Predictors for Mortality in Patients with Antineutrophil Cytoplasmic Autoantibody-associated Vasculitis: A Study of 398 Chinese Patients

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ABSTRACT. ***Objective.*** Patients with antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) have high mortality despite the introduction of immunosuppressive therapy. We investigated factors associated with mortality of patients with AAV in a single Chinese cohort.

Methods. A total of 398 consecutive patients with AAV diagnosed in our center were recruited. Clinical and laboratory data were collected retrospectively. The predictive values of variables associated with mortality were analyzed.

Results. During followup of a median duration 25.5 months (range 1–196 mo), 135 out of 398 patients (33.9%) died, with 83 deaths within the first 12 months after diagnosis. Independent predictors of all-cause mortality were age ($p < 0.001$), secondary infection ($p < 0.001$), pulmonary involvement of AAV ($p = 0.012$), and initial renal function ($p = 0.001$). Secondary infection was the leading cause of death (53/153, 39.3%) during the first year after diagnosis, while cardiovascular event was the leading cause of death (15/53, 28.8%) after 12 months from diagnosis. Independent predictors of secondary infection were age ($p = 0.002$), initial renal function ($p = 0.041$), lymphocyte counts in the peripheral blood ($p = 0.03$), and underlying pulmonary involvement of AAV ($p = 0.001$).

Conclusion. Secondary infection is the overall leading cause and independent predictor of death in patients diagnosed with AAV. Cardiovascular event is a major cause of death during the late followup. Prudent monitoring should be given to patients of advancing age with renal dysfunction to reduce adverse events, especially infectious complications. (First Release Aug 1 2014; J Rheumatol 2014;41:1849–55; doi:10.3899/jrheum131426)

Key Indexing Terms:
ANTINEUTROPHIL CYTOPLASMIC AUTOANTIBODY VASCULITIS
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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of necrotizing vasculitis associated with ANCA, and in particular, specific for myeloperoxidase (MPO) or proteinase-3 (PR3). AAV affects predominantly small vessels with few or no immune deposits[1]. The major clinical and pathological variants of AAV include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA; previously Churg-Strauss syndrome), and renal-limited vasculitis (RLV)[1]. Left untreated, patients with active AAV have poor prognosis, with a mortality of around 80% at 1 year[2]. The introduction of immunosuppressive therapy with corticosteroids and cyclophosphamide (CTX) has led to dramatic improvement in prognosis, with a remission rate of 80%–90% during the past decades[3].

However, patients with AAV are still at increased risk of death compared with an age- and sex-matched population despite immunosuppressive therapy[4]. Therefore, it is relevant to analyze the causes of death and to identify patients at high risk of death. Studies from Europe and the USA demonstrated that several variables were independent predictors of mortality in patients with AAV, including advanced age, adverse events of treatment (such as infection and leukopenia), decreased renal function, higher scores on the Birmingham Vasculitis Activity Score (BVAS), PR3-ANCA positivity, and pulmonary hemorrhage[4,5,6,7,8]. However, our previous studies demonstrated distinctive differences in the disease spectrum of AAV between Chinese and white patients. For example, Chinese patients

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were characterized by MPA preponderance, while a majority of patients in Western countries were diagnosed as having GPA[9,10,11,12]. Therefore, it is reasonable to investigate whether the above predictors for mortality in white patients are suitable for Chinese patients, or whether there are some other predictors of mortality in Chinese patients. Moreover, since secondary infection has been suggested to be an important factor associated with mortality in AAV[4,5,7,8], the predictors and major causes of secondary infection require clarification.

MATERIALS AND METHODS

Patients. Three hundred ninety-eight consecutive patients newly diagnosed with AAV at the Institute of Nephrology, Peking University First Hospital, from 1997 to 2011, were analyzed retrospectively. Renal biopsy was performed at the time of diagnosis. All patients met the criteria of the Chapel Hill Consensus Conference definition for AAV[1]. Exclusion criteria were defined as follows[13]: (1) patients with EGPA, since EGPA is increasingly considered a distinct type of AAV with different manifestations and outcomes as compared to GPA, MPA, and RLV[14]; (2) patients with secondary vasculitis such as propylthiouracil-induced AAV, or with comorbid renal diseases, such as anti-glomerular basement membrane disease, IgA nephropathy, diabetic nephropathy, lupus nephritis, or membranous glomerulopathy.

