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Kidney transplantation in childhood-onset ANCA-associated vasculitis: long-term outcomes and prognostic factors

--Manuscript Draft--

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Abstract:	Background. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is extremely rare in children, and results in kidney failure in up to one third of cases. There is very limited knowledge on kidney transplantation in the context of childhood-onset AAV. We assessed outcomes of kidney transplantation and prognostic factors in an international, multicentre cohort of patients with childhood-onset AAV. Methods Patients diagnosed with AAV during childhood (≤18 years) who received a kidney transplant were included in a retrospective study. We determined patient and graft survival, rates of chronic graft dysfunction (defined as an eGFR <60 mL/min/1.73 m2 for ≥3 months) and AAV relapse, and assessed determinants of outcome with logistic regression models. Patients were matched 1:2 for age, sex, and era of transplantation with non-AAV recipients from The Hospital for Sick Children in Toronto, Canada, and their graft survival was compared. Results We included 72 patients, of whom 53 (74%) had microscopic polyangiitis and 19 (26%) granulomatosis with polyangiitis. Their median age (interquartile range, IQR) at the time of diagnosis and transplantation was 12 (9-14) and 14 (12-16) years, respectively. After a median post-transplant follow-up of 53 months (IQR 25-97), 70 patients (97%) were alive, 62 (86%) had a functioning graft, 28 (39%) had developed chronic graft dysfunction, and eight (11%) had experienced AAV relapse. Graft survival was comparable between AAV and non-AAV recipients. Acute rejection was the only independent predictor of graft failure. Positive ANCA at the time of transplantation was significantly associated with a higher risk of chronic graft dysfunction and AAV relapse. Conclusions Patients with childhood-onset AAV show good overall and graft survival after kidney transplantation and a low rate of post-transplant relapse. Further studies are warranted to confirm whether positive ANCA at the time of transplantation is associated with poorer graft outcomes.
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Question	**Response**
Declaration of Helsinki	N/A

For all clinical experimentation described in the manuscript, I adhered to the Declaration of Helsinki and indicated my response below accordingly.	
Declaration of Istanbul My study is related to clinical organ transplantation, and the clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.	The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.
Animal Experimentation Animal experimentation is discussed in this manuscript, and I have adhered to the NIH Guide for the Care and Use of Laboratory Animals or the equivalent.	N/A
Clinical Trial Registration My study was a clinical trial and is registered in one of the registries recommended by the International Committee of Medical Journal Editors (ICMJE).	No
Please provide the reason why it was not registered: as follow-up to "Clinical Trial Registration My study was a clinical trial and is registered in one of the registries recommended by the International Committee of Medical Journal Editors (ICMJE)."	Not a trial
Institutional Review Board or Ethics Committee Oversight For all clinical experimentation described in this manuscript, I received approval by an Institutional Review Board or equivalent Ethics Committee and responded regarding patient consent, or I provided the reason for the exemption.	Yes
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Study Group/Organization Name: as follow-up to "Study Group: Does your paper include study group(s)? If yes, please provide a list of study group(s) and members that have contributed to or participated in the submitted work in some way. This list may contain either a collaboration of individuals (e.g., investigators) and/or the name of an organization (e.g., a laboratory, educational institution, corporation, or department) and its members."	CIBREO study group
Study Group Members' Names (Members' names should be entered as first name and last name, with individual names separated by commas. If the list of group members' names exceeds 4250 characters, the group members' names will appear in the Supplemental Material but will be indexed in PubMed.) as follow-up to "Study Group: Does your paper include study group(s)? If yes, please provide a list of study group(s) and members that have contributed to or participated in the submitted work in some way. This list may contain either a collaboration of	List of collaborators: Biplab, Maji Chantida, Subun Luigi, Cirillo Carmela, Errichiello Ilaria, Fibbi Marta, Calatroni Edoardo, La Porta Steve, Balgobin Rae, Yeung Nowrin, Aman

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Declaration of Helsinki For all clinical experimentation described in the manuscript, I adhered to the Declaration of Helsinki and indicated my response below accordingly.	This study includes clinical experimentation and complies with the Declaration of Helsinki.
Declaration of Istanbul My study is related to clinical organ transplantation, and the clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.	The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.
Animal Experimentation Animal experimentation is discussed in this manuscript, and I have adhered to the NIH Guide for the Care and Use of Laboratory Animals or the equivalent.	N/A
Scale of Data Generated *(select all that apply)*	N/A
Data Availability *(select all that apply)**Additional information: Original data generated for the study will be made available upon reasonable request to the corresponding author: This is not recommended for large datasets but is acceptable for low-throughput experimental data. If data are not deposited in a public access repository, or access will otherwise be subject to partial	Original data generated for the study will be made available upon reasonable request to the corresponding author.*

