Comparison of the factors associated with the short-term prognosis between elderly and non-elderly patients with anti-neutrophil cytoplasmic antibody-associated vasculitis: a retrospective observational study

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Abstract

Objective

The difference in factors associated with the prognosis between elderly and non-elderly patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is uncertain. We aimed to elucidate the clinical factors associated with the short-term prognosis (within 6 months from the start of the treatment) and investigate the differences in the associated factors between elderly and non-elderly individuals.

Methods

We performed a dual centre retrospective observational study of patients newly treated with AAV (eosinophilic granulomatous with polyangiitis was excluded). The primary outcome was all-cause death, and the secondary outcome was end-stage renal disease (ESRD) and infectious complications within 6 months after the start of treatment. We analysed factors associated with these outcomes using logistic regression analyses.

Results

Of the 79 patients, patients aged ≥75 years were defined as elderly (n=41), whereas those aged <75 years were defined as non-elderly (n=38). In elderly patients, age was significantly associated with all-cause mortality. In the non-elderly patients, the geriatric nutritional risk index was significantly associated with all-cause death. The estimated glomerular filtration rate (eGFR) before the start of treatment was significantly associated with ESRD in elderly and non-elderly patients. In elderly patients, the Birmingham vasculitis score 3, eGFR, methylprednisolone pulse use, and cyclophosphamide use were significantly associated with infectious complications. Factors other than the serum albumin level were not significantly associated with infectious complications in the non-elderly population.

Conclusion

The factors associated with all-cause death and infectious complications differed between elderly and non-elderly patients. Awareness of these differences may contribute to better management of AAV.

Key words

anti-neutrophil cytoplasmic antibody, anti-neutrophil cytoplasmic antibody-associated vasculitis, elderly, geriatric nutritional risk index

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic small-vessel vasculitis characterised by ANCA positivity, and it often causes severe kidney and/or lung injury that results in life-threatening conditions (1, 2). AAV is mainly categorised as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), or eosinophilic granulomatosis with polyangiitis (EGPA) (1, 2). In Japan, MPA is common, and the mean age of patients who developed MPA was >70 years, although some studies have reported the mean age as >75 years (3-6). The mean age of the patients who developed MPA was 55–75 years, whereas that of patients who developed GPA was 45-65 years (1). Thus, in cases of AAV treatment, particularly MPA, physicians may manage elderly patients at a high frequency. The main induction therapy against AAV is a glucocorticoid and cyclophosphamide or rituximab, which are strong immunosuppressants (1, 2). Because many elderly patients with AAV are treated with strong immunosuppressive therapy, infectious complications are one of the most important problems in the therapeutic course of AAV (3, 4). However, insufficient immunosuppressive therapy may not suppress disease activity, resulting in end-stage renal disease (ESRD) or severe lung injury. This is a dilemma for the treatment of patients with AAV.

The important clinical outcomes in patients with AAV are the short-term and long-term prognoses (all-cause death, occurrence of ESRD, and infectious complications). Clarifying the factors associated with these clinical outcomes is important for better treatment of patients with AAV. In addition, these factors may differ depending on the patient's age. In clinical settings, physicians often decide the strength of immunosuppressive therapy against AAV according to the patient factors, such as age. However, it is uncertain whether there are differences in the factors associated with prognosis between elderly and non-elderly patients with AAV.

Herein, we aimed to elucidate the clinical factors associated with the short-term prognosis (within 6 months from the start of immunosuppressive therapy) in patients who developed AAV and investigate the differences in the factors associated with prognosis between elderly and non-elderly patients who developed AAV. These findings may contribute to personalised medicine in elderly and non-elderly patients with AAV.

Materials and methods

Study design and patients

This dual-centre, retrospective observational study screened patients who were newly diagnosed with AAV. Since the prognosis, treatment pattern, and frequency of kidney and lung injuries in patients with EGPA are different from those in patients with MPA and GPA (1, 2), patients with EGPA were excluded. Patients with AAV (except for EGPA) who were treated at the Department of Nephrology, Shinshu University Hospital between January 2013 and December 2019 and those who were treated at the Department of Nephrology, Nagano Red Cross Hospital between January 2010 and December 2017 were included. Patients younger than 20 years of age or those who had been treated with immunosuppressive therapy prior to AAV induction therapy were excluded. In addition, patients positive for the anti-glomerular basement membrane (GBM) antibody in addition to ANCA (myeloperoxidase and/or proteinase 3) were excluded because these patients appear to receive stronger immunosuppressive therapy. Of the 95 eligible patients, 16 were excluded because of prior treatment, anti-GBM antibody positivity, drug-induced AAV, and receipt of no treatment. The final analyses included 79 patients; patients who were 75 years or older were defined as elderly (n=41), whereas those who were younger than 75 years of age were defined as non-elderly (n=38) (Fig. 1).

