Predictors of Treatment Resistance and Relapse in Chinese Patients with Antineutrophil Cytoplasmic Antibody-associated Disease

Yali Cao, Zhigang Tian, Wenge Li, Li Ma, Yongchao Yu, and Wenwen Ren

ABSTRACT. ***Objective.*** The prevalence and significance of treatment resistance and relapse in patients from China with antineutrophil cytoplasmic antibody-associated (ANCA) disease are poorly understood.

Methods. A total of 98 patients with ANCA vasculitis, diagnosed between January 2003 and December 2009 in the China-Japan Friendship Hospital, were enrolled in this retrospective study.

Results. Fifteen patients (15.3%) were categorized as having cytoplasmic and/or proteinase 3 (PR3) ANCA and 83 patients (84.7%) had perinuclear and/or myeloperoxidase (MPO) ANCA. After the induction phase treatment, the disease was resistant to therapy in 24 (25%) of the patients. A response to initial treatment occurred in 74 patients (75%). Of these 74 patients, remission was achieved and sustained with or without maintenance therapy in 41 patients (55%). Multivariable logistic regression models revealed that female sex was a statistically significant predictor of treatment resistance (OR 2.85; 95% CI: 1.06–2.86; p = 0.036). Additionally, elevated serum creatinine level, with each increment of 150 μmol/l, predicted resistance (p = 0.002). Among the 74 patients where remission was achieved, Cox proportional hazards models detected that those with PR3 ANCA were 1.31 times more likely to experience a relapse than were patients with MPO ANCA (95% CI: 1.01–5.35; p = 0.0001). Lung involvement was associated with an increased risk of relapse (HR 1.87; 95% CI: 1.12–4.35; p = 0.014). Although not significant, advanced age tended to be associated with relapse (p = 0.08).

Conclusion. Our findings highlight the important effect of female sex and severity of renal disease at presentation as predictors of treatment resistance, and PR3 ANCA and lung involvement as predictors of relapse. (J Rheumatol First Release March 15 2014; doi:10.3899/jrheum.130758)

Key Indexing Terms:
ANTINEUTROPHIL CYTOPLASMIC ANTIBODY TREATMENT RESISTANCE
RELAPSE PROTEINASE 3 REMISSION

Antineutrophil cytoplasmic antibody (ANCA) disease is characterized by necrotizing inflammation of small blood vessels. Disorders belonging to the group mainly include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilia granulomatosis with polyangiitis (EGPA)[1]. Therapy for ANCA disease typically includes induction therapies with corticosteroids and cyclophosphamide and maintenance therapies with azathioprine, mycophenolate mofetil, and cyclosporine[2]. Rituximab has been given to increasing numbers of patients especially after the publication of 2 randomized-controlled trials, showing that it was as effective as cyclophosphamide at inducing disease remission[3,4]. The majority of patients respond well to these therapies; remission is achieved in 85%. However, some of those patients who reached remission (about 11% to 57%) experienced a relapse. Some relapses are severe and may result in life-threatening infection and endstage kidney disease (ESKD)[3,4,5,6,7]. Fear of relapsing has resulted in physicians prescribing prolonged maintenance therapies to the majority of patients. Unfortunately, longterm use of immunosuppressive therapy will often result in unnecessary treatment and therapy-related risks that may outweigh the benefits of preventing relapse. Therefore, it is necessary to find predictors of treatment resistance and relapse to personalize the treatment.

Previous studies have demonstrated that female sex, African American ethnicity, older age, and the severity of renal disease at presentation are predictors of therapy

From the Department of Nephrology, Department of Rheumatology, China-Japan Friendship Hospital; Department of Surgery, Beijing LuHe Hospital, Beijing, China.

Supported by the National Natural Science Foundation of China (grant number 81200535) and the Scientific Research Foundation for Returned Chinese Scholars, Ministry of Human Resources and Social Security (grant number 2012).

Y. Cao, MD, PhD, Department of Nephrology, China-Japan Friendship Hospital; Z. Tian, MD, Department of Surgery, Beijing LuHe Hospital; W. Li, MD, PhD, Department of Nephrology, China-Japan Friendship Hospital; L. Ma, MD, Department of Rheumatology, China-Japan Friendship Hospital; Y. Yu, MD; W. Ren, MD, Department of Nephrology, China-Japan Friendship Hospital.