restriction, provide details in the textbox.- Data belong to a third party, and authors are not authorized to share the data: If data cannot be shared because they belong to a third party, specify the identity of the third party and reason for the restriction (e.g., proprietary data, administrative data governed by regulatory or legal frameworks).- Original data cannot be shared: This choice is allowable in select instances only, such as for research that applies to the CARE Principles — Global Indigenous Data Alliance, and requires editor approval.	
Data Type: as follow-up to "Data Availability *(select all that apply)****Additional information:** Original data generated for the study will be made available upon reasonable request to the corresponding author: This is not recommended for large datasets but is acceptable for low-throughput experimental data. If data are not deposited in a public access repository, or access will otherwise be subject to partial restriction, provide details in the textbox.- Data belong to a third party, and authors are not authorized to share the data: If data cannot be shared because they belong to a third party, specify the identity of the third party and reason for the restriction (e.g., proprietary data, administrative data governed by regulatory or legal frameworks).- Original data cannot be shared: This choice is allowable in select instances only, such as for research that applies to the CARE Principles — Global Indigenous Data Alliance, and requires editor approval."	Aggregated Data; Observational Data
Reason for Restricted Access: as follow-up to "Data Availability *(select all that apply)****Additional information:** Original data generated for the study will be made available upon reasonable request to the corresponding author: This is not recommended for large datasets but is acceptable for low-throughput experimental data. If data are not deposited in a public access repository, or access will otherwise be subject to partial restriction, provide details in the textbox.-	no restricted access

Data belong to a third party, and authors are not authorized to share the data: If data cannot be shared because they belong to a third party, specify the identity of the third party and reason for the restriction (e.g., proprietary data, administrative data governed by regulatory or legal frameworks).- Original data cannot be shared: This choice is allowable in select instances only, such as for research that applies to the CARE Principles — Global Indigenous Data Alliance, and requires editor approval."	
Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and not duplications of your keywords or index terms. At least two key points are required.	Key Point 1; Key Point 2
Key point #1: as follow-up to "Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and not duplications of your keywords or index terms. At least two key points are required."	In patients with childhoohd-onset ANCA-vasculitis, kidney transplantation was a good option as patients showed good transplant outcomes
Key point #2: as follow-up to "Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and not duplications of your keywords or index terms. At least two key points are required."	Positive ANCA at the time of transplantation was not associated with graft failure but with a risk of DGF, chronic graft dysfunction, and relapse

We would like to express once again our sincere gratitude to the Associate Editor and the reviewers for their thorough and encouraging comments to our revised manuscript. We have read with particular interest the considerations on infections among AAV and non-AAV recipients and have managed to retrieve further data of the controls to compare their burden in these groups. We believe that these findings are interesting and further support the feasibility of transplantation in children with AAV.

Here we provide a point-by-point reply to all the requests made.

Associate Editor Comments:
Thank you for submitting these extensive, responsive and thoughtful revisions. The manuscript reads quite well and will be a valuable contribution to the literature. There are just a few additional requests.

1. Please clarify the timeline inconsistencies/lack of clarity regarding start and end points noted by reviewer 1. P

REPLY: This has been done (please see our reply to Reviewer 1).

2. Please edit Table S4 to make it clearer which patient had three relapses and what treatment course and response was for each relapse.

REPLY: This has been done (please see our reply to Reviewer 1).

3. In this version, it is striking to this reader that the infection rates were quite high with two fatalities. Since the authors are doing matched control analysis for important outcomes, can they compare infection rates with the matched controls? One would expect infection rates may be higher due to more immunosuppression preceding transplant with vasculitis, but the control group also had 44 patients with glomerulonephritis who may have had pre-transplant immunosuppression before transplant. It would be helpful to understand how much to worry about the risk of infection? This may be something actionable - are the data granular enough to provide any insight into timing of infections or types of organisms? This would help inform whether we should be providing different or longer prophylaxis in vasculitis patients post-transplant.

REPLY: We thank the Associate Editor for this insightful comment. We have interrogated the transplant database of SickKids and identified those non-AAV recipients who developed CMV, EBV or BK viraemia or were hospitalised due to infectious complications. Although it could be possible that some events were not captured as patients were admitted to other hospitals, we believe that this is a relatively uncommon situation and these data reflect quite accurately the burden of infections.

We have compared CMV, EBV, BK virus reactivations and infection-related hospitalisations between cases and controls (see new Table S10 and the new Kaplan-Meier curve in Figure 3). Surprisingly, non-AAV recipients had numerically higher percentage of bacterial infections, EBV and BK reactivations, while the frequencies of CMV and hospitalisations due to viral infections were similar in the two groups. Controls also had a non-significantly shorter time to hospitalisation than cases. There may be a few factors that contributed to these unexpected results including variation of practice and capacity between SickKids and the other hospitals, a higher percentage of patients with CAKUT in the non-AAV group that are known to be at higher risk of UTI, eg reflux, posterior urethra valves, a higher proportion of B cell-depleted patients among AAV recipients, which could reduce the risk of EBV viraemia.

We also reported the type and frequency of infections during the first year post-transplant (left columns of Table S3). Most infections were due to UTI and CMV, while respiratory infections occurred in less than 5% of cases and none had Pneumocystis jirovecii pneumonia.

