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ORIGINAL ARTICLE

Epidemiology and clinical features of childhood-onset anti-neutrophil cytoplasmic antibody–associated vasculitis: a clinicopathological analysis

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Abstract

Background This study was performed to determine the clinical features and outcomes of childhood-onset anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), particularly microscopic polyangiitis (MPA).

Methods A retrospective Japanese multicenter study was performed in patients diagnosed with AAV before 16 years of age.

Results Of 49 patients with AAV, 36 were female. The diagnoses were as follows: MPA ($n = 38$, 78%), granulomatosis with polyangiitis (GPA; $n = 9$, 18%), eosinophilic granulomatosis with polyangiitis (EGPA; $n = 1$, 2%), and other ($n = 1$, 2%). The median age at onset was 10.7 years, and median time to diagnosis was 2.0 months. Twenty-seven (55%) patients were identified through a school urinary screening program. Initial symptoms included fever and fatigue (45%), and renal (71%), pulmonary (29%), ocular (20%), and mucocutaneous involvement (22%). Although 27 (55%) patients achieved remission and none had died at the last follow-up, at least one recurrence occurred in 13 (48%) patients after a median of 48 months and was more common in patients with GPA ($P < 0.01$). After a median follow-up of 43 months, seven (14%) patients (all with MPA) progressed to end-stage renal disease (ESRD).

Conclusions Childhood-onset AAV has an estimated prevalence of 3.41–4.28 per million children and is characterized by female predominance and high frequency of detection in school urinary screening programs. More than 10% of patients with childhood-onset AAV still progress to ESRD without achieving remission. Histological chronicity is a factor associated with ESRD.

Keywords Anti-neutrophil cytoplasmic antibody–associated vasculitis · Microscopic polyangiitis · Pediatric patient · Vasculitis · Epidemiology

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is a group of disorders characterized by necrotizing inflammation of small- to medium-sized vessels. It has been classified into three entities: granulomatosis with polyangiitis (GPA, previously Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, previously Churg–Strauss syndrome). AAV generally occurs in adults and rarely in pediatric populations, with peak age at onset commonly between the fifth and seventh decades of life. Therefore, AAV has generally been studied in adults. Reports of large pediatric series are limited, and those that have been published to date have focused mainly on GPA [1–4]. Our knowledge of AAV in pediatric patients is based mostly on small cohort studies and case series [5–11]. In addition, reliable epidemiological data on pediatric patients with MPA are scarce because these diseases

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rarely occur in children. Therefore, the epidemiology of AAV in pediatric patients, such as annual incidence, prevalence, and disease course, is poorly understood.

The present study was a nationwide survey conducted to investigate the principal clinical and demographic features of pediatric AAV at presentation, to determine the course of the disease, and to identify factors associated with progression to end-stage renal disease (ESRD).

Materials and methods

Study design and population

We conducted a cross-sectional, nationwide retrospective survey in patients diagnosed with AAV before 16 years of age. Two questionnaires were sent in 2014 and 2015 to 1701 institutions in Japan, including all institutions that are members of the Japanese Society for Pediatric Nephrology and the Pediatric Rheumatology Association of Japan, all university and children's hospitals, and all general hospitals with > 200 beds. The inclusion criteria were all children < 16 years of age with AAV treated between 2012 and 2014.

The first questionnaire was designed to record the approximate number of children with AAV in each institution, whereas the second questionnaire was designed to collect data of each patient, including sex, age at initial symptoms, age at diagnosis, clinical and laboratory characteristics at disease onset, treatments received, duration of follow-up, relapse, and final outcome. Clinical characteristics included symptoms, signs, and organ involvement at presentation. The results of histological investigations were also collected.

Diagnosis and classification of AAV

AAV was diagnosed and classified based on the American College of Rheumatology or the 2012 Revised International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis [12] and the Endorsed Consensus Criteria for the Classification of Childhood Vasculitides of the European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society (PRES) [13]. The EULAR/Paediatric Rheumatology International Trials Organisation (PRINTO)/PRES proposed validated classification criteria were also used to update the classification criteria for childhood GPA [14].

