


ORIGINAL RESEARCH

Association between different infection profiles and one-year outcomes in ANCA-associated vasculitis: a retrospective study with monthly infection screening

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ABSTRACT

Objectives This study aimed to explore clinical features of early infection in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and to identify the association between the infection profile of patients with AAV during the first 3 months and 1-year survival.

Methods A total of 415 newly diagnosed patients with AAV in the Department of Nephrology at Shanghai Ruijin Hospital from 2000 to 2018 were included. Four Cox regression models were used to analyse the association based on demographics, comorbidities, laboratory baseline index and therapy parameter. Infection screening was carried out monthly during the first 3 months after diagnosis.

Results In all, 377 episodes of infection were identified among 220 patients during the first 3 months. The overall survival after 1 year was 73.0%. Respiratory infection (210 episodes/164 persons) accounted for more than half of infections. Infection was independently associated with 1-year mortality (adjusted HR 2.32, 95% CI 1.27 to 4.23, $p=0.006$) after adjustment. Respiratory infection (adjusted HR 4.36, 95% CI 2.86 to 8.06, $p<0.001$), Gram-negative bacterial infection (adjusted HR 1.71, 95% CI 1.01 to 2.91, $p=0.047$) and fungal infection (adjusted HR 1.77, 95% CI 1.07 to 2.94, $p=0.026$) was identified as a risk factor for 1-year mortality. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis (adjusted HR 0.55, 95% CI 0.31 to 0.97, $p=0.040$) was protective for 1-year mortality.

Conclusions Infections, particularly respiratory infections, are a common and important class of complication in patients with AAV and are associated with early mortality. TMP-SMX prophylaxis might be necessary to improve short-term outcome. More consideration of infectious risk and regular infection screening should be given.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disease characterised by necrotising lesions of small vessels,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Infection is closely related to early mortality in antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

WHAT THIS STUDY ADDS

⇒ The study showed that infection during the first 3 months, especially respiratory infection and Gram-negative bacterial and fungal infection, was an independent risk factor for 1-year mortality.
⇒ Trimethoprim-sulfamethoxazole prophylaxis might be beneficial to improve 1-year survival.
⇒ Insufficient control of disease activity probably poses just as much infection risk as the therapies themselves.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ More attention should be paid to systematic and comprehensive infection screening in the treatment of AAV.

extravascular inflammation and a paucity of immune deposits. This group of disorders includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA).¹ Despite improved survival rates of patients with AAV, infection remains a critical complication during the treatment of AAV.

In observational studies, approximately 20%–60% of patients with ANCA-associated vasculitis had infection episodes during treatment.^{2–6} According to previous literature, several features, such as older age, more comorbidities, disease severity, renal deficiency at baseline, pulmonary involvement or intensity of therapy (cumulative dose of steroids

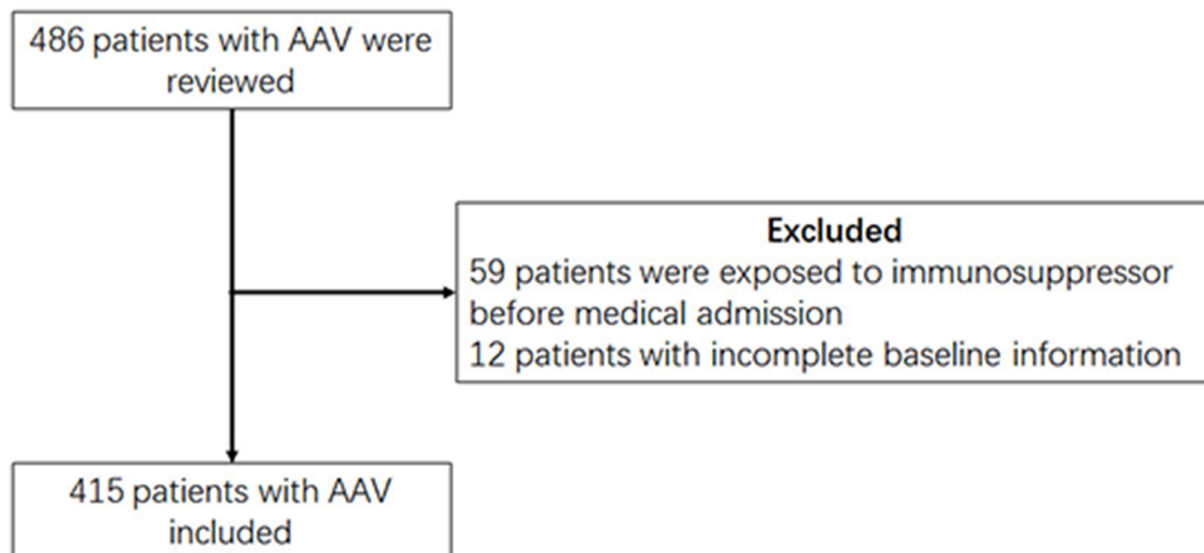


Figure 1 Flow chart of the inclusion of patients with AAV of the cohort. AAV, antineutrophil cytoplasmic antibody-associated vasculitis.

or cyclophosphamide (CYC)), have been identified as risk factors for infection in patients with AAV.^{5–15} These factors are intertwined, which places clinicians in a therapeutic dilemma. A better understanding of infection-related factors helps to balance the benefits and risks associated with treatment. Infection, together with active vasculitis, is the main reason for first-year mortality.^{16–18} Most infection episodes occurred in the first 3 months.^{18–20} Respiratory infection is the most frequent infection type, regardless of age, dialysis dependence or given treatment.^{21–28} Gram-negative bacteria are the leading causative pathogens, and opportunistic infections are common in patients with AAV.^{18–20–25–29} Trimethoprim-sulfamethoxazole (TMP-SMX) was previously thought to protect patients with AAV from *Pneumocystis jirovecii* either with CYC or rituximab (RTX) treatment.^{15–30–31} TMP-SMX was recommended by EULAR³² and the British Society for Rheumatology (BSR).³³ However, more studies are still needed to increase the knowledge of infection-related factors and infection profiles, which will be a great help to reduce the burden of disease in the early stage of disease.

In our study, a large retrospective cohort of patients with AAV was followed. We explored the different characteristics of the infection and non-infection groups. We assumed that infection episodes that occurred in the first 3 months of AAV diagnosis were related to 1-year mortality. We analysed the correlation between mortality and the first 3 months of infection (infection site and causative pathogens) and the association with TMP-SMX prophylaxis. The aim of this study was to gain better knowledge of the disease and to provide insights into disease management, especially in the early stage of the disease.

