Original article

Comparison of severity classification in Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study

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ABSTRACT

Objective: To compare disease severity classification systems for 6-month outcome prediction in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

Methods: Patients with newly diagnosed AAV from 53 tertiary institutions were enrolled. Six-month remission, overall survival, and end-stage renal disease (ESRD)-free survival were evaluated.

Results: According to the European Vasculitis Study Group (EUVAS)-defined disease severity, the 321 enrolled patients were classified as follows: 14, localized; 71, early systemic; 170, generalized; and 66, severe disease. According to the rapidly progressive glomerulonephritis (RPGN) clinical grading system, the patients were divided as follows: 60, grade I; 178, grade II; 66, grade III; and 12, grade IV. According to the Five-Factor Score (FFS) 2009, 103, 109, and 109 patients had <1, 2, and ≥3 points, respectively. **No significant difference in remission rates was found in any severity classification.** The overall and ESRD-free survival rates significantly differed between grades I/II, III, and IV, regardless of renal involvement. Severe disease was a good predictor of 6-month overall and ESRD-free survival. The FFS 2009 was useful to predict 6-month ESRD-free survival but not overall survival.

Conclusions: The RPGN grading system was more useful to predict 6-month overall and ESRD-free survival than the EUVAS-defined severity or FFS 2009.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA), are characterized by ANCA production and small vessel inflammation [1]. Previous reports showed interesting geographic and ethnic differences in the incidence and myeloperoxidase (MPO)-ANCA or peroxidase-3 (PR3)-ANCA positivity [2-4].

To characterize the clinical and laboratory features, and the prognosis of Japanese patients with AAV, we implemented a nationwide prospective cohort study of remission induction therapy in Japanese patients with ANCA-associated vasculitides (RemIT-JAV). In the RemIT-JAV study, we confirmed that MPO-ANCA-positive MPA/renal limited vasculitis RLV) was the most common form of AAV in Japanese patients and revealed that one-half of patients with GPA had MPO-ANCA positivity and that interstitial lung disease (ILD) was an important clinical manifestation in Japanese patients with AAV [5, 6]. This high MPO-ANCA positivity in patients with GPA was also confirmed in a recent retrospective report [7]. In addition, we proposed MPO-ANCA positivity in AAV patients and ILD as a novel variant of MPA. As for clinical course, we elucidated that most Japanese patients with MPA and GPA received treatment with high-dose glucocorticoid and limited-dose cyclophosphamide **(CY)**, and showed high remission and relapse-free survival rates. However, remission with prednisolone at <10 mg/day was observed only in 40% of the patients with remission at 6 months [8, 9]. To further analyze the

characteristics of Japanese patients with AAV, Research Committee of Intractable Vasculitis Syndrome and Research Committee of Intractable Renal Disease of the Ministry of Health, Labour, and Welfare of Japan collaboratively implemented a subsequent nationwide prospective cohort study of remission induction therapy in Japanese patients with ANCA-associated vasculitides and rapidly progressive glomerulonephritis (RemIT-JAV-RPGN).

The extent and pattern of organ involvement were quite different between patients with AAV, and the European League Against Rheumatism (EULAR) recommends that patients with vasculitis should be categorized into clearly defined disease states. Currently, the European Vasculitis Study Group (EUVAS)-defined disease severity, Five-Factor Score (FFS), and RPGN clinical grading system could be used for this purpose [10-12]. The RemIT-JAV study revealed that the EUVAS-defined disease severity, especially the severe form, was useful for predicting poor renal and vital prognoses [9].

In the present study, we compared the usefulness of the three disease severity classification systems for predicting 6-month outcome in patients with AAV enrolled in the RemIT-JAV-RPGN study.