This study was approved by the institutional review board of the ethical committee of Shinshu University School of Medicine (approval number: 4997) and was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for written informed consent was waived because

of the retrospective nature of the study.

Data collection and definitions

Clinical data were collected from patients' medical records. We set the primary outcome as all-cause death within 6 months after the start of immunosuppressive therapy, and the secondary outcome was the development of ESRD and infectious complications within 6 months after the start of immunosuppressive therapy. ESRD was defined as patients who required renal replacement therapy (receiving maintenance dialysis for >30 days or kidney transplantation). Infectious complications were defined as severe conditions requiring antibiotic, antimycotic, and antiviral therapy to treat a bacterial, fungal, or viral infection, respectively. AAV was defined according to the algorithm suggested by Watts *et al*. (7). We categorised each patient as having GPA, MPA, or unclassifiable vasculitis. Diabetes mellitus was defined as a high glycated haemoglobin A1c level (>6.5%), an insulin or hypoglycaemic agent prescription, and/or a history of diabetes mellitus listed in the patient's medical records. Hypertension was defined as an antihypertensive drug prescription and/or a history of hypertension, as described in the medical records. As for the lung lesions, interstitial infiltrates were defined as bilateral interstitial lesions on computed tomography images. Alveolar haemorrhage was defined as haemoptysis and lung abnormalities on computed tomography that corresponded to haemorrhage. Neurological symptoms were defined as numbness and muscle weakness.

The maximum dose of prednisolone (PSL) was adjusted according to the ideal body weight. A high dose of PSL was defined as patients who received more than the median dose of PSL in each group of patients (elderly or non-elderly). In a previous Japanese nationwide study, rapid PSL reduction was defined as a decrease in the necessary daily PSL dose to <20 mg/day within 8 weeks (3). Methylprednisolone pulse therapy consisted of intravenous methylprednisolone (500–1000 mg/day) administered for 3 consecutive days. Cyclophosphamide (CY) was administered intravenously (IVCY). The severity of AAV was evaluated according to the Birmingham vasculitis score 3 (BVAS-3) at the time of hospital admission (8). AAV treatment was performed according to the Japanese guidelines for ANCA-positive, rapidly progressive glomerulonephritis (3).

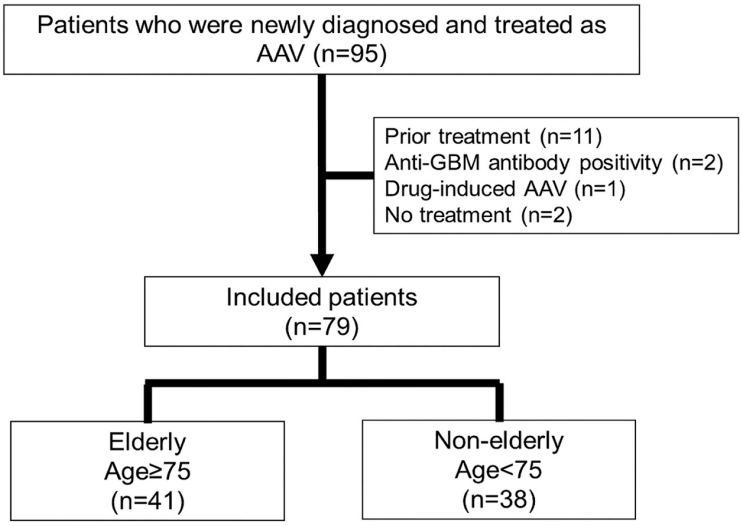

Fig. 1. Study flow chart.
Of the 95 eligible patients, 16 were excluded because of prior treatment (n=11), anti-glomerular basement membrane (GBM) antibody positivity (n=2), drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) (n=1), and receipt of no treatment (n=2). The final analyses included 79 patients; patients who were 75 years or older were defined as elderly (n=41), whereas those who were younger than 75 years of age were defined as non-elderly (n=38).