We acknowledge that our analysis has several limitations. Our results confirm that infections are frequent among AAV recipients but do not support the hypothesis that these patients have a significantly higher risk of infection than the general transplant population. Furthermore, the type and pattern of infections in our AAV groups was very reminiscent of that commonly seen in transplant recipients. Therefore, we feel that based on our data we cannot make any recommendation on prophylactic antibiotic therapy. We have discussed these results in the relevant sections.

4. For the tables/figures, since there is a matched control component in the manuscript but the main study tables only show AAV patients, please add into the titles "among AAV patients".

REPLY: This has been added as requested.

5. For table 4, please add a footnote noting that 3 patients were missing ANCA status data and were excluded.

REPLY: This has been added as requested.

Reviewer Comments:
Reviewer 1: The revised manuscript titled "Kidney transplantation in childhood-onset ANCA-associated vasculitis: long-term outcomes and prognostic factors" is responsive to the initial round of peer review. Since the data show infrequent changes in ANCA status after KTx, it seems reasonable to include ANCA status up to 3 months prior to transplant as "ANCAs status @ time of transplant."

Remaining concerns that could influence potential impact:
Table 1, table S6: The median time since remission induction therapy is listed in table 1, but months since completion of induction therapy is listed in table S6. This is confusing. Is this the time between start of induction therapy and date of kidney transplantation? Time from end of induction therapy? Or is it the time between AAV remission and date of kidney transplantation. The most important of these would seem to be the time between AAV remission and date of transplantation, since 99% of the cohort achieved complete remission prior to transplant.

REPLY: We thank Reviewer 1 for noting this. Table 1 also refers to months since completion of remission induction therapy, like Table S6. The item in Table 1 has been changed to clarify this. We have focused on time of completion of remission induction therapy since this can be more precisely tracked retrospectively than clinical remission and has been implicated as a risk factor for death post-transplant in adult AAV recipients (Little M 2010).

Page 54, line 8: p-value should be changed from 0.057 to 0.6 rather than to 0.05 in order to conform to journal formatting guidelines.

REPLY: This has been changed accordingly.

Suppl Table 4: would prefer listing 10 rows, one for each relapse, as opposed to the 8 patients. Please add a footnote explaining the listed age. Is it age at latest follow-up? Age at relapse? Or age at transplantation? Another footnote could indicate which 3 relapses occurred in the same patient.

REPLY: The table has been revised as requested.

Reviewer 2: I congratulate the authors.
REPLY: Thanks very much.

Reviewer 3: Thank you for revising this important work.

The manuscript details a great deal of information about the patient group and their respective outcomes of transplantation, a complex topic with multiple confounding variables.
The bulk of the results present not only this specific patient population variables and outcomes but also seem to focus on a comparison between ANCA positive v ANCA negative (now re-defined as persistently positive v persistently negative) patients.
A few correlations seem to be emerging from this data, however, in conclusion, further work needs to be done to elucidate the role of ANCA in kidney transplantation.

The conclusion also highlights that one of the main messages is to show that overall patient and graft survival after kidney transplantation in patients with AAV are comparable to that of the pediatric kidney transplant population at large.
We encourage the authors to highlight this message, as it may be lost.
With that understanding, we welcome the additional information provided about the matched controls, in particular their diagnoses and time to chronic dysfunction.
REPLY: Thank you for reminding us to highlight the main message of this work. We keep this at the heart of our discussion.

Kidney transplantation in childhood-onset ANCA-associated vasculitis: long-term outcomes and prognostic factors

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Abstract

Background. ANCA-associated vasculitis (AAV) is rare in children, and results in kidney failure in up to one third of cases. There is very limited knowledge on kidney transplantation in childhood-onset AAV. We assessed kidney transplantation outcomes and prognostic factors in a multicentre cohort of patients with childhood-onset AAV.

Methods Patients diagnosed with AAV during childhood (≤18 years) who received a kidney transplant were included in this retrospective study. We determined patient and graft survival, rates of chronic graft dysfunction (defined as eGFR<60 mL/min/1.73 m^2 for ≥3 months) and AAV relapse, and assessed determinants of outcome with logistic regression models. Patients were matched 1:2 for age, sex, and era of transplantation with non-AAV recipients from The Hospital for Sick Children in Toronto, Canada, and their graft survival was compared.