Our research was in compliance with the Declaration of Helsinki and approved by the ethics committee of our hospital. Informed consent was obtained from each patient.

Detection of ANCA. ANCA tests were performed by both indirect immunofluorescence (IIF) assay and antigen-specific ELISA for all patients at the time of presentation and before immunosuppressive treatment was instituted. Standard IIF assay was performed according to the manufacturer's instructions (Euroimmun, Lübeck, Germany). In the antigen-specific ELISA, 2 ANCA antigens, PR3 and MPO, highly purified as described[15], were used in solid-phase assays.

Treatment. Induction therapy included corticosteroids in combination with CTX. Oral prednisone was prescribed at an initial dosage of 1 mg/kg/day for 4–6 weeks, with reducing doses over time to 12.5–15 mg by 3 months, and to 10 mg by 6–9 months, then with reducing doses over time to 5 mg or less by 18–24 months. The mean total prednisone dosage was 15.1 g (SD 13, range 8–20 g). CTX was administered by daily oral dose 2 mg/kg/day or intravenously 0.5–0.7 g/m^2 every month. For daily oral CTX, it continued for 3–4 months. Intravenous CTX continued for 6–9 months, usually 6–9 pulses. Therefore, the total amount was 9–12 g for daily oral CTX and 6–8 g for monthly intravenous CTX. A 25% dose reduction of CTX was carried out for those over age 65 years or those with renal insufficiency, and CTX was temporarily withdrawn for those who developed leukocytopenia (< 4000 cells/mm^3). Patients with acute renal failure or pulmonary hemorrhage received 3 pulses of intravenous methylprednisolone (7–15 mg/kg/day) before the standard induction therapy. Patients with severe pulmonary hemorrhage or acute renal failure requiring dialysis at diagnosis received additional plasma exchanges. For maintenance therapy, daily oral azathioprine (AZA) was given (2 mg/kg/day) for at least 2 years. Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) was recommended but was not mandatory, especially for those with severe renal impairment.

Data collection and definitions. Data were collected at the time of diagnosis and during followup. Disease activity was assessed with the BVAS[16].

We analyzed predictors of mortality, in particular, early mortality, defined as mortality within 12 months after diagnosis[5]. We also assessed events during followup including major infectious episodes and cardiovascular (CV) events. Major infectious episodes were defined as those requiring hospitalization or treatment with intravenous and/or prolonged antibiotics, as described[17]. Additionally, herpes zoster recurrences were also considered as major infections as they reflected consistent treatment-induced immunosuppression[17]. Mild infections such as rhinitis or bronchitis were not considered. All the major infections were classified broadly according to the site of infection and pathogenic organisms. CV events were defined as death from any CV cause, nonfatal stroke, nonfatal myocardial infarction, and coronary artery bypass graft or percutaneous coronary intervention, as described[18].

Statistical analysis. Differences of quantitative variables between groups were tested with the Student t-test (for normally distributed data) or nonparametric test (for data not normally distributed) as appropriate. Differences of qualitative results were compared using the chi-square test. Multivariate analysis of all-cause mortality and infection was performed with the CoX regression model. Since events during the followup were affected by baseline factors, we first assessed baseline factors (e.g., age, sex, disease type, ANCA type, disease severity, initial renal function, BVAS at diagnosis, involvement of major organs), and then assessed factors occurring during the followup (e.g., secondary infection, CV events, treatment) in separate CoX models. Then we used baseline factors with significance in the first model to adjust followup factors in the second model. We created segmental time-dependent covariates according to whether or not an individual patient developed certain events (e.g., major infectious episodes and CV events) during certain timeframes of followup as described[19,20]. We also evaluated the predictive performance of the 2009 Five Factor Score (FFS) in our cohort[21]. Variables assessed as potential predictors of infection included age, initial renal function, disease type, ANCA type, disease severity, initial laboratory findings in peripheral blood (e.g., complete blood counts), major organ involvement of AAV, and treatment. Variables associated with a given outcome at a p value < 0.1 in Kaplan-Meier analysis (categorical variables) or univariable CoX regression (continuous variables) were entered into the final multivariable model. Results were expressed as hazard ratios with 95% confidence intervals. The difference was considered significant if the p value was < 0.05. Analysis was performed with SPSS software (v 10.0; SPSS, Chicago, IL, USA).