Address correspondence to Dr. W. Li, Professor of Medicine, Department of Nephrology, China-Japan Friendship Hospital, No. 2 Yinghua St., Chaoyang District, Beijing, 100029, P.R. China. E-mail: wenge_lee2002@126.com

Accepted for publication December 19, 2013.

resistance, while relapse is associated with proteinase 3 (PR3) ANCA and disease involvement of the lungs and upper respiratory tract[8,9]. It is not known whether these predictors, which have been demonstrated in US and other Western cohorts, apply to Chinese patients with ANCA disease. Substantial evidence suggests that geographical and genetic factors both play a part in the pathogenesis of ANCA disease. In northern Europe and Germany there are many more patients with GPA than with MPA[10,11]. But a study from Spain suggested that, in southern Europe, patients with MPA comprised about 2 to 3 times as many patients with GPA[12]. Assessment of disease by ethnic distributions in US cohorts has suggested GPA is more prevalent in whites than in African Americans[13]. MPA is more common in Asian countries, such as China and Japan[14,15]. Therefore, it is of interest to evaluate whether Chinese patients with ANCA disease share similar predictors of outcome with Westerners.

MATERIALS AND METHODS

Patients. A total of 102 patients with ANCA disease, diagnosed between January 2003 and December 2009 at the China-Japan Friendship Hospital, Beijing, and followed up by specialists in nephrology and rheumatology, were identified in our retrospective study. The end of the followup period was December 2012. Study patients gave informed written consent and participated according to China-Japan Friendship Hospital Institutional Review Board guidelines. Our hospital is affiliated with China's Ministry of Health and is a teaching hospital of Peking University and Beijing University of Chinese Medicine. We designed a consent form that allows for the files of hospitalized patients to be used for teaching medical students and material for retrospective research.

To be included in the study, patients were required to be positive for ANCA, as determined by both immunofluorescence microscopy and ELISA[16]. Standard indirect immunofluorescence assays were performed according to the manufacturer's instructions (Euroimmun). Ethanol-fixed human polymorphonuclear leukocytes were used to detect ANCA and monkey liver sections were used to exclude antinuclear antibodies. Cytoplasmic ANCA and perinuclear ANCA were distinguished according to staining patterns by 2 experienced technicians. Antigen-specific PR3 and MPO ELISA were determined by the ELISA kit (Euroimmun). Patients were categorized as having cytoplasmic and/or PR3 ANCA or perinuclear and/or myeloperoxidase ANCA (MPO ANCA). Patients who had perinuclear ANCA alone had to be negative for antinuclear antibodies to be included in the study. Two patients with target antigen specificities to both MPO and PR3 were excluded (Figure 1).

All of the patients met the criteria of the Chapel Hill consensus conference definition (for GPA, MPA, and EGPA). Patients with systemic lupus erythematosus, Henoch-Schönlein purpura, and rheumatoid arthritis were excluded. Two patients with EGPA were also excluded because of the small number (Figure 1). Organ involvement was determined by biopsy or by described criteria[8,17,18].

Methods. The induction therapy included corticosteroids in combination with cyclophosphamide. Prednisone was started at a dose of 1 mg/kg for the first month, and tapered progressively over 12–24 months. Cyclophosphamide was administered monthly either by intravenous (IV) pulse (0.5–1 g/m^2) or orally (1–2 mg/kg/day). A 25% dose reduction of cyclophosphamide was made for those participants aged 65 years and those with renal insufficiency. Patients with acute renal failure or pulmonary hemorrhage received 3 pulses of IV methylprednisolone (7–15 mg/kg/day) before standard induction treatment. Some patients with severe pulmonary hemorrhage received plasma exchanges. Azathioprine (2 mg/kg/day with a reduction for those with renal insufficiency) or mycophenolate mofetil (1 g/day) was given in maintenance treatment.

Histopathologic renal evaluations included 4 general categories: focal, crescentic, sclerotic, and mixed[19]. Briefly, the categories labeled focal, crescentic, and sclerotic are based on the predominance of normal glomeruli (≥ 50% normal glomeruli that are not affected by the disease process), cellular crescents (≥ 50% of glomeruli with cellular crescents), and globally sclerotic glomeruli (≥ 50% of glomeruli with global sclerosis), respectively. The mixed category represents a heterogeneous glomerular phenotype wherein no glomerular feature predominates (< 50% normal, < 50% crescentic, < 50% globally sclerotic glomeruli).

Treatment categories were based on the first therapy regimen used at diagnosis. Primary outcomes included treatment resistance, remission during or outside therapy, and relapse. Treatment resistance was determined at least 1 month after the start of treatment and defined as a progressive decline in kidney function with persistence of active urine sediment, or unchanged or new appearance of any extra renal manifestations of active vasculitis despite immunosuppressive therapy. Remission was defined as the absence of clinical signs or symptoms or laboratory evidence of vasculitis activity for more than 1 month. Relapse was considered only in patients in whom remission was reached (on and off therapy) and was defined as the return of clinical signs or symptoms or laboratory evidence of disease activity sufficient to warrant a sustained increase in immunosuppressive treatment. ESKD was defined by dialysis dependence for greater than 3 months or kidney transplantation. The disease activities were quantified by Birmingham Vasculitis Activity Score.