Blood and urine samples obtained at the time of hospital admission were also evaluated. Proteinuria was defined as a urinary protein level >0.15 g/gCr. Haematuria was defined as a red blood cell sediment count of >5/high-power field. The geriatric nutritional risk index (GNRI), which assesses nutritional status, was calculated using the following formula: 14.89×serum albumin (g/dL)+41.7×body mass index/22 (9). The GNRI was suggested to evaluate the prognosis of elderly inpatients. Actually, GNRI effectively predicts the mortality in patients with ESRD requiring haemodialysis treatment and heart failure (10,11). For risk evaluation, it was classified as follows: major nutrition-related risk (GNRI: <82), moderate nutrition-related risk (GNRI: 82 to <92), and a low nutrition-related risk (GNRI: 92 to ≤98) (9). Serum creatinine based estimated glomerular filtration rate (eGFR) was calculated following previously reported formulas (12).

Statistical analysis

Continuous variables are presented as median and interquartile range, and categorical variables are presented as number (n) and percentage (%). Continuous variables were compared using the Mann-Whitney-U test, and categorical variables were compared using the Fisher exact test. We analysed the association between clinical events such as all-cause death, ESRD, or infectious complications, and clinical factors such as nutritional factors (body mass index, serum albumin, and GNRI), disease severity (BVAS-3, estimated glomerular filtration rate [eGFR], and C-reactive protein level), and treatment pattern (dose of PSL, rapid PSL reduction, methylprednisolone pulse use, cyclophosphamide use, and cyclophosphamide and/or rituximab use) using logistic regression analyses. Statistical significance was set at $P<0.05$. Analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (13), and IBM SPSS Statistics software package v. 26 for Windows (IBM Corp., Armonk, NY, USA).

Results

A comparison of the clinical characteristics between elderly and non-elderly patients is presented in Table I. The

incidence of hypertension was significantly higher in elderly patients than in non-elderly patients (p=0.043). The dose of maximum PSL, frequency of methylprednisolone pulse use, and cyclophosphamide use were significantly lower in elderly patients than in non-elderly patients (p=0.001, p=0.002, p=0.017, respectively). The frequency of rapid decrease of the PSL dose was significantly higher in elderly patients than in non-elderly patients (p=0.023). In addition, kidney biopsy was less frequently performed in elderly patients than in non-elderly patients (p=0.013). In contrast, the clinical classification of AAV, disease severity, laboratory data, and nutritional status were not significantly different between elderly and non-elderly patients with AAV. Although no significant difference in the frequency of double positivity of ANCA was detected between elderly and non-elderly patients who developed AAV (p=0.24), all three patients who had double positivity were elderly (8% of the total patients). Two patients were categorised as unclassifiable and one as microscopic polyangiitis. These three patients were treated by oral prednisolone alone (without methylprednisolone pulse or other immunosuppressant), and their prognosis was good (none resulted in ESRD or death). Table II shows the analyses of the factors associated with all-cause death within 6 months after the start of immunosuppressive therapy in both elderly and non-elderly patients with AAV (Table II). In elderly patients, age was significantly associated with all-cause death (p=0.032), but not in non-elderly patients. In non-elderly patients, the GNRI was significantly associated with all-cause death (p=0.045), but not in elderly patients. Disease severity and treatment patterns were not significantly associated with all-cause death in both elderly and non-elderly patients.

The details of the causes of death are presented in Supplementary Table S1. Infectious complications, complications due to AAV, and cardiovascular diseases were the main causes of death in both elderly and non-elderly patients with AAV.

Table I. Comparison of the clinical characteristics between elderly and non-elderly patients with AAV.