RESULTS

General data. Among the 398 patients with AAV, 193 were male and 205 were female, with a median age of 66 years (range 17–90) at diagnosis. Among them, 357 (89.7%) were MPO-ANCA-positive while the other 41 (10.3%) patients were PR3-ANCA-positive. According to the Chapel Hill Consensus Conference definition[1], 269 out of 398 (67.6%) of these patients were classified as having MPA, 104/398 (26.1%) as GPA, and 25/398 (6.3%) as RLV. The median and average durations of followup were 25.5 and 37.1 months (range 1–196), respectively. In terms of treatment, 47 patients received plasma exchange, and 304 received monthly intravenous and 94 received daily oral CTX. The detailed general data is summarized in Table 1.

Predictors of mortality. During the followup, 135 out of 398 patients (33.9%) died. The cumulative proportion of survival at 1, 2, and 5 years was 77.4% (95% CI 73.1% to 81.7%), 70.3% (95% CI 65.5% to 75.1%), and 61.9% (95% CI 56.2% to 67.6%), respectively (Figure 1). There was no significant difference in mortality between patients diagnosed before (including) and after year 2004 (HR 0.920, 95% CI 0.632–1.34, p = 0.664). Independent predictors of all-cause mortality at baseline included age (increased by 10

Table 1. General data for the study population.

Characteristic	N
Sex, female/male	205/193
Age*, yrs	66 (53, 72)
ANCA by ELISA (MPO/PR3)	357/41
Diagnosis, MPA/GPA/RLV	269/104/25
Serum creatinine*, μmol/l	333.5 (127.8, 638.5)
Creatinine clearance rate*, ml/min	16.08 (7.13, 42.74)
BVAS*	20 (15–24)
Five Factor Score*	1 (1, 2)
Fever, n (%)	226/398 (56.8)
Fatigue, n (%)	258/398 (64.8)
Weight loss, n (%)	215/398 (54.0)
Muscle pain, n (%)	110/398 (27.6)
Arthralgia, n (%)	125/398 (31.4)
Rash, n (%)	77/398 (19.4)
Pulmonary involvement, n (%)	280/398 (70.4)
Pulmonary hemorrhage, n (%)	138/398 (34.67)
Pulmonary nodules/cavities, n (%)	71/398 (17.84)
Pulmonary interstitial fibrosis, n (%)	147/398 (36.93)
Renal involvement, n (%)	371/398 (93.2)
Ophthalmic, n (%)	84/398 (21.1)
Ear, nose, throat manifestations, n (%)	177/398 (44.5)
Upper respiratory tract, n (%)	90/398 (22.7)
Gastrointestinal**, n (%)	58/398 (14.6)
Nervous system, n (%)	82/398 (20.6)

*Data are 50th centile (25th, 75th centiles); **Gastrointestinal bleeding, perforation, infarction and/or pancreatitis[26]. BVAS: Birmingham Vasculitis Activity Score; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RLV: renal-limited vasculitis; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase-3.

yrs; HR 1.8, 95% CI 1.512–2.142, p < 0.001), pulmonary involvement of AAV (HR 1.796, 95% CI 1.137–2.836, p = 0.012), and initial renal function (increase of 24-hour creatinine clearance rate by 10 ml/min; HR 0.889, 95% CI 0.832–0.950, p = 0.001). Independent predictors during followup of all-cause mortality included secondary infection (HR 3.316, 95% CI 2.289–4.805, p < 0.001) and CV events (HR 2.285, 95% CI 1.388–3.764, p = 0.001). However, after adjustment by age, pulmonary involvement of AAV, and initial renal function, only secondary infection (HR 2.918, 95% CI 1.988–4.284, p < 0.001) remained an independent predictor of mortality. The most common cause of death was secondary infection (53/135, 39.3%), followed by CV events (25/135, 18.5%) and active vasculitis (25/135, 18.5%; Table 2). The 2009 version of the Five Factor Score also showed significant prognostic value in our patients. Five-year survival rates for scores of 0, 1, and ≥ 2 were 95%, 69% (compared to FFS = 0; p = 0.015), and 35% (compared to FFS = 0; p < 0.0001), respectively.