Statistical analysis. Comparisons among the 3 treatment response groups included chi-square tests or Fisher's exact tests for small sample size for categorical measures. Continuous measures were compared using Wilcoxon rank sum tests. Multivariate analyses of the treatment resistance were evaluated using logistic regression models, and results were expressed as OR with 95% CI and p values. Multivariate analyses of the time to relapse were performed using Cox proportional hazards models, and results were expressed as hazards ratios (HR) with 95% CI and p values. Kaplan-Meier analysis was used to assess patient and renal survival.

Demographic characteristics and other variables to be assessed as potential predictors of treatment resistance and relapse were determined before the study and are shown in Table 1. Selection of multivariable models was an iterative process that first included backward selection of variables that were statistically significant at $p < 0.05$. These measures were retained in the model; each additional measure of interest was added to the model 1 at a time and was retained if the measure changed the outcome by 20% or more compared with the univariate effect of that measure. A $p < 0.05$ was considered statistically significant. Analysis was performed using SPSS statistical software package (version 11.0).

RESULTS

Prevalence and demographic features. Cohort characteristics are shown in Table 1. Of the 98 patients, 54 (55.1%) were male and 44 (44.9%) were female. The average age was 60.7 ± 14.1 years (range 20–89). The median serum creatinine at presentation was 174.5 (range 74–568) μmol/l. Fifteen patients (15.3%) were categorized as having cytoplasmic and/or PR3 ANCA and 83 patients (84.7%) had perinuclear and/or MPO ANCA (Appendix 1). Twenty-five patients (25.5%) were GPA and 73 (74.5%) were MPA. Twelve patients (48%) were diagnosed as GPA with positive perinuclear-ANCA (pANCA)/MPO ANCA. The median length of followup was 36 months and ranged from 2 months (for those who presented with ESKD or who died of disease complications) to 9 years.

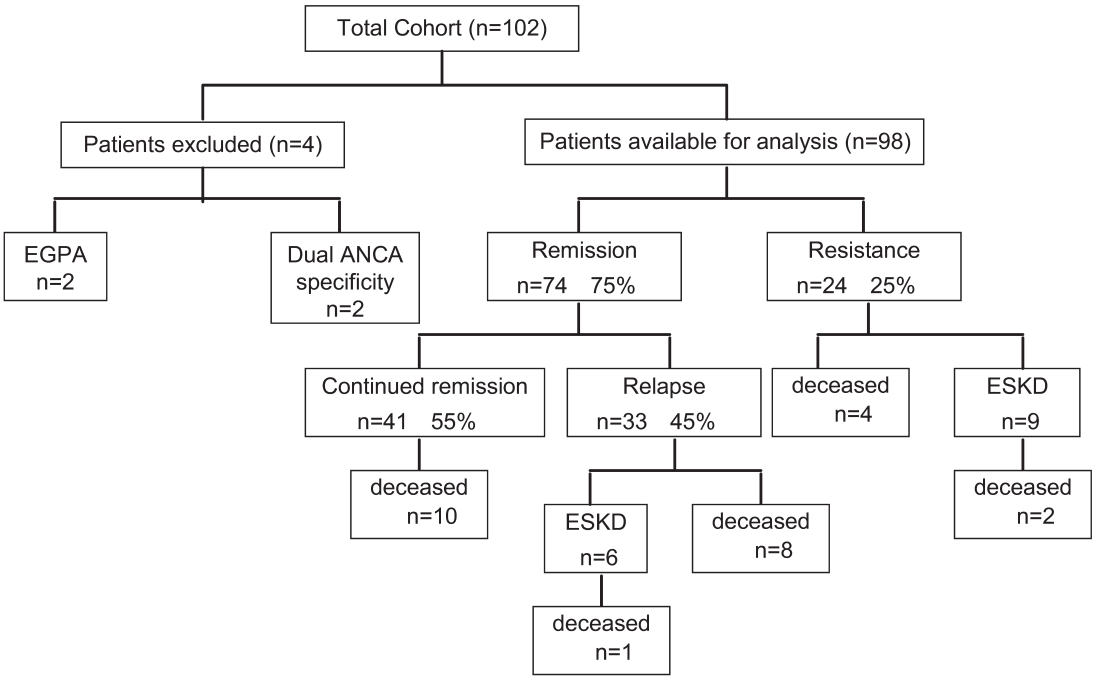

Figure 1. Characteristics of the Chinese patients with ANCA disease followed by nephrologists and rheumatologists at the China-Japan Friendship Hospital. EGPA: eosinophil granulomatosis with polyangiitis; ANCA: antineutrophil cytoplasmic antibody; ESKD: endstage kidney disease.

