

Initial high-dose corticosteroids and renal impairment are risk factors for early severe infections in elderly patients with antineutrophil cytoplasmic autoantibody-associated vasculitis

A retrospective observational study

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Abstract

Recent large observational studies of antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV) show that severe infection is a major cause of death and that the majority of infections occur during the early phase of initiating remission-induction therapy. Many risk factors for severe infection have been suggested, but these have been inconsistent. Nevertheless, infectious risk factors in elderly patients with AAV have not been adequately investigated in previous studies.

In this retrospective observational study, we examined potential predictors of severe infection within 90 days (early severe infections) after remission-induction therapy in patients with AAV aged 65 years or older. We included 167 consecutive elderly patients with AAV admitted to our hospital. Data from medical history and remission-induction therapy were analyzed for predictive risk factors associated with early severe infections. The relationship between initial doses of corticosteroids and cumulative incidence of severe infections was also analyzed. A multivariate analysis of risk factors for early severe infections was performed using logistic regression analysis. The Kaplan–Meier method was used to estimate the overall survival, and the log-rank test was used to evaluate the differences between patients with and without early severe infections. Gray method was used to compare the cumulative incidence of severe infections in patients who did and did not receive initial high-dose corticosteroids.

Logistic regression analysis showed that initial high-dose corticosteroid administration (prednisolone ≥ 0.8 mg/kg/d) (odds ratio [OR] 3.86, $P = .030$) and serum creatinine levels at diagnosis ≥ 1.5 mg/dL (OR 5.13, $P = .003$) were independent predictors of early severe infection although administration of cyclophosphamide or rituximab was not. The cumulative incidence of severe infections was also significantly higher in patients who received initial high-dose corticosteroids ($P = .042$), and patients with early severe infections exhibited a high mortality rate within 6 months ($P < .001$).

Our findings suggest that initial high-dose corticosteroids and renal impairment at diagnosis are associated with a higher risk of early severe infections and early death in elderly patients with AAV.

Abbreviations: AAV = antineutrophil cytoplasmic autoantibody-associated vasculitis, ANCA = antineutrophil cytoplasmic autoantibody, AZA = azathioprine, BVAS = Birmingham vasculitis activity score, CKD = chronic kidney disease, CMV = cytomegalovirus, CYC = cyclophosphamide, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, EGPA = eosinophilic granulomatosis with polyangiitis, FFS = five factor score, GPA = granulomatosis with polyangiitis, MPA = microscopic polyangiitis, MPSL = methylprednisolone, MTX = methotrexate, RLV = renal-limited vasculitis, RTX = rituximab.

Keywords: age, antineutrophil cytoplasmic autoantibody, corticosteroids, elderly, infection, mortality, vasculitis

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1. Introduction

Combined immunosuppressive therapy with corticosteroids and cyclophosphamide (CYC) has improved the prognosis for patients with antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV). Rituximab (RTX) has also provided high remission rates and low relapse rates, equal to CYC.^[1,2] Despite these advances in treatment, the mortality rate for patients with AAV remains higher than that for age- and sex-matched persons in the general population.^[3] Recent large observational studies have shown that severe infection is a major cause of death, more so than active vasculitis, and 38% to 73% of infectious episodes occur within the first 2 to 6 months of initiating remission-induction therapy.^[4–8] Moreover, infectious episodes have been reported to be independent risk factors for death in some studies of AAV.^[4,5,8–10] Based on the results of these studies, there is a strong correlation between mortality and severe infections in the early phase of treatment.

Many risk factors for severe infection have been suggested, including older age, female sex, renal impairment at the time of diagnosis, high disease activity, pulmonary involvement, severe lymphopenia during treatment, and a therapeutic regimen including CYC and RTX.^[4–7,9–14] However, the parameters for severe infection and follow-up periods have varied between studies, and risk factors were inconsistent between each report. In addition, few studies focused on the risk factors for severe infections in the early phase of treatment, especially regarding initial doses of corticosteroids in elderly patients with AAV.