As shown in Figure 1, the survival curve of patients with AAV was especially steep mainly within the first 12 months after diagnosis. Indeed, 83 of the 135 deaths (61.5%) happened within the first 12 months after diagnosis. Therefore, we further analyzed factors associated with early mortality, i.e., mortality within the first 12 months. Age (increased by 10 yrs; HR 1.623, 95% CI 1.314–2.006, p < 0.001), pulmonary involvement of AAV (HR 1.880, 95% CI 1.018–3.471, p = 0.044), and initial renal function (increase of 24-hour creatinine clearance rate by 10 ml/min; HR 0.861, 95% CI 0.785–0.943, p = 0.001) were baseline independent predictors of 1-year mortality in the Cox regression. Independent predictors during followup of 1-year mortality included secondary infection (HR 5.030, 95% CI 3.154–8.021, p < 0.001) and CV events (HR 2.21, 95% CI 1.2–4.070, p = 0.011). After adjustment for age, pulmonary involvement of AAV, and initial renal function, secondary infection (HR 4.062, 95% CI 2.518–6.554, p < 0.001) remained to be an independent predictor of mortality

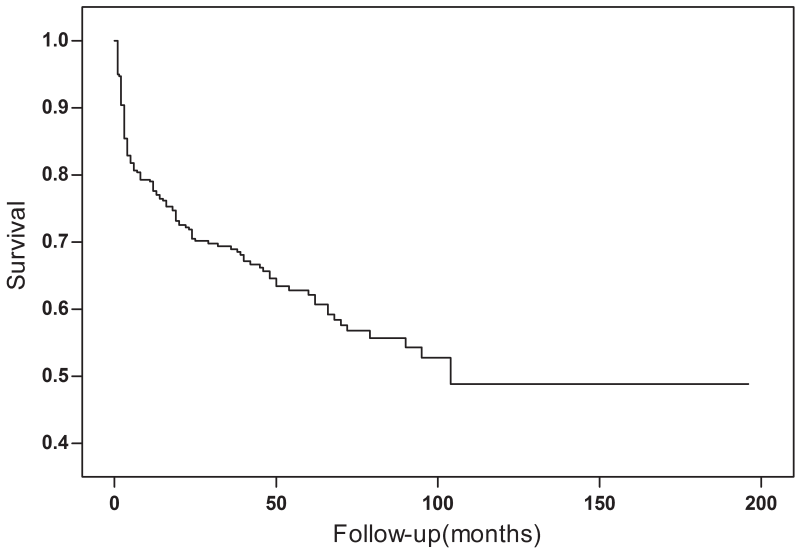

Figure 1. Survival of patients with AAV during followup.

Table 2. Causes of death within and after the first year of followup.

	Death Within 1 Year, n (%)	Death After 1 Year, n (%)	Total, n (%)
Active AAV	18/83 (21.7)	7/52 (13.5)	25/135 (18.5)
Infection	39/83 (47.0)	14/52 (26.9)	53/135 (39.3)
Pneumonia infection	37/83 (44.6)	10/52 (19.2)	47/135 (34.8)
Peritonitis/GI tract infection	2/83 (2.4)	3/52 (5.8)	5/135 (3.7)
Undefined	—	1/52 (1.9)	1/135 (0.7)
Cardiovascular events	10/83 (12.0)	15/52 (28.8)	25/135 (18.5)
Malignancy	3/83 (3.6)	3/52 (5.8)	6/135 (4.4)
Miscellaneous	3/83 (3.6)	4/52 (7.7)	7/135 (5.2)
GI hemorrhage	2/83 (2.4)	1/52 (1.9)	3/135 (2.2)
Complication of ESRD	1/83 (1.2)	3/52 (5.8)	4/135 (3.0)
Unknown	10/83 (12.0)	9/52 (17.3)	19/135 (14.1)
Total	83/135 (61.5)	52/135 (38.5)	135 (100)

AAV: antineutrophil cytoplasmic autoantibody-associated vasculitis; ESRD: endstage renal disease; GI: gastrointestinal.

