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# Anti-neutrophil cytoplasmic antibody seropositivity in young adults aged up to 35 years: kidney histopathological findings and patient outcomes

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## Abstract

**Objective:** To investigate the clinical features, pathological renal findings, and outcomes in young adults with anti-neutrophil cytoplasmic antibody (ANCA) seropositivity.

**Methods:** Adults aged ≤35 years, with ANCA seropositivity, who underwent renal biopsy and received treatment comprising a combination of corticosteroids and cyclophosphamide between January 2004 and May 2018, were retrospectively enrolled.

**Results:** Thirteen patients with ANCA seropositivity were included, all of whom presented with kidney disease at diagnosis: 10 (76.9%) with ANCA-associated pauci-immune glomerulonephritis, one with ANCA-associated crescentic glomerulonephritis with immune complex deposition, one with immunoglobulin A nephropathy, and one with membranous nephropathy. The median serum creatinine level was 183.2 μmol/l (range, 55.0–1024.0 μmol/l). Respiratory symptoms (9/13 [69.2%]) and nonspecific gastrointestinal symptoms (5/13 [38.5%]) were the most common extrarenal manifestations. Remission was achieved in 10 (91%) of 11 ANCA-associated nephritis cases, and median interval from diagnosis to relapse was 30 months (range, 9–63 months). Cumulative relapse-free survival rates at 1 and 5 years were 100% and 88.9%, respectively. Overall, 1-year and 5-year renal survival rates were 80.8% and 58.9%, respectively.

**Conclusion:** Renal histopathology varied in young adults with ANCA seropositivity. Although relapse rates in this young adult population were generally low, long-term renal survival rates remain unsatisfactory.

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## Introduction

The incidence of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), a common condition of the elderly, increases with age.[1,2] AAV exhibits variable manifestations that are often unpredictable and potentially life-threatening,[3] and the disease frequently affects the kidneys.[4] Renal involvement is an important factor in patient morbidity and mortality.[5]

Since the 1970s, a combination of corticosteroids (CS) and cyclophosphamide (CYC) has been used to induce remission in AAV,[6] transforming the outcome of this condition from an 80% 1-year mortality rate in untreated patients to remission in more than 90% of affected patients.[7] The dose of CYC is recommended to be adjusted for age due to an increased risk of adverse events.[3,8–10]

An increased risk of death and end-stage renal disease (ESRD) has been reported in older patients with AAV.[11–13] However, data regarding clinicopathological features and outcomes in younger age groups are limited, as AAV rarely affects young individuals. Whether clinical characteristics and outcomes of AAV differ between young adults and older individuals remains unknown. The aim of the present study was to examine young adult Chinese patients with AAV to characterize these rare cases and investigate their outcomes.

## Patients and methods

### Study population and setting

In this single-centre, retrospective, observational study, consecutive young adults with AAV, who received treatment at the China-Japan Friendship Hospital, Beijing, China, between January 2004 and May 2018, were identified from data within the China-Japan Friendship Hospital electronic medical record system. Patients were eligible for inclusion if they were aged $\leq$35 years at diagnosis; had undergone renal biopsy; had positive serum ANCA findings; and had undergone treatment with a combination of CS and CYC to induce remission. Any patient with eosinophilic granulomatosis with polyangiitis was excluded because AAV and eosinophilic granulomatosis with polyangiitis are presumed to have distinct clinical outcomes.[8,14] Patients with double-seropositivity for ANCA and anti-glomerular basement membrane (GBM) antibodies were also excluded.

The study protocol adhered to the Declaration of Helsinki and was approved by the ethics committee of the China-Japan Friendship Hospital (2021-113-K71). All patient data were deidentified for this study, and the reporting of the study conforms to STROBE guidelines.[15] As this was a retrospective observational study of deidentified data, patient informed consent was not required.