The purpose of this study was to identify the potential predictors of severe infections in the early phase of treatment and to investigate the relationship between initial doses of corticosteroid and severe infection in elderly patients with AAV.

2. Methods

2.1. Study population

We enrolled 313 consecutive patients based on the International Classification of Diseases diagnostic codes assigned during their inpatient stay at the Kurashiki Central Hospital between January 2006 and January 2019. We screened patients who were hospitalized with AAV, as well as newly diagnosed cases, and collected the data retrospectively.

All patients were diagnosed and classified according to the European Medicines Agency algorithm into microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and unclassified AAV.^[15] Clinical manifestations and laboratory data were recorded at the time of diagnosis.

ANCA-negative patients who had necrotizing vasculitis in small or middle caliber vessels and who satisfied the clinical characteristics of AAV were also included. Patients with secondary vasculitis were excluded from this study. Patients who died within 1 week after diagnosis were also excluded, since it is usually difficult to identify whether these patients had infections as part of their critical condition, and the impact of treatment was unclear.

Finally, 167 patients were included in this retrospective observational cohort study. Our research was performed according to the principles set forth in the Declaration of Helsinki and was approved by the ethics committee of our hospital (approval number 3128). Informed consent was obtained from all participants.

2.2. Data collection and definitions

Patient data were recorded at each follow-up visit and collected from medical records until loss to follow-up or completion of follow-up. The date of diagnosis was defined as the day that remission-induction therapy was started. Past history of lung diseases was defined as chronic lung damage (eg, chronic obstructive pulmonary disease, bronchiectasis, and interstitial pneumonia) at least 6 months before the date of diagnosis; past history of heart disease was defined as chronic myocardial dysfunction (eg, congestive heart failure, acute myocardial infarction, moderate or severe cases of valvular heart disease, and chronic myocarditis) at least 6 months before the date of diagnosis. History of chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m² at least 6 months before the date of diagnosis. The eGFR was calculated according to the Japanese eGFR equation based on standardized serum creatinine levels.^[16] The Birmingham vasculitis activity score (BVAS) at the time of diagnosis was calculated according to BVAS version 3, and pulmonary and renal involvement were also scored according to the BVAS.^[17] Indirect immunofluorescence or antigen-specific enzyme-linked immunosorbent assay tests were used to detect ANCA. The data that support the findings of this study are available from the corresponding author upon reasonable request.

We defined “severe infections” as viral, bacterial, or fungal infections requiring hospitalization or intravenous antibiotics and “early severe infections” as severe infections occurring within 90 days of treatment onset. Disseminated herpes zoster recurrences, pneumocystis pneumonia, cytomegalovirus (CMV) hepatitis, gastrointestinal infections with CMV, mycobacterium tuberculosis, expanded nontuberculous mycobacterium infection, and febrile neutropenia were also counted as severe infections because they may cause significant disability. The first episode of early severe infection and severe infection after 90 days were recorded in each patient. None of the patients had received any immunosuppressive therapy before the diagnosis of AAV. Remission-induction therapy included oral or intravenous CYC, RTX, mycophenolate mofetil, methotrexate (MTX), azathioprine (AZA), calcineurin inhibitors, intravenous immunoglobulin, and plasma exchange, in addition to corticosteroids. Other immunosuppressants (including CYC or RTX), in addition to corticosteroids, were administered at the discretion of each physician. In general, initial doses of corticosteroids were continued for 2 weeks, with gradual tapering every 2 weeks to 5 to 10 mg/d of prednisolone (or equivalent).

We analyzed the risk factors for early severe infections in this cohort. Patient characteristics and overall survival rates within 6 months were compared between the patients with, and those without, early severe infections. To evaluate the impact of initial doses of corticosteroids on overall severe infections, we also compared the cumulative incidence of severe infections between the patients who received initial high-dose corticosteroid (prednisolone \geq 0.8 mg/kg/d) and those who did not. Different types of corticosteroids were converted to equivalent doses of prednisolone, as some patients were prescribed dexamethasone rather than prednisolone.