(Table 3). The most common cause of early death was still secondary infection (39/83, 47.0%), followed by active vasculitis (18/83, 21.7%) and cardiovascular events (10/83, 12.0%). After 12 months from diagnosis, the leading cause of death was CV events (15/53, 28.8%), while secondary infection (14/53, 26.9%) was the second cause (Table 2).

Predictors of secondary infection. We further investigated factors associated with secondary infection, the leading cause of death in patients with AAV.

In our study, there were a total of 223 major infectious episodes in 175 patients (175/398, 44.0%) during the followup. The median and average durations from diagnosis to each infectious episode were 2 months and 13.4 months, respectively (range 1–106 mo). Most infectious episodes (158/223, 70.9%) occurred within the first 12 months, especially the first 3 months (129/223, 57.8%) after initiation of immunosuppressive therapy (Figure 2). Further, most of the patients who had infection developed their first major infectious episodes within the first 12 months after diagnosis (144/175, 82.3%). The median and average times to the first major infectious episodes during followup were 2 and 7.6 months, respectively (range 1–84 mo). The 12-month infection-free survival rate was 60.9% (95% CI 55.9% to 65.9%).

Table 3. Factors associated with early mortality. Hazard ratios for each variable were derived using Cox regression.

Factor	Hazard Ratio (95% CI)	p
Baseline predictors		
Age*	1.623 (1.314–2.006)	< 0.001
Initial creatinine clearance rate**	0.861 (0.785–0.943)	0.001
Pulmonary involvement of AAV***	1.88 (1.018–3.471)	0.044
Followup predictors		
Infection***	5.03 (3.154–8.021)	< 0.001
Cardiovascular events***	2.21 (1.2–4.070)	0.011
Followup predictors adjusted by baseline factors		
Infection***	4.062 (2.518–6.554)	< 0.001

*For every decade increase; ** for every 10 ml/min increase; ***yes versus no. AAV: antineutrophil cytoplasmic autoantibody-associated vasculitis.

In the Cox regression analysis, the independent predictors of infection within 1 year were age (increase by 10 yrs; HR 1.268, 95% CI 1.095–1.468, p = 0.002), initial renal function (increase of 24-hour creatinine clearance rate by 10 ml/min; HR 0.925, 95% CI 0.858–0.997, p = 0.041), lymphocyte counts in peripheral blood at diagnosis (increased by 1×10^9/l; HR 0.695, 95% CI 0.501–0.965, p = 0.03), and underlying pulmonary involvement of AAV (HR 2.323, 95% CI 1.427–3.782, p = 0.001). The total dosage of corticosteroids was not a predictor for infection. And there was no significant difference of the infection risk between patients receiving daily oral CTX and those receiving monthly intravenous CTX (HR 1.351, 95% CI 0.922–1.978, p = 0.123).

Then the pathogens of infection were analyzed. Bacterial infection was the most prevalent cause of the infectious episodes (127/223, 57.0%), including 7 (3.1%) cases of tuberculosis. Fungal infection took second place (36/233, 16.1%), 9 (4.0%) of which were caused by *Pneumocystis jirovecii*. None of the patients who developed PCP pneumonia were treated with PCP prophylaxis, mainly due to severe impairment of renal function. Viral infection amounted to a total of 12 (5.4%) episodes of infection, with herpes zoster being the leading cause (9 cases), followed by Epstein-Barr virus (2 cases), and cytomegalovirus (1 case) infections (Table 4).

Regarding the site of infection, pulmonary infection was the leading infection (170/223, 76.2%), followed by genitourinary and gastrointestinal infection (19/223, 8.5%, and 13/223, 5.8%, respectively). There were 12 events of sepsis (12/223, 5.4%), including 11 events caused by pulmonary infection and 1 by gastrointestinal infection, leading to 8 deaths in total (Table 2 and Table 4).