Table 1. The clinical characteristics of the 3 groups stratified by the treatment response.

Characteristic	Remission			
	Treatment Resistance, n = 24	Relapse, n = 33	Non-relapse, n = 41	p
Age, yrs				
Mean ± SD	72.7 ± 11.4	58.5 ± 13.2	54.7 ± 11.7	< 0.0001
Median (range)	74 (46–89)	60 (20–79)	58 (26–78)	—
Median followup, mos	36	37	36	0.89
Male/female	4/20	27/6	23/18	< 0.0001
ANCA phenotype, n (%)				0.02
PR3 ANCA seropositive	4 (17)	9 (27)	2 (5)	
MPO ANCA seropositive	20 (83)	24 (73)	39 (95)	
Disease type, n (%)				0.52
GPA	6 (25)	7 (21)	12 (29)	
MPA	18 (25)	26 (79)	29 (71)	0.52
Serum creatinine level, μmol/l*				
Mean ± SD	508.6 ± 200.8	167.7 ± 110.7	169.4 ± 138.6	< 0.0001
Median (range)	495 (46–789)	154 (56–632)	163 (55–749)	—
BVAS, median (range)	20 (13–29)	17 (15–27)	20 (15–25)	0.58
Renal biopsy measures				0.038
Focal	0	1	2	
Crescentic	4	6	8	
Mixed	1	2	1	
Sclerotic	6	1	0	
Organ involvement				
Lung	17	24	14	0.001
Upper respiratory tract	8	12	5	0.036
ESKD, n (%)	9 (38)	6 (18)	0 (0)	0.01
Mortality, n (%)	6 (25)	9 (27)	10 (24)	0.96

*Peak serum creatinine level at diagnosis. ANCA: antineutrophil cytoplasmic antibody; PR3: proteinase 3; MPO: myeloperoxidase; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; BVAS: Birmingham Vasculitis Activity Score; ESKD: endstage kidney disease.

A total of 91 cases (93%) had renal involvement, of which 84 (92%) had hematuria; 74 (81%) had proteinuria [with 7 (8%) proteinuria > 3.5 g/d]; 77 (85%) had raised serum creatinine, with 56 (62%) cases diagnosed with acute renal failure; and 4 cases (4%) with nephrotic syndrome. Altogether there were 32 cases (32.7%) of renal biopsy, of which 7 (22%) were classified as sclerotic ANCA-associated glomerulonephritis. Of the 25 biopsies left, 3 (9%) were classified as focal. After taking out the biopsies that were identified as sclerotic and focal, 18 (56%) were classified as crescentic. The remaining 4 (13%) were classified as a mixed phenotype. Seventeen cases (17%) had gastrointestinal involvement and 55 patients (56%) had manifestations of lung diseases. The involvement of other organs including joint, upper respiratory tract, skin, eye, and nerve were 27%, 25%, 18%, 16%, and 11%, respectively.

Of the 98 patients, 32 and 66 cases received prednisone together with daily oral or monthly IV cyclophosphamide, respectively. In response to the induction phase of treatment, disease was resistant to therapy in 24 (25%) of the patients. A response to initial treatment occurred in 74 patients (75%). Of these 74 patients, remission was achieved and sustained with or without maintenance therapy in 41 patients (55%). The median duration of the maintenance therapy was 2.3 years. Thirty-three patients (45%) experienced a relapse over a median of 23 months from the time therapy was initiated. Characteristics of the patients stratified by the treatment outcomes are summarized in Table 1. With respect to demographic features, patients with treatment resistance were the eldest ($p < 0.0001$). The median followup times were similar among the 3 groups ($p = 0.89$). There were more women in the treatment resistance group than in the others ($p < 0.0001$). For ANCA specificity, there were more patients with PR3 ANCA in the relapse group (27%) compared to the treatment resistant (17%) and sustained remission (5%) groups ($p = 0.02$). However, there were no differences among the 3 groups when stratified by the disease category. Mean serum creatinine of patients with treatment resistance was the highest compared to those who responded to treatment and relapsed or remained in remission ($p < 0.0001$). The renal biopsy categories were also different among the 3 groups with more sclerotic phenotype in the treatment resistance patients ($p = 0.038$). As to organ involvement, lung ($p = 0.001$) and upper respiratory tract ($p = 0.036$) involvement were statistically different among the 3 groups. There were no substantial differences in other organs, including renal, gastrointestinal, joint, skin, eye, and nerve (data not shown). For the patients with treatment resistance, the progression to ESKD was more frequent ($p = 0.01$). The number of deceased patients with all-cause mortality was similar in the 3 groups ($p = 0.96$).