MATERIALS AND METHODS

Settings and patient population

Database

Fifty-three tertiary care institutions (university and referring hospitals) participated in this study and

enrolled consecutive patients with newly diagnosed AAV from April 2011 to March 2014. The criteria for enrolment in this study were as follows, which are the same as those in the RemIT-JAV study: 1) diagnosis of AAV by the site investigators, 2) fulfilling the criteria for primary systemic vasculitis as proposed by the European Medicines Agency (EMEA) algorithm [13], and 3) starting immunosuppressive treatment based on the discretion of the site investigators. The exclusion criteria were 1) age younger than 20 years, 2) recurrent AAV, 3) serological evidence of hepatitis B or C virus infection, and 4) a history of malignancy because 3) and 4) may influence treatment selection and the prognosis of patients with AAV. We conducted this study according to the Declaration of Helsinki and the ethical guidelines for Epidemiological Research in Japan. Written informed consent was obtained from each participant, and the study protocol was approved by the ethics committee of each participating hospital. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000005136).

Data collection

The baseline data of each patient included demographic information; general performance categorized using the World Health Organization performance status scale, except category 5 (death) [14]; comorbidities; laboratory data; disease activity according to the Birmingham Vasculitis Activity Score (BVAS) 2003 [15]; imaging data (e.g., findings of chest radiography, thoracic computed tomography, renal histology, and magnetic resonance imaging of the head); and respiratory function data. RPGN was

defined as an abrupt or insidious onset of macroscopic hematuria, proteinuria, anemia, and rapidly progressing renal failure [16].

At months 3, 6, 12, 18, and 24 and at relapse, the following data were collected: vital status, BVAS 2003, laboratory data, treatments, and adverse events. The Vascular Damage Index score [17] was recorded at months 6, 12, and 24. Chest radiography and respiratory function data were collected at months 12 and 24, and thoracic computed tomography data were collected at months 3, 6, 12, and 24 in patients with pulmonary involvement. Observation will be completed in March 2016.

The site investigators completed and sent the electronic case report form for each patient to the RemIT-JAV-RPGN data center at the Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, in Okayama, Japan.

Outcome measures

The primary outcome measure of the present study was cumulative remission rate within 6 months. Remission was defined as the complete absence of disease activity attributable to active vasculitis. The absence of disease activity was determined systematically using a BVAS of 0 on two occasions at least 1 month apart according to the EULAR recommendations [18].

Secondary outcome measures included cumulative overall and end-stage renal disease (ESRD)-free survival rates at 6 months. ESRD was defined as dependence on dialysis or an irreversible increase in serum creatinine level of >5.6 mg/dL (500 mol/L).

Disease severity

The disease severity of the enrolled patients was classified as localized, early systemic, generalized, or severe according to the EUVAS-defined disease severity [18]. The patients with threatened vital organ function were classified as having a generalized disease, and the patients with organ failure were classified as having severe disease. Detailed definitions of disease severity were described in our previous report [5].

We also classified the patients into 4 groups according to Japanese RPGN clinical grading [11]. The parameters included in RPGN clinical grading were as follows: serum creatinine level (<3 mg/dL = 0 point, 3–6 mg/dL = 1 point, >6 mg/dL = 2 points, and dialysis dependent = 3 points), age (≤59 years = 0 point, 60–69 years = 1 point, and ≥70 years = 2 points), lung involvement (negative = 0 point and positive = 2 points), and serum C-reactive protein **(CRP)** level (<2.6 mg/dL = 0 point, 2.6–10.0 mg/dL = 1 point, and >10 mg/dL = 2 points). Lung involvement was defined as presence of chest symptoms in BVAS or ILD. ILD was diagnosed by site investigators using chest radiography and/or thoracic computed tomography in the present study. The points of these 4 parameters were summed, and patients were divided into 4 groups as follows: grade I, 0 to 2 points; grade II, 3 to 5 points; grade III, 6 to 7 points; and grade IV, 8 to 9 points.

For calculation of FFS 2009, we defined each parameter as follows: renal insufficiency was defined as a serum creatinine level > 1.7 mg/dL; cardiac insufficiency, as presence of cardiac symptoms in BVAS;

gastrointestinal involvement, as presence of abdominal symptoms in BVAS; and ear, nose, and throat (ENT) involvement, as presence of ENT symptoms in BVAS. Age older than 65 years, cardiac insufficiency, gastrointestinal involvement, and renal insufficiency were accorded +1 point, and absence of ENT manifestations was accorded +1 point. The patients were divided into 3 groups according to the sum of the points of these 5 parameters as follows: <1, 2, and ≥3.