Results We included 72 patients, of whom 53 (74%) had microscopic polyangiitis and 19 (26%) granulomatosis with polyangiitis. Their median age (interquartile range, IQR) at the time of diagnosis and transplantation was 12 (9-14) and 14 (12-16) years, respectively. After a median post-transplant follow-up of 53 months (IQR 25-97), 70 patients (97%) were alive, 62 (86%) had a functioning graft, 28 (39%) had developed chronic graft dysfunction, and eight (11%) had experienced AAV relapse. Graft survival was comparable between AAV and non-AAV recipients. Acute rejection was the only independent predictor of graft failure (HR 12.11, 95% CI 1.19-122.49). Positive ANCA at the time of transplantation was significantly associated with a chronic graft dysfunction (HR 4.16, 95% CI 1.71-10.13) and AAV relapse (HR 23.1, 95% CI 2.67-200.28)

Conclusions Patients with childhood-onset AAV show good overall and graft survival after kidney transplantation and a low rate of post-transplant relapse. Further studies are warranted to confirm whether positive ANCA at the time of transplantation is associated with poorer graft outcomes.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses rare disorders including microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), characterised by pauci-immune small vessel vasculitis and positive ANCA, which usually targets myeloperoxidase (MPO) or proteinase 3 (PR3).[1] AAV has an annual incidence of 11-47 cases per million persons and mostly affects adults and elderly individuals.[2,3] However, both MPA and GPA also occur in childhood and adolescence, albeit with a significantly lower incidence, and their clinical phenotype is similar to that of adults, including a high frequency of kidney involvement.[4–11] In a previous study on children with ANCA-associated glomerulonephritis,[12] we observed a distribution of kidney histological classes and a rate of kidney failure comparable to those of adult cohorts.[13,14] Other studies reported that 28-40% of children with AAV required chronic kidney replacement therapy (KRT).[8,11,12,15]

Kidney transplantation is regarded as the preferred modality of KRT for patients with AAV. In adults, it has been consistently associated with good patient and graft survival, and a low post-transplant relapse.[16–29] Currently, it is recommended to defer transplantation until patients are in stable remission and have completed induction therapy for at least 6-12 months, while ANCA positivity should not preclude transplantation, although the role of ANCA status in relapse risk and graft outcomes is unclear.[22,30] However, data on kidney transplantation in children with AAV are lacking. Two single-centre case series (seven patients each) and one registry study reported excellent results, but little is known about long-term prognosis and baseline predictors of graft outcome, including ANCA.[31–33] To mitigate this gap, we assessed long-term outcomes and prognostic factors of kidney transplantation in a large, multicentre cohort of patients with childhood-onset AAV and compared their graft survival with that of matched non-AAV controls.

Methods

Patients

Physicians with expertise in childhood-onset AAV were contacted in order to identify patients who received a kidney transplant. To be included, patients had to: i) fulfil the European League Against Rheumatism

(EULAR) and Paediatric Rheumatology European Society (PRES) classification criteria for childhood MPA and GPA, the 2008 Ankara classification criteria endorsed by EULAR/PRES/Paediatric Rheumatology International Trials Organization (PRINTO) for GPA;[34,35] ii) be diagnosed at age ≤18 years; iii) have received a kidney transplant; iv) have a post-transplant follow-up period of at least six months. Cases with vasculitis secondary to drugs, infections, or other autoimmune diseases and cases with kidney failure not attributable to AAV were excluded.

Experts from 18 European centres, mostly belonging to the European Vasculitis Society (EUVAS) network, and from The Hospital for Sick Children (SickKids) of Toronto, Canada, and Tonji Hospital, Wuhan, China, contributed cases (**Table S1**). Eleven patients had previously been included in the paper by Calatroni *et al.*, which focused on ANCA-associated glomerulonephritis but did not report data on kidney transplantation.[12] Furthermore, seven patients had been described in the transplant series by Noone *et al.*; their post-transplant follow-up has been extended by a median of 11 months (range 0-46) in the current study.[31] The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Meyer Children's Hospital, Florence, Italy (protocol #l120/2019), and was shared with the participating centres.

Data collection and definitions

Patient data were retrieved from electronic records or archived medical charts. We collected demographic characteristics, features of AAV, information regarding donor, recipient, and transplant immunosuppressive therapy, and reviewed post-transplant follow-up, which was continued until graft failure, death, last available visit or December 2022. Data on second transplants were not collected.

Results of enzyme-linked immunosorbent assay (ELISA) were used to define ANCA status (positive or negative) and specificity (MPO or PR3). ANCA pattern on immunofluorescence, *i.e.* cytoplasmic (C-ANCA) or perinuclear (P-ANCA), was considered for those whose ELISA results were not available. For the purpose of the analysis, P-ANCA was grouped with MPO-ANCA and C-ANCA with PR3-ANCA, in view of their usual correspondence. ANCA status at transplantation was defined according to the results of the most recent ANCA test, provided this had been performed within three months prior to transplant.

Remission was defined as absence of clinical vasculitis activity, measured by the Paediatric Vasculitis Activity Score (PVAS), and relapse as new or recurrent manifestation of active disease.[36] The occurrence of new or worsening graft dysfunction and/or urinary abnormalities were considered as relapse with graft involvement if graft biopsy showed compatible histological changes (*e.g.*, pauci-immune crescentic glomerulonephritis not secondary to rejection), or, in the absence of histological confirmation, if extra-renal manifestations of AAV were present.