METHOD

Study design

This was a single-centre study based on a retrospective cohort. All patients with AAV newly diagnosed in the Department of Nephrology at Shanghai Ruijin Hospital from 1 January 2000 to 31 December 2018 were included. The diagnosis was established according to the International Chapel Hill Consensus Conference Nomenclature of Vasculitides.¹

A total of 486 newly diagnosed patients were initially included in the study. Then, all their medical documents were reviewed. Patients with incomplete baseline information (12 patients) or immunosuppressor exposure history before medical admission (59 patients) were excluded. After selection, 415 patients were selected for further analysis (figure 1). In this retrospective study, the primary objective was 1-year survival. Mortality within 12 months after diagnosis was checked and confirmed individually by phone. For those who were lost to follow-up and had incomplete information on 1-year survival, the date of the last medical record was assigned as their drop-out date. The drop-out rate of this study was 7.2% (30 patients).

Determination of infection events

Based on the literature, we chose an infection within the first 3 months as our event of interest.^{16–18–25} Information on infection events was carefully registered, including the time of infection, infection site (such as respiratory infection, urinary infection, gastrointestinal infection, oral infection, bloodstream infection, etc), associated serological results and pathogens identified by culture.

Every positive screening of infection in the first 3 months was registered based on the medical record. Notably, in our centre, the screening of infection was systematic at the time of admission and after diagnosis.

For every patient with AAV, regardless of clinical presentation, monthly serological examinations (such as herpes simplex virus I/II, Epstein-Barr virus, cytomegalovirus, influenza A, influenza B, Q-fever virus, *Mycoplasma*, *Legionella*, etc), a galactomannan test, a 1-3- β -D-glucan test, a nasal throat swab and a urine culture were performed. If there was suspicion of infection or aggravated infection symptoms, cultures of samples (swab, sputum, blood, urine and stool) as well as viral serological examinations were carried out repetitively.

The diagnosis of infection was judged by two independent experienced clinicians; if there was a disagreement, a third opinion from senior physicians was sought. The judgement was made after comprehensive analysis based on multiple dimensions: clinical presentation, laboratory result, imaging, serological test and pathogen culture. According to clinical presentation, infection episodes were classified by infection site, including respiratory infection, urinary infection, gastrointestinal infection, oral infection, bloodstream infection, soft tissue infection, nail infection, biliary duct infection, cholecystitis, pancreatitis, meningitis and catheter-related infection and endocarditis. Those infected patients who did not present clinical signs or symptoms but were positive for viral IgM were recorded as having non-specific infection sites. Depending on the causative pathogens, infection was categorised as bacterial, viral, fungal or others. Causative pathogens were recorded only after a confirmation of infection. Viral infection was determined from positive serological antibody results and corresponding symptoms.

Data collection

The following clinical data at baseline were collected: age, sex, subtype of AAV (MPA, GPA and EGPA), comorbidities (hypertension, diabetes, chronic bronchitis, tuberculosis history, other autoimmune disease, chronic kidney disease), routine blood analysis results, levels of serum immunoglobulins (IgG, IgA, IgM and IgE) and complement (C3 and C4), erythrocyte sedimentation rate (ESR), C reactive protein (CRP) level, serum creatinine (Scr) level, 24-hour urine protein excretion (24Upro) and albumin-to-creatinine ratio (ACR). All the infection screening results at baseline and follow-up were also collected. The estimated glomerular filtration rate (eGFR) was calculated by using the Kidney Disease Improving Global Outcomes-Epidemiology Collaboration equation. The Birmingham Vasculitis Activity Score (BVAS) was calculated at the time of diagnosis. Renal replacement therapy (RRT), plasma exchange (PE), medical induction strategy, cumulative prednisone and CYC doses of the first 3 months, antifungal drug use, antiviral drug use and TMP-SMX prophylaxis were recorded. Antifungal drugs and antiviral drugs were generally prescribed under the circumstance of

high suspicion of related infection with or without positive culture results. The use of TMP-SMX was not systematic and relied on the decision of the clinician. TMP-SMX prophylaxis lasted at least 3 months.

Statistical analysis

In this study, the baseline data were shown to be non-normally distributed; therefore, we used the median (IQR) to describe the metric variables. The demographic and clinical characteristics of the participants are presented as the frequency (percentage, %) for categorical variables and as the median (IQR) for continuous variables.

All the subjects were divided into two groups: the infection group (those who had at least one infection during the first 3 months) and the non-infection group (those who never acquired an infection during the first 3 months). The χ^2 test was used for the categorical variables, and the Mann-Whitney U test was used for the metric variables to compare the clinical characteristics of the infection group and the non-infection group.

One-year Kaplan-Meier curves were plotted for the infection group and the non-infection group. Cox models were developed to analyse the association between infection events and 1-year mortality. To calibrate an appropriate model, factors including general demographic variables, comorbidities, laboratory results at baseline and therapy were assessed; age; sex; the presence of hypertension, diabetes, other autoimmune disease and chronic bronchitis; white blood cell levels; neutrophil counts; lymphocyte counts; levels of IgG, IgA, IgM, IgE, C3 and C4; ESR; CRP levels and Scr levels; 24Upro; eGFR levels; BVAS; RRT; PE; cumulative prednisone doses during the first 3 months; cumulative CYC doses during the first 3 months of antifungal drug use; antiviral drug use and TMP-SMX prophylaxis were tested for univariate analysis. For those variables with a p value <0.1, they were included in the multivariate analysis. Factors with significance (age, neutrophil counts, 24Upro, eGFR, BVAS, cumulative CYC doses during the first 3 months and antifungal drug use) in multivariate analysis and sex were used as a constant parameter for adjustment. Three adjusted models were finally established with the adjustment of parameters under different conditions: (1) demographics: age and sex; (2) demographics and baseline data: age, sex, neutrophil counts, 24Upro, eGFR and BVAS; (3) demographics, baseline data and therapy: age, sex, neutrophil counts, 24Upro, eGFR, BVAS, cumulative CYC doses during the first 3 months and antiviral drug use. Unadjusted model and three adjusted models were then used for statistical analysis.