Predictors of treatment resistance. Based on findings obtained from the above comparison, the following factors were evaluated in multivariable logistic regression models: age, sex, ANCA specificity, disease categories, serum creatinine, lung, and upper respiratory tract involvement. Female sex was a statistically significant predictor of treatment resistance (OR 2.85; 95% CI: 1.06–2.86; $p = 0.036$). Additionally, elevated serum creatinine level was found to be a predictor of treatment resistance, with each increment of 150 μmol/l associated with a 5.27 OR of resistance ($p = 0.002$). Controlling for sex and serum creatinine, age, ANCA specificity, disease categories, and organ involvement were not statistically significant for predicting treatment resistance (Table 2).

Predictors of relapse. Among the 74 patients where remission was achieved, those with PR3 ANCA were 1.31 times more likely to experience a relapse than were patients with MPO ANCA (95% CI: 1.01–5.35; $p = 0.0001$). Lung involvement was associated with an increased risk of relapse (HR 1.87; 95% CI: 1.12–4.35; $p = 0.014$). Advanced age tended to be associated with relapse ($p = 0.08$), whereas specific diagnosis or organ involvements did not show evidence of influencing the risk of resistance (Table 2).

Effect of treatment resistance and relapse on longterm outcome. ESKD occurred in 38% of patients who were resistant to therapy (9 of 24), 18% of those who were in remission but relapsed (6 of 33) in median intervals of 10.9 and 29.2 months, respectively. None of the patients who did not relapse experienced ESKD during the followup. The Cox model with time-dependent covariates revealed that the likelihood of progression to ESKD was 2.3 times (95% CI: 1.7 to 8.4 times) higher among those patients who were resistant to treatment compared with those who were not ($p = 0.001$). A Kaplan-Meier curve of kidney survival reflected a treatment response effect ($p = 0.001$), with the treatment resistance group progressing to ESKD faster than the remission groups with and without relapse, and those experiencing a relapse were more likely to progress to ESKD than those who had a sustained remission (Figure 2).

The patients' 1-year survival was 91.8% in this cohort. There were 5 and 20 patients who died during the induction and maintenance phase, respectively. Death from any cause was observed in 25% (6 of 24) of patients who were treatment resistant, 27% (9 of 33) of those who responded to the therapy but relapsed, and 24% (10 of 41) of those who did not relapse in the median times of 4.9, 20.2, and 39.2 months, respectively. The Kaplan-Meier curve reflected that there was no statistical evidence for a difference in all-cause mortality among the 3 groups ($p = 0.425$; Figure 3).

DISCUSSION

ANCA disease is a common multisystem autoimmune disease and is an important cause of mortality (if untreated) and morbidity (despite current aggressive treatment). To limit the incidence and severity of treatment resistance and

Table 2. Multivariable predictors of treatment resistance and relapse.

Predictor	Predictors of treatment resistance, n = 98*		Predictors of relapse, n = 74†	
	OR (95% CI)‡	p‡	Hazard Ratio (95% CI)‡	p‡
Female vs male	2.85 (1.06, 2.86)	0.036	0.72 (0.65, 6.87)	0.18
Age per 20 yrs	1.35 (0.43, 3.45)	0.99	1.45 (0.97, 3.59)	0.08
PR3 ANCA vs MPO ANCA	0.66 (0.11, 7.26)	0.86	1.31 (1.01, 5.35)	0.0001
GPA vs MPA	4.87 (0.63, 6.36)	0.52	0.81 (0.55, 3.27)	0.31
Lung involvement	0.52 (0.18, 3.28)	0.49	1.87 (1.12, 4.35)	0.014
Upper respiratory involvement	0.55 (0.12, 2.93)	0.85	1.01 (0.25, 2.33)	0.66
Serum creatinine (per 150 μmol/l)#	5.27 (1.29, 6.34)	0.002	0.89 (0.73, 3.56)	0.39

*Estimated using logistic regression. †Estimated using cause-specific proportional hazard models. ‡Evaluated in a model that controlled for all other measures identified by backward selection. #Peak serum creatinine level at diagnosis. ANCA: antineutrophil cytoplasmic antibody; PR3: proteinase 3; MPO: myeloperoxidase; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

