Title: The reclassification of patients with previously diagnosed eosinophilic granulomatosis with polyangiitis based on the 2022 ACR/EULAR criteria for ANCA-associated vasculitis

Category: Original Article

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Conflict of Interest

The authors declare that they have no competing interests.

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Running head: Reclassification of EGPA

ABSTRACT

Objectives: The American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) have proposed the 2022 classification criteria for eosinophilic granulomatosis with polyangiitis (EGPA). This study applied the 2022 ACR/EULAR criteria to Korean patients with previously diagnosed EGPA to investigate the concordance rate between the 2022 ACR/EULAR criteria and the old criteria for EGPA.

Methods: Fifty-one patients with EGPA, who fulfilled the 1990 ACR criteria, the 2007 EMA algorithm, and the 2012 CHCC definitions were reclassified based on the 2022 ACR/EULAR criteria.

Results: Of the 51 patients, 44 patients (86.3%) were reclassified as EGPA according to the 2022 ACR/EULAR criteria. Among the 7 patients who failed to meet the 2022 ACR/EULAR criteria, 3 patients were reclassified as having MPA, 1 as having GPA based on the 2022 ACR/EULAR criteria, and 3 as unclassifiable vasculitis. Moreover, 6 patients who met the 2022 ACR/EULAR criteria for EGPA simultaneously met the criteria for microscopic polyangiitis (MPA), and 1 patient met the criteria for GPA based on the 2022 ACR/EULAR criteria for MPA and GPA.

Conclusion: The concordance rate between the 2022 ACR/EULAR criteria for EGPA and the old criteria was 86.3%. The most important factor in the failure to reclassify patients as EGPA was the exclusion of non-fixed pulmonary infiltrates in the 1990 ACR criteria for EGPA. We carefully suggest that non-fixed pulmonary infiltrates should be reconsidered in cases reclassified as unclassifiable vasculitis and additional classification strategies are needed for patients who simultaneously satisfy both AAV subtypes.

Keywords: eosinophilic granulomatosis with polyangiitis, the 2022 ACR/EULAR criteria, the 2007 EMA algorithm, the 2012 CHCC definitions, concordance

INTRODUCTION

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is small vessel vasculitis which is characterised by necrotising vasculitis with few or no immune deposits and includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). EGPA primarily induces necrotising vasculitis in small to medium vessels in the respiratory tract and is often associated with asthma and peripheral eosinophilia (**1, 2)**. Unlike other AAV subtypes such as microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA), EGPA consists of three phases: prodromal, eosinophilic, and vasculitic phases. The prodromal phase may precede the eosinophilic phase by months to years and exhibit the upper respiratory tract symptoms such as asthma, nasal polyps, and sinusitis, are often observed in this phase. In the eosinophilic phase, lung, heart, and gastrointestinal manifestations are predominant, whereas in the vasculitic phase, nerve, kidney, and skin manifestations are apparent, along with an improvement in asthma (**3)**.

In 1951, Churg and Strauss first described the characteristics observed in 13 cases of EGPA through pathological findings obtained by autopsy (**4)**, and in 1984, Lanham and colleagues reported the clinical findings of 16 cases of EGPA, including asthma, peripheral eosinophilia, and vasculitis (**5)**. However, these two studies only described the clinical features of patients with EGPA but could not provide the well-structured classification criteria for EGPA.

In 1990, the American College of Rheumatology (ACR) proposed the first classification criteria for EGPA (the 1990 ACR criteria). The 1990 ACR criteria are composed of six items, which are listed in order of specificity as follows: i) eosinophilia > 10% (specificity 96.6%); ii) asthma (96.3%); iii) non-fixed pulmonary infiltrate (92.4%); iv) extravascular eosinophils (84.4%); v) mono or polyneuropathy (79.8%); and vi) paranasal sinus abnormality (79.3%). These criteria have been used most frequently thus far, because the overall sensitivity and specificity are as high as 85.0% and 99.7%, respectively (**6**).