Infection sites (respiratory infection, urinary tract infection, gastrointestinal infection and oral infection), causative pathogens (Gram-positive bacteria, Gram-negative bacteria, fungi and virus) and TMP-SMX were then analysed by univariate and adjusted regression models. All variables in the final model were tested, and they met the proportional hazards assumption. The

Table 1 The clinical characteristics, laboratory results and treatment at baseline in overall, infected and non-infected patients with AAV

	Overall (n=415)	Non-infection group (n=195)	Infection group (n=220)	P value
Demographics				
Male, n (%)	171 (41.2)	79 (40.5)	92 (41.8)	0.865
Age, years (median (IQR))	61.00 (49.50, 69.00)	56.00 (45.00, 67.00)	64.00 (53.75, 71.00)	<0.001***
Comorbidities				
Hypertension, n (%)	145 (34.9)	71 (36.4)	74 (33.6)	0.625
Diabetes, n (%)	70 (16.9)	23 (11.8)	47 (21.4)	0.014*
Chronic bronchitis, n (%)	84 (20.2)	21 (10.8)	63 (28.6)	<0.001***
Tuberculosis, n (%)	34 (8.2)	15 (7.7)	19 (8.6)	0.864
Other autoimmune disease, n (%)	63 (15.2)	41 (21.0)	22 (10.0)	0.003**
Chronic kidney disease, n (%)	99 (23.9)	49 (25.1)	50 (22.7)	0.647
Laboratory results				
WBC, $\times 10^9/L$ (median (IQR))	7.70 (5.94, 11.2)	7.10 (5.70, 9.60)	8.60 (6.20, 12.05)	<0.001***
N, $\times 10^9/L$ (median (IQR))	5.49 (3.80, 8.76)	4.70 (3.40, 6.86)	6.14 (4.23, 9.90)	<0.001***
L, $\times 10^9/L$ (median (IQR))	1.43 (1.00, 2.00)	1.61 (1.21, 2.20)	1.26 (0.85, 1.70)	<0.001***
IgG, mg/dL (median (IQR))	1470 (1223, 1850)	1420 (1190, 1790)	1520 (1260, 1970)	0.032*
IgA, mg/dL (median (IQR))	285 (208, 382)	283 (207, 381)	288 (209, 384)	0.855
IgM, mg/dL (median (IQR))	112 (78, 164)	119 (81, 179)	103 (77, 156)	0.086
IgE, mg/dL (median (IQR))	78 (29, 222)	60 (19, 140)	107 (38, 289)	<0.001***
C3, mg/dL (median (IQR))	89 (73, 108)	91 (73, 108)	87 (72, 108)	0.345
C4, mg/dL (median (IQR))	23 (18, 28)	23 (19, 28)	23 (17, 28)	0.446
ESR, mm/hour (median (IQR))	74 (34, 107)	46 (19, 90)	87 (52, 115)	<0.001***
CRP, mg/L (median (IQR))	10.10 (2.40, 44.89)	3.90 (1.37, 15.20)	20.55 (6.77, 65.48)	<0.001***
Scr, $\mu\text{mol/L}$ (median (IQR))	237 (99, 524)	192 (78, 395)	306 (136, 598)	<0.001***
eGFR-EPI, mL/min/1.73 m ² (median (IQR))	20.64 (8.43, 63.01)	29.56 (11.41, 84.79)	15.07 (6.90, 40.90)	<0.001***
24Upro, mg/24 hours (median (IQR))	1001 (436, 1870)	826 (332, 1726.00)	1041 (495, 1955)	0.076
ACR, mg/g (median (IQR))	89.00 (23.91, 199.40)	81.70 (18.25, 164.18)	107.77 (31.50, 229.07)	0.021*
BVAS (median (IQR))	22 (17, 26)	19 (14, 24)	23 (19, 28)	<0.001***
Treatment				
Intravenous CYC, n (%)	322 (77.6)	136 (69.7)	186 (84.5)	0.991
Steroid-based induction, n (%)	329 (79.3)	139 (71.3)	190 (86.4)	<0.001***
Cumulative dose of prednisone, mg (median (IQR))	681.1 (514.8, 820.2)	579.6 (425.7, 728.9)	735.1 (604.9, 927.6)	<0.001***
Cumulative dose of CYC, g (median (IQR))	1.6 (0.6, 2.4)	1.6 (0, 2.4)	1.8 (0.8, 2.4)	0.056
RRT, n (%)	72 (17.3)	22 (11.3)	50 (22.7)	<0.001***
PE, n (%)	37 (8.9)	14 (7.2)	23 (10.5)	0.007**
Antifungal drug, n (%)	126 (30.4)	21 (10.8)	105 (47.7)	<0.001***
Antiviral drug, n (%)	57 (13.7)	15 (7.7)	42 (19.1)	<0.001***
TMP-SMX prophylaxis, n (%)	92 (22.2)	33 (16.9)	59 (26.8)	<0.001***

Other autoimmune disease: Hashimoto's thyroiditis, rheumatoid arthritis, Sjögren's syndrome, uveitis, psoriasis, etc. The p value indicates whether there is a significant difference between the infection group and the non-infection group.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ACR, albumin-to-creatinine ratio; BVAS, Birmingham Vasculitis Activity Score; C3, complement C3; C4, complement C4; CRP, C reaction protein; CYC, cyclophosphamide; eGFR-EPI, estimated glomerular filtration rate-Epidemiology Collaboration equation; ESR, erythrocyte sedimentation rate; L, lymphocyte counts; N, neutrophil counts; PE, plasma exchange; RRT, renal replacement therapy; Scr, serum creatinine; TMP-SMX, trimethoprim-sulfamethoxazole; 24Upro, 24-hour urine protein; WBC, white blood cell.