### Data collection

The following data were retrospectively extracted from the China-Japan Friendship Hospital Electronic Medical Record System: date/patient age at diagnosis; date/patient age at biopsy; sex; comorbidities; duration of symptoms prior to diagnosis; organ system involvement at disease onset; relevant laboratory data at diagnosis, including ANCA serotype, C-reactive

protein, serum creatinine (at diagnosis or before initiation of dialysis for patients who needed acute dialysis during the first hospital admission), 24-h urinary protein excretion, serum albumin and haemoglobin levels; histopathology; radiological examinations; relapses; treatment at time of diagnosis and relapse; and mortality data, including likely cause of death and comorbidities that may have contributed towards death. Disease activity at diagnosis, assessed according to the Birmingham Vasculitis Activity Score version 3,[16] was retrospectively computed by the same investigator (SJ). ANCA serotype was evaluated by indirect immunofluorescence or antigen-specific enzyme linked immunosorbent assay, as previously described.[17]

Renal biopsy specimens were evaluated using light microscopy, immunofluorescence staining, and electron microscopy. The investigators (SJ and GZ) recorded and classified the lesions according to the pathological description. The total number of glomeruli was defined as the maximum number of glomeruli in one tissue section (per case), excluding incomplete glomeruli on the edge. Normal glomeruli included glomeruli with minor mesangial or ischemic changes that did not exhibit significant proliferation, scarring, or crescent formation. 'Cellular' crescents were defined according to the presence of purely cellular lesions, or lesions with cellular components. Renal histopathology was grouped into four classes, based on the International Working Group of Renal Pathologists criteria:[20] focal ($\geq$50% normal glomeruli), crescentic ($\geq$50% glomeruli with cellular crescents), mixed (<50% normal, <50% crescentic, <50% globally sclerotic glomeruli) and sclerotic (>50% globally sclerotic glomeruli). The intensity of immunofluorescence staining of immunoglobulin and complements deposits was graded using a semi-quantitative method on a scale of 0–4+. When the staining was detected at $\geq$1+ (seemingly visible at low magnification but clearly visible at high magnification), it was regarded as positive.

## Data parameters and definitions

Renal involvement was defined according to the presence of haematuria (macroscopic or microscopic, red blood cell casts) or proteinuria (24-h urinary protein excretion >150 mg), an elevated serum creatinine level (out of reference range, >106 μmol/l) attributable to the disease, or histological evidence of pauci-immune necrotizing and/or crescentic glomerulonephritis. Lung involvement was considered likely in the presence of pulmonary hemorrhage;[18] respiratory failure; or radiographic evidence of infiltrates, nodules, or cavities without infection. The date of diagnosis was defined as the initiation of treatment with prednisone $\geq$30 mg/day, plasma exchange, or CYC; or day of biopsy, if never treated; or day of the first positive ANCA test result, if biopsy was not performed. Diagnoses were confirmed by reviewing patient records. Renal replacement therapy at presentation was defined as the need for acute dialysis during the first hospital admission. The estimated glomerular filtration rate (eGFR) was calculated for each patient at the time of diagnosis using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[19]

## Treatment regimens

Standard AAV treatment at the China-Japan Friendship Hospital during the study period comprised the following: Initiation of oral CS at a starting dose of 1.0 mg equivalent prednisone/kg/day (maximum 60 mg/day) for 4–6 weeks; Tapering of CS after initial therapy, depending on the clinical response and the results of laboratory assessments; Initiation of CYC at 10–14 days after CS, either with daily oral

CYC at 2 mg/kg/day (maximum 100 mg/day), fortnightly intravenous CYC at 0.4 g, or monthly intravenous CYC at 0.6–0.8 g; Continuation of oral CYC therapy for 3–6 months, or continuation of intravenous CYC for 8–12 months, up to total administered doses for oral or intravenous CYC of 8–10 g or 6–8 g, respectively. Patients with acute renal failure or pulmonary haemorrhage received pulses of intravenous methylprednisolone (500 mg/kg/day for 3 days, one to three courses) before standard induction treatment. Patients with rapidly progressive glomerulonephritis or severe pulmonary haemorrhage received additional plasma exchange therapy. Remission was maintained with a combination of low-dose CS (usually 5–10 mg/day) and other immunosuppressive agents, such as mycophenolate mofetil (1.0–2.0 g/day) or azathioprine (100 mg/day). Maintenance immunosuppression was continued for at least 2 years after the induction of sustained remission.