Definitions

The estimated glomerular filtration rate (eGFR) was determined using the modified Schwartz formula [15]. Patients with urine protein to creatinine ratio of ≥ 0.15 g/gCr and of ≥ 2.0 g/gCr were classified as positive for proteinuria and nephrotic-range proteinuria, respectively. Hematuria was defined as ≥ 5 red blood cells/high-power field in centrifuged specimens. The Birmingham Vasculitis Activity Score (BVAS) was used to quantify disease activity [16]. For some data, such as serum creatine level and blood pressure, the Pediatric VAS was used in place of BVAS [17]. Remission was defined as a score of zero using the BVAS. Treatment failure was characterized as no improvement or deterioration of clinical symptoms and renal function. Relapse was diagnosed in patients showing reappearance or deterioration of clinical symptoms after achieving initial remission.

Statistical analysis

Basic demographic characteristics, clinical features, and laboratory findings were primarily extracted for patients who were uniquely classified as having MPA, GPA, or others. Depending on the type of data, patient characteristics at diagnosis were expressed as median with interquartile range (IQR) or percentage. Kaplan–Meier plots were used to assess time to ESRD, and time to first relapse. The log-rank test was used to compare relapse-free survival between different groups. Multiple logistic regression analysis was used to identify factors associated with ESRD.

The number of patients with AAV in Japan was estimated by dividing the number of cases reported in the first questionnaire by the response rate. However, as it is presumed that AAV is managed concentrating on the facilities of pediatric nephrologists and pediatric rheumatologists in each area, the patients were stratified based on the type of institution (i.e., university hospital, children's hospital, and general hospital), the number of beds (< 500 vs. ≥ 500), and the presence of pediatric nephrologists on staff (yes vs. no), assuming that the response rate was independent of the number of patients in each stratified category [18, 19]. Next, we weighted the number of patients in each category by the reciprocal of the predicted response rate and summed to estimate the total number of patients in Japan. To account for the inverse probability weights, robust standard errors were estimated for confidence intervals (CIs). Prevalence rate was calculated by dividing the total estimated number of patients by the size of the population at risk in Japan at the end of 2016, based on the report of the Statistics Bureau of the Ministry of Internal Affairs and Communications of Japan [20]. All statistical analyses were performed using STATA 12.0 (StataCorp, College Station, TX). In all analyses, $P < 0.05$ was taken to indicate statistical significance.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the ethical guidelines for epidemiological studies issued by the Ministry of Health, Labour and Welfare, Japan. The study was approved by the Ethics Review Committee of Graduate School of Medicine, Yokohama City University (institution of the

principal investigator, SI, ID: B151201009) before commencement. Informed consent was not deemed necessary because the data were obtained retrospectively from the patient charts.

Results

Cohort description

Responses to the first questionnaire were obtained from 1077 of 1701 institutions (response rate, 63.3%), and 63 children with AAV were reported. Consent for the secondary survey was obtained for 49 children (13 males and 36 females), and they were included in the present study. Therefore, 49 children were included for detailed patient background, treatment, and prognostic surveillance studies, while prevalence rate was calculated from 49 (consent for the secondary survey) to 63 (all patients with responses to the first questionnaire) children. Therefore, the prevalence of reported cases was then estimated to be 3.41–4.28 (95% CI, 2.33–6.19) per million children. Tables 1 and 2 summarize the patient characteristics. Median age at onset was 10.7 years (interquartile range (IQR), 8.3–12.4); median time to diagnosis was 2.0 months (IQR, 1.0–4.0). The 49 patients included in the study consisted of 38 (78%) with MPA, nine (18%) with GPA, one (2%) with EGPA, and one with drug-induced AAV. Children with MPA were significantly younger than those with GPA (10.0 vs. 12.8 years, respectively, $P < 0.01$). MPA was detected by a school urinary screening program in 27 of the 38 patients with MPA (71%). On serological analysis, 37 patients (76%) were positive for MPO-ANCA, eight (16%) were positive for PR3-ANCA, and two (4%) were negative for ANCA. Data for the remaining two (4%) patients were not available.