Delayed graft function (DGF) was defined as the temporary need for dialysis in the first post-transplant week and primary non-function (PNF) as being unable to discontinue dialysis for ≥3 months, or no sign of improvement in kidney function in case of pre-emptive transplantation. Graft failure was defined as the need to resume or start dialysis after a dialysis-free post-transplant period ≥3 months. The modified Schwartz formula and the chronic kidney disease (CKD) epidemiology (CKD-EPI) equation were used to calculate estimated glomerular filtration rate (eGFR) in patients aged <18 and ≥18 years, respectively.[37,38] Chronic graft dysfunction was defined as an eGFR <60 mL/min/1.73 m^2 for ≥3 months, and the day of the first test showing eGFR <60 mL/min/1.73 m^2 was considered as the incidence date.

Biopsy reports were reviewed and findings scored according to the 2022 Banff Meeting for Allograft Pathology.[39] For the purpose of the analysis, borderline and acute T-cell mediated rejection (TCMR) and active antibody-mediated rejection (ABMR) were grouped together as acute rejection, while chronic active TCMR, chronic active ABMR and chronic ABMR were grouped as chronic rejection.

Infections were defined as severe when they required hospitalization, administration of intravenous antimicrobial therapy, change in the regimen of anti-rejection therapy, or resulted in death. Cytomegalovirus (CMV), Epstein-Bar virus (EBV) or BK Polyoma virus (BKV) infections were all considered severe. Malignancy was defined as any malignant neoplastic diseases, including post-transplant lymphoproliferative disorder (PTLD), while cardiovascular events as any acute coronary syndrome, cerebrovascular accident, or peripheral artery disease complication.

Controls

Propensity score matching was used to match AAV patients with recipients who were transplanted for causes other than AAV in a 1:2 ratio, for age, sex and era of the transplant. All non-AAV recipients were followed at SickKids. We retrieved the date of transplant, death, graft failure or last follow-up and analysed longitudinal eGFR values to identify those who developed chronic graft dysfunction. Data on severe infections were also collected, while since protocol biopsy was standard of care at SickKids but not in most other centres, rates of rejection were not considered for comparison.

Statistical analysis

Continuous variables are presented as median (range or interquartile range, IQR), and differences between groups were assessed using the Mann-Whitney or Kruskal-Wallis tests, as appropriate. Categorical variables are presented as numbers (%) and were compared using Fisher's exact test or Chi Square test. Death-censored graft survival and time to chronic graft dysfunction, acute rejection and relapse were assessed using the Kaplan-Meier method. The log-rank test was used to compare survival between groups, *e.g.*, patients with positive vs negative ANCA at transplantation and AAV vs non-AAV recipients.

Univariate Cox proportional logistic regression models were used to estimate the effect of demographic, AAV-related and transplant-related covariates on time to graft failure, chronic graft dysfunction, relapse, acute rejection and severe infections. Post-transplant covariates, such as relapse, were fitted into the models as time-dependent variables. Only variables significantly associated with the outcome were included into the multivariate Cox regression models. Results were reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Statistical analyses were performed using STATA software version 14 (StataCorp). Two-sided P values <0.05 were considered statistically significant.

Results

Patients

We included 72 patients, of whom 53 (74%) had MPA and 19 (26%) GPA; 52 (72%) were female, and the median age at diagnosis was 12 years (IQR 9-14) (**Table 1**). Six patients had negative ANCA or no available

ANCA test results, but all had kidney biopsy or extra-renal features consistent with AAV. As expected, patients with MPA had a significantly higher frequency of positive P-ANCA/MPO-ANCA than those with GPA, who conversely were more frequently C-ANCA/PR3-ANCA positive. Sex, age at diagnosis, and type of induction therapy, *e.g.*, cyclophosphamide or rituximab, did not differ significantly between MPA and GPA, while patients with GPA more frequently had extra-renal involvement (**Table S2**).

Characteristics at transplantation

Transplantation was performed between 1985 and 2021, with 43 patients (60%) transplanted between 2010 and 2021 (**Table 1**). The median age at the time of transplantation was 14 years (IQR 11-16) and five patients (7%) were >18 years old. Two patients (3%) underwent pre-emptive transplantation while the remainder were transplanted a median of 15 months (IQR 10-25) after starting dialysis. Twenty-five transplants were from living donors (34%) with the remainder from deceased donors (donation after brain death).

All patients were in vasculitis remission (PVAS=0) at the time of transplantation and the median time since completion of the most recent induction regimen was 19 months (IQR 12-35). Of 69 patients with available results at the time of transplantation, 15 (22%) had positive ANCA. The frequency of positive ANCA did not differ significantly between patients with P-ANCA/MPO-ANCA and C-ANCA/PR3-ANCA.

Forty-nine patients (72%) received IL2-receptor antagonists or anti-thymocyte globulins as transplant induction therapy (**Table 1**). Maintenance regimen was based on a calcineurin inhibitor (CNI) plus an anti-metabolite and glucocorticoids in 64 patients (89%). Six patients (8%) had DGF but their grafts eventually gained independent function and none had PNF. eGFR at 1 month was >60 mL/min/1.73 m^2 in all but two patients.