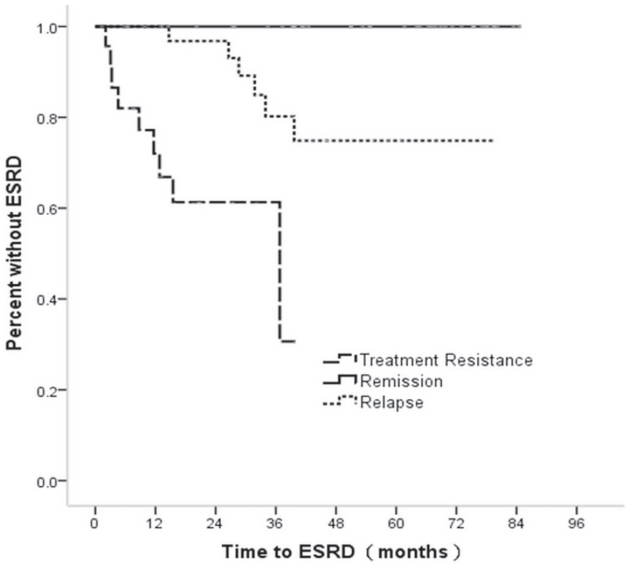

Figure 2. The Kaplan-Meier curve of kidney survival reflecting the treatment response effect. Log-rank analysis tested the null hypothesis that survivor functions are statistically different among the 3 groups ($p < 0.0001$), with treatment resistance group progressing to endstage kidney disease faster than the groups in remission with and without relapse. ESRD: endstage renal disease.

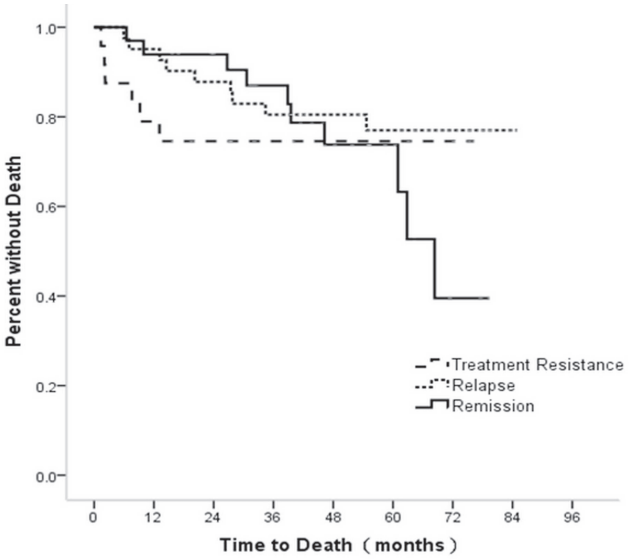

Figure 3. The Kaplan-Meier curve reflected no statistical evidence for a difference in all-cause mortality among the 3 groups ($p = 0.425$).

relapse, longterm maintenance therapy with immunosuppressive agents is commonly used. Unfortunately, the immunosuppressants currently used for maintenance therapy are associated with risks of infection and malignancy. Many studies were performed to identify the predictors of treatment resistance and relapse. However, most of the previous studies were primarily focused on white populations with ANCA disease. There was 1 study that focused on the role of certain HLA alleles and addressed the treatment resistance in Chinese patients[20].

In our study, patients with ANCA disease were followed up by physicians specializing in nephrology and rheumatology. The 75% remission rate was comparable with previously reported rates of 70% to 92%[2,5,8,21,22]. Treatment resistance was most common among patients presenting with higher serum creatinine levels, greater disease chronicity, and vascular sclerosis on renal biopsy. In previous reports, cumulative organ damage[23], glomerular sclerosis, interstitial infiltrates, tubular necrosis, atrophy[24], and other markers of chronic disease were consistently labeled as predictors of treatment resistance, despite differences in statistical models and outcome definitions. We also analyzed renal biopsies using the recent classification system by Dr. Berden[19] and found there were statistical differences among the 3 groups as to the renal pathology. However, this could not be included in the regression analyses for treatment response because much data was missing. In this cohort, we observed that female patients or those with severe kidney diseases might be resistant to initial treatment more often than other patients with ANCA disease. In our clinical practice, we speculated that female sex was associated with a diagnostic delay due to lower socioeconomic levels of women compared with men.

Information on socioeconomic indicators and access to care was not available. These factors should be explored to assess their potential role in delayed diagnosis and therefore in presumed treatment resistance among female patients. In the early 2000s, after the use of commercial indirect immunofluorescence-ANCA kits, and purified MPO and PR3 became routine in ANCA screening assays, ANCA disease was more easily recognized by physicians in some of the larger hospitals in China. Many patients with ANCA disease who could not be diagnosed in rural areas were referred to us. Unawareness of the systemic disease by physicians resulted in late diagnosis that might be attributable to the chronicity and severity of the disease. This showed that awareness of this disease still needs to be improved among clinicians in China. Earlier diagnosis and initiation of treatment might reduce the chronicity of the disease and increase the remission rate.