In 1994, the first International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (the 1994 CHCC definition) was held to specify the name and definition of systemic vasculitis (1). In 2007, the European Medicines Agency proposed a diagnostic tool using an algorithm for the classification of AAV (the 2007 EMA algorithm), which consisted of EGPA, GPA, MPA, polyarteritis nodosa, and unclassifiable vasculitis in order. The 1990 ACR criteria for EGPA are applied as the first step of the 2007 EMA algorithm; if these criteria are met, the algorithm is terminated (**7**). Thereafter, the understanding of vasculitis has advanced and the tendency to not use eponyms in terminology has increased, CHCC revised the names and definition of systemic vasculitis as appropriated in 2012 (the 2012 CHCC definitions), and ANCA was first included in eligibility criteria used in the MIRRA trial (2, 8).

In addition, a group of diagnostic and classification criteria for primary systemic vasculitis (DCVAS) proposed the ACR/European League Against Rheumatism (EULAR) provisional criteria for GPA at the ACR session in 2016. These criteria were primarily designed to distinguish GPA from EGPA by assigning the differently weighted scores to nine items. When a patient achieves a total score of 5 or greater, the patient may be classified as

GPA preferentially. A previous study applied these provisional criteria to Korean patients with AAV and reclassified 90.0% of GPA, 5.6% of MPA, and 3.3% of EGPA patients as GPA. Moreover, that previous study confirmed the clinical significance of proteinase 3 (PR3)-ANCA to distinguish between GPA and EGPA (9**)**. However, these criteria had a limitation in that they had only aimed to differentiate GPA from EGPA and were not officially published.

In March 2022, the ACR and European Alliance of Associations for Rheumatology (EULAR) suggested the new classification criteria for EGPA (the 2022 ACR/EULAR criteria) based on a differently weighted score system. These criteria consist of 7 items, and the classification of EGPA can be performed only when a total score of ≥6 is obtained (**10)**. Because it is a recent publication, there is no study on how many of the patients diagnosed with EGPA in Korea meet the 2022 ACR/EULAR criteria yet. Hence, this study applied the 2022 ACR/EULAR criteria to Korean patients with previously diagnosed EGPA according to all of the 1990 ACR criteria, the 2007 EMA algorithm, and the 2012 CHCC definitions to determine the number of patients who could be reclassified as having EGPA.

PATIENTS AND METHODS

Patients

The term ‘a patient with previously diagnosed EGPA’ was defined as one who was diagnosed with EGPA prior to this study. This study screened 53 patients with previously diagnosed EGPA who were enrolled in the Severance Hospital ANCA associated VasculitidEs

(SHAVE) cohort, which is an observational cohort of Korean patients with AAV and was established in November 2016, according to the inclusion criteria described in previous studies (**11, 12)**. The inclusion criteria were i) patients who were first classified or reclassified as EGPA at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine and Severance Hospital; ii) patients who fulfilled all of the 1990 ACR criteria, the 2007 EMA algorithm, and the 2012 CHCC definitions (**1, 6, 7)**; iii) patients who had well-documented medical records that included the clinical, laboratory, radiologic, and histopathologic data to apply the 2022 ACR/EULAR criteria for EGPA; iv) patients who did not have serious medical conditions, such as malignancies, infectious diseases requiring hospitalisation, and other systemic diseases mimicking EGPA or confusing EGPA diagnosis; v) patients who had never been exposed to immunosuppressive drugs for the treatment of EGPA before EGPA diagnosis; vi) patients who had been followed up for at least three months after EGPA diagnosis.

Of the 53 patients with previously diagnosed EGPA, two patients were excluded because they met only 3 items of the 1990 ACR criteria for EGPA although EGPA was highly suspected based on histopathologic features and asthmatic history. Finally, 51 patients with previously diagnosed EGPA were included in this study. Co-existing serious medical conditions and immunosuppressive drugs that were administered were identified using the 10th revised International Classification Diseases (ICD-10) and the Korean Drug Utilization Review (DUR) system, respectively. The present study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea, IRB No. 4-2020-1071), and conducted according to the Declaration of Helsinki. Given the retrospective design of the

study and the use of anonymised patient data, the requirement for written informed consent was waived by the IRB.