2.3. Statistical analyses

Differences between the groups were analyzed using the Mann-Whitney *U* test for nonparametric data and the Chi-square or Fisher exact test for categorical data. All analyses excluded patients

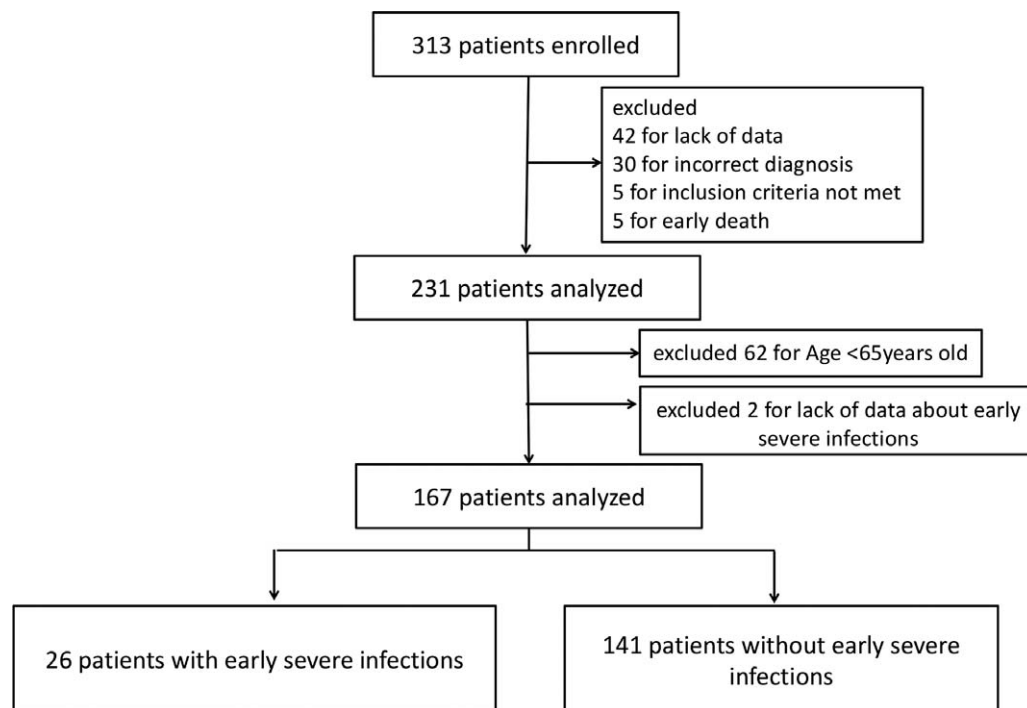


Figure 1. Flow diagram of patient selection. Patients were selected retrospectively based on the International Classification of Diseases diagnostic codes assigned during their inpatient stay at our hospital. In total, 146 patients were excluded due to lack of data, inadequate inclusion criteria, early death, incorrect diagnosis, or if younger than 65 years old. Finally, 167 patients were included and categorized into 2 groups, according to the occurrence of severe infections within 90 days of starting treatment.

with missing data. The Kaplan–Meier method was used to estimate the overall survival, and the log-rank test was used to evaluate the differences between the groups. Censoring was performed on the day of loss to follow-up or completion of follow-up. A multivariate analysis of risk factors for early severe infections was performed using a logistic regression analysis. A receiver operating characteristic curve analysis was performed to determine the threshold for renal impairment at diagnosis. The following variables were assessed as potential risk factors for early severe infections: BVAS ≥ 20 , renal impairment at the time of diagnosis, receipt of initial high-dose corticosteroids, revised five factor score (revised FFS), and receipt of CYC or RTX. These variables were selected with reference to previous studies.^[4–14] To assess for the presence of collinearity, we calculated the variance inflation factor and conservatively classified values of ≥ 5 as suggestive of collinearity. The cumulative incidence of severe infections in patients who received initial high-dose corticosteroids and those who did not was compared using Gray method, considering death without severe infections as a competing risk.^[18] The differences were considered significant if the 2-tailed P value was $< .05$. All analyses were performed using R statistical software (3.1.1).