Statistical analysis

We used baseline and follow-up data at 3 and 6 months of the enrolled patients in this study for statistical analysis. Categorical variables were compared using the Fisher direct probability test, and continuous variables were compared using the Mann-Whitney *U* test. The cumulative remission, overall survival, and ESRD-free survival rates were analyzed using the Kaplan-Meier method and compared using the log-rank test.

A *p* value of <0.05 was considered significant for statistical analyses. When comparing three or four categories, statistical significance was determined by <0.05/3 or <0.05/**6** by Bonferroni correction to adjust for multiple testing. All statistical analyses were performed by a biostatistician using the JMP version 10.0.2 statistical package for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

In total, 321 patients with AAV were initially enrolled in the RemIT-JAV-RPGN study. Using the EMEA algorithm, we identified 28 patients with EGPA, 53 with GPA, 198 with MPA/RLV, and 42 who were unclassifiable (Figure 1). The **median** ages of the patients with EGPA (male/female, 9/19), GPA (20/33), MPA/RLV (93/105), and unclassifiable disease (15/25) were **60.5, 68, 73, and 74** years, respectively (Table 1). **The patients with MPA/RLV and unclassifiable patients** were significantly older at the time of presentation than those with EGPA ($p < 0.017$ for both). A female predominance was observed for all AAV diseases. MPO-ANCA was positive in 42.9% of the patients with EGPA, 62.3% of those with GPA, and 98.5% of those with MPA/RLV. In contrast, PR3-ANCA was positive in 3.6% with EGPA, 35.9% with GPA, and 3.5% with MPA/RLV. Renal manifestations developed in 256 patients (79.8%). Of the 42 unclassifiable patients, 37 (88.1%) had MPO-ANCA positivity and 31 (73.8%) had ILD.

Disease severity classification

Disease severity was classified using the three different classification systems (Table 2). According to the EUVAS-defined disease severity, 14 patients (4.3%) had localized disease, 71 (22.1%) had early systemic disease, 170 (53.0%) had generalized disease, and 66 (20.6%) had severe disease. The RPGN clinical grading system divided the patients as follows: 60 (19.0%) with grade I, 178 (56.3%) with grade II, 66 (20.9%) with grade III, and 12 (3.8%) with grade IV. **Five patients was excluded because data of CRP levels were missing.** With the use of FFS 2009, 103 (32.1%) patients had $\leq$1 point, 109 (34.0%) had 2 points, and the other 109 (34.0%) had $\geq$3 points. Cardiac symptom was found only in 27 AAV patients

(8.4%); and abdominal symptom, only in 6 AAV patients (1.9%).

Clinical course

Of the 321 patients, 2 (1 patient with EGPA and 1 patient with MPA) were excluded from the outcome analysis because follow-up data were not obtained. **The median initial daily prednisolone dose was 40 mg, and methylprednisolone pulse therapy was used in 145 (45%) patients. Concomitant CY was used during the initial 3 weeks of remission induction therapy in 105 (33%) patients and plasmapheresis was implemented in 16 (5%) patients.**

By 6 months, 22 (81.5%) of the 27 EGPA patients, 48 (90.6%) of the 53 GPA patients, 150 (76.1%) of the 197 MPA patients, and 40 (95.2%) of the 42 unclassifiable patients achieved remission, as defined by a BVAS of 0 on two occasions at least 1 month apart. A statistical difference in remission was observed between the disease classifications ($p = 0.04$). The patients with unclassifiable disease exhibited a significantly higher remission rate than the patients with MPA after Bonferroni correction ($p = 0.006$; Figure 2a). No statistically significant difference in remission rate was found between the groups when we used the other three severity classification criteria. In 29 patients who were alive at 6 months without achieving remission, manifestations were found in the kidney, neurological system, chest, cardiovascular system, and ENT in 18 (62.1%), 4 (13.8%), 3 (10.3%), 2 (6.9%), and 1 (3.5%), respectively, at 6 months.

