seasonal pattern (24–26). The high incidence of AAV during summer may be caused by exposure to sunlight or air pollutants. Spring and summer are common seasons for various allergy-related diseases. Furthermore, AAV-related nasal disease may be caused by an immune response driven by Th2 cells. However, more studies are needed to confirm these speculations (27–29). Seasonal inconsistency may be due to differences in AAV disease subtypes, geographic regions, patient records, onset time deviations, and regional differences in medical levels in each study. Our study contributes to this discussion by highlighting that patients in our country were predominantly diagnosed in the spring months, with attacks occurring more frequently in autumn and spring. Kemna et al. in their study, where they examined the risk factors for flare in patients with kidney involvement, they found that the decrease in vitamin D level was an important risk factor for the flare of the disease, especially in the autumn season (20). Another study concluded that winter is a period when the incidence of respiratory diseases is high and infection may trigger the formation of AAV (30). In the light of previous studies related to chronic inflammatory pulmonary diseases, the reasons for frequent infections in pulmonary involvement might also be considered as a factor in AAV cases, as they help provide critical nutrients that increase vascular leakage into the lungs, thus facilitating the growth of bacteria, resulting in development of inflammation in the lungs (31). Uslu Yurteri et al. (2023) found that immunosuppression due to renal involvement may have limited effect, but the combination of renal and pulmonary involvement acts as a compounding factor that significantly increases the risk of serious infection in ANCA-associated vasculitis (32). We believe that this may be related to the added burden of immunosuppressive therapy, especially with multisystem involvement in vital organs. Our findings align with these observations, with lung involvement being more prevalent in patients during attacks, suggesting a potential link between respiratory infections and GPA flare. As reported by Uslu Yurteri et al., half of AAV patients developed serious infections, with 31% occurring in the first six months, likely due to intensive immunosuppression or complications from active disease (32). Microbial infection is considered to be an important risk factor for the development of AAV. Intranasal staphylococcus aureus (S. aureus) infection is most closely associated with AAV (33). The early symptoms of patients with GPA are mainly runny nose, nosebleeds, and other symptoms, because the most prominent feature of the disease is the granulomatous inflammation of the respiratory tract. S. aureus infection that colonizes the respiratory tract may trigger GPA disease activity (34). Previous studies (35) have found that the detection rate of S. aureus in patients with GPA is significantly higher than that in healthy individuals, and patients with GPA with chronic S. aureus infection have a significantly increased risk of flare. Few studies have been conducted on other microorganisms in AAV. A Japanese study (36) reported that Aspergillus infections, including Candida, Candida, and Fusarium, were found in patients with both allergic bronchopulmonary mycosis (ABPM) and EGPA. Kuwabara et al. (37) found that *Mycobacterium tuberculosis* infection and anti-tuberculosis drugs may be related to AAV. Fujita et al. (38) found that the positive rate of *Chlamydia pneumoniae* in patients with MPO-AAV was 33%. Currently, the effect of these microorganisms on AAV is only speculative, and further large-scale studies are needed to verify. Trimethoprim/sulfamethoxazole (TMP/SMX) use has been shown to reduce the risk of infection in studies (39). Although we did not use these data from our patients in our study, it is important to note that in our clinical setting, there is a consistent protocol to ensure that patients receive the necessary vaccinations and prophylactic treatments before starting immunosuppressive therapy. This proactive approach aims to reduce the risk of infection and manage potential flare triggers in patients with GPA. Numerous studies have highlighted the variation in relapse rates between different subtypes of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), with granulomatosis with polyangiitis (GPA) patients experiencing more frequent relapses compared to those with microscopic polyangiitis (MPA) (40). Additionally,

PR3-ANCA positivity has been associated with a higher risk of relapse compared to MPO-ANCA positivity, irrespective of the initial classification of GPA or MPA (41,42). The initiation of maintenance therapy while patients are ANCA-positive has been linked to a twofold increase in the risk of relapse compared to when patients are ANCA-negative (41,42). However, a subset of patients undergoing induction therapy may become ANCA-negative and remain so permanently, exhibiting a lower risk of relapse (43,44). We also aimed to investigate whether PR3-ANCA titer levels were associated with organ involvement and exacerbation frequency. We investigated the relationship between initial PR3-ANCA ELISA titers and relapse but did not observe a significant association between titer levels and relapse. This approach is consistent with the findings of Houben et al., who observed an association between higher ANCA levels, multiorgan involvement and AAV severity (45). The utility of measuring ANCA titers to predict disease activity or guide treatment remains controversial, as absolute titers only weakly correlate with disease severity. Nevertheless, increased PR3-ANCA titers during clinical remission have been shown to predict relapse in GPA patients (46,47). It's worth noting that in our study, we did not assess PR3-ANCA ELISA levels prior to flare-ups during patient follow-up. Consequently, while the risk of relapse after a documented ANCA rise is notable, it is not absolute, and relapses may occur even in the absence of a preceding ANCA rise.The utility of measuring ANCA titers to predict disease activity or guide treatment remains controversial, as absolute titers only weakly correlate with disease severity. Nevertheless, increased PR3-ANCA titers during clinical remission have been shown to predict relapse in GPA patients (46,47). It's worth noting that in our study, we did not assess PR3-ANCA ELISA levels prior to flare-ups during patient follow-up. Consequently, while the risk of relapse after a documented ANCA rise is notable, it is not absolute, and relapses may occur even in the absence of a preceding ANCA rise.

In conclusion, while these limitations should be considered, we believe that our study provides valuable preliminary data, particularly as it is the first study to present findings on this topic from our country. Future studies with larger sample sizes, prospective designs, and more comprehensive data on treatments, vaccinations, and confounding factors are needed to confirm our results and further elucidate the factors influencing seasonal flare patterns in GPA.

Study Limitations

This study has several important limitations that must be considered when interpreting the results.

Sample size

The relatively small sample size of our cohort may affect the generalizability of our findings. A larger sample size would provide greater statistical power, allowing for more robust conclusions.

Retrospective nature

As a retrospective study, our analysis relied on existing medical records, which may be subject to incomplete data, inconsistencies, and recall bias. These factors introduce potential bias that may influence the accuracy and validity of our findings.

Short follow-up duration

The relatively short duration of follow-up in this study limits our ability to assess long-term seasonal patterns or the lasting effects of treatments on flare rates.

Lack of treatment and vaccination data

One of the most significant limitations of our study is the lack of detailed data on treatments and vaccinations. These factors are essential for understanding potential confounding variables that could influence flare rates and disease progression. The absence of this information means we cannot assess the impact of specific treatments or prophylactic measures (e.g., vaccinations) on seasonal flare patterns or long-term disease control. Including these variables in future studies would allow for a more nuanced interpretation of how treatments affect flare frequency and the overall course of GPA.

Confounding variables

This study does not deeply investigate other potential confounding factors, such as comorbidities or

environmental exposures, which could impact flare rates. For example, infections or seasonal environmental factors (e.g., temperature, allergens) might play a role in triggering flares but were not specifically analyzed.

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