3. Results

3.1. Demographics

Of the total of 313 patients that were enrolled in this cohort study, 42 were excluded because of insufficient data (unknown involved organ at the time of diagnosis or unclear treatment regimen for remission-induction therapy); 5 were excluded owing to inadequate inclusion criteria (mainly ANCA-negative and

unproven necrotizing vasculitis); 5 were excluded owing to death within 1 week after diagnosis; 30 were excluded owing to incorrect diagnoses; 2 were excluded owing to lack of data concerning early severe infections; and 62 were excluded as their age at diagnosis was under 65 (Fig. 1). Finally, 167 patients were included in the study, of whom 115 were diagnosed with MPA, 30 with GPA, 16 with EGPA, and 6 with unclassified AAV. No patients with classic polyarthritis nodosa were identified.

The patient data at baseline are described in Table 1. All patients received corticosteroids. In addition to corticosteroids, 42 patients were treated with CYC (36 with intravenous CYC and 6 with oral CYC) and 10 with RTX. In addition, 15 patients were treated with AZA, 1 with MTX, 12 with plasma exchange, and 1 with 1 dose of intravenous CYC (not included as having received CYC or RTX). In total, 100 patients were treated with corticosteroids alone.

Patients with early severe infections, compared to those without, had a higher prevalence of CKD history ($P = .032$), BVAS ≥ 20 ($P = .021$), serum CRP levels at diagnosis (10.2 ± 7.7 vs 7.4 ± 5.8 mg/dL, $P = .037$), serum creatinine levels at diagnosis (median 2.37 vs 0.97 mg/dL, $P = .012$), and higher FFS/revised FFS at diagnosis ($P = .037$, $P = .003$, respectively). The initial doses of corticosteroids and the prevalence of CYC or RTX administration were significantly higher in patients with early severe infections ($P = .003$, and $P = .036$, respectively) although the prevalence of methylprednisolone pulse therapy administration was not significantly different between the 2 groups ($P = .671$). Interestingly, early severe infections had a significant association with severe infections after 90 days ($P = .012$) (Table 1). Details of the patients with early severe infections are listed in the Supplemental Table, <http://links.lww.com/MD/D829>.