Clinical features

Table 1 shows the differences between MPA and GPA presentation. GPA is frequently heralded by the presence of systemic symptoms, such as fever (78%) and weight loss (33%). Otolaryngological (78%), ocular (56%), and pulmonary (44%) involvements were also common in patients with GPA. In contrast, renal involvement was the most common manifestation in patients with MPA (82%) and these patients showed a more severe clinical course than those with GPA.

Histopathological findings

The results of renal biopsies were available for 40 children with AAV. The detailed histopathological findings are presented in Table 3. Among these 40 patients, 77%, 58%, 40%, 75%, 70%, and 53% showed cellular crescent, fibrocellular crescent, fibrous crescent, global sclerosis, interstitial inflammation, and interstitial fibrosis, respectively. In addition, a kidney biopsy showing chronic lesions (global sclerosis + fibrocellular crescent + fibrous crescent) involving > 50% of glomeruli was associated with a significantly higher rate of progression to ESRD ($P < 0.01$). With regard to tubulointerstitial lesions, 70% and 53% had interstitial inflammation and interstitial fibrosis, respectively.

Treatment

Almost all children received corticosteroid induction therapy, with 39/49 (80%) receiving intravenous methylprednisolone pulse therapy. Thirty-one (63%) patients received a combination of corticosteroid and cyclophosphamide (intravenously (iv) in 14 patients with median total dose of 3000 mg (IQR, 2500–4500 mg)). Other induction therapies included azathioprine ($n = 18$, 37%), mizoribine ($n = 16$, 33%), plasma exchange ($n = 9$, 19%), rituximab ($n = 2$, 6%), mycophenolate mofetil ($n = 2$, 6%), tacrolimus ($n = 2$, 6%), cyclosporin A ($n = 2$, 6%), and methotrexate ($n = 2$, 6%). Maintenance therapy consisted of oral corticosteroids alone or in combination with other immunosuppressive agents in seven (14%) and 42 (86%) patients, respectively. Three patients (6%) were treated with rituximab.

Outcome after induction therapy

Data regarding remission were available for 47 patients. Of these, 27 (55%) achieved remission after induction therapy. Thirteen patients (28%) had at least one relapse after a median follow-up period of 3.6 years. Median time to relapse was 48 months (IQR, 23–79). Although the relapse-free survival rate for MPA was higher than that for GPA ($P < 0.01$), renal prognosis was very poor in MPA (Figs. 1 and 2). When the patients relapsed, corticosteroid therapy alone or in combination with another immunosuppressant (mycophenolate mofetil ($n = 3$), azathioprine ($n = 2$), mizoribine ($n = 2$), methotrexate ($n = 2$), and tacrolimus ($n = 1$)) was prescribed. Eight of 13 patients (62%) received corticosteroid therapy for relapse, with 5/13 (38%) receiving intravenous methylprednisolone pulse therapy. Four patients received cyclophosphamide (iv in all four patients). Other therapies for relapse included rituximab ($n = 7$), azathioprine ($n = 4$), mycophenolate mofetil ($n = 3$), and mizoribine ($n = 1$). During follow-up, 11 (22%) patients had chronic kidney disease (CKD) stages 3–5. Although no patients died during the study period, seven of 38 (18%) patients with MPA progressed to ESRD. In contrast, none of the patients with GPA progressed to ESRD. Figure 3 shows the Kaplan–Meier curve for patients with ESRD. In univariate analysis, sex, age at onset, and diagnosis delay were not associated with risk of progression to ESRD. However, type of AAV, nephrotic-range proteinuria, and histological chronicity indices were factors associated with renal outcome.

Table 1 Demographic and clinical features at the time of diagnosis (n (%) or median (IQR))