### Outcomes

Follow-up data were extracted from electronic medical records, from diagnosis until the following endpoints: relapse, patient death and/or ESRD, or study termination (May 2018). Remission was defined as the absence of disease activity (complete remission) or >50% reduction in Birmingham Vasculitis Activity Score and the absence of new manifestations (partial remission).[21] For patients with only renal involvement, remission was defined as stabilization or improvement in kidney function and resolution of haematuria, with no other manifestations of vasculitis. Treatment resistance was defined as unchanged or increased disease activity in acute AAV cases after 4 weeks of treatment with standard therapy; or lack of response, defined as ≤50% reduction in the Birmingham Vasculitis Activity Score after 6 weeks of treatment; or chronic, persistent disease, defined as the presence of at least one major or three minor items on the Birmingham Vasculitis Activity Score list after ≥12 weeks of treatment.[21] Relapse was defined as the return of clinical signs or symptoms, or laboratory evidence of disease activity sufficient to warrant a sustained increase in immunosuppressive therapy. Renal death, regarded as ESRD, was defined as the need for maintenance dialysis or kidney transplantation.

### Selection of previously published studies

The PubMed database was searched for previous studies published up to 6 April 2018. The search terms included "ANCA", OR "anti-neutrophil cytoplasmic antibody-associated vasculitis", OR "anti-neutrophil cytoplasmic antibody", AND "corticosteroids" AND "cyclophosphamide". Other search terms, such as "prednisone" or "prednisolone", were also used. Only reports published in English that explored outcomes in older adults receiving CS and CYC as the remission-inducing drugs, were included.

### Statistical analyses

Continuous data are presented as median (range) and categorical variables are presented as *n* (%) prevalence. Survival rates were analysed using Kaplan-Meier curves. All descriptive statistical analyses were performed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA).

## Results

### General demographic and clinical characteristics

A total of 18 young adults with AAV were initially identified to have received treatment at the China-Japan Friendship

Hospital between 2004 and 2018, and had undergone renal biopsies. Five patients were excluded: one due to diagnosis of eosinophilic granulomatosis with polyangiitis; one with only a clinical diagnosis; one double-seropositive for ANCA and anti-GBM antibodies; and two who received CS only or a combination of CS and mycophenolate mofetil. Thus, 13 young adults (aged $\leq$35 years) with ANCA seropositivity were enrolled into the study. The median age at AAV onset was 29 years (range, 22–35 years) and 12 female patients were included. For comparison, each patient case was allocated a number: P1–P13. Two cases had been previously diagnosed elsewhere before admission for treatment at the China-Japan Friendship Hospital: one male patient (P10) presented during his second relapse, while the other (P5) presented with treatment failure.

Of the 13 patients, 10 were myeloperoxidase-ANCA-positive (76.9%), and three were proteinase 3-ANCA-positive (23.1%).

## Renal and extra-renal manifestations

Key clinical features and serological findings at presentation are summarized in **Supplementary Table 1**. All patients had kidney abnormalities at presentation, with a median peak serum creatinine level of 183.2 µmol/l (range, 55.0–1024.0 µmol/l) and a median eGFR of 40.6 ml/min/1.73 $m^2$ (range, 4.0–134.7 ml/min/1.73 $m^2$). One patient (7.7%) required renal replacement therapy at presentation. Eight patients (61.5%) presented with rapidly progressive glomerulonephritis; five patients (P1, P2, P7, P10 and P11; 38.5%) presented with chronic kidney disease. All patients, except one (P7) with proteinuria only, presented with haematuria and proteinuria. Urine protein levels ranged from 0.23 to 4.5 g/24 h (median 2.25 g/24 h). Three patients (P4, P5 and P6; 23.1%) presented with nephrotic range proteinuria, while five patients (P1, P3, P6, P12 and P13; 38.5%) had gross haematuria.