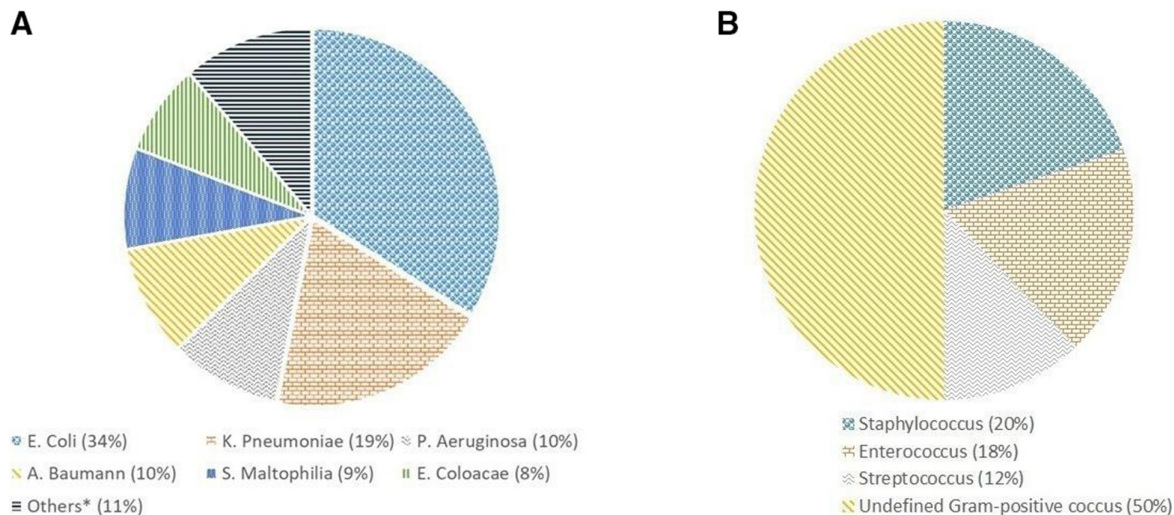


Figure 2 Pie chart of the bacterial composition of cultures from patients with AAV during the first 3 months after diagnosis. Pie chart of the Gram-negative bacterial composition of cultures from patients with AAV during the first 3 months after diagnosis. *Others include *Proteus mirabilis*, *Enterobacter aerogenes*, *Morganella morganii*, *Pseudomonas fluorescens*, *Haemophilus influenzae*, *F. indoleans* and *A. qiongensis*. Pie chart of the Gram-positive bacterial composition of cultures from patients with AAV during the first 3 months after diagnosis. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; *A. baumannii*, *Acinetobacter baumannii*; *E. cloacae*, *Enterobacter cloacae*; *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. maltophilia*, *Stenotrophomonas maltophilia*.

significant difference in this study was set as $p < 0.05$, and the CIs were calculated at 95%. All statistical analyses were performed by R studio V.4.0.3.

RESULTS

General data of patients with AAV

Four hundred fifteen patients were enrolled in our study, including 304 patients with MPA, 53 patients with GPA and 16 patients with EGPA. Thirty patients (7.2%) dropped out. The overall survival after 1 year was 73.0%. The median age was 61 years. Among them, 171 (41%) were male, and 244 (59%) were female. Most of the patients (322 patients, 78%) received monthly intravenous CYC as a strategy for induction. At the time of diagnosis, 72 patients (17%) received RRT, 37 patients (9%) received PE, 57 patients (14%) received antiviral drugs, 98 (24%) received antifungal drugs and 73 (18%) received TMP-SMX prophylaxis. The clinical characteristics and treatment for all the patients are shown in [table 1](#).

Overall infection episodes and characteristics

Among the 415 patients, 220 experienced 377 episodes of infection. Two hundred and twenty patients developed at least one infection during the first 3 months after diagnosis. Thirty-seven patients experienced three episodes of infection or more. Compared with those in the non-infection group, the patients in the infection group were older ($p < 0.001$), and more of them had diabetes ($p = 0.014$), chronic respiratory disease ($p < 0.001$) and other autoimmune diseases ($p = 0.003$). The infection group had relatively higher IgG ($p = 0.032$), IgE ($p < 0.001$), ESR ($p < 0.001$) and CRP ($p < 0.001$) levels. Additionally, patients with infection episodes had more severe

renal damage at onset (ie, Scr level, $p < 0.001$; eGFR-EPI, $p < 0.001$; ACR, $p = 0.021$) and higher BVAS ($p < 0.001$). Regarding therapy and medication use, the infection group had a larger proportion of patients that underwent RRT ($p < 0.001$), PE ($p = 0.007$), antifungal drug treatment ($p < 0.001$), antiviral drug treatment ($p < 0.001$) and TMP-SMX prophylaxis ($p < 0.001$). Furthermore, patients in the infection group had a higher cumulative dose of prednisone ($p < 0.001$) during the first 3 months. Detailed data on the patients in the infection and non-infection groups are shown in [table 1](#).

Infection sites and pathogens in the patients with AAV

In a total of 377 episodes of infection, 330 episodes had identified infection sites, and the rest had non-specific infection sites. Respiratory infection (210 episodes/164 persons) dominated more than half of infections, followed by urinary infection (74 episodes/63 persons), gastrointestinal infections (13 episodes/11 persons), oral infection (10 episodes/10 persons) and bloodstream infection (7 episodes/7 persons) (online supplemental figure 1).

Among 377 episodes of infection, 337 pathogens could be tested or cultivated positive. There were 168 (110 persons) bacterial infections, 41 (37 persons) viral infections, 122 (88 persons) fungal infections and 6 (5 persons) *Mycoplasma* infections (online supplemental figure 2). Gram-negative bacteria (115 episodes, eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, etc) were the main bacterial pathogens, with 39 episodes (34%) of *E. coli*, 22 episodes (19%) of *K. pneumoniae*, 11 episodes (10%) of *P. aeruginosa*, 11 episodes (10%) of *A. baumannii*, 10 episodes

(9%) of *Stenotrophomonas maltophilia*, 9 episodes (8%) of *Enterobacter cloacae* and 13 episodes (11%) of others (figure 2A).

Gram-positive bacterial pathogens (106 episodes) comprised 21 episodes (20%) of *Staphylococcus*, 19 episodes (18%) of *Enterococcus* and 13 episodes (12%) of *Streptococcus*. Half of the Gram-positive bacteria could not be classified because the culture results suggested only a Gram-positive coccus and provided no further specifics (figure 2B). The most common cause of viral infections was CMV (26 episodes), followed by herpes simplex virus I/II (10 episodes), herpes varicella-zoster virus (2 episodes), influenza A virus (2 episodes) and Q-fever virus (1 episode) (online supplemental figure 3). *Candida* caused a large number (88 episodes, 72%) of fungal infections, and the rest could not be identified by subtype. We also recorded one episode of *Aspergillus fumigatus* (online supplemental figure 4).

Association between infections and 1-year mortality

During follow-up, 82 deaths were recorded, and 30 patients dropped out. The overall survival after 1 year was 73.0%. The median time until death was 2.6 months. The Kaplan-Meier curves of 1-year mortality for the infection group and non-infection group are shown in figure 3A. The results showed that there was a significant difference in 1-year mortality between the groups during the first 3 months and the group without infection (log-rank test $\chi^2=37.8$; $p<0.001$).

To better examine the association between infection and 1-year mortality, Cox regression models were calibrated. General demographics, comorbidities, laboratory results at baseline, therapy and infection were used for univariate analysis. All factors with a p value <0.1 were entered into multivariate analysis. Other than infection, age (HR 1.03, 95% CI 1.01 to 1.05, $p=0.003$), neutrophil counts (HR 1.09, 95% CI 1.04 to 1.15, $p=0.001$), 24Upro (HR 1.00, 95% CI 1.00 to 1.00, $p<0.001$), eGFR (HR 0.97, 95% CI 0.95 to 0.98, $p<0.001$), BVAS (HR 1.08, 95% CI 1.04 to 1.12, $p<0.001$), cumulative CYC doses during the first 3 months (HR 0.53, 95% CI 0.41 to 0.68, $p<0.001$) and antiviral drug use (HR 0.22, 95% CI 0.09 to 0.54, $p=0.001$) were associated with 1-year mortality with a statistical significance (table 2). These factors, together with sex, were used for adjustment. Based on their characteristics—including demographics, baseline data or therapy—one unadjusted model and three adjusted Cox models were generated (online supplemental table 1).