Variables	MPA ($n = 38$)	GPA ($n = 9$)	Others ($n = 2$)	Total ($n = 49$)
Gender				
Male	8 (21%)	4 (44%)	1 (50%)	13 (27%)
Female	30 (79%)	5 (56%)	1 (50%)	36 (73%)
Age at diagnosis (median in years)	10.0 (7.7–12.0)	12.8 (11.7–13.7)	10.5 (10.0–11.0)	10.7 (8.3–12.4)
Time from initial symptom to diagnosis (median in months)	2.0 (1.0–4.0)	2.0 (2.0–5.0)	1.0 (1.0)	2.0 (1.0–4.0)
Detected by school urinary screening program	27 (71%)	0 (0%)	0 (0%)	27 (55%)
Organ involvements				
General symptom	13 (34%)	7 (78%)	2 (100%)	22 (45%)
Fever	10	7	2	19
Weight loss	3	3	0	6
Renal involvement	31 (82%)	3 (33%)	1 (50%)	35 (71%)
Proteinuria	31	3	1	35
Nephrotic range proteinuria	13	0	0	13
Hematuria	15	2	1	18
Macroscopic hematuria	15	2	0	17
Oliguria	2	0	0	2
Renal insufficiency	5	0	0	5
Pulmonary involvement	10 (26%)	4 (44%)	0 (0%)	14 (29%)
Alveolar hemorrhage	7	1	–	8
Pleural effusion	1	0	–	1
Abnormal chest imaging	2	2	–	4
Dyspnea	1	2	–	3
Cardiovascular involvement	3 (8%)	0 (0%)	1 (50%)	4 (8%)
Otolaryngology involvement	1 (3%)	7 (78%)	1 (50%)	9 (18%)
Eyes involvement	4 (11%)	5 (56%)	1 (50%)	10 (20%)
Mucocutaneous involvement	8 (21%)	2 (22%)	1 (50%)	11 (22%)
Joint involvement	3 (8%)	1 (11%)	0 (0%)	4 (8%)
Gastrointestinal involvement	5 (13%)	1 (11%)	2 (100%)	8 (16%)
Central nervous system involvement	0 (0%)	2 (22%)	1 (50%)	3 (6%)

Table 2 Laboratory findings at the time of diagnosis

Variables	MPA ($n = 38$)	GPA ($n = 9$)	Others ($n = 2$)	Total ($n = 49$)
Hematological tests				
WBC (/μl)	7400 (5800–9360)	8013 (4450–11,440)	23,140 (12800–33,480)	7600 (5800–9490)
Hemoglobin (g/dl)	10.6 (8.0–11.6)	11.5 (9.2–13.2)	12.6 (11.7–13.4)	10.7 (8.5–12.1)
Erythrocyte sedimentation rate (mm/h)	58 (22–82)	37 (6–48)	33 (32–34)	48 (22–81)
Serum albumin (g/dl)	3.8 (3.2–4.0)	3.7 (3.0–3.9)	3.7 (3.1–4.2)	3.8 (3.1–4.0)
CRP (mg/dl)	0.3 (0.06–1.8)	2.3 (0.06–10.98)	12.6 (11.3–13.8)	0.47 (0.75–3.50)
Urinary protein excretion (uPCR g/gCr)	1.21 (0.51–3.02)	0.4 (0.03–0.43)	–	0.81 (0.41–2.57)
Serology (ANCA status)				
MPO-ANCA	36 (95%)	0	1 (50%)	37 (76%)
PR3-ANCA	0	8 (89%)	0	8 (16%)
No data available	2 (5%)	0	0	2 (4%)

Table 3 Histopathological findings at diagnosis ($n = 40$)*

No. of glomeruli*	Glomerular lesions†				Tubulointerstitial lesions†	
	Cellular crescent (%)	Fibrocellular crescent (%)	Fibrous crescent (%)	Global sclerosis (%)	Interstitial inflammation (%)	Interstitial fibrosis (%)
29.5 (19–43)	31 (77%)	23 (58%)	16 (40%)	30 (75%)	28 (70%)	21 (53%)

*Results are expressed as median (IQR)

† Percentage of total patients

Histological chronicity was significantly correlated with nephrotic-range proteinuria ($\rho = 0.50$, $P < 0.01$) and was an independent factor associated with ESRD on logistic regression analysis (odds ratio, 24.20; 95% CI, 1.12–520.56; $P = 0.042$) (Table 4).

Discussion

Few reliable epidemiological data are available regarding pediatric patients with AAV, particularly MPA, due to the rarity of these diseases in children. To date, four large pediatric studies in which outcomes were described showed relatively low rates with MPA patients ranging from 13 to 58% [1–4], because of regional and ethnic differences in AAV types [21]. Therefore, the present study was performed to investigate the outcomes of this group of diseases in pediatric patients to date.