Clinical data and ANCA measurements

The clinical variables are shown in **Table 1**. Birmingham vasculitis activity score (BVAS) and five-factor score (FFS) were collected as AAV-specific indices and clinical manifestations were evaluated based on the 9 systemic categories of BVAS (**13, 14)**. Myeloperoxidase (MPO)-ANCA and PR3-ANCA were measured using the novel anchor-coated highly sensitive (hs) Phadia Elia (Thermo Fisher Scientific/Phadia, Freiburg, Germany) and human native antigens, on the Phadia250 analyser. Immunoassays were used as the primary screening method for ANCA; however, when patients were found to be negative for ANCA by an antigen-specific assay but positive for perinuclear (P)-ANCA or cytoplasmic (C)-ANCA with an indirect immunofluorescence assay, they were considered to have MPO-ANCA or PR3-ANCA when AAV was strongly suspected based on the clinical and laboratory features (**11, 15)**.

2022 ACR/EULAR criteria for EGPA

There are two entry requirements: the presence of small- or medium-vessel vasculitis, and the exclusion of other diseases mimicking vasculitis. Differently weighted scores are assigned to each criterion. The clinical criteria include obstructive airway disease (+3), nasal polyps (+3), and mononeuritis multiplex (+1), whereas the laboratory and biopsy criteria include blood

eosinophil count ≥ 1 × 10^9/litre (+5), extravascular eosinophilic-predominant inflammation on biopsy (+2), PR3-ANCA (or C-ANCA) positivity (-3), and haematuria (-1). When a total score of ≥6 is achieved, the EGPA can be classified (**10**).

Application of the 2022 ACR/EULAR criteria for MPA and GPA

When a patient with previously diagnosed EGPA was not reclassified as EGPA, the 2022 ACR/EULAR criteria for MPA and GPA were further applied (**16, 17**). Moreover, when patients could not be reclassified as MPA or GPA, they were reclassified as unclassifiable vasculitis.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians with interquartile ranges, whereas categorical variables were expressed as numbers (percentages).

RESULTS

Characteristics

The median age of the 51 patients with previously diagnosed EGPA was 53.7 years and 16 of them were men. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were detected in

25 (49.0%) and 5 (9.8%) patients, respectively. Three patients (5.9%) had both MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA). The median BVAS and FFS were 13.0 and 1.0, respectively. The most common clinical manifestation was otorhinolaryngological (80.4%), followed by pulmonary (68.6%) and nervous systemic manifestations (58.8%) (**Table 1**).

Frequencies of each criterion of the 2022 ACR/EULAR criteria for EGPA

Obstructive airway disease was the most frequently observed clinical criterion (90.2%), followed by mononeuritis multiplex (43.1%). Among the laboratory and biopsy criteria, eosinophilia was most commonly found (88.2%), followed by extravascular eosinophil-predominant inflammation (54.9%). One point was deducted in 17 patients for the presence of haematuria, while 3 points were deducted in 5 patients for PR3-ANCA (or C-ANCA) positivity. Finally, 44 patients achieved a total score of ≥6, which indicates the concordance rate regarding the classification of EGPA between the 2022 ACR/EULAR criteria and the old criteria for EGPA was 86.3% (**Table 2**).

Total scores of the application of the 2022 ACR/EULAR criteria for EGPA

The highest total score of 14 was achieved in 2 patients. Among the 51 patients with previously diagnosed EGPA, 7 patients could not be reclassified as EGPA according to the 2022 ACR/EULAR criteria for EGPA. Three patients with previously diagnosed EGPA received a total score of 5 points, 3 patients received 4 points, and 1 patient received 3 points (**Table 3**).

Itemised analysis of patients with previously diagnosed EGPA who failed to be reclassified as EGPA

All 7 patients who did not meet the 2022 ACR/EULAR criteria for EGPA had obstructive airway disease but no nasal polyps. Three patients obtained a score of -1 due to haematuria and 2 patients received a score of -3 due to PR3-ANCA (or C-ANCA) positivity. Because of their negative scores, these items had a critical negative impact on the reclassification of patients B, C, and D as EGPA, but not the remainder. It is noteworthy that an important factor that prevented the reclassification into EGPA was the exclusion of non-fixed pulmonary infiltrates and paranasal sinus abnormality in the 1990 ACR criteria for EGPA (**Table 4**).