Using the Cox regression model, we found that overall infection was independently associated with 1-year mortality with or without adjustment (unadjusted HR 4.87, 95% CI 2.74 to 8.66, $p<0.001$; HR 3.79, 95% CI 2.11 to 6.80, $p<0.001$ after adjustment for age and sex; HR 2.18, 95% CI 1.17 to 4.08, $p=0.014$ after adjustment for age, sex, neutrophil counts, 24Upro, eGFR and BVAS; HR 2.55, 95% CI 1.37 to 4.74,

$p=0.003$ after adjustment for age, sex, neutrophil counts, 24Upro, eGFR, BVAS, cumulative CYC doses during the first 3 months and antiviral drug use).

In the subgroup analysis based on the infection site, the four most frequent infections in our study (respiratory infection, urinary tract infection, gastrointestinal infection and oral infection) were selected for further investigation. The Kaplan-Meier curve for the analysis of respiratory infection is shown in figure 3B (log-rank test $\chi^2=70.77$, $p<0.001$). Using Cox regression, patients with respiratory infection (HR 7.67, 95% CI 4.44 to 13.25, $p<0.001$) or gastrointestinal infection (HR 3.60, 95% CI 1.45 to 8.93, $p=0.006$) had a higher 1-year mortality. After adjustment for age and sex, gastrointestinal infection (HR 3.26, 95% CI 1.32 to 8.08, $p=0.011$) was positively associated with 1-year mortality. However, respiratory infection was a risk factor for 1-year mortality in all adjusted models (HR 6.01, 95% CI 3.44 to 10.52, $p<0.001$ after adjustment of age and sex; HR 3.50, 95% CI 1.91 to 6.43; $p<0.001$ after adjustment for demographics and baseline data; HR 4.37, 95% CI 2.86 to 8.06; $p<0.001$ after adjustment for demographics, baseline data and therapy).

With the same statistical method, subgroup analysis of pathogens (Gram-positive bacteria, Gram-negative bacteria, fungi and viruses) was reviewed. Infection with Gram-negative bacteria (unadjusted HR 2.01; 95% CI 1.27 to 3.19, $p=0.003$) and fungi (unadjusted HR 2.09, 95% CI 1.32 to 3.31; $p=0.002$) increased the risk of 1-year mortality. With adjustment for demographics, baseline analysis and therapy, Gram-negative bacteria (adjusted HR 1.71; 95% CI 1.01 to 2.91, $p=0.047$) and fungi (adjusted HR 1.77; 95% CI 1.07 to 2.94, $p=0.026$) infections were still a risk factor of 1-year mortality. Moreover, fungi (adjusted HR 1.76; 95% CI 1.11 to 2.79, $p=0.017$) were associated with 1-year mortality after adjustment for demographics. The results of the subgroup analysis for 1-year mortality with unadjusted model and adjusted model of demographics, baseline analysis and therapy are presented in a forest plot (figure 4). The result of subgroup analysis for infection and 1-year mortality in four models is shown in online supplemental table 2.

Association between prophylactic TMP-SMX use and 1-year mortality

In our study, 92 patients received TMP-SMX prophylaxis. Twenty out of 92 patients were dead at the 1-year point, whereas 62 out of 323 patients without TMP-SMX prophylaxis were registered as dead. There was no difference between the 1-year Kaplan-Meier curves of the two groups (log-rank test $\chi^2=0.1$, $p=0.78$). Without adjustment, TMP-SMX prophylaxis showed no significant association with mortality (unadjusted HR 1.07, 95% CI 0.65 to 1.78, $p=0.783$). No association was observed in model adjusted for demographics or for demographics and baseline data. However, after adjustment for demographics, baseline and therapy variables, TMP-SMX prophylaxis (adjusted HR 0.55, 95% CI 0.31 to 0.97, $p=0.040$) had negative