Lungs were the most commonly involved extrarenal organs, affected in nine patients (P3–P6; P8; P10–P13; 69.2%), with haemoptysis in three patients (P3, P4 and P10; 23.1%), interstitial lung disease in one patient (P8; 7.1%), pulmonary nodules in one patient (P12; 7.7%), and radiographic infiltrates without evidence of infection in four patients (P5, P6, P11 and P13; 31.8%). The digestive tract was the second most commonly involved extrarenal organ (affected in 5 patients [38.5%]), with mostly nonspecific symptoms characterized by loss of appetite, nausea or vomiting. Other involved organs included the ears, nose, throat, eyes, joints, skin and central nervous system (Table 1).

## Histopathology

All patients underwent renal biopsy (Table 2), which showed ANCA-associated pauci-immune glomerulonephritis in 10 patients (P2–4, P6–9, P11–13; 76.9%). These cases constituted pauci-immune glomerulonephritis because electron microscopy results showed few or no electron-dense deposits, while

**Table 1.** Extra-renal involvement in 13 young adults with anti-neutrophil cytoplasmic antibody seropositivity.

| Parameter | Prevalence |
|---|---|
| Lung | 9 (69.2%) |
| Digestive tract | 5 (38.5%) |
| Upper respiratory tract | 4 (30.8%) |
| Skin purpura | 3 (23.1%) |
| Joint pain | 3 (23.1%) |
| Weight loss | 2 (15.4%) |
| Eye | 3 (23.1%) |
| Ear, nose and throat | 2 (15.4%) |
| Central nervous system | 1 (7.7%) |

Data presented as *n* (%) prevalence.

**Table 2.** Renal histopathology findings in 13 young adults with anti-neutrophil cytoplasmic antibody seropositivity.

| | Case number | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10* | P11 | P12 | P13 |
| Age at biopsy, years | 35 | 29 | 30 | 31 | 22 | 26 | 27 | 26 | 35 | 25 | 34 | 35 | 27 |
| Sex, M or F | F | F | F | F | F | F | F | F | F | M | F | F | F |
| Renal status at biopsy | | | | | | | | | | | | | |
| Required RRT | No | No | Yes | No | No | No | No | No | No | No | No | No | No |
| eGFR, ml/min/1.73m$^2$ | 117.1 | 96.21 | 3.95 | 8.18 | 17.46 | 12.87 | 94.28 | 66.72 | 17 | 89.74 | 113.64 | 16.57 | 40.55 |
| Peak SCr, μmol/l | 55 | 73 | 1024 | 554 | 311.8 | 392.3 | 75.1 | 183.2 | 295 | 100 | 61.5 | 296.8 | 150.9 |
| Glomerular findings | | | | | | | | | | | | | |
| Total glomeruli, n | 24 | 17 | 53 | 27 | 21 | 31 | 59 | 43 | 12 | 20 | 21 | 32 | 29 |
| Normal glomeruli, % | 83.33 | 35.29 | 0 | 0 | 0 | 6.45 | 16.95 | 0 | 0 | 40 | 4.17 | 12.5 | 68.96 |
| Fibrinoid necrosis, % | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 14.28 | 0 | 3.45 |
| Crescents, % | 8.33 | 52.9 | 98.1 | 100 | 100 | 93.55 | 66.1 | 100 | 100 | 30 | 57.14 | 68.75 | 20.68 |
| • Cellular, % | 8.33 | 0 | 43.4 | 100 | 42.86 | 64.52 | 11.86 | 100 | 91.67 | 10 | 57.14 | 25 | 13.79 |
| • Fibrous, % | 0 | 42.9 | 54.7 | 0 | 57.14 | 29.03 | 54.24 | 0 | 8.33 | 20 | 0 | 43.75 | 6.89 |
| Global sclerosis, % | 0 | 11.76 | 0 | 0 | 0 | 0 | 5.08 | 0 | 0 | 15 | 0 | 3.12 | 0 |
| IFTA | Mild | Mild | Mod | Mod | Mod | Mod | Mod | Mild | Mod | Mild | Mild | Mod | Severe |
| Histopathologic class | – | Mixed | Cres | Cres | Mixed | Cres | Mixed | Cres | Cres | – | Cres | Cres | Focal |

M, male; F, female; RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; IFTA, interstitial fibrosis and tubular atrophy (mild, 5–24%; moderate, 25–50%; severe, >50%); Mod, moderate; Cres, crescent.