The main findings of this nationwide survey in Japanese children were as follows. (i) More than 10% of patients still do not achieve remission, and progress to ESRD. (ii) The worst renal outcomes were observed in patients with chronic histological lesions involving > 50% of all glomeruli detected on renal biopsy. (iii) The prevalence of childhood-onset AAV was estimated to be 3.41–4.28 (95% CI: 2.33–6.19) per million children.

After a median follow-up of 43 months, of 49 patients, 11 (22%) progressed to CKD stages 3–5 and seven (14%) developed ESRD. In previous studies in pediatric AAV cases, the rates of ESRD were reported to be 10–50% [2, 6, 11, 22]. ESRD was also reported to occur at 29% in a study conducted in Japan in 1999 [23]. However, we could not compare renal outcomes with these previous studies as the populations were very different. Consistent with a previous report [23], no correlation was observed between detection at school urinary screening programs and favorable outcome on multivariate analysis. Of seven patients with ESRD, four (57%) were detected by school urinary screening programs. However, the time to diagnosis was shorter and prognosis was better in the present study than in previous studies in countries with a higher proportion of MPA and without annual urine screening programs [10, 11, 24]. In addition, the rates of renal insufficiency at diagnosis were high in previous reports, ranging from 29 to 80% [10, 11, 24], and were related to later ESRD. However, in the present study, renal insufficiency was detected in only five of 38 (13%) patients at diagnosis. Early diagnosis is important to improve long-term outcome in patients with AAV, particularly in those with MPA. Renal

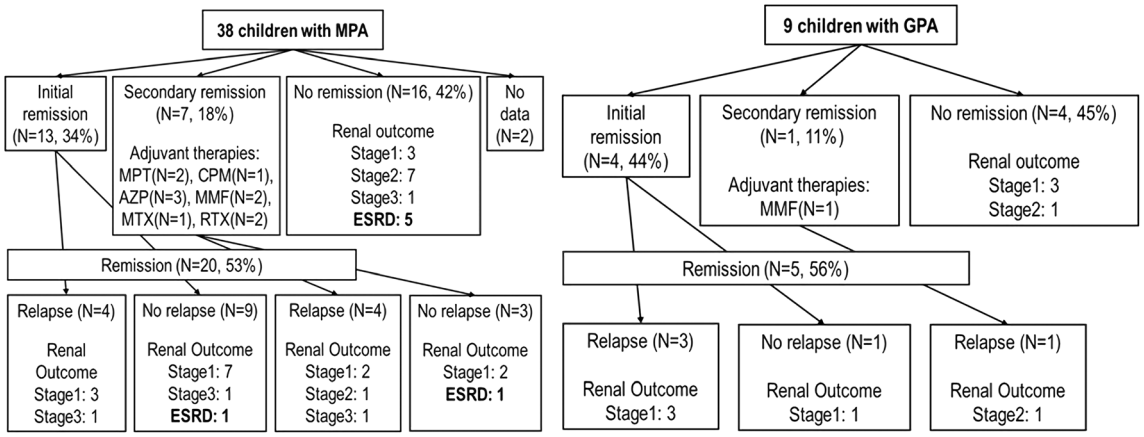

Fig. 1 Disease course of childhood-onset AAV. AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; CPM, cyclophosphamide; MPT, methylprednisolone pulse therapy; AZP, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; ESRD, end-stage renal disease