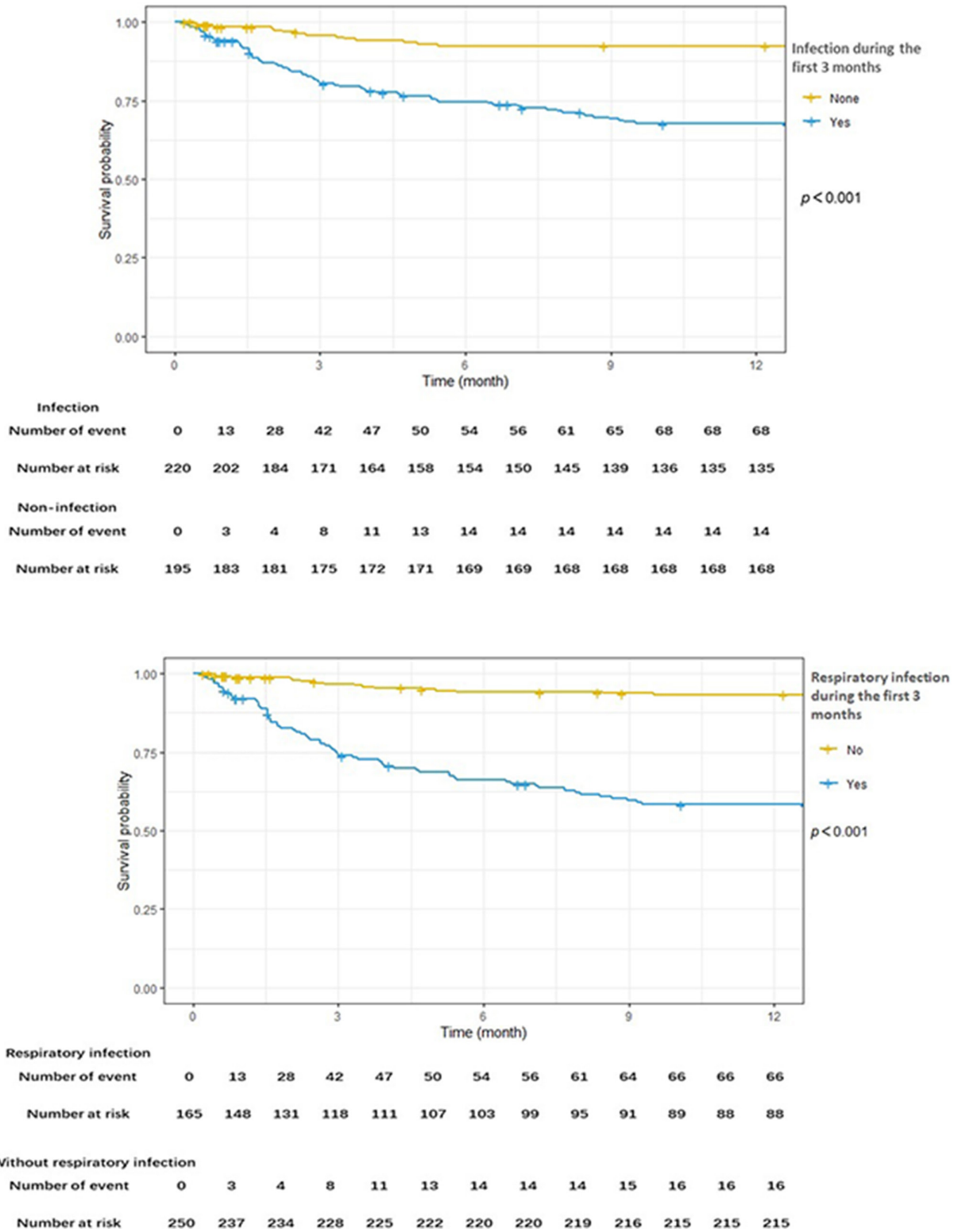


Figure 3 One-year Kaplan-Meier curve for patients with AAV with (respiratory) infection and without (respiratory) infection during the first 3 months. One-year Kaplan-Meier curve for patients with AAV with infection and without infection during the first 3 months. One-year Kaplan-Meier curve for patients with AAV with and without respiratory infection during the first 3 months. AAV, antineutrophil cytoplasmic antibody-associated vasculitis.

Table 2 The Cox analysis of 1-year mortality and parameters

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Demographics						
Age, years	1.05	1.03 to 1.07	<0.001***	1.03	1.01 to 1.05	0.003**
Sex (male)	1.21	0.78 to 1.87	0.389			
Comorbidities						
Hypertension	1.59	1.03 to 2.45	0.037*			
Diabetes	1.91	1.17 to 3.12	0.009**			
Other autoimmune disease	0.19	0.06 to 0.59	0.004**			
Chronic bronchitis	1.66	1.03 to 2.67	0.036*			
Laboratory results						
WBC, $\times 10^9/L$	1.06	1.02 to 1.11	0.005**			
N, $\times 10^9/L$	1.09	1.04 to 1.14	<0.001***	1.09	1.04 to 1.15	0.001**
L, $\times 10^9/L$	0.78	0.61 to 1.00	0.046*			
IgG, mg/dL	1.00	1.00 to 1.00	0.358			
IgA, mg/dL	1.00	1.00 to 1.00	0.562			
IgM, mg/dL	1.00	0.99 to 1.00	0.019*			
IgE, mg/dL	1.00	1.00 to 1.00	0.010*			
C3, mg/dL	0.99	0.98 to 1.00	0.013*			
C4, mg/dL	0.98	0.95 to 1.01	0.235			
ESR, mm/hour	1.01	1.00 to 1.01	0.012*			
CRP, mg/L	1.00	1.00 to 1.01	0.044*			
Scr, $\mu\text{mol/L}$	1.00	1.00 to 1.00	<0.001***			
24Upro, mg/24 hours	1.00	1.00 to 1.00	0.004**	1.00	1.00 to 1.00	<0.001***
eGFR-EPI, mL/min/1.73 m ²	0.95	0.94 to 0.97	<0.001***	0.97	0.95 to 0.98	<0.001***
BVAS	1.12	1.09 to 1.15	<0.001***	1.08	1.04 to 1.12	<0.001***
Treatment						
RRT	3.78	2.43 to 5.90	<0.001***			
PE	1.52	0.78 to 2.94	0.218			
Cumulative dose of prednisone, mg	1.00	1.00 to 1.00	<0.001***			
Cumulative dose of CYC, g	0.80	0.66 to 0.96	0.018*	0.53	0.41 to 0.68	<0.001***
Antifungal drug	2.86	1.86 to 4.42	<0.001***			
Antiviral drug	0.43	0.19 to 1.00	0.049*	0.22	0.09 to 0.54	0.001**
TMP-SMX prophylaxis	1.07	0.65 to 1.78	0.783			
Infection	4.87	2.74 to 8.66	<0.001***	2.58	1.39 to 4.79	0.003**