	Elderly (age ≥75 y) n=41		Non-elderly (age <75 y) n=38		p-value
Age (y)	81	78–85	68	64–72	<0.001*
Male sex (n, %)	21	51	19	50	1.00
Body mass index (kg/m^2)	21.8	19.9–23.4	22.1	20.9–24.0	0.22
Systolic BP (mmHg)	131	123–146	129	114–158	0.77
Diastolic BP (mmHg)	74	66–84	73	65–84	0.98
Heart rate (/min)	79	70–86	82	72–91	0.37
Diabetes mellitus (n, %)	11	27	7	18	0.43
Hypertension (n, %)	27	66	16	39	0.043*
History of smoking (n, %)	11	27	8	20	0.30
Malignancy (n, %)	7	17	4	10	0.52
Interstitial pneumonitis (n, %)	19	46	19	50	0.82
Alveolar haemorrhage (n, %)	4	10	5	13	0.73
Neurological disorder (n, %)	5	12	2	5	0.43
Purpura (n, %)	2	5	5	13	0.25
Clinical classification					
GPA (n, %)	1	2	3	8	0.35
MPA (n, %)	34	83	33	80	0.76
Unclassifiable vasculitis (n, %)	6	15	2	5	0.27
Clinical severity (BVAS-3)	16	12-18	16	12-18	0.80
Nutritional status (GNRI)	87.1	80.8–96.6	90.1	80.0–96.3	0.51
Laboratory results					
Albumin (g/dL)	3.0	2.2–3.3	2.9	2.3–3.3	0.93
Blood urea nitrogen (mg/dL)	35.3	24.9–61.4	33.0	18.4–55.9	0.50
Serum creatinine (mg/dL)	2.36	1.21–4.70	2.53	1.01–3.99	0.78
Estimated GFR (mL/min/1.73 m^2)	18.0	9.5–33.5	20.0	10.9–49.7	0.58
C-reactive protein (mg/dL)	5.2	1.0–10.2	4.7	0.7–10.2	0.77
White blood cell count (/μL)	8790	5840–12 600	8145	6310–10 855	0.93
Haemoglobin (g/dL)	9.6	8.2–10.4	10.5	7.9–11.2	0.38
Platelet count (×10^4/μL)	28.4	20.8–35.2	30.9	23.0–40.8	0.43
Haematuria (n, %)	34	83	33	80	0.76
Proteinuria (n, %)	36	88	32	78.0	0.75
Positivity in MPO-ANCA (n, %)	39	95	33	80.0	0.25
Positivity in PR3-ANCA (n, %)	5	12	5	13.0	1.00
Double positivity in ANCA (n,%)	**3**	8	0	0	0.24
Treatment pattern					
PSL (maximum) (mg/kg/day)	0.61	0.53–0.71	0.75	0.61–0.81	0.001*
Rapid PSL dose reduction (n, %)	23	56	11	29	0.023*
PSL alone (n, %)	21	51	6	15	0.001*
mPSL pulse (n, %)	18	44	30	79	0.002*
Cyclophosphamide (n, %)	5	12	14	37	0.017*
Rituximab (n, %)	2	5	4	11	0.42
Plasma exchange (n, %)	4	10	6	16	0.51
TMP-SMX (n,%)	38	93	34	89	0.47
Clinical events					
Kidney biopsy (n, %)	14	34	24	63	0.013*
Steroid diabetes (n, %)	10	24	12	32	0.62
Infectious complications (n, %)	11	27	9	24	0.80
ESRD (n, %)	8	20	8	21	1.00
All-cause death (n, %)	8	20	5	13	0.55

Continuous variables are presented as median and interquartile range, and categorical variables are presented as number (n) and percentage (%). Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared using the Fisher exact test. Differences were considered statistically significant at p<0.05.

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; ANCA: anti-neutrophil cytoplasmic antibody; BP: blood pressure; BVAS-3: Birmingham vasculitis activity score 3; ESRD: end-stage renal disease; GFR: glomerular filtration rate; GNRI: geriatric nutritional risk index; GPA: granulomatous with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; mPSL: methylprednisolone; PR3: proteinase 3; PSL: prednisolone; RIT: rituximab; TMP-SMX: trimethoprim-sulfamethoxazole.

Table II. Factors associated with all-cause death within 6 months after the start of immunosuppressive therapy in both elderly and non-elderly patients with AAV.

	Elderly (age ≥75 y)			Non-elderly (age <75 y)		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.25	1.02–1.54	0.032*	1.02	0.88–1.20	0.76
Male sex	0.25	0.04–1.40	0.11	4.80	0.48–47.7	0.18
Nutritional status						
Body mass index	0.89	0.67–1.18	0.42	0.80	0.58–1.12	0.19
Albumin level	0.40	0.13–1.29	0.13	0.24	0.05–1.12	0.07
Geriatric nutritional risk index	0.93	0.86–1.01	0.07	0.89	0.79–0.99	0.045*
Disease severity						
BVAS-3	1.05	0.89–1.24	0.59	1.14	0.93–1.40	0.21
eGFR	0.94	0.87–1.02	0.12	0.98	0.94–1.02	0.36
C-reactive protein level	1.06	0.94–1.20	0.31	0.96	0.82–1.12	0.61
Treatment pattern						
Median maximum PSL dose	0.57	0.12–2.76	0.48	4.80	0.48–47.7	0.18
Rapid PSL dose reduction	1.39	0.28–6.79	0.69	0.575	0.06–5.81	0.64
mPSL use	0.35	0.06–2.02	0.24	1.08	0.10–11.2	0.95
CY use	1.04	0.10–10.8	0.98	0.39	0.04–3.84	0.42
CY and/or RIT use	0.64	0.07–6.25	0.70	0.26	0.03–2.64	0.26

Differences were considered statistically significant at $p<0.05$.
AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; BVAS-3: Birmingham vasculitis activity score 3; CY: cyclophosphamide; eGFR: estimated glomerular filtration rate; mPSL: methylprednisolone; PSL: prednisolone; RIT: rituximab.