Table 1**Patient characteristics.**

	Patients with early severe infections (n = 26)	Patients without early severe infections (n = 141)	P-value
Sex, n (%)			.132
Women	11 (42.3)	84 (59.6)	
Men	15 (57.7)	57 (40.4)	
Age at diagnosis, mean ± SD	77.7 ± 5.0	76.9 ± 6.4	.507
Past history of smoking, n (%)	11 (42.3)	54 (44.6)	.861
Past history of lung disease, n (%)	10 (38.5)	64 (46.4)	1.000
Past history of CKD, n (%)	10 (40.0)	24 (18.5)	.032
Past history of DM, n (%)	2 (7.7)	22 (16.1)	.373
Past history of heart disease, n (%)	6 (23.1)	20 (14.5)	.257
ANCA, n (%)			.307
MPO-ANCA/p-ANCA	23 (88.5)	119 (84.4)	
PR3-ANCA/c-ANCA	3 (11.5)	9 (6.4)	
Both negative	0	12 (8.5)	
Type of AAV, n (%)			.514
MPA	21 (80.8)	94 (66.7)	
GPA	3 (11.5)	27 (19.1)	
EGPA	1 (3.8)	15 (10.6)	
unclassified	1 (3.8)	5 (3.5)	
BVAS* mean ± SD	15.9 ± 6.0	14.0 ± 5.6	.124
BVAS* ≥ 20, n (%)	9 (34.6)	20 (14.2)	.021
CRP mg/dL mean ± SD	10.2 ± 7.7	7.4 ± 5.8	.037
Serum creatinine mg/dL, median [IQR]	2.37 [0.98–3.99]	0.97 [0.64–3.04]	.012
FFS† mean ± SD	1.3 ± 1.0	0.9 ± 0.9	.037
Revised FFS† mean ± SD	2.6 ± 0.6	2.1 ± 0.8	.003
Renal involvement, n (%)	19 (73.1)	86 (61.0)	.276
Pulmonary involvement, n (%)	16 (61.5)	62 (44.0)	.134
Initial doses of CS mg/d [‡] mean ± SD	48.5 ± 15.6	40.3 ± 12.3	.003
Initial doses of CS/Weight mg/kg/d [‡] mean ± SD	0.94 ± 0.2	0.77 ± 0.2	< .001
Initial doses of CS/Weight ≥ 0.8 mg/kg/d [‡] , n (%)	19 (73.1)	62 (44.0)	.008
MPSL pulse therapy, n (%)	15 (57.7)	73 (51.8)	.671
Received CYC or RTX, n (%)	13 (50.0)	39 (27.7)	.036
Received HD, n (%)	4 (15.4)	18 (12.8)	.754
Severe infections after 90 d, n (%)	9 (60.0)	30 (24.6)	.012

Interquartile range (IQR): data were median [1st quartile to 3rd quartile].

AAV = antineutrophil cytoplasmic autoantibody-associated vasculitis, ANCA = anti-neutrophil cytoplasmic antibody, BVAS = Birmingham vasculitis activity score, CKD = chronic kidney disease, CRP = C-reactive protein, CS = corticosteroids, CYC = cyclophosphamide, DM = diabetes mellitus, EGPA = eosinophilic granulomatosis with polyangiitis, GPA = granulomatosis with polyangiitis, HD = hemodialysis, MPA = microscopic polyangiitis, MPO = myeloperoxidase, MPSL = methylprednisolone, p = perinuclear, R3 = proteinase-3, RTX = rituximab, SD = standard deviation.

* BVAS = Birmingham vasculitis activity score version 3.^[17]

† FFS = 5 factor scores reported in 1996,^[19] and revised FFS = the revised five factor scores reported in 2009.^[20]

‡ Different types of corticosteroid were converted to equivalent doses of prednisolone.

3.2. Risk factors for early severe infections and long-term impact of initial high-dose corticosteroids on overall severe infections

According to previous studies, the following variables were assessed as potential risk factors for early severe infections and were included as variables for the multivariate analysis: BVAS ≥ 20, renal impairment (Cr ≥ 1.5 mg/dL) at the time of diagnosis, administration of initial high-dose corticosteroids, revised FFS, and administration of CYC or RTX.^[4–14] Multivariate analysis showed that initial high-dose corticosteroids (≥ 0.8 mg/kg/d) (odds ratio [OR] 3.86; 95% confidence interval [CI]: 1.14–13.10; *P* = .030) and serum creatinine levels ≥ 1.5 mg/dL (OR 5.13; 95% CI: 1.75–15.00; *P* = .003) were independent prognostic factors for early severe infections. By contrast, higher BVAS (≥ 20) at diagnosis (OR 1.52; 95% CI: 0.52–4.46; *P* = .449), revised FFS ≥ 2 at diagnosis (OR 1.28; 95% CI: 0.53–3.13; *P* = .582), and administration of CYC or RTX in addition to corticosteroids were not significant risk factors for early severe infections (OR 1.76; 95% CI: 0.57–5.40; *P* = .322) (Table 2).

Collinearity diagnostics did not identify any variables with a variance inflation factor ≥ 5. Cumulative incidences of severe infections were significantly higher in the patients who received initial high-dose corticosteroids (*P* = .042) (Fig. 2).