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

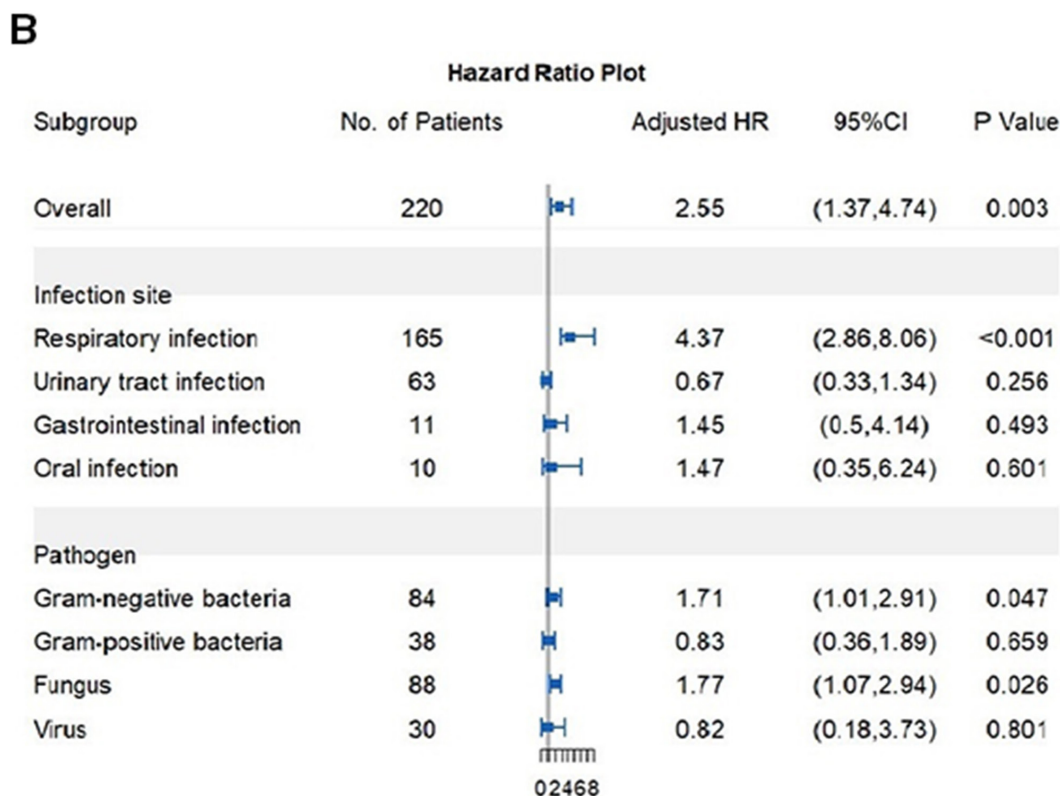
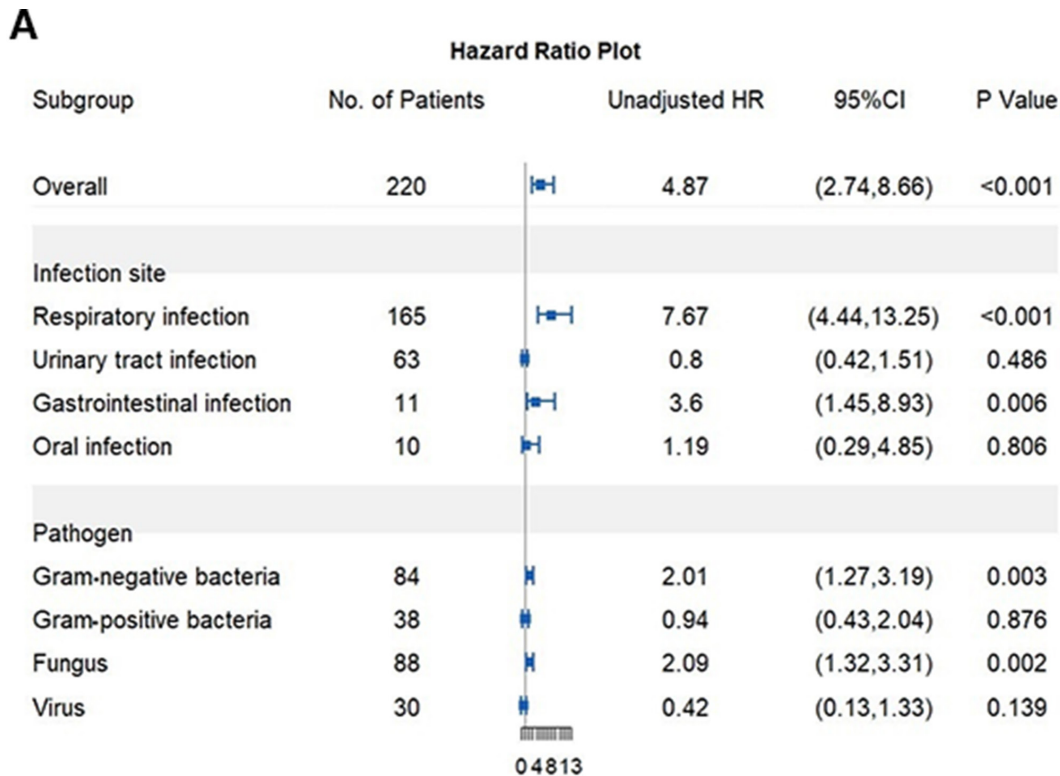
BVAS, Birmingham Vasculitis Activity Score; C3, complement C3; C4, complement C4; CRP, C reaction protein; CYC, cyclophosphamide; eGFR-EPI, estimated glomerular filtration rate-Epidemiology Collaboration equation; ESR, erythrocyte sedimentation rate; L, lymphocyte counts; N, neutrophil counts; PE, plasma exchange; RRT, renal replacement therapy; Scr, serum creatinine; TMP-SMX, trimethoprim-sulfamethoxazole; 24Upro, 24-hour urine protein; WBC, white blood cell.

correlation with 1-year mortality. The TMP-SMX results are shown in [table 3](#).

DISCUSSION

As widely acknowledged in other studies,^{5–7 17 20 25–27 34–36} infection is a critical complication in the management of AAV and is closely related to deteriorative outcomes,

especially in the early stage of the disease. Therefore, more attention to infection-related factors needs to be addressed, and recognition of death-related infection types or causative pathogens provides clinicians with more chances to reduce mortality. In our study, we described the sites and pathogens of infection episodes in the first 3 months after initial treatment in a large



Adjusted for age, sex, neutrophil counts, 24h urine protein, eGFR, BVAS, cumulative use of CYC and antiviral drug

Figure 4 Forest plots with subgroup analysis for infection and 1-year survival in patients with AAV. Forest plot with subgroup analysis for infection and 1-year survival with an unadjusted model. Forest plot with subgroup analysis for infection and 1-year survival after adjustment for age, sex, neutrophil counts, 24 hours urine protein, eGFR, BVAS, cumulative use of CYC and antiviral drug. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate.

Table 3 HR of TMP-SMX prophylaxis in Cox regression model

	Model 1			Model 2			Model 3			Model 4		
	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
TMP-SMX prophylaxis	1.07	0.65 to 1.78	0.783	0.98	0.59 to 1.63	0.945	0.6	0.35 to 1.04	0.069	0.55	0.31 to 0.97	0.040*

Model 1: unadjusted; model 2: adjusted for age and sex; model 3: adjusted for age, sex, neutrophil counts, 24 hours urine protein, eGFR and BVAS; model 4: adjusted for age, sex, neutrophil counts, 24 hours urine protein, eGFR, BVAS, cumulative use of CYC and antiviral drug. * $p < 0.05$.
 BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; TMP-SMX, trimethoprim-sulfamethoxazole.

AAV cohort with good screening for infection. Respiratory infection episodes dominated more than half of infections, followed by urine tract infection, gastrointestinal infection, oral infection and bloodstream infection. During the first 3 months after diagnosis, infection episodes, especially respiratory infection and infections due to Gram-negative pathogens or fungi, were a risk factor for 1-year mortality in patients with AAV. Furthermore, patients who received TMP-SMX prophylaxis during the first 3 months may have improved outcomes at the 1-year point.

One of our major findings was the significant association between the infection during the first 3 months and 1-year mortality in all four regression models. Most of the infection events occurred during the first 3 months after disease diagnosis.^{18 19 25} Our study showed that infection in the early stage of disease increases the risk of death by 2.55 times. This result is in accordance with the results of other literature.^{18–20 34} Data from McGregor *et al* indicated that patients with severe infections were 4.2 times more likely to die within 12 months after controlling for age, sex and kidney function.²⁰ Another study identified infection as an independent predictor of 1-year mortality with an adjusted HR of 3.316.¹⁸ Similar results were also reported by Little *et al*. They found that the infection score was independently associated with 1-year mortality.¹⁹ Additionally, statistical data from a recent meta-analysis based on patients with AAV under RTX treatment confirmed that general mortality related to infection was estimated at 0.7%.³⁴ In summary, this conclusion is consistent across recent studies. Therefore, there is need for early detection of infection in patients with AAV, and prompt and effective therapeutic measures against infection may improve disease outcome.