Table III demonstrates the analyses of the factors associated with the occurrence of ESRD within 6 months after the start of immunosuppressive therapy in both elderly and non-elderly patients with AAV. Nutritional factors and treatment patterns were not significantly associated with ESRD in both elderly and non-elderly patients. However, the BVAS-3 and eGFR (indicators of disease severity) before the start of the treatment were significantly associated with the occurrence of ESRD in elderly patients (p=0.020, p=0.017, respectively). The eGFR before the start of treatment was also significantly associated with the occurrence of ESRD in non-elderly patients (p=0.035). Thus, the eGFR before the start of treatment was an important factor that may predict renal prognosis. Receiver operating analyses indicated a cut-off value of the eGFR that predicted ESRD. In elderly patients, an eGFR <14.6 mL/min/1.73 m^2, which was calculated by the Youden index, predicted the occurrence of ESRD (area under the curve [AUC]: 0.905 [95% confidence interval 0.813–0.998], sensitivity: 1.000, specificity: 0.788). In non-elderly patients, an eGFR <11.4 mL/min/1.73 m^2, calculated by the Youden index, predicted the occurrence of ESRD (AUC: 0.975 [95% confidence interval 0.933–0.999], sensitivity: 1.000, specificity: 0.867) (Suppl. Fig. S2a, b).

Table IV shows the analysis of the factors associated with the occurrence of infectious complications within 6 months after the start of immunosuppressive therapy in both elderly and non-elderly patients with AAV. In elderly patients, the BVAS-3 and eGFR (indicators of disease severity), methylprednisolone pulse use, and cyclophosphamide use were significantly associated with the occurrence of infectious complications (p=0.018, p=0.049, p=0.032, p=0.019, respectively). However, factors other than the serum albumin level (p=0.045) were not significantly associated with the occurrence of infectious complications in non-elderly patients. The details of the infectious complications were similar in both the elderly and non-elderly patients (Suppl. Table S2).

Concerning the association between infectious complication and TMP/SMX treatment, a previous study has demonstrated the importance of TMP/SMX for the prevention of infectious complications (14, 15). However, no significant association was detected between infectious complication and the primary use of TMP/SMX in non-elderly patients (odds ratio: 0.92, 95% confidence interval: 0.08-10.2, p=0.95). As for the elderly patients, because of the separation of the events in elderly patients, logistic regression analyses could not statistically evaluate the results (all of the patients who developed infectious complications received TMP/SMX treatment). Concerning the dose of TMP/SMX in the current study, the following kinds of prophylactic TMP/SMX doses were prescribed: TMP: 160 mg/SMX: 800 mg /day, TMP: 160 mg/SMX: 800 mg /every other day, TMP: 160 mg/SMX: 800 mg /twice a week, TMP: 80 mg/SMX: 400 mg /day, TMP: 80 mg/SMX: 400 mg /every other day, TMP: 80 mg/SMX: 400 mg /three times a week, TMP: 80 mg/SMX: 400 mg / twice a week, TMP: 40 mg/SMX: 200 mg /day. Because, in general, prophylactic TMP/SMX dose was recommended that TMP: 80 mg/SMT: 400 mg to TMP: 160 mg/SMT: 800 mg daily or TMP: 160 mg/SMT: 800 mg / three times per week (14). We divided patients in the current study into two groups (Group A and B) according to the dose of TMP/ SMX. A) Standard-dose TMP/SMX group: patients who received TMP: 160 mg/SMT: 800 mg / day, TMP: 160 mg/SMT: 800 mg /every other day, TMP: 160 mg/SMT: 800 mg /twice a week, and TMP: 80 mg/SMT: 400 mg /day, B) reduced or without TMP/SMX group: patients who received TMP: 80 mg/SMT: 400 mg / every other day, TMP: 80 mg/SMT: 400 mg /three times a week, TMP: 80 mg/SMT: 400 mg /twice a week, TMP: 40 mg/SMT: 200 mg /day, and without TMP/SMX (details are presented in Suppl. Table S3). We then investigated the association between the dose of TMP/SMX and pulmonary/ear-nose-throat (ENT) super-infections or all infectious complications within six months. As a result, the dose of TMP/SMX was not significantly associated with the development of both pulmonary/ENT infections or all infectious complications within six months in elderly (p=0.13 and p=0.55, respectively) and non-elderly (p=0.55 and p=0.18, respectively) (Suppl. Table S4).