Transplant outcomes

The median post-transplant follow-up was 53 months (IQR 25-97). **Table 2** presents outcomes while **Figures 1** and **2** show survival curves. At last follow-up, all but two patients (97%) were alive. These two patients died of infectious complications 106 and 200 months after transplantation, respectively, and the graft had already

failed in one of them. Ten patients (14%) lost their graft a median of 45 months (IQR 28-95) after transplantation due to acute rejection (5/10), chronic rejection (2/10), relapse (1/10) while two had no established cause. Twenty-eight patients (39%) developed chronic graft dysfunction a median of 19 months (IQR 6-67) after transplantation. There was a trend towards better graft survival and a lower incidence of chronic graft dysfunction among patients transplanted after 2010 (**Figure S1**).

Twenty-six patients (36%) experienced 32 episodes of acute rejection, of which 28 (87%) were classified as TCMR (**Table S3**). All received standard-of-care treatment according to centre policy. Eight patients (11%) were diagnosed with chronic rejection, which in 6/8 (75%) was due to ABMR. The frequencies of acute and chronic rejection and those of TCMR and ABMR were comparable between patients that were treated with or without rituximab for induction therapy of AAV (**Figure S2**).

Forty-two patients (59%) experienced 64 severe infections, with urinary tract infections accounting for almost 40% of the episodes (**Table S3**). Three patients developed CMV disease, while there were no cases of *Pneumocystis jirovecii* pneumonia and BKV nephropathy. Excluding the two fatal infections, all episodes resolved with no permanent complications. Neither malignancy nor cardiovascular events were reported.

AAV relapse

Eight patients (11%) experienced a relapse, and one of them suffered from three episodes (**Table S4**). The median time from transplantation to first relapse was 71 months (range 7-182) and the relapse rate was 0.02 per patient-year. All patients had positive ANCA at the time of relapse (MPO-ANCA in 5/8 and PR3-ANCA in 3/8) and were taking a CNI and an antimetabolite as transplant immunosuppression therapy, while 5/8 had previously discontinued glucocorticoids. Two patients experienced a graft-limited relapse, three only had extra-renal manifestations, while three had both graft and extra-renal involvement. Four patients presented with acute graft dysfunction (median eGFR 33 mL/min/1.73 m^2). All were treated with intravenous pulses of methylprednisolone and three additionally received rituximab, one cyclophosphamide and two plasma exchange. All but one patient achieved remission and graft function recovery, while one developed graft failure.

Prognostic factors

In the univariate analysis, only cold ischemia time (HR 1.14, 95% CI 1.02-1.27, p=0.02) and acute rejection (HR 13.77, 95% CI 1.73-109.35, p=0.01) were significantly associated with a higher risk of graft failure (**Table 3**). The association with acute rejection remained significant in the multivariate analysis (HR 12.11, 95% CI 1.19-122.49, p=0.03).

The univariate analysis for chronic graft dysfunction showed significant associations with age at transplantation (HR 1.09, 95% CI 1.00-1.18, p=0.04), positive ANCA at transplantation (HR 4.16, 95% CI 1.71-10.13, p=0.002) and DGF (HR 5.91, 95% CI 2.29-15.26, p<0.001; **Table 3**). The association between acute rejection and chronic graft dysfunction was of borderline significance (HR 1.91, 95% CI 0.90-4.06, p=0.09), while there was no association between this outcome and relapse. However, 7/8 patients had already developed chronic graft dysfunction at time of relapse and only one was considered exposed. In the multivariate analysis, the association between DGF and chronic graft dysfunction remained significant (HR 4.33, 95% CI 1.52-12.35, p=0.006), while that of positive ANCA status fell short (HR 2.54, 95% CI 0.97-6.63, p=0.06).

Positive ANCA at time of transplantation was also significantly associated with a higher risk of relapse in the univariate analysis (HR 23.1, 95% CI 2.67-200.28, p=0.004), while having MPA compared to GPA with a lower risk (HR 0.23, 95% CI 0.05-0.96, p=0.044; **Table S5**). Furthermore, glucocorticoid withdrawal showed a non-significant association with relapse (HR 3.85, 95% CI 0.91-16.29, p=0.06). Neither AAV-related features nor the type of immunosuppressive therapy or time elapsed since the completion of the previous remission induction regimen were associated with acute rejection and severe infection (**Tables S6-7**).

Associations with ANCA status at transplantation

Since ANCA status emerged as a possible prognostic factor, we compared patients with positive and negative ANCA at transplantation (**Table 4**). Age at transplantation, use of cyclophosphamide or rituximab, era of transplantation, type of donor, and cold ischemia time were comparable in the two groups, while patients with

positive ANCA had a significantly higher frequency of DGF and a lower eGFR at month 1 after transplant. Furthermore, when we compared patients who developed DGF with those who did not, the only significant difference we detected was a higher frequency of ANCA positivity at transplantation among DGF patients, while other factors, such as cold ischemia time, were comparable (**Table S8**).

In keeping with the results of the logistic regression analysis, time to chronic graft dysfunction and time to relapse were significantly shorter in patients with positive ANCA, while graft survival did not differ significantly according to ANCA status (**Figures 1-2**). Patients with positive ANCA had also a non-significantly shorter time to acute rejection compared to those with negative ANCA (**Figure 2**).