Itemised analysis of applying the 2022 ACR/EULAR criteria for MPA and GPA to patients who failed to be reclassified as EGPA

We attempted to apply the ACR/EULAR criteria for MPA and GPA in patients who failed to be reclassified as EGPA, and found that 3 were reclassified as MPA and 1 as GPA. Based on the 2022 ACR/EULAR criteria for MPA, patients C and E received a total score of 9 due to MPO-ANCA (or P-ANCA) positivity (+6) and pauci-immune glomerulonephritis on biopsy (+3). Patient G obtained a total score of 9 due to MPO-ANCA (or P-ANCA) positivity (+6) and interstitial lung disease (+3). In addition, based on the 2022 ACR/EULAR criteria for GPA, patient F obtained a total score of 7 due to nasal involvement (+3), cartilaginous

involvement (subglottic stenosis) (+2), pulmonary nodule and cavitation (+2), paranasal sinusitis (+1) and MPO-ANCA (or P-ANCA) positivity (-1). However, the remaining patients did not meet the ACR/EULAR criteria for MPA, GPA, and EGPA, and were finally reclassified as unclassifiable vasculitis (**Supplementary Table 1**).

Itemised analysis of patients who were reclassified as both EGPA and MPA and those reclassified as both EGPA and GPA based on the 2022 ACR/EULAR criteria for EGPA, MPA and GPA

Among the 44 patients reclassified as EGPA, 6 fulfilled the ACR/EULAR criteria for MPA simultaneously. All patients achieved a score of +6 due to MPO-ANCA (or P-ANCA) positivity but received a score of -4 because of peripheral eosinophilia. None of the patients were positive for PR3-ANCA (or C-ANCA). Nevertheless, they could be reclassified as MPA because of the presence of fibrosis or interstitial lung disease on chest imaging (+3) and/or pauci-immune glomerulonephritis on biopsy (+3). Meanwhile, 1 patient reclassified as EGPA met the ACR/EULAR criteria for GPA simultaneously. The patient received positive scores for nasal involvement (+3), conductive or sensorineural hearing loss (+1), PR3-ANCA (or C-ANCA) positivity (+5), and paranasal sinusitis (+1) but negative scores for MPO-ANCA (or P-ANCA) positivity (-1) and peripheral eosinophilia (-4). Finally, the patient obtained a total score of 5 which is the cut-off value (**Supplementary Table 2**).

DISCUSSION

This study investigated the number of patients who could be reclassified as having EGPA by the 2022 ACR/EULAR criteria in Korean patients with previously diagnosed with EGPA according to the 1990 ACR criteria, the 2007 EMA algorithm, and the 2012 CHCC definitions. Our findings include the following: first, forty-four of 51 patients (86.3%) were reclassified as EGPA and 7 patients could not be reclassified as EGPA based on the 2022 ACR/EULAR criteria for EGPA. Second, PR3-ANCA (or C-ANCA) positivity and haematuria, to which negative scores were assigned, had a critical negative impact on the reclassification; furthermore, an important factor in the failure to reclassify patients as EGPA was the exclusion of non-fixed pulmonary infiltrates and paranasal sinus abnormality in the 1990 ACR criteria for EGPA. Third, when the ACR/EULAR criteria for MPA and GPA were applied to patients not reclassified as EGPA, 3 patients were reclassified as MPA and one as GPA. The remaining patients did not meet the 2022 ACR/EULAR criteria for MPA, GPA, and EGPA, and were finally reclassified as unclassifiable vasculitis. Fourth, among the 44 patients who were reclassified as EGPA, 6 patients were also reclassified as MPA. In addition, 1 patient with EGPA also fulfilled the ACR/EULAR criteria for GPA.