Disease relapse occurred in 45% of patients who reached remission; this is within the range of reported rates of 11% to 57%. In our study, the risk for relapse increased in the presence of anti-PR3 antibodies. This has also been demonstrated by research from the southeastern United States[8]. Two recent studies showed, both clinically and genetically, that ANCA specificity is extremely important and plays a pivotal role in the course of the disease[25,26]. Our finding of ANCA specificity predicting relapse also supported the cited studies. A European study reported that patients with GPA were more likely to relapse than patients with MPA[27]. We did not find that the specific disease diagnoses predicted relapse. We concluded that this difference in the predictive values of specific disease diagnosis might reflect differences in the relative frequency of the 2 diseases between Europe and China. Although cytoplasmic ANCA/PR3 ANCA was mainly found in patients with GPA and pANCA/MPO ANCA was mainly found in patients with MPA, these findings were not exclusive. There were more Asian patients diagnosed with GPA with positive pANCA/MPO ANCA than white patients.

An association between lung involvement and relapse was previously reported in 1 study of GPA[28] and 1 study of ANCA disease[8]. Generally, presence of active disease or lung involvement from vasculitis may foster an environment for *Staphylococcus aureus* infection. Nearly two-thirds of patients presenting with GPA are nasal carriers of *S. aureus* (significantly higher incidence than the general population) and nasal colonization with *S. aureus* greatly increases the risk of disease relapse, suggesting direct involvement[29]. Further, in a randomized controlled trial, prophylactic treatment with co-trimoxazole reduced relapse rates by 60%[30]. Pendergraft, *et al* suggested that exposure to *S. aureus* induced anti-complementary PR3 antibodies that, in turn, induced anti-PR3 antibodies and ANCA disease[31]. This study also demonstrated that advanced age was associated with a higher likelihood of relapse, although the difference was not statistically significant. In clinical practice, a dilemma exists concerning how to control active disease in older patients with ANCA disease effectively with fewer adverse events, especially infection. The strength of immunosuppressive therapy is weaker in older patients than in younger patients.

It has been previously suggested that prevention of relapse confers a benefit to longterm outcomes[8]. Similarly, we found an association between treatment resistance/relapse and subsequent progression to ESKD that was attributable to recurrent nephritis because no patient with non-renal relapse progressed to ESKD. In our study, there were more than 5 times as many patients with MPO ANCA than patients with PR3 ANCA. A total of 91 cases (93%) had renal involvement. The high prevalence of renal involvement may be, to some extent, a result of the high prevalence of MPO ANCA, which might be attributable to the delay in diagnosis. More patients who were PR3 ANCA-positive had upper respiratory and ophthalmic involvements, which probably reduced the patients' and doctors' delay. Earlier diagnosis and start of treatment might reduce the frequency of renal involvement[32]. Persistent undetected active nephritis may be an important risk factor for ESKD among patients without overt signs of systemic vasculitis.

Our study was limited in that the research was conducted in a prosperous city in China and some patients were referred to us from rural areas. Information regarding the clinical course at the rural hospitals was limited. In China, the recognition of ANCA disease by physicians in the city and those in the impoverished areas was totally different owing to the imbalance in the distribution of healthcare resources. The unawareness of ANCA disease by physicians in the rural areas and the resulting late diagnosis might contribute to the treatment response. Thus, the utility of these risk factors for decisions regarding treatment needs to be prospectively validated. Besides, the number of the included patients was quite small to be representative of the Chinese population. Further studies are required using a large cohort of patients to validate this result.

We observed that females and those with higher serum creatinine levels were more likely to be resistant to initial treatment. The presence of anti-PR3 antibodies and lung involvement were risk factors for relapse. Therefore, the ability to distinguish patients according to the response to treatment opens the possibility of more effective immunosuppressive therapy for those at higher risk and less toxic treatment for those at lower risk.

ACKNOWLEDGMENT

The authors acknowledge Dr. Susan L. Hogan from the Kidney Center of the University of North Carolina at Chapel Hill for her revision and correction of this manuscript. We also thank the State Key Laboratory of Kidney Disease (Chinese PLA General Hospital, 2011DAV00088) for its participation.

APPENDIX 1. Antineutrophil cytoplasmic antibody (ANCA) results of serum samples from IIF-ANCA kits and ELISA.

	Anti-PR3	Anti-MPO	Anti-PR3 and MPO (+)	PR3 and MPO (–)	Total
cANCA	14	0	1	1	16
pANCA	0	83	1	2	86
Total	14	83	2	3	102

PR3: proteinase 3; MPO: myeloperoxidase; cANCA: cytoplasmic ANCA; pANCA: perinuclear ANCA.