Since pulmonary infection was the leading cause of

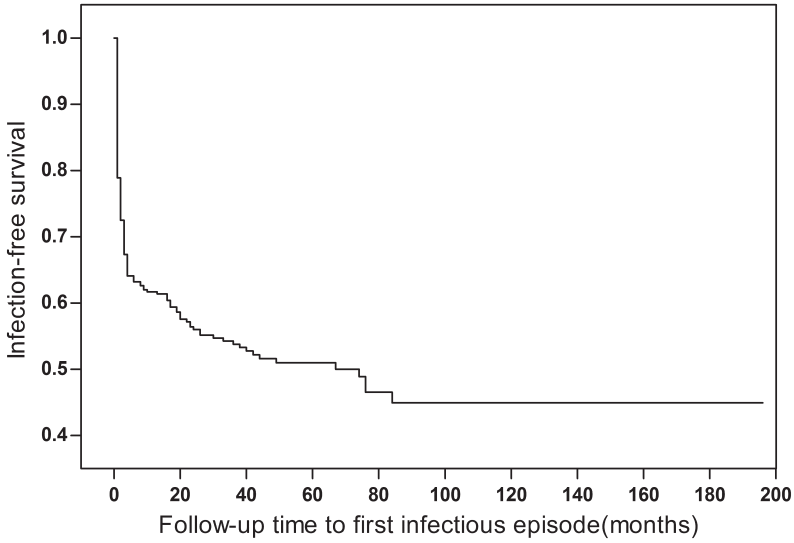

Figure 2. Infection-free survival of patients with AAV during followup.

Table 4. Details of major infectious episodes within and after 1-year followup.

	Infection Within 1 Year, n (%)	Infection After 1 Year, n (%)	Total, n (%)
Infection pathogens			
Bacterial	99 (62.7)	28 (43.1)	127 (57.0)
Viral	9 (5.7)	3 (4.6)	12 (5.4)
Varicella zoster	7 (4.4)	2 (3.1)	9 (4.0)
CMV	1 (0.6)	—	1 (0.4)
EBV	1 (0.6)	1 (0.4)	2 (0.9)
Fungus infection	25 (15.8)	11 (16.9)	36 (16.1)
Pneumocystis jirovecii	8 (5.1)	1 (1.5)	9 (4.0)
Other*	25 (15.8)	23 (35.4)	48 (21.5)
Locations of infection			
Pulmonary	116 (73.4)	54 (83.1)	170 (76.2)
Genitourinary	16 (10.1)	3 (4.6)	19 (8.5)
GI tract	12 (7.6)	1 (1.5)	13 (5.8)
Skin**	8 (5.1)	2 (3.1)	10 (4.5)
Other***	6 (3.8)	5 (7.7)	11 (4.9)
Total	158 (70.9)	65 (29.1)	223 (100)

*Clinically diagnosed infection without positive culture results. **Includes herpes zoster, cellulitis, etc. ***Includes infectious endocarditis, catheter-associated infection, meningitis, etc. CMV: cytomegalovirus; EBV: Epstein-Barr virus; GI: gastrointestinal.

infection, we further analyzed the factors associated with pulmonary infection. The independent predictors of pulmonary infection were age (increase by 10 yrs; HR 1.470, 95% CI 1.226–1.762, $p < 0.001$), initial lymphocyte count in peripheral blood (increased by 1×10^9/l; HR 0.487, 95% CI 0.339–0.701, $p < 0.001$), and pulmonary hemorrhage (HR 1.997, 95% CI 1.343–2.970, $p < 0.001$).

Predictors of CV events. CV event was another important cause of death in patients with AAV, especially after 12 months since diagnosis. In this retrospective study, a total of 35 CV events were recorded during followup.

In the Cox regression analysis, the independent predictors of CV events were age (increased by 10 yrs; HR 1.896, 95% CI 1.319–2.726, $p = 0.001$), hypertension (HR 2.333, 95% CI 1.062–5.129, $p = 0.001$), and initial BVAS (increased by 1 point; HR 1.095, 95% CI 1.039–1.54, $p = 0.001$).

DISCUSSION

Currently, patients with AAV still have much higher mortality compared with the general population in spite of immunosuppressive therapy. It is of great clinical importance to analyze the causes of death and to recognize patients at high risk of death.