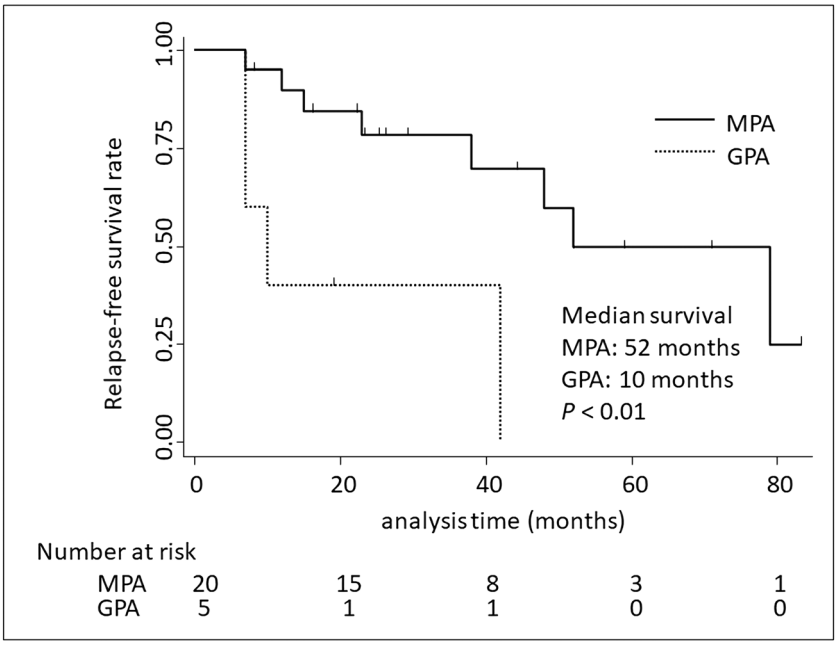

Fig. 2 Kaplan–Meier curves for relapse-free survival in patients with MPA and GPA. Kaplan–Meier plots were used to assess time to first relapse. The log-rank test was used to compare relapse-free survival between different groups. GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis

disease, which is the primary manifestation of MPA, is seen at onset in almost all pediatric patients diagnosed with this disease [25, 26]. Although our results did not indicate a significant effect of the annual urine screening program, such screening would allow earlier intervention in childhood-onset AAV before the development of renal insufficiency.

We found that not a few patients with childhood-onset AAV still do not achieve remission and progress to ESRD because there are no specific guidelines for therapeutic management of such cases [27]. Rituximab, which has recently been shown to be as effective as cyclophosphamide, high-dose steroids, and plasmapheresis [28] as an induction agent for treatment of childhood-onset AAV, was used to treat 20% of patients in our cohort, particularly in cases with recurrent disease. This high percentage of treatment with rituximab may have improved the overall prognosis in this study. Chronic T cell activation occurring in AAV has been suggested to promote maturation of autoreactive B cells, thereby leading to ANCA production. Maintenance therapy with mycophenolate mofetil after rituximab induction was reported to significantly improve maintenance of remission and to prevent relapse in pediatric MPA [29]. Therefore, treatment regimens based on rituximab and mycophenolate mofetil may be good alternatives to cyclophosphamide-based protocols for the treatment of childhood-onset AAV.

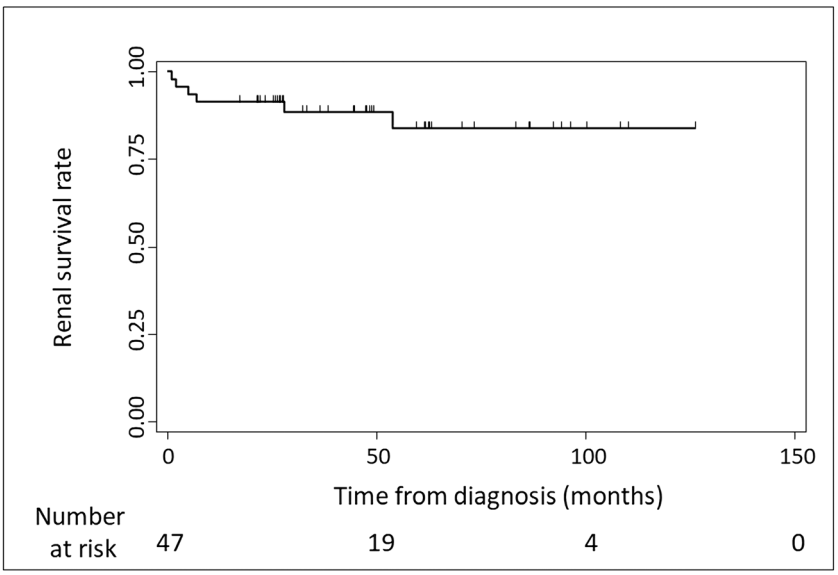

Fig. 3 Kaplan–Meier curves for patients with ESRD ($n = 49$). Kaplan–Meier plots were used to assess time to ESRD. AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; ESRD, end-stage renal disease