We also analysed ANCA status of 39 patients who had available results during follow-up. ANCA remained persistently positive in 8/11 (73%) with positive ANCA at the time of transplantation and persistently negative in 26/28 (93%) who already were ANCA negative at the time of transplantation. As expected, survival curves of patients with persistently positive and persistently negative ANCA were comparable to those of patients with positive and negative ANCA status at the time of transplantation, respectively (**Figure S3**).

Comparison with matched non-AAV recipients

Kaplan-Meier analysis showed that AAV recipients had a comparable patient and graft survival and a longer time to chronic graft dysfunction compared to non-AAV recipients (**Figure 3**). It must be acknowledged that the non-AAV recipients had a significantly shorter follow-up due to the local policy of discharging patients older than 18 years from paediatric to adult care (**Table S9**). Furthermore, we compared severe infections in the two groups. AAV recipients had a non-significantly better survival free from infection-related hospitalisation (**Figure 3**) and a lower frequency of EBV viraemia than non-AAV recipients, while the incidence of CMV viraemia was similar in the two groups (**Table S10**). It should be noted that a substantial proportion of individuals of the control group had vescico-ureteral reflux or congenital anomalies of the kidneys and the urinary tract, which are known to be associated with urinary tract infections, while more patients of the AAV group received rituximab that reduces the risk of EBV reactivation.

Discussion

Since mortality due to vasculitis has dramatically decreased but the rate of kidney failure remains high, KRT has become key to the care of patients with AAV.[14] Despite concerns about high cumulative burden of immunosuppression and persisting risk of disease relapse, kidney transplantation has shown favourable outcomes and appears to be the best modality of KRT in this population.[16,17] However, no study has assessed long-term outcomes of kidney transplantation and prognostic factors in large cohorts of children with AAV, for whom a transplant is a high priority, given the benefits on length and quality of life and on neuro-physical development.

Here, we present the results of an international, multicentre cohort of 72 patients with childhood-onset AAV that received kidney transplantation. Most children were treated with cyclophosphamide for induction of remission of AAV and received a standard transplant immunosuppressive regimen based on basiliximab, glucocorticoids, CNI and antimetabolites. After a median follow-up of almost five years, cumulative patient and graft survival were 97% and 86%, respectively, and were comparable to a matched control population. Furthermore, disease relapse occurred in a small number of patients and in most cases years after transplantation. Relapses were successfully managed with immunosuppressive treatment and only one patient developed graft failure. Infections were frequent and were fatal in two cases, but AAV recipients did not appear to be at higher risk of severe infections as compared to non-AAV recipients. Importantly, neither malignancies nor cardiovascular events were reported.

Our findings are reassuring about efficacy and safety of kidney transplantation in childhood-onset AAV and in line with results of adult studies.[19,20,40] Furthermore, they compare well with results of the one study on children with AAV based on a US registry, which reported better patient and graft survival among AAV recipients compared to non-AAV recipients.[33] Consistent with previous studies is also the fact that relapse is an uncommon cause of graft failure in these patients.[21–25,28]

We did not find an association between graft failure and AAV-related factors. Only acute rejection was identified as a negative independent predictor of graft survival. Rejection is indeed a main contributor to adverse transplant outcomes in adolescence and young adulthood, likely due to several factors, such as a lower

therapeutic adherence and a more robust immune system.[41–44] Our patients were transplanted at a median age of 14 years and largely fell into this "high-risk window".

Since the low number of events might have hampered our ability to detect associations with graft failure, we applied the regression model to chronic graft dysfunction (permanent eGFR <60 mL/min/1.73 m^2), which occurred in almost 40% of patients. This condition may precede graft failure, albeit by variable time, and is clinically significant for a child or young adult. Recipient age at transplantation, positive ANCA status at transplantation and DGF were significantly associated with a higher risk of chronic graft dysfunction in the univariate model and the association with DGF remained significant in the multivariate analysis, while that of positive ANCA status fell short in the multivariate model (p=0.06). Furthermore, being ANCA positive at the time of transplantation was significantly associated with a higher probability of relapse, as reported by previous studies.[23,24,26,27] However, relapse was not associated with chronic graft dysfunction in the univariate analysis, likely because it occurred after chronic graft dysfunction had been detected in almost all relapsing patients. Patients with positive and negative ANCA at the time of transplantation did not differ significantly in baseline features, including type of donor and cold ischemia time. However, those with a positive ANCA status developed DGF more frequently.