*Patient underwent renal biopsy at time of second relapse rather than at first clinical diagnosis of anti-neutrophil cytoplasmic antibody-associated vasculitis. Thus, peak SCr level differs between Table 2 and supplemental Table 1.

immunofluorescence showed negative or false-positive staining results for immunoglobulins (e.g., IgA, IgG and IgM) and/or complement components (e.g., C3 and C1q). One patient (P5) displayed crescentic glomerulonephritis with both immunoglobulin (≥2+) and complement (≥2+) deposition in the glomeruli, constituting ANCA-associated crescentic glomerulonephritis with immune complex deposition.

The remaining two patients were pathologically diagnosed with either membranous nephropathy (P10), characterized by subepithelial/intramembranous deposits and granular capillary wall deposits of polyclonal IgG and C3, with extensive foot process effacement; or focal proliferative IgA nephropathy (P1). The key pathological features in P1 were a variable appearance on light microscopy with mesangial proliferation to the endocapillary hypercellularity; IgA-dominant deposits on immunofluorescence, predominantly in the mesangium; and mesangial deposits on electron microscopy.

A median of 29 glomeruli (range, 12–59) were observed in biopsy tissue sections from the 11 cases of ANCA-associated nephritis. A spectrum of histological classes of disease was noted, although none of the patients had sclerotic-class disease. One case (9%) was classified as focal, seven (64%) were crescentic, and three (27%) were mixed. Biopsy tissue from all cases (100%) showed glomerular crescents with median crescents of 93.5% (range, 20.7–100%). None of the patients who underwent biopsy showed a sclerotic category. Two patients (18%) had fibrinoid necrosis, while three patients (27%) had global sclerosis. Cases of interstitial fibrosis and tubular atrophy were more severe in patients with eGFR $<60\,ml/min/1.73\,m^2$ (moderate, 86%; severe, 14%) than in those with eGFR $\geq 60\,ml/min/1.73\,m^2$ (mild, 75%; moderate, 25%).

### *Treatment summary in 11 cases of ANCA-associated nephritis*

Two cases (P1 and P10) were excluded from further analyses because they represented types of renal disease other than ANCA-associated nephritis. Among the remaining 11 cases (**Supplementary Table 1**), 10 had not received any immunosuppressive agents prior to admission; one case (P5) had received intermittent single-dose methotrexate. During the first visit to the China-Japan Friendship Hospital, all patients received a combination of CS and CYC (oral or intravenous) to induce remission in new-onset or relapsing organ-threatening AAV. Two patients (18%) received a lower dose of CYC due to leucopenia (P8), or concerns regarding ESRD progression (P5). The median cumulative dose of CYC was 8 g (range, 3–12 g). Eight patients (73%) received pulse intravenous methylprednisolone (500 mg/kg/day for 3 days, one to three courses). Four patients (36%) received additional plasma exchange (median four sessions; range, 2–18 sessions).

### *Follow-up of 11 cases with ANCA-associated nephritis*

Three patients (P2, P6 and P12) were lost to follow-up within a median interval of 41 months (range, 13–53 months). No deaths occurred during follow-up. The median duration of follow-up after diagnosis of ANCA-associated nephritis was 41 months (range, 9–171 months). Resistance to induction therapy developed in one case (P5; 9%). Among the 10 patients (91%) who achieved remission, seven (70%) and three (30%) achieved complete and partial remission, respectively.