Table 2**Risk factors affecting early severe infections.**

Risk factor	Odds ratio	95% CI	P-value
BVAS* ≥ 20	1.52	(0.52–4.46)	.449
Initial dose of corticosteroids/weight ≥ 0.8 mg/kg/d	3.86	(1.14–13.10)	.030
Revised FFS† ≥ 2	1.28	(0.53–3.13)	.582
Serum creatinine ≥ 1.5 mg/dL	5.13	(1.75–15.00)	.003
Received CYC or RTX‡	1.76	(0.57–5.40)	.322

* BVAS = Birmingham vasculitis activity score version 3.^[17]

† Revised FFS = the revised five factor scores reported in 2009.^[20]

‡ CYC = cyclophosphamide, RTX = rituximab.

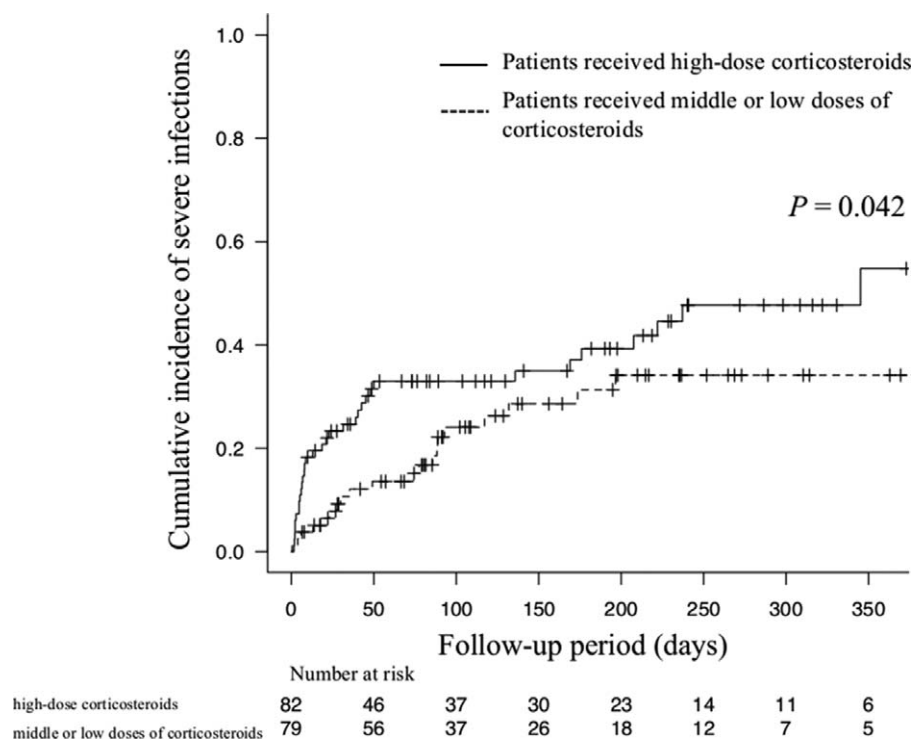


Figure 2. Cumulative incidences of severe infections in patients who received initial high-dose corticosteroids and those who did not. Cumulative incidences of severe infections were significantly higher in patients who received initial high-dose corticosteroids, considering death without severe infections as a competing risk ($P = .042$).

3.3. Etiologies of early severe infections

We identified 26 early severe infections and 67 severe infections during follow-up. Nine patients had both early and late severe infections after 90 days. Early severe infections included bacterial and viral pneumonias ($n=9$), sepsis of unknown origin ($n=3$), diverticulitis ($n=1$), skin and soft tissue infections ($n=2$), biliary tract infections ($n=1$), CMV infections ($n=5$), disseminated herpes zoster recurrences ($n=2$), pneumocystis pneumonia ($n=1$), and fungal infections ($n=2$).