Patients with AAV have been shown to have an increased infection risk in comparison with a matched background population.⁹ To our knowledge, this is the first article to report the association between the infection profile (site and causative pathogens) during the first 3 months and early outcome of AAV. Our results suggested that respiratory infection and Gram-negative bacterial and fungal infection during the first 3 months were independently associated with 1-year mortality. Respiratory infection in AAV, as the most common infection type, is almost unanimous in all studies.^{4–7 10 16 18 19 25–28} Due to the fact that patients with AAV often exhibit pulmonary involvement at the onset, which presents as interalveolar haemorrhage, the function of the endothelium is possibly damaged. The immunosuppressive status resulting from the induction treatment suppresses the immunity processes of the local pulmonary barrier. This cumulative effect could be a plausible explanation for the higher incidence of respiratory infection and higher association with early mortality. Regarding causative pathogens, there is heterogeneity in the literature results, although most of them have reported opportunistic pathogens.^{18 20 25 29} Immunodeficient or immunocompromised patients, such as

those with HIV, transplant status or long-term use of immunosuppressive drugs, consistently have a higher risk of opportunistic infection. In our article, Gram-negative bacteria and fungi were the main causative pathogens in our patients. Opportunistic infection usually indicated a disrupted immune system or severely altered microbial flora and should be considered with vigilance as a predictor of poor outcome.

Older age, diabetes, impaired renal function, lymphopenia, immunosuppressive therapy and a high cumulative dose of steroids were reported to be independent risk factors for infection in previous studies.^{46–14 18 37 38} Consistent with these findings, our results revealed that patients with infection were older, had more comorbidities, had a higher BVAS at the time of diagnosis, had more severe renal damage and received a higher dose of prednisone. The cumulative dose of prednisone was higher in patients who had experienced at least one infection event during the first 3 months in our study. Fast control of AAV in the early stage of the disease usually demands a higher dose of steroids and immunosuppressant therapy. However, high-dose glucocorticoid therapy also increases the risk of infection events. Recently, a randomised clinical trial in Japan compared the doses of high-dose prednisone (1 mg/kg/day) and reduced-dose prednisone (0.5 mg/kg/day) in patients with AAV assigned to RTX therapy. The results indicated that the severe infection risk of the high-dose group was augmented by 12.8% (95% CI 1.3% to 24.2%) compared with that of the reduced-dose group, with a non-inferior remission rate at 6 months.¹¹ Similar results were given in the well-known PEXIVAS trial¹², in which steroid dosing was assessed during treatment of AAV. Steroid reduced-dose group reported less severe infection event compared to standardised-dose group (incidence rate ratio, 0.69; 95% CI, 0.52 to 0.93). Taken together, the evidence shows that it is necessary to balance the control of vasculitis activity and the infection events secondary to a high dose of immunosuppressive treatment. Clinicians should be more cautious of cumulative prednisone doses in elderly patients with AAV with high disease activity or renal impairment. Although the use of a methylprednisone bolus and immunosuppressor agent is quite effective in reducing disease damage at onset, the infection risk should also be weighed beforehand out of prudence.

To improve the survival outcome, based on the experience from non-HIV severe immunosuppressed patients, prophylactic use of TMP-SMX is suggested in patients with AAV. A dose of 800/160 mg on alternate days or 400/80 mg/day is recommended by EULAR³² and 960 mg thrice weekly by BSR.³³ However, data specific for AAV are scarce. Available data from Kronbichler *et al* showed that TMP-SMX reduces the risk of infection in RTX.¹⁵ Moreover, Stegeman *et al* reported that TMP-SMX is associated with prolonged disease-free survival at the 2-year time point.³⁹ Another recent retrospective study including 3524 patients in Korea also indicated TMP-SMX prophylaxis reduced the incidence of *P.*

jirovecii infection in patients receiving RTX treatment.³¹

In our article, after adjustment for demographics, baseline features and therapy variables, TMP-SMX prophylaxis was found to be a protective factor of short-term survival. However, the long-term effect on survival, infection or relapse could not be examined by our existing data. In earlier studies, a higher mortality was reported in those without TMP-SMX prophylaxis. The causes of death were usually due to severe infectious complications, and these patients were often simultaneously infected with multiple pathogens.^{30 40} Improved disease outcome might result from a multifactorial combination of drugs, compromising new therapeutic regimens, a reduction in the corticosteroid dose used, closer patient follow-up, early detection of infections and infection prophylaxis. Therefore, our results should be cautiously interpreted. Prolonged follow-up for assessments of the infection rate and relapse might be needed when the effect of TMP-SMZ prophylaxis is reviewed. Moreover, more high-quality studies should be designed to standardise the dose and duration of TMP-SMZ prophylaxis in patients with AAV.

Our study had many strengths. To the best of our knowledge, this study is the largest cohort of patients with AAV in southern China. Then, regardless of suspicion, infections were screened monthly. Clinical presentation, serological results, imaging and culture of samples in this study were taken together to identify the infection site and its causative pathogens. It provided more reliable and close information. An intact record prevents physicians from neglecting latent infection. However, this study had some limitations. First, the intrinsic problem of this study is that as a clinical observation, it was consistently difficult to clearly distinguish whether infection was related to treatment or secondary to disease activity. More prudence must be given in regard to the interpretation of the results. Second, another well-discussed problem in patients with AAV, the association between infectious events and different immunosuppressive regimens, especially CYC and RTX, could not be presented with our existing data because of the skewed distribution of the induction strategy in our cohort (only one patient received RTX for induction therapy until 2018 in our data set). The last limitation of this study is that only the infection and 1-year mortality were analysed. The association of long-term survival, renal progression or disease remission has not been a focus.

In conclusion, infection is a common and important complication in patients with AAV, especially in those with respiratory infection and opportunistic infections of Gram-negative bacteria and fungi. They are associated with early mortality. TMP-SMX prophylaxis might improve short-term outcome. In addition, the balance of early disease control and potential infection risk should be treated with delicacy, and we recommend that patients with AAV undergo systematic screening for infection before starting immunosuppressive therapy.

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Competing interests None declared.

Patient and public involvement statement Patients were not involved in the study execution phase; however, the study aim and design were communicated with patients either in person or on phone. They were encouraged to provide feedback on treatment and infection screening to ensure sensible reporting. As clinicians and researchers, we also provided basic educational materials and evidence-based opinions, which contributed to the optimization of patient care.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by the Ethics Research Committee of Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University (2012-40). This study was performed in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data are available on reasonable request. Requests can be sent to pinkyfinger@126.com.

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