Table III. Factors associated with the occurrence of ESRD within 6 months after the start of immunosuppressive therapy in both elderly and non-elderly patients with AAV.

	Elderly (age ≥75 y)			Non-elderly (age <75 y)		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	0.91	0.74–1.11	0.34	0.96	0.86–1.07	0.48
Male sex	1.77	0.36–8.65	0.48	0.26	0.04–1.48	0.13
Nutritional status						
Body mass index	0.92	0.70–1.20	0.52	0.96	0.77–1.19	0.68
Albumin level	0.78	0.26–2.39	0.67	1.18	0.35–4.03	0.79
Geriatric nutritional risk index	0.97	0.91–1.04	0.46	1.00	0.94–1.06	0.96
Disease severity						
BVAS-3	1.42	1.06–1.91	0.020*	1.12	0.95–1.33	0.17
eGFR	0.79	0.66–0.96	0.017*	0.47	0.23–0.95	0.035*
C-reactive protein level	1.05	0.93–1.18	0.44	0.87	0.73–1.05	0.14
Treatment pattern						
Median maximum PSL dose	2.00	0.41–9.78	0.39	1.90	0.38–9.44	0.43
Rapid PSL reduction	0.74	0.16–3.47	0.70	3.29	0.65–16.7	0.15
mPSL use	2.56	0.52–12.6	0.25	2.13	0.22–20.4	0.51
CY use	3.33	0.46–24.4	0.24	0.19	0.02–1.71	0.14
CY and/or RIT use	4.35	0.74–25.6	0.10	0.13	0.01–1.14	0.07

Differences were considered statistically significant at $p<0.05$.
AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; BVAS-3: Birmingham vasculitis activity score 3; CY: cyclophosphamide; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; mPSL: methylprednisolone; PSL: prednisolone; RIT: rituximab.

Table IV. Factors associated with the occurrence of infectious complications within 6 months after the start of immunosuppressive therapy in both elderly and non-elderly patients with AAV.

	Elderly (age ≥75 y)			Non-elderly (age <75 y)		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.03	0.88-1.21	0.71	0.99	0.88-1.10	0.81
Male sex	0.73	0.18-2.92	0.66	0.41	0.08-1.95	0.26
Nutritional status						
Body mass index	1.11	0.88-1.39	0.38	1.06	0.87-1.29	0.55
Albumin level	0.67	0.24-1.82	0.43	0.27	0.07-0.97	0.045*
Geriatric nutritional risk index	0.99	0.93-1.06	0.83	0.96	0.90-1.03	0.25
Disease severity						
BVAS-3	1.33	1.05-1.69	0.018*	1.19	0.99-1.43	0.06
eGFR	0.92	0.85-1.00	0.049*	0.97	0.93-1.01	0.12
C-reactive protein	1.04	0.94-1.17	0.44	1.02	0.92-1.13	0.75
Treatment pattern						
Median maximum PSL dose	1.37	0.34-5.49	0.66	0.75	0.17-3.36	0.70
Rapid PSL dose reduction	0.92	0.23-3.68	0.90	1.31	0.26-6.55	0.74
mPSL use	5.33	1.16-24.6	0.032*	2.55	0.27-24.1	0.42
CY use	16.6	1.59-172	0.019*	0.41	0.07-2.30	0.31
CY and/or RIT use	5.14	0.93-28.5	0.06	0.54	0.11-2.56	0.44

Differences were considered statistically significant at $p<0.05$.
AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; BVAS-3: Birmingham vasculitis activity score 3; CY: cyclophosphamide; eGFR: estimated glomerular filtration rate; mPSL: methylprednisolone; PSL: prednisolone; RIT: rituximab.