Fifteen deaths were reported during the 6-month observation period (14 MPA patients and 1 GPA patients). The causes of death reported by the site investigators were vasculitis (3 patients), infection (7

patients), and others (cardiovascular in 2 patients, gastrointestinal bleeding in 2 patients, and subacute fulminant hepatic failure in 1 patient). In terms of overall survival rate, the patients with MPA tended to have worse prognosis than those with EGPA, GPA, and unclassifiable disease, but the differences were not statistically significant ($p = 0.07$; Figure 3a). In the EUVAS-defined disease severity spectrum, survival rate significantly differed across the groups ($p = 0.005$). The patients with severe disease had a poorer prognosis than those with generalized disease, with a statistically significant difference after Bonferroni correction ($p = 0.0006$; Figure 3b). Using the RPGN clinical grading, we found a significant difference in survival rate across the four groups ($p < 0.0001$). The patients categorized as grade I had a statistically better prognosis than those categorized as either grade III ($p = 0.0076$) or IV ($p < 0.0001$). The patients categorized as grade II had statistically better prognosis than those categorized as either grade III ($p = 0.004$) or IV ($p < 0.0001$). The patients categorized as grade III tended to have better prognosis than those categorized as grade IV, but the difference was not significant after Bonferroni correction ($p = 0.03$). No significant difference in survival rate according to FFS 2009 was found between the three groups ($p = 0.09$).

Twenty-nine cases of ESRD developed during the observation period (25 patients with MPA, 2 with GPA, and 2 with unclassifiable disease). The median (range) time to ESRD was 26.2 days (0–173 days). As for EUVAS-defined disease severity, ESRD-free survival rate significantly differed between the four groups. The patients with severe disease showed significantly poorer renal outcome than those with early

systemic disease ($p < 0.0001$) and those with generalized disease ($p < 0.0001$). A statistically significant difference was found between the four groups when the RPGN clinical grading was used ($p < 0.0001$), and all intergroup comparisons, except grades I and II, showed significant differences after Bonferroni correction (grade I vs grade III, $p = 0.0012$; grade I vs grade IV, $p < 0.0001$; grade II vs grade III, $p < 0.0001$; grade II vs grade IV, $p < 0.0001$; and grade III vs grade IV, $p < 0.0001$, respectively). A statistically significant difference in ESRD-free survival was found between the three FFS 2009 groups ($p < 0.0001$). Patients with $\geq$3 points in the FFS 2009 showed significantly poorer renal outcome than the other 2 groups after Bonferroni correction (vs patients with $\leq$1 point in the FFS 2009, $p<0.0001$ and vs patients with 2 points in the FFS 2009, $p=0.001$, respectively).

DISCUSSION

This is the first prospective cohort study that compared between several disease severity classification systems in AAV patients. The RPGN clinical grading system was a good predictor of 6-month overall survival and ESRD-free survival not only in RPGN patients but also in AAV patients.

In both this study and the RemIT-JAV study, the **majority** of the patients were positive for MPO-ANCA and diagnosed with MPA. The proportion of MPA patients, however, was higher (**60% vs. 50%**), and the proportion of patients with unclassifiable disease were lower (**13% vs. 20%**) in the RemIT-JAV-RPGN study than in the RemIT-JAV study. **Almost same number of the rheumatologists**

and the nephrologists participated in the RemIT-JAV-RPGN study while more rheumatologists participated than the nephrologists in the RemIT-JAV study, which probably accounts for **the difference of the proportion of each disease between the two studies**. Because **numbers of the board-certified nephrologists and rheumatologists are substantially equal in Japan,** the proportion of each disease in the RemIT-JAV-RPGN study may reflect the real-world situation in Japan more accurately than that in the RemIT-JAV study.

The 6-month remission rate in the present study was 10% lower than that in the RemIT-JAV study (76% in RemIT-JAV-RPGN vs 85% in RemIT-JAV). Renal manifestations were observed at 6 months in 62.1% of the patients who did not achieve remission. Considering that the patients with renal damage exhibited large fluctuation in serum creatinine or urinary protein level, making a precise judgment of the vasculitis activity for the renal components of the BVAS system seemed difficult for the site investigators. The higher frequency of renal involvement in the present study (80% in RemIT-JAV-RPGN vs 70% in RemIT-JAV) may have affected the lower remission rate in the present study.