3.4. Mortality and cause of death

In the total cohort, the mean follow-up period was 28 months (range, 0–166 months). During follow-up, 36 patients (21.3%) died, and the cumulative proportions of survival at 1, 3 and 5 years were 0.858 (95% CI: 0.793–0.903), 0.839 (95% CI: 0.770–0.889), and 0.738 (95% CI: 0.637–0.815), respectively. The most frequent causes of death were infection (14 patients) and active vasculitis (8 patients). Of the 26 patients with early severe infections, 13 died during follow up, 8 from infections, 3 from active vasculitis, and 2 from unknown causes (see Supplemental Table, <http://links.lww.com/MD/D829>). The patients with early severe infections exhibited a significantly higher mortality rate at 6 months than those without ($P < .001$) (Fig. 3).

4. Discussion

Our study revealed several important findings. First, severe infections in the early phase of treatment were significantly associated with early mortality in elderly patients with AAV. Second, initial high-dose corticosteroids and renal impairment at

diagnosis were predictive risk factors for early severe infections. This association was independent of the severity of vasculitis and administration of CYC or RTX. Finally, initial high-dose corticosteroids were associated with later severe infections during follow-up.

These results are in keeping with previous studies indicating that therapy-associated infection is an independent risk factor for death in patients with AAV. Little et al reported that half the infections occurred within the first 2 months.^[5] They also reported that infections and episodes of leucopenia (mainly as a side effect of CYC) were risk factors for death within the first year. Lai et al also reported that secondary infections were independent predictors of 1-year mortality in Chinese patients with AAV in their study.^[4] All their patients received corticosteroids with CYC, and 70.9% of infections occurred within the first 3 months after the initial treatment. This evidence led us to consider that CYC administration in the early phase of treatment may be associated with severe and fatal infections. However, most of these previous studies did not consider the effect of corticosteroid doses, and it is unclear which immunosuppressive drug was more likely to cause early severe infections. Moreover, few studies focus on infections in older patients with AAV, although aging has been assumed to be the most robust risk factor for severe infection. Accordingly, there is a therapeutic dilemma, especially in elderly patients with AAV.

The early infection risk of initial high-dose corticosteroids was reported from a multicenter cohort of patients with AAV in Japan.^[14] In the study, initial prednisolone dosage ≥ 0.8 mg/kg/d, smoking history, and severe AAV were significant risk factors for severe infections within 6 months after remission-induction therapy. Bomback et al reported that patients receiving