The duration of the TMP/SMX treatment in both elderly and non-elderly patients is presented in Supplementary Table S5. Next, we investigated the association between the duration of TMP/SMX (full length of TMP/SMX treatment: more than six months or total follow-up period) and pulmonary/ENT super-infections or all infectious complications within six months. As a result, in non-elderly patients, duration of TMP/SMX treatment was significantly associated with the development of pulmonary/ENT super-infections within six months (p=0.034) (Suppl. Table S6). On the other hand, because of the separation of the events in elderly patients, logistic regression analyses could not statistically evaluate the results (all the patients who developed pulmonary/ENT super-infections or all infectious complications received full length of the TMP/SMX treatment).

Discussion

In the current study, the factors associated with each clinical event (all-cause death, ESRD, and infectious complications) were different between elderly and non-elderly patients. Age was significantly associated with all-cause death in elderly patients, whereas the GNRI was significantly associated with all-cause death in non-elderly patients. The eGFR before the start of immunosuppressive therapy was significantly associated with the occurrence of ESRD in both elderly and non-elderly patients with AAV. The eGFR and BVAS-3 (indicators of disease severity) and methylprednisolone pulse use were associated with infectious complications in elderly patients with AAV. It is thought that the patients who presented with severe disease activity (including severe kidney dysfunction) tended to be treated with strong immunosuppressive therapy such as methylprednisolone pulse therapy, cyclophosphamide, or rituximab. However, in non-elderly patients with AAV, although the serum albumin level was associated with the occurrence of infectious complications, disease activity or treatment patterns were not associated. Thus, in non-elderly patients with AAV, nutritional conditions may be influenced by clinical events such as all-cause death and the occurrence of infectious complications.

In non-elderly patients with AAV, although disease activity and treatment patterns were not significantly associated with clinical events, nutritional factors were significantly associated with clinical events. Concerning the mortality at six months, Monti *et al.* have reported that 1.49% of the deaths were observed in younger onset patients (<65 years), while 4.8% were seen in older onset patients (≥ 65 years)

(16). Age, impaired renal function, and respiratory failure were significantly associated with mortality (16). Ni *et al*. have reported that survival rate at six months was 88.6%, and older age, (≥ 65 years), high leukocyte counts, high BVAS, infection, and a low serum albumin level were significantly associated with the mortality at six months (17). Harris *et al*. have reported that the comorbidity score is a significant predictive factor for early mortality (< 90 days) (18). Itabashi *et al*. have reported that survival rate at six months after onset of AAV was 84.8%, and the PR-3 ANCA positivity and BVAS at one and three months were independent risk factors influencing survival time (19). In the current study, the survival rate in elderly patients with AAV at six months was 80%, and was 87% in the non-elderly. These results were similar to previous studies. The only factors that significantly associated with the mortality in elderly patients was age and in non-elderly patients was GNRI. A few studies have investigated the relationship between nutritional factors and the prognosis of patients with AAV (20, 21). Ahn *et al*. conducted two studies. One retrospective observational study in Korea indicated that the controlling nutritional status score (calculated by the serum albumin level, lymphocyte count, and total cholesterol level) was associated with all-cause mortality but not ESRD (20). Another study suggested that the prognostic nutritional index (calculated by the serum albumin level and lymphocyte count) was significantly associated with disease severity and relapse (21). The population of these studies was younger than that in our study (the median age of the former study was 56.6 years and that of the latter study was 55.2 years). These results were similar to those of our study, and nutritional evaluation may be a complementary tool for evaluating the prognosis of non-elderly patients who develop AAV. However, nutritional factors were not significantly associated with clinical outcomes in elderly patients. Significant correlation between age and GNRI was detected in elderly patients (Spearman's rank correlation coefficient, rs=-0.386, p=0.013), while no correlation was detected in non-elderly patients (Spearman's rank correlation coefficient, rs=-0.189, p=0.26). In short, it is thought that age is strongly associated with GNRI in elderly patients than in non-elderly.