The RPGN clinical grading system was a good predictor of 6-month overall and ESRD-free survival in the present study. The RPGN clinical grading was created with 844 Japanese patients (including 502 patients with MPA/RLV) with RPGN from 1989 to 1998 and validated in 888 patients with RPGN from 1999 to 2007 (including 587 patients with MPA/RLV) [11]. The overall and ESRD-free survival rates significantly differed between grades I/II, III, and IV in this study even though some patients did not have

renal involvement. A previous report also showed that score based on this system was a good predictor of mortality in patients with MPO-AAV [19]. As for the EUVAS-defined disease severity, severe disease was a good predictor of 6-month overall and ESRD-free survival, but the difference of these outcomes was not apparent among limited, early systemic, and generalized diseases. The EUVAS-defined disease severity was categorized based on the extent of organ damage and renal function. Organ failure classified as severe disease was defined according to the presence of any of the following BVAS manifestations: massive hemoptysis/alveolar hemorrhage, respiratory failure, congestive cardiac failure, ischemic abdominal pain, or stroke. These symptoms may be good predictors of 6-month survival because they are potentially fatal if not responsive to treatment. Categorization according to FFS 2009 was useful to predict 6-month ESRD-free survival but not overall survival. This may be explained by the fact that cardiac or abdominal manifestations, which are incorporated in FFS 2009, were rarer in the AAV patients enrolled in the RemIT-JAV-RPGN study than those enrolled in a Western clinical study [20].

Our study has several limitations. First, selection bias should be considered because this study was performed in university and referral hospitals in Japan. **However,** patients with AAV are frequently referred to specialists in Japan and 53 institutions participated in the RemIT-JAV-RPGN; thus, the results of this study have generalizability to some extent. Second, our data might have been affected by indication bias, which could influence treatment selection and outcomes of the patients in each classification group of disease severity **therefore further analysis need to be elucidate the effectiveness**

and the safety of the treatment for AAV. Third, the 6-month observation period could be too short to evaluate true outcomes of AAV.

In conclusion, the Japanese RPGN clinical grading system was more useful for predicting 6-month overall and ESRD-free survival in Japanese AAV patients than the EUVAS-defined disease severity or FFS 2009.

COMPETING INTERESTS

MH received research grants from Teijin Pharma, Ltd. and received research grants and/or honoraria from Abbott Japan Co., Ltd., Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma, Ltd., and Pfizer Japan Inc. TA received Honoraria and/or Research funding from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Daiichi Sankyo Co. Ltd., Otsuka Pharmaceutical Co., Ltd. HM is a consultant for AbbVie, Astellas, and Teijin; receives speaker honoraria from Astellas, Boehringer-Ingelheim, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Kyowa Hakko Kirin, MSD, Novartis, Pfizer, Takeda, and Tanabe Mitsubishi; and receives grant support from Astellas, Boehringer-Ingelheim, Daiichi Sankyo, Dainippon Sumitomo, Kyowa Hakko

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FIGURE LEGENDS

Figure 1 Classification of the 321 patients with ANCA-associated vasculitis according to the EMEA algorithm in this cohort study.

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; EMEA, European Medicines Agency; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RLV, renal-limited vasculitis.

Figure 2. Cumulative remission rates according the EUVAS-disease severity, RPGN clinical grading, and Five-Factor Score 2009 disease classification systems

Cumulative remission rates were analyzed using the Kaplan-Meier method. The log-rank test was used for intergroup comparison. (a) Remission rates according to disease classification. (b) Remission rates according to the EUVAS-defined disease severity. (c) Remission rates according to the RPGN clinical grading. (d) Remission rates according to the Five-Factor Score 2009.

Figure 3. Cumulative overall survival rates according to the EUVAS-disease severity, RPGN clinical grading, and Five-Factor Score 2009 disease classification systems

Cumulative survival rates were analyzed using the Kaplan-Meier method. The log-rank test was used for intergroup comparison. (a) Survival rates according to disease classifications. (b) Survival rates according to EUVAS-defined disease severity. (c) Survival rates according to the RPGN clinical grading. (d) Survival rates according to the Five-Factor Score 2009.