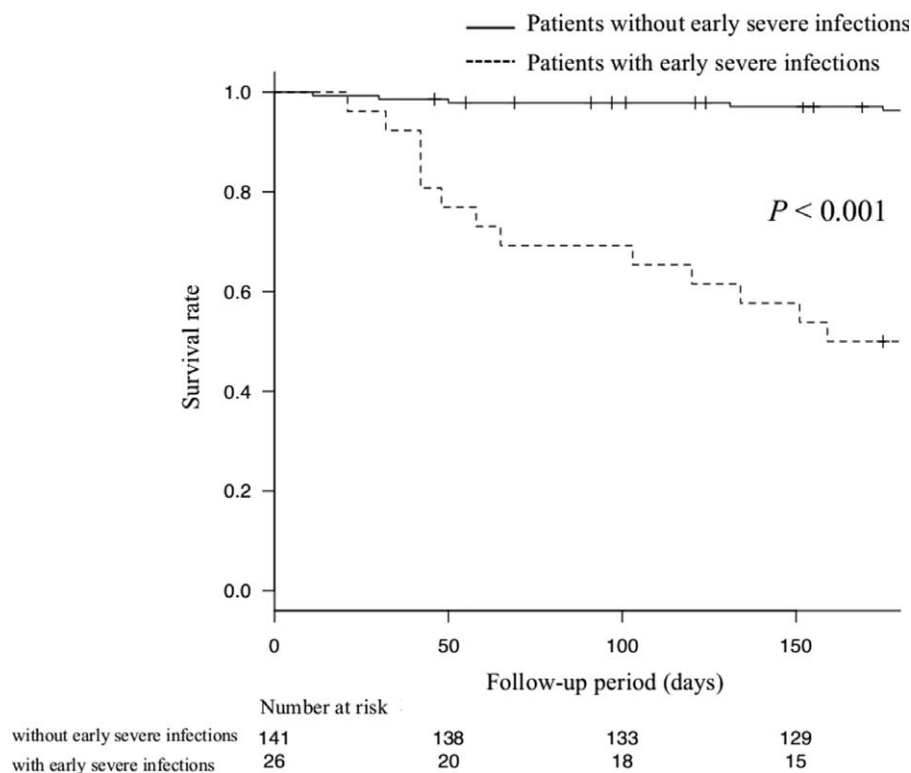


Figure 3. Overall survival rates within 6 months for patients with and without early severe infections. Kaplan–Meier curve showing an association between survival and early severe infections ($P < .001$).

immunosuppressive therapy were more likely to have infections among very elderly individuals (≥ 80 years old) with ANCA-associated pauci-immune glomerulonephritis although details of the immunosuppressive therapy were not described.^[21] Consistent with their results, our study confirmed initial high-dose corticosteroids are a robust risk factor for early severe infections rather than treatment with CYC or RTX and that the serious infection risk from initial high-dose corticosteroids may persist long-term in elderly patients with AAV.

We found that renal impairment at diagnosis was a predictive risk factor for early severe infections even in older patients with AAV. Various prior reports show correlations between renal impairment at diagnosis and severe infections in AAV. Mohammad et al. proposed that the triad of older age, higher serum creatinine levels at diagnosis, and the occurrence of infections have a synergistic effect on mortality in patients with AAV.^[9] We speculate that renal damage also amplifies the side effects of immunosuppressive drugs, which exacerbate life-threatening severe infections.

We acknowledge that there were several limitations in our study. First, our study was a retrospective single-center observational study that included patients for whom MPA was the predominant diagnosis. However, we think these characteristics reflect the clinical background of AAV in Japan.^[22–24] The Japanese AAV registry reported that a large proportion of patients with AAV in Japan were classified as having MPA similar to Korean and Chinese patients.^[4,12] Second, treatment outcomes (eg, remission rates and relapse-free survival) were not measured in our study. Rapid tapering of corticosteroids and fixed low-dose CYC therapy for elderly patients with AAV reduced serious

adverse events (including infections) and kept the same remission rate compared to conventional therapy in the CORTAGE trial.^[25] The French Vasculitis Study Group reported that a systemic corticoid alone as first-line treatment and AZA as second-line therapy offered acceptable efficacy compared to CYC in patients with MPA, polyarteritis nodosa, or EGPA without poor prognostic factors.^[26,27] A further prospective study to evaluate the efficacy of these less-intensive therapies, including more restrictive use of glucocorticoids, is warranted in elderly patients with AAV. Third, other immunosuppressants (including CYC or RTX), in addition to corticosteroids, were administered at the discretion of each physician in our study. The patients with life-threatening organ involvement or higher BVAS tended to receive CYC or RTX, which physicians tended to avoid using in patients with dementia and low activities of daily living (data not shown). Although these clinical judgments are in keeping with current guidelines for the management of AAV, toxicity of CYC or RTX may be underestimated in this study.^[28–30] Finally, we could not verify all the potential predictors of early severe infections to develop a risk scoring system because the study was statistically under-powered. In the future, a scoring system for predicting severe infections will improve clinical decision-making when choosing therapeutic strategies in elderly patients with AAV.

To conclude, early severe infection is an independent predictor of death in elderly patients with AAV, and initial high-dose corticosteroids are associated with the risk of early severe infections, which also leads to a higher cumulative incidence of severe infections. Optimal treatment strategies that include lower corticosteroid doses in the early phase of treatment should be

considered in order to improve outcomes in elderly patients with AAV.

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