Regarding the renal prognosis, an eGFR <14.6 mL/min/1.73 m^2 in elderly patients and an eGFR <11.4 mL/min/1.73 m^2 in non-elderly patients carried a high risk of the development of ESRD. Ni *et al*. have reported that renal survival rate at six months from onset of AAV was 72.9%, and eGFR, BVAS, and daily urine protein levels were significantly associated with the development of ESRD (17). In the current study, the renal survival rate in elderly patients with AAV at six months was 80% and in non-elderly was 79%. The factors that significantly associated with the renal prognosis in elderly patients were BVAS and eGFR and those in non-elderly was only eGFR. These results were similar to those reported by previous study. Previous studies have suggested that the evaluation of kidney biopsy specimens and the combined evaluation of kidney tissue with the eGFR are reliable methods that can appropriately evaluate the possibility of the recovery of kidney function or renal prognosis (22-26). However, as our study showed, not all patients were able to undergo a kidney biopsy, particularly the elderly patients with AAV (only 34% of elderly patients underwent a kidney biopsy, as shown in Table 1). In cases that cannot be evaluated by a kidney biopsy, the eGFR before the start of immunosuppressive therapy may be a useful marker to evaluate renal prognosis. In patients who presented with a severely decreased eGFR, recovery or maintenance of kidney function may be difficult despite strong immunosuppressive therapy. The cut-off value suggested in the current study was similar between the elderly and non-elderly patients. In addition, the cut-off value of the eGFR was similar to that in a previous study (24). However, not all patients who presented with a severely decreased eGFR did not recover or maintain their kidney function. Therefore, biomarkers that can identify patients who respond well to treatment in terms of kidney function will be desirable, and clinical physicians should carefully decide the strength of immunosuppressive therapy in AAV patients with a severely decreased eGFR.

Concerning to the infectious complications in AAV patients, previous studies have reported that 26 to 46% of the patients with AAV develop severe infectious complications (27, 28). Mohammad *et al*. have reported that only age at the time of diagnosis of AAV was associated with severe infection (28). In the current study, incidence of infectious complications in elderly patients was 27% and that in non-elderly was 24% at six months from onset of AAV. The factors that significantly associated with development of infectious complications within six months in elderly patients was BVAS, eGFR, mPSL use, and CY use and those in non-elderly was low level of serum albumin. There were only small number of patients who were treated with rituximab in the current study (two patients were in the elderly patients' group, and four patients were in the non-elderly group). In addition, in our data set, the use of rituximab was seen as gradually increasing with time, and most patients who were treated with rituximab were non-elderly. We will need to accumulate elderly cases of AAV who were treated with rituximab. Because methylprednisolone pulse use and cyclophosphamide use in elderly patients were significantly associated with the occurrence of infectious complications, clinicians should pay attention when prescribing strong immunosuppressive therapy that includes these treatments. Concerning the IVCY treatment, there were five patients who were treated with IVCY in the elderly patient group. Three patients were treated with 500 mg doses of IVCY, and two with 300 mg doses, while the median dose of IVCY in the non-elderly patient group was 700 mg, the range was 500 to 1000 mg. Thus, in the current study, the dose of IVCY was less in elderly than in non-elderly patients, and the dose of IVCY in elderly patients was almost the same or slightly less than the sug-

gestion by the CORTAGE study that recommended fixed low-dose IVCY in elderly patients (29).

Concerning the TMP/SMX prophylactic treatment, the prophylactic dose of TMP/SMX should be decreased for patients who developed kidney dysfunction or have an overall small body size (14). In the current study, the dosage was decided by the treating physicians based on the patients' kidney function (eGFR), height, and body weight. Since the dose of TMP/SMX was not significantly associated with the infectious complications in the current study, appropriate reduction of the TMP/SMX dosage may not have influenced the infectious complications in both elderly and non-elderly patients with AAV. However, it is possible that the duration of the TMP/SMX treatment in non-elderly patients is important to prevent pulmonary/ENT superinfections.

There are several limitations to the current study. First, there were small numbers of patients in the study groups, and we could not perform multivariate analyses adjusted for confounding factors. Second, the current study was a short observational study performed over 6 months; thus, it is possible that factors associated with all-cause death, ESRD, and infectious complications are different between short-term and long-term observations. The frequency of infectious complications differs between short-term and long-term observations (4, 5, 30). In short, we did not assess the long-term prognosis and its associated factors, including maintenance therapy. These are future challenges. Third, it is possible that the treatment strategy is not always unified in a retrospective manner. However, most of the physicians in the faculties that belonged to the current study treated the patients in accordance with the Japanese guidelines for rapid glomerulonephritis due to AAV.

Conclusions

In conclusion, the factors associated with all-cause death and infectious complications were different in elderly and non-elderly patients. In elderly patients, circumspection will be needed at the time of the assessment of disease activity, particularly in cases with a severely decreased eGFR, and when deciding the strength of immunosuppressive therapy, such as methylprednisolone pulse and cyclophosphamide therapy. In non-elderly patients, nutritional factors such as the GNRI and serum albumin levels may be useful markers for assessing the risk of all-cause death and infectious complications, respectively.

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