Figure 4. Cumulative ESRD-free survival rate according to the EUVAS-disease severity, RPGN clinical grading, and Five-Factor Score 2009 disease classification systems

Cumulative ESRD-free survival rates were analyzed using the Kaplan-Meier method. The log-rank test was used for intergroup comparison. (a) ESRD-free survival rates according to disease classification. (b)

ESRD-free rates according to the EUVAS-defined disease severity. (c) ESRD-free survival rates according to the RPGN clinical grading. (d) ESRD-free survival rates according to the Five-Factor Score 2009.

Table 1 Demographic characteristics of the patients with AAV disease

	EGPA (n = 28)	GPA (n = 53)	MPA/RLV (n = 198)	Unclassifiable (n = 42)
Male/female, n	9/19	20/33	93/105	17/25
Mean (median) age (years)[#,‡]	57.4 ± 16.0 (60.5)	66.8± 15.5 (68)	70.5 ± 12.2 (73)	72.8 ± 10.1 (74)
MPO-ANCA positive[#,†,‡,§,¶]	12 (42.9)	33 (62.3)	195 (98.5)	37 (88.1)
PR3-ANCA positive*[,†,‡,§]	1 (3.6)	19 (35.9)	7 (3.5)	3 (7.1)
ANCA negative*[,#]	16 (57.1)	4 (7.6)	2 (1.0)	3 (7.1)
Serum creatinine (mg/dL)*[,#,†,¶]	0.63 ± 0.18	1.60 ± 1.77	3.20 ± 3.20	1.27 ± 1.48
General performance 0/1/2/3/4	3/9/5/10/1	7/23/10/11/2	41/82/31/31/13	4/21/8/8/1
RPGN*[,#,†,‡,¶]	0 (0)	19 (35.9)	144 (72.7)	8 (19.1)
Interstitial lung disease[†,‡,§,¶]	8 (28.6)	10 (18.9)	89 (45.0)	31 (73.8)

Values are expressed as mean ± standard deviation or n (%) unless otherwise noted. Comparisons between the EGPA, GPA, and MPV/RLV groups were made using the Mann-Whitney *U* test. Statistical significance was determined based on <0.05/**6** using Bonferroni correction: *EGPA versus GPA. [#]EGPA

versus MPA/RLV. †GPA versus MPA/RLV. **‡EGPA versus unclassifiable AAV. §GPA versus unclassifiable AAV. ¶MPA/RLV versus unclassifiable AAV.**

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, peroxidase-3; RLV, renal-limited vasculitis; RPGN, rapidly progressive glomerulonephritis.

Table 2 Disease severity classification according to EUVAS-defined disease severity, RPGN clinical grading, and Five Factor Score 2009

	EGPA	GPA	MPA/RLV	Unclassifiable
EUVAS-defined disease severity	(n = 28)	(n = 53)	(n = 198)	(n = 42)
Localized	0 (0)	6 (11.3)	7 (3.5)	1 (2.4)
Early systemic	1 (3.6)	7 (13.2)	45 (22.7)	18 (42.9)
Systemic	23 (82.1)	31 (58.5)	96 (48.5)	20 (47.6)
Severe	4 (14.3)	9 (17.0)	50 (25.3)	3 (7.1)
RPGN clinical grading	(n = 27)	(n = 53)	(n = 194)	(n = 42)
I	14 (51.9)	8 (15.1)	34 (17.5)	4 (9.5)
II	11 (40.7)	32 (60.4)	107 (55.2)	28 (66.7)
III	2 (7.4)	13 (24.5)	42 (21.7)	9 (21.4)
IV	0 (0)	0 (0)	11 (5.7)	0 (2.4)
Five-Factor Score 2009	(n = 28)	(n = 53)	(n = 198)	(n = 42)
≤1	24 (85.7)	40 (75.5)	30 (15.2)	9 (21.4)
2	3 (10.7)	12 (22.6)	67 (33.8)	27 (64.3)
≥3	1 (3.6)	1 (1.9)	101 (51.0)	6 (14.3)

Values are expressed as n (%).

EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, peroxidase-3; RLV, renal-limited vasculitis; RPGN, rapidly progressive glomerulonephritis.

APPENDIX

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