### *Relapse-free survival*

The clinical features of each relapse are summarized in Table 3. Among 10 patients

**Table 3.** Details of relapse or ESRD during follow-up of 11 young adults with ANCA-associated nephritis.

| Relapse* (Case No) | Time to relapse, months | Treatment at time of relapse | Treatment for relapse | Relapse frequency | Follow-up, months |
|---|---|---|---|---|---|
| P9 | 13 | CS only | CS, CYC | 4 | 122 |
| P11 | 63 | Off treatment 2 years | CS, CYC | 4 | 171 |
| ESRD# (Case No) | Time to ESRD, months | eGFR at presentation | Relapse before ESRD | Relapse after ESRD | Follow-up, months |
| P3 | 10 | $<60$ ml/min/1.73 $m^2$ | No | No | 16 |
| P4 | 33 | $<60$ ml/min/1.73 $m^2$ | No | No | 61 |
| P5 | 6 | $<60$ ml/min/1.73 $m^2$ | No | No | 35 |
| P6 | 13 | $<60$ ml/min/1.73 $m^2$ | No | – | 13 |
| P11 | 140 | $>60$ ml/min/1.73 $m^2$ | Yes | No | 171 |

ESRD was defined as a need for maintenance dialysis or kidney transplantation.
ANCA, anti-neutrophil cytoplasmic antibody; CS, corticosteroids; CYC, cyclophosphamide; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate.
*The follow-up interval of the other eight patients with relapse as the end point was 53 (P2), 16 (P3), 61 (P4), 13 (P6), 19 (P7), 9 (P8), 41 (P12), and 59 (P13) months, respectively.
#The follow-up interval of the other six patients with ESRD as the end point was 53 (P2), 19 (P7), 9 (P8), 122 (P9), 41 (P12), and 58 (P13) months, respectively.

who achieved remission during the treatment period, two (20%) experienced multiple relapses (4 times each). The median interval from diagnosis to first relapse was 30 months (range, 9–63 months). The overall 1-year and 5-year relapse-free survival rates were 100% and 88.9%, respectively.

### *Renal survival*

One patient (P3; 9%) began renal replacement therapy at the time of diagnosis, but stopped active treatment at the 10th month and the patient's renal function did not recover during the follow-up period. By the end of the study, five out of 11 patients (45%) had progressed to ESRD (Table 3). The median follow-up interval for ESRD was 33 months (range, 6–140 months). The cumulative renal survival rates at 1 and 5 years were 80.8% and 58.9%, respectively.

### *Relapse- and ESRD-free survival*

The median follow-up interval for the composite of ESRD and relapse was 19 months (range, 6–63 months), with six patients reaching the composite end point (four ESRD, one relapse, and one ESRD and relapse). The 1- and 5-year composite end-point (ESRD or relapse)-free survival rates were 80.8% and 48.5%, respectively.

### *Comparison with prognosis of elderly patients*

The prognosis of young adult patients with ANCA-associated nephritis was compared with that of elderly patients (median age $>50$ years) described in previously published reports (**Supplementary Table 2**).[22–26] Remission rates were found to be approximately 90% in both young adults and the elderly. In elderly patients, the relapse rates ranged between 32% and 45%, which was higher than the relapse rate for young adult patients who achieved remission in the present study (20%). The cumulative renal survival rates (81% and 59% at 1 and 5 years, respectively) in the present cohort were

comparable with the findings in published reports.

## Discussion

To the best of our knowledge, this is the first published series of patients with AAV aged ≤35 years. The median follow-up interval was 3.4 years, and several important observations were made in this young adult population with ANCA seropositivity: nonspecific gastrointestinal manifestations may be a distinctive extrarenal trait; renal involvement shows varied histopathology; and long-term renal survival is unfavourable, despite lower relapse and overall mortality rates compared with elderly patients.