The biggest difference between the 1990 ACR criteria and the 2022 ACR/EULAR criteria for EGPA is that two items, non-fixed pulmonary infiltrates and paranasal sinus abnormality, were deleted (**Supplementary Table 3**). Paranasal sinus abnormality is currently included only in the 2022 ACR/EULAR criteria for GPA. Since the 2007 EMA algorithm also indicated that it is a GPA surrogate marker, and a considerable number of asthma patients have allergic rhinitis and paranasal sinusitis, paranasal sinus abnormality may not be a sufficiently specific symptom to suggest EGPA (**7, 18**). However, non-fixed pulmonary infiltrates could be a predictive marker for EGPA because they are rarely

observed in patients with MPA and GPA. In the 1990 ACR criteria for EGPA, the sensitivity of non-fixed pulmonary infiltrates was only 40.0%, but the specificity was as high as 92.4% (**6**). Moreover, in the 2022 ACR/EULAR criteria for EGPA, the entry requirement specifies that the criteria should be applied after excluding infectious pulmonary infiltrates mimicking AAV (10**)**. For these reasons, we would like to argue that migratory and rapidly changing pulmonary infiltrates indicate the eosinophilic phase of EGPA (**19)**.

The 2022 ACR/EULAR classification criteria is designed to identify homogenous patients for inclusion in clinical studies, therefore, excluding ambiguous item from the classification might be appropriate, because it is difficult to define 'non-fixed pulmonary infiltrates'. Since the patients included in this study were diagnosed with EGPA for clinical practice and not for clinical trial purposes, the diagnosis may differ from the classification criteria for identifying homogenous patients. In this study, all 7 patients, who could not be reclassified as EGPA based on the 2022 ACR/EULAR criteria, clearly exhibited non-fixed and rapidly migratory pulmonary infiltrates at the first classification. All the patients had asthma and all but one had peripheral eosinophilia or mononeuritis multiplex, ensuring that the initial diagnosis was correct. The sensitivity of the 2022 ACR/EULAR criteria for EGPA was 84.9%, which was lower than that of the 2022 ACR/EULAR criteria for GPA or MPA. We believe that excluding the item 'non-fixed pulmonary infiltrates' is a factor that lowers the sensitivity. Although the purpose of the classification criteria is to identify homogeneous patients for clinical studies, EGPA is a rare disease and it is important to register as many patients as possible. Therefore, we suggest that the addition of non-fixed and rapidly migratory pulmonary infiltrates to the 2022 ACR/EULAR criteria for EGPA should be reconsidered carefully.

Since the 2007 EMA algorithm applied the criteria to patients in the order of EGPA, GPA, MPA, polyarteritis nodosa, and unclassifiable vasculitis, there have been no cases of classification into 2 AAV subtypes (**7**). However, if the 2022 ACR criteria for AAV are applied to patients simultaneously, several cases can be classified into 2 AAV subtypes, as seen in the results of this study. Herein, it is questionable as to which subtype should be focused on for managing patients classified as MPA or GPA along with EGPA. This is because the treatment strategy for EGPA is different from that for MPA or GPA (**8, 20, 21**). Therefore, we believe that the principle as to the order of applying the 2022 ACR/EULAR criteria for AAV and initiating the treatment strategy should be established. Here, we provide the following 3 clinical examples: First, the classification order may be determined in a top-down format in the same order as in the 2007 EMA algorithm (**7**). Second, because the treatment strategy of MPA and GPA is stronger than that of EGPA, the treatment order may be determined from MPA and GPA to EGPA in a bottom-up manner in the 2007 EMA algorithm, a direction from MPA and GPA to EGPA (**20**). Third, in patients with patients classified as having both EGPA and active severe MPA or GPA, the treatment strategy of active severe MPA and GPA should be considered first. However, in patients classified as both EGPA and active non-severe MPA or GPA simultaneously, the treatment strategy of active non-severe EGPA including mepolizumab may be considered in addition to that of active non-severe MPA and GPA (**8, 20**). It is important to quickly establish a common opinion among experts regarding this topic.