Our study revealed that advanced age, impaired renal function, pulmonary involvement of AAV, and the presence of infectious episodes were independent predictors of mortality in patients with AAV. Age and impaired renal function have also been identified as independent predictors for mortality in European cohorts[4,7]. However, the survival probability of patients with AAV in the first year was much lower in our study than that reported from the European cohorts[4,5,7]. This might be at least partly explained by the predominance of MPA in Chinese patients with AAV. MPA patients have more severe renal involvement and fewer ear, nose, and throat manifestations compared with GPA patients[22]. This characteristic leads to patients with MPA experiencing delayed diagnosis as well as more chronic and severe lesions in kidneys, which respond poorly to treatment[23,24]. The baseline serum creatinine levels in our study were much higher than those of the European cohort (median values 333.5 vs 203 μmol/l, respectively), indica-

ting more severe renal involvement[4]. We also found the early mortality of patients with AAV, i.e., within the first 12 months, is a great challenge to physicians. A majority of deaths (61.5%) occurred within the first year after diagnosis, when both the intensity of immunosuppression and the burden of infection were the greatest. In our study, infection, rather than active vasculitis *per se*, was the leading cause of both early and longterm overall death in patients with AAV. However, a study by Bourgarit, *et al* showed that active vasculitis was the leading cause of early death followed by infection as the second cause in European patients with PAN, MPA, and EGPA[25]. Only 32.2% (192/595) of their patients had received immunosuppressants. Others received only steroid or plasmapheresis. Their treatment protocols were tailored according to different diagnoses and disease severity. This may have decreased the risk of infection while at the same time leaving active disease uncontrolled.

Probably due to the predominance of MPA in our patients, pulmonary involvement (280/398, 70.4%) was another common organ manifestation in our cohort. The pulmonary involvement was not only an independent prognostic factor for mortality, but also an independent predictor for secondary infection. The underlying pulmonary involvement of AAV might make the lungs vulnerable to infection, thus increasing the risk of mortality. The Five Factor Score proved to be a prognostic indicator in our cohort. Most of our patients presented scores for renal insufficiency (creatinine ≥ 150 μmol/l; 290/398, 72.9%), while only 19% (206/1108) of patients in the French cohort had such scores[21]. However, pulmonary involvement was not assessed by the 2009 Five Factor Score. Therefore, it is possible to investigate a more precise prognostic score system including pulmonary involvement as an item to fit the distinct disease spectrum in our cohort.

We found that the initial peripheral blood lymphocyte count was another independent predictor of secondary infection in our cohort. A previous study also reported that the severity of lymphopenia was associated with the risk of infectious complications[26]. Therefore, patients with underlying pulmonary involvement in AAV require extra attention to prevent infection, especially pulmonary infections. Thus, peripheral lymphocyte count is a potential measure to predict infectious complications in patients with AAV.

The use of corticosteroids has long been investigated as an important risk factor for infectious complications. Studies described that glucocorticoid therapy was associated with increased risk of infection in patients with autoimmune diseases[27,28]. However, our study did not prove the total dosage of corticosteroid as a predictor of infection. Since our study was retrospective, the results concerning the relationship between infection and treatment might not be convincing, and remain to be clarified in large-scale prospective studies. Nevertheless, prudent management and careful dosing of immunosuppressant by weighing the efficacy and side effects are called for in treating patients with AAV, especially older patients and those with renal dysfunction. In addition, preventive methods should be employed, especially administration of trimethoprim sulfamethoxazole for *P. jirovecii* prophylaxis[29].

In our study, CV disease was another major concern, representing the leading cause of death after 12 months from diagnosis when immunosuppressive therapy was gradually tapering. Further investigation of the underlying pathophysiology and methods to improve patients' CV outcomes are required.

There were some limitations in our study. First, most patients were recruited in a single nephrology center; therefore, referral bias might have influenced the risk of mortality as well as infection. Second, since PCP prophylaxis was not administered routinely, especially for those with severe renal impairment, this might have increased the infection rate. Further, disease relapses were not examined in the current study, and their contribution to risk of infection and overall mortality needs further investigation.

Secondary infection is the overall leading cause and independent predictor of death in patients with AAV. Cardiovascular events were a major cause of death during the late followup. Prudent monitoring should be given to patients of advanced age and those who have renal dysfunction to reduce adverse events, especially infectious complications.

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