REFERENCE

1. Falk RJ, Jennette JC. ANCA disease: where is this field heading? J Am Soc Nephrol 2010;21:745-52.
2. Chen M, Kallenberg CG. ANCA-associated vasculitides—advances in pathogenesis and treatment. Nat Rev Rheumatol 2010;6:653-64.
3. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
4. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.
5. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351–61.
6. Reinhold-Keller E, Fink CO, Herlyn K, Gross WL, de Groot K. High rate of renal relapse in 71 patients with Wegener's granulomatosis under maintenance of remission with low-dose methotrexate. Arthritis Rheum 2002;47:326–32.
7. Bacon PA. The spectrum of Wegener's granulomatosis and disease relapse. N Engl J Med 2005;352:330–2.
8. Hogan SL, Falk RJ, Chin H, Cai J, Jennette CE, Jennette JC, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann Intern Med 2005;143:621–31.
9. Pagnoux C, Hogan SL, Chin H, Jennette JC, Falk RJ, Guillevin L, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody–associated small-vessel vasculitis. Arthritis Rheum 2008;58:2908-18.
10. Watts RA, Scott DGI. Epidemiology of the vasculitides. Curr Opin Rheumatol 2003;15:11-6.
11. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gutfleisch J, Peter HH, Raspe HH, et al. No difference in the incidences of vasculitides between north and south Germany: first results of the German vasculitis register. Rheumatology 2002;41:540-9.
12. Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, Rodriguez-Ledo P, Llorca J. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. Arthritis Rheum 2003;49:388-93.
13. Cao Y, Schmitz JL, Yang J, Hogan SL, Bunch D, Hu Y, et al. DRB1*15 allele is a risk factor for PR3-ANCA disease in African Americans. J Am Soc Nephrol 2011;22:1161-7.
14. Chen M, Yu F, Zhang Y, Zhao MH. Antineutrophil cytoplasmic autoantibody-associated vasculitis in older patients. Medicine 2008;87:203-9.
15. Fujimoto S, Uezono S, Hisanaga S, Fukudome K, Kobayashi S, Suzuki K, et al. Incidence of ANCA-associated primary renal vasculitis in the Miyazaki Prefecture: the first population-based, retrospective, epidemiologic survey in Japan. Clin J Am Soc Nephrol 2006;1:1016-22.
16. Hagen EC, Ballieux BE, van Es LA, Daha MR, van der Woude FJ. Antineutrophil cytoplasmic autoantibodies: a review of the antigens involved, the assays, and the clinical and possible pathogenetic consequences [review]. Blood 1993;81:1996-2002.
17. Flossmann O, Bacon P, de Groot K, Jayne D, Rasmussen N, Seo P, et al. Development of comprehensive disease assessment in systemic vasculitis. Ann Rheum Dis 2007;66:283-92.
18. Suppiah R, Mukhtyar C, Flossmann O, Alberici F, Baslund B, Batra R, et al. A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis. Rheumatology 2011;50:899-905.
19. Berden A, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010;21:1628-36.
20. Chang D, Luo H, Zhou X, Chen M, Zhao M. Association of HLA genes with clinical outcomes of ANCA-associated vasculitis. Clin J Am Soc Nephrol 2012;7:1293-9.
21. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniené J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.
22. Guillevin L, Cordier JF, Lhote F, Cohen P, Jarrousse B, Royer I, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997;40:2187-98.
23. Koldingsnes W, Nossent JC. Baseline features and initial treatment as predictors of remission and relapse in Wegener's granulomatosis. J Rheumatol 2003;30:80-8.
24. Bajema IM, Hagen EC, Hermans J, Noël LH, Waldherr R, Ferrario F, et al. Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. Kidney Int 1999;56:1751-8.
25. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012;367:214-23.
26. Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides. Arthritis Rheum 2012;64:3452-62.
27. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis 2003;41:776-84.
28. Kyndt X, Reumaux D, Bridoux F, Tribout B, Bataille P, Hachulla E, et al. Serial measurements of antineutrophil cytoplasmic autoantibodies in patients with systemic vasculitis. Am J Med 1999;106:527-33.
29. Stegeman CA, Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG. Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. Ann Intern Med 1994;120:12-7.
30. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprimsulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996;335:16-20.
31. Pendergraft WF 3rd, Preston GA, Shah RR, Tropsha A, Carter CW Jr, Jennette JC, et al. Autoimmunity is triggered by cPR-3(105-201), a protein complementary to human autoantigen proteinase-3. Nat Med 2004;10:72-9.
32. Hauer HA, Bajema IM, van Houwelingen HC, Ferrario F, Noël LH, Waldherr R, et al. Renal histology in ANCA-associated vasculitis: differences between diagnostic and serologic subgroups. Kidney Int 2002;61:80–9.