In addition, for the research purposes, when it is important to recruit homogenous patients and increase the specificity, we carefully suggest that excluding the patients who met more than on criteria may be appropriate. In our study population, 6 patients met both criteria

of EGPA and MPA and 1 patient met both criteria for EGPA and GPA based on the 2022 ACR/EULAR criteria for AAV. Of the 6 patients who met both criteria for EGPA and MPA, 5 patients were positive for MPO-ANCA and kidney biopsy showed pauci-immune glomerulonephritis, suggesting the possibility of MPA. However, all these patients also had asthma and peripheral eosinophilia, which is specific for EGPA. Similarly, the patient who met both criteria for EGPA and GPA, showed nasal involvement as well as hearing loss and PR3-ANCA positive, suggesting the possibility of GPA. However, this patient also had asthma, nasal polyp, and peripheral eosinophilia, which is specific finding of EGPA. Therefore, either diagnosis is considered reasonable in clinical practice. However, for the research purpose, these patients are a factor in reducing specificity. Further consensus should be reached by gathering expert opinions.

STRENGTHS

The merit of this study that it applied the 2022 ACR/EULAR criteria for AAV to patients with previously diagnosed EGPA, and investigated the concordance rate between the 2022 ACR/EULAR criteria and the old criteria in a well-structured cohort. In addition, we identified patients with unclassifiable vasculitis and those with 2 subtypes of AAV, and suggested strategies for AAV classification and treatment.

LIMITATIONS

However, this study has several limitations. Although there were few inter-observer variations and selection biases, the number of patients with EGPA was small due to the single-centre prospective and observational cohort study, and validation in a separate group could not be done. Furthermore, since there was no separate control group in this study and EGPA patients who did not meet the 1990 ACR criteria were not included, the sensitivity and specificity of the 2022 ACR/EULAR criteria could not be analyzed. A retrospective study design may also reduce the reliability of the results of the present study. However, since all the patients were first classified as EGPA, in this hospital, by the same three rheumatologists, it is believed that the clinical, laboratory, radiologic, and histopathologic data used in applying the 2022 ACR/EULAR criteria for MPA, GPA, and EGPA, could be reliable. Lastly, the follow-up period of patients reclassified as unclassifiable vasculitis was not long enough to confirm that they could be differentiated into AAV subtypes. A future prospective study with a larger number of patients and for a longer follow-up period will overcome these limitations and provide sequential and more reliable information on the reclassification and alteration of AAV subtypes.

CONCLUSION

Among the 51 patients previously diagnosed with EGPA, 86.3% were reclassified as EGPA based on the 2022 ACR/EULAR criteria for EGPA. While 5.9% and 2.0% of patients were reclassified as MPA and GPA, respectively, 5.9% of them were reclassified as unclassifiable vasculitis. Moreover, 11.8% of the patients were reclassified as having both EGPA and MPA simultaneously, and 2.0% were classified as having EGPA and GPA

simultaneously. We suggest that non-fixed pulmonary infiltrates should be reconsidered in cases reclassified as unclassifiable vasculitis and further highlight the need for diagnostic and therapeutic strategies for patients with 2 AAV subtypes.

DECLARATIONS

Ethics

This study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea, IRB No. 4-2020-1071) and was conducted according to the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Data availability

The authors will provide raw data will on request.

Authors' contributions

All authors contributed to data analyses and data interpretation. JYP and SWL acquisition of data, interpretations of data. JYP, SSA and SWL participate in the preparation of the draft manuscript. SSA, JJS, YBP participated in the interpretation of the results. All authors read and approved the final manuscript.

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Table 1. Characteristics of patients with previously diagnosed EGPA (N=51)

AAV patients	Values
At the time of the first classification	
Demographic data	
Age (years)	53.7 (22.0)
Male sex (N (%))	16 (31.4)
ANCA positivity (N (%))	
MPO-ANCA (or P-ANCA) positivity	25 (49.0)
PR3-ANCA (or C-ANCA) positivity	5 (9.8)
Both ANCA positivity	3 (5.9)
ANCA negativity	24 (47.1)
AAV-specific indices	
BVAS	13.0 (10.0)
FFS	1.0 (1.0)
Clinical manifestations at diagnosis (N (%))	
General	17 (33.3)
Cutaneous	17 (33.3)
Muco-membranous /Ocular	2 (3.9)
Otorhinolaryngological	41 (80.4)
Pulmonary	35 (68.6)
Cardiovascular	11 (21.6)
Gastrointestinal	5 (9.8)
Renal	14 (27.5)
Nervous systemic	30 (58.8)

Values are expressed as median (interquartile range) or number (percentage).