Table 4 Logistic regression model with factors possibly associated with end-stage renal disease

	95% confidence interval			
	Odds ratio	Lower	Upper	*P* value
Gender (male)	3.91	18.18	112.86	0.43
Age	0.73	0.44	1.23	0.24
Detected by school urinary screening	2.55	0.14	44.87	0.52
Nephrotic-range proteinuria	6.92	0.54	88.12	0.14
Chronic histological lesion > 50%	24.20	1.12	520.56	0.042

A number of factors, including older age, female sex, elevated serum creatinine level, and chronic histological lesions, have been reported to predict poor renal outcome in adult AAV patients [30–34]. Here, histopathological analysis of renal biopsy specimens at diagnosis was shown to predict the risk of progression to ESRD. That is, the rates of progression to ESRD during long-term follow-up were higher in pediatric patients with chronic histological lesions involving > 50% of all glomeruli (OR, 24.20 (95% CI: 1.12–520.56), $P = 0.042$). Histological classification of ANCA-associated glomerulonephritis was reported to predict prognosis regarding both renal function and patient outcome in adult patients [31, 35–42]. However, limited data are available on the association between histopathology and ESRD in childhood-onset AAV, with only two studies reported to date [2, 31]. The histological chronicity of ANCA-associated glomerulonephritis indicates dysfunction of the majority of glomeruli and heavy reliance on the compensatory ability of the kidneys. Sacri et al. reported that patients with sclerotic or mixed lesions had a threefold greater risk of ESRD than those with focal or crescentic patterns [2]. Noone et al. also reported progression to ESRD in all cases of childhood-onset AAV with sclerosis at diagnosis despite early aggressive therapy [31]. Such patients may not respond to drug therapy, and therefore early diagnosis and commencement of immunomodulatory therapy would be important to improve renal outcome.

The prevalence of childhood-onset AAV remains unclear due to the rarity of this condition in children. The results of the present study indicated a prevalence rate of childhood-onset AAV (before 16 years old) of 3.41–4.28 cases/million in Japan. Although this prevalence rate was very small compared to that in adults (46–184 cases/million) [43, 44], it may increase in the future because of increased awareness of the disease among pediatricians, and improved identification of cases due to health insurance coverage of the ANCA test.

This study had several limitations. First, this was a retrospective study using data collected over a long period, resulting in heterogeneity in the availability and accuracy of medical records. We also could not obtain information on the precise doses and durations of drugs used for therapy. In addition, all patients included in the study were Japanese. Therefore, our results may not be generalizable to non-Asian populations. Second, in this study, remission was defined as zero score in BVAS. Serum Cr and blood pressure matched to age and gender were used for BVAS in this study. However, some patients showed elevated serum Cr and proteinuria due to chronic renal scarring despite no disease activity. Such patients cannot achieve a zero score in BVAS. Therefore, the proportion of remission was lower than expected. Third, as 14 of 63 patients (22%) for whom consent was not provided were not included in the secondary survey, this may have led to overestimation of renal survival. Therefore, further studies are required to develop a prediction model and to determine the outcome of childhood-onset AAV. In conclusion, renal replacement therapy was not required in approximately 90% of the cohort at a median follow-up of 3.6 years. This observation indicated more than 10% of patients with childhood-onset did not achieve remission and progressed to ESRD. In addition, patients with chronic histological lesions involving > 50% of all glomeruli showed the best renal outcome.

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Compliance with ethical standards

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the ethical guidelines for epidemiological studies issued by the Ministry of Health, Labour and Welfare, Japan. The study was approved by the Ethics Review Committee of Graduate School of Medicine, Yokohama City University (institution of the principal investigator, SI, ID: B151201009) before commencement. Informed consent was not deemed necessary because the data were obtained retrospectively from the patient charts.

Conflict of interest S.I. has received consulting fees from Novartis Pharma and Loche. S.I. has also received research grants from Asahi Kasei Pharma, Astellas Pharma, and Chugai Pharmaceutical. T.S. has received consulting fees from Takeda Pharmaceutical Company Limited. T.S. has also received lecture fees from Takeda Pharmaceutical Company Limited and Statcom Company Limited.

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