In the current study, five patients (38%) presented with nonspecific gastrointestinal symptoms, an extrarenal manifestation that is unusual in the elderly.[27] This may be a distinctive extrarenal trait in relatively young patients with AAV. Two cases were represented by other types of renal disease, and renal biopsy in one of these cases demonstrated IgA nephropathy. In addition to proteinuria and gross haematuria, this patient had upper respiratory tract infection, and ear and nose symptoms without rash, joint symptoms and gastrointestinal symptoms that were unlikely due to Henoch-Schonlein purpura. These findings may have been fortuitous, because the incidence of IgA nephropathy in the general population is high. The other case was membranous nephropathy with ANCA seropositivity (proteinase-3 positive), which is also infrequently encountered. Proteinase-3-positive ANCA may be involved in the pathogenesis of membranous nephropathy through the formation of immune complexes.[28]

All patients in the present study presented with renal involvement at diagnosis. On renal biopsy, other renal diseases, such IgA nephropathy and membranous nephropathy, were frequently found (at least 15%), although they are infrequent in older patients.[20] This suggests that renal damage may be variable in young patients with AAV, however, the high prevalence of renal involvement might have partially resulted from selection bias, because many included patients were from the Department of Nephrology.

The prevalence of different histopathological classifications, proposed by Berden et al.,[20] was also described in the 11 young adults with ANCA-associated vasculitis. In the present cohort, there were smaller proportions of the focal (9% versus 16%) and sclerotic classes (0% versus 13%), and larger proportions of the mixed (27% versus 16%) and crescentic classes (64% versus 55%), compared with the findings by Berden et al.[20] The histopathological classes were related neither to kidney function at presentation nor to renal outcome. However, due to the small number of patients, the present findings must be interpreted cautiously.

During the follow-up period, the remission rate was 91% in survivors at 3 months. This was similar to previously reported results from elderly patients in the Czech Republic,[24] Japan,[25] and China,[26] suggesting that the treatment regimen is equally effective in both young and older patients with AAV. AAV is also a chronic relapsing condition, and in the present study, relapse occurred in 20% of the patients at a median of 30 months. Compared with previous studies in older patients,[24,26,29] young individuals generally had a lower relapse rate, the reason for which requires further investigation.

Relapse in AAV is a well-recognized, independent risk factor for subsequent progression to ESRD.[30] The association between poor renal function and a lower risk of relapse was first observed in a small series,[31] and was later confirmed by a large cohort study from the European

Vasculitis Study Group (EUVAS) therapeutic trials.[32] The present study also showed that AAV associated with renal insufficiency was less likely to relapse. Among five patients who progressed to ESRD, four did not experience any relapse. These cases had renal dysfunction at presentation. Another patient without renal dysfunction at presentation experienced relapse four times before progression to ESRD.

Renal involvement is frequently encountered in patients with AAV and is an important cause of ESRD. At the end of the follow-up period, nearly one-half of the living patients had independent renal function in the present study, and ESRD developed in 45% of the cohort. The cumulative renal survival rates (81% and 59% at 1 and 5 years, respectively) were comparable with previously published findings in elderly patients with AAV (**Supplementary Table 2**), suggesting poor renal survival in young adults.

The strengths of the present study include the young adult patient age, the use of a highly standardized CYC-based treatment regimen, and the long-term follow-up period. However, the results may be limited by several factors. First, the intrinsic limitation of the single-centre and retrospective study design may have led to bias. Secondly, the sample size was small. Finally, all patients were serum ANCA-positive, thus, differences between ANCA-positive and -negative vasculitis were not compared. These factors may have affected the assessments of clinical features, outcomes and treatment efficacy in young adult patients with AAV, and the results may not be generalisable to the wider population.

In conclusion, gastrointestinal involvement was an unusual feature of AAV in young patients, and renal involvement displayed diverse renal histology. A CYC-based regimen in young patients was associated with generally lower relapse rates compared with findings in the elderly. However, the long-term renal survival of young patients with AAV remains unfavourable. Further multicentre studies are required to determine whether the use of this classical regimen differs in efficacy between young and elderly patients with AAV.

## Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

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## Supplemental material

Supplemental material for this study is available online.

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