EGPA: eosinophilic granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five-factor score.

Table 2. Frequencies of each criterion of the 2022 ACR/EULAR criteria for EGPA fulfilled by patients with previously diagnosed EGPA (N=51)

Variables		Values
At the time of the first classification	**Score**	
Items for the 2022 ACR/EULAR criteria for EGPA and assigned scores to each item (N (%))		
Clinical criteria		
Obstructive airway disease	**+3**	46 (90.2)
Nasal polyps	**+3**	8 (15.7)
Mononeuritis multiplex	**+1**	22 (43.1)
Laboratory, imaging and biopsy criteria		
Serum eosinophil count ≥ 1000/μL	**+5**	45 (88.2)
Extravascular eosinophilic-predominant inflammation on biopsy	**+2**	28 (54.9)
PR3-ANCA (or C-ANCA) positivity	**-3**	5 (9.8)
Hematuria	**-1**	17 (33.3)
Total score for 7 items above		8.0 (3.0)
Patients with total score ≥ 6 (N (%))		44 (86.3)

Values are expressed as number (percentage).

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; EGPA: eosinophilic granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic.

Table 3. Total scores of the application of the 2022 ACR/EULAR criteria for EGPA to patients with previously diagnosed EGPA

	Score for the 2022 ACR/EULAR classification criteria for EGPA															
	0	**1**	**2**	**3**	**4**	**5**	**6***	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**
Number of patients with previously diagnosed EGPA	0	0	0	1	3	3	4	5	10	7	8	5	1	2	2	51

*: the cut-off of total scores for the classification of MPA based on the 2022 ACR/EULAR criteria for EGPA

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; EGPA: eosinophilic granulomatosis with polyangiitis

Table 4. Clinical manifestations of patients who were not reclassified as EGPA based on the 2022 ACR/EULAR criteria for AAV

Patients number	Detailed descriptions of the patients who failed to be reclassified as EGPA based on the 2022 ACR/EULAR criteria for EGPA [decisive clues for previously diagnosed EGPA]	Scores based on the 2022 ACR/EULAR criteria for EGPA	Final classification based on the 2022 ACR/EULAR criteria for AAV
A	Obstructive airway disease (+3); Extravascular eosinophilic inflammation on biopsy (+2) [Asthma, non-fixed pulmonary infiltrates, sinusitis, extravascular eosinophils on biopsy]	5	Unclassifiable vasculitis
B	Obstructive airway disease (+3); Serum eosinophil count ≥ 1000/μL (+5); PR3-ANCA positive (-3) [Asthma, peripheral eosinophilia, non-fixed pulmonary infiltrates, sinusitis]	5	Unclassifiable vasculitis
C	Obstructive airway disease (+3); Mononeuritis multiplex (+1); Extravascular eosinophilic inflammation on biopsy (+2); Hematuria (-1) [Asthma, mononeuritis multiplex, non-fixed pulmonary infiltrates, extravascular eosinophils on biopsy]	5	MPA
D	Obstructive airway disease (+3); Serum eosinophil count ≥ 1000/μL (+5); PR3-ANCA positive (-3); Hematuria (-1) [Asthma, peripheral eosinophilia, non-fixed pulmonary infiltrates, sinusitis]	4	Unclassifiable vasculitis
E	Obstructive airway disease (+3); Mononeuritis multiplex (+1) [Asthma, mononeuritis multiplex, non-fixed pulmonary infiltrates, sinusitis]	4	MPA
F	Obstructive airway disease (+3); Mononeuritis multiplex (+1) [Asthma, mononeuritis multiplex, non-fixed pulmonary infiltrates, sinusitis]	4	GPA
G	Obstructive airway disease (+3); Mononeuritis multiplex (+1); Hematuria (-1) [Asthma, mononeuritis multiplex, non-fixed pulmonary infiltrates, sinusitis]	3	MPA