The association between positive ANCA and worse graft function is novel but difficult to explain since relapse does not appear to be involved. It is possible that it is entirely coincidental due to a random imbalance in the rate of DGF, facilitated by the low numbers. However, the fact that the association between chronic graft dysfunction and ANCA status remained almost significant after adjustment for DGF might suggest a true effect. Since ANCA positivity has been associated with a higher risk of relapse in this and other cohorts,[23,24,26,27,45–47] one could speculate that disease activity was not fully controlled in recipients with positive ANCA, resulting in subclinical graft function deterioration. Of note, chronic graft dysfunction is established before relapse in almost all relapsing patients, suggesting that subclinical involvement precedes apparent active disease. Furthermore, subclinically active disease might have exacerbated ischemia-reperfusion injury, leading to DGF.[48,49] Intriguingly, a previous study reported an association between positive ANCA status at the time of transplantation and chronic vascular changes in the graft biopsy, *i.e.* transplant vasculopathy.[22] We were unable to assess transplant vasculopathy in our cohort but are mindful that ANCA may contribute in various ways to kidney damage. Finally, patients with positive ANCA showed a non-significantly higher tendency to

develop acute rejection, which could have contributed to chronic graft dysfunction. Whether the increased rate of acute rejection in those with positive ANCA was coincidental or due to a more intense immune response remains unknown.

ANCA status did not change in most patients with available longitudinal post-transplant results. Current guidelines do not recommend deferring transplantation until ANCA becomes negative, and we believe that our findings do not yet warrant a change in this practice, since positive ANCA was not associated with graft failure and the rate of relapse remained low.[30] However, our results suggest that in the absence of more accurate biomarkers, ANCA status helps identify patients at higher risk of adverse graft outcomes, who may benefit from closer monitoring, including surveillance graft biopsies. Such an association has not been previously reported in adult studies and may represent a true difference with children. Notwithstanding, we believe that these findings are also of interest to adults as it is plausible that we were able to detect an effect in children due to fewer confounding factors, such as donor and recipient comorbidity, and ANCA plays a role also in older recipients.

Our study has limitations, including its retrospective nature and the fact that patients were transplanted over a span of almost 30 years and followed at various centres, with potential heterogeneity in practice and ANCA test assays, while controls were selected from only one centre. We acknowledge that the management of AAV has changed significantly during this time and only a minority of our patients were treated with rituximab, which is now increasingly used compared to cyclophosphamide. Hence, our cohort may not be representative of patients from the most recent era. Furthermore, several data were missing or were not analysed, such as donor age and sex, and details of histological lesions, *e.g.* transplant vasculopathy. Finally, the subgroups, such as ANCA positive patients, and the number of events of interest, including graft failure, were small, preventing firm conclusions. However, it must be acknowledged that in the context of childhood-onset AAV being a rare condition, our cohort is of considerable size.

In conclusion, this is the first study to assess outcomes of kidney transplantation and prognostic factors in a large, multicentre cohort of patients with childhood-onset AAV. We observed good patient and graft survival and low rates of disease relapse. Positive ANCA at the time of transplantation was not associated with graft failure but was significantly associated with a higher risk of DGF, chronic graft dysfunction, and relapse,

highlighting the need for increased vigilance. Our findings support kidney transplantation as a safe and effective modality of KRT in AAV and encourage further study on the role of ANCA in transplant outcomes.

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Conflicts of interest

None of the authors has conflicts to disclose.

Table 1 Main patient and transplant features of AAV recipients.

	All N=72	MPA N=53	GPA N=19	P value
Before transplantation				
Demographics				
Female, n (%)	52 (72)	40 (75)	12 (63)	0.37
White, n (%)	50 (69)	34 (64)	16 (84)	0.14
Age at diagnosis, median (IQR) - years	12 (9-14)	12 (9-14)	12 (10-14)	0.77
Type of ANCA				
P-ANCA/MPO ANCA, n (%)	48 (66)	45 (84)	3 (16)	**<0.001**
C-ANCA/PR3 ANCA, n (%)	18 (25)	4 (8)	14 (74)	**<0.001**
Negative, n (%)	4 (6)	3 (6)	1 (5)	1
Not available, n (%)	2 (3)	1 (2)	1 (5)	
Remission induction therapy for AAV				
Cyclophosphamide, n (%)	59 (82)	43 (81)	16 (84)	1
Rituximab, n (%)	17 (24)	10 (19)	7 (39)	0.12
Other immunosuppressive therapies, n (%)	4 (6)	3 (6)	1 (5)	1
None/glucocorticoids only, n (%)	3 (4)	3 (6)	0	0.56
At the time of transplantation				
Era of transplantation				
Before 2000, n (%)	8 (11)	6 (11)	2 (11)	1
2000-2009, n (%)	21 (29)	17 (32)	4 (21)	0.55
After 2009, n (%)	43 (60)	30 (57)	13 (68)	0.42
Donor				
Living, n (%)	25 (35)	17 (32)	8 (42)	0.57
Deceased, n (%)	47 (65)	36 (68)	11 (58)	0.57
Recipient				
Age, median (IQR) – years	14 (11-16)	14 (11-16)	14 (13-16)	0.56
Months since completion of remission induction therapy for vasculitis, median (IQR)	19 (12-35)	18 (11-36)	22 (16-35)	0.30
Complete AAV remission (PVAS=0), n (%)	71 (99)	53 (100)	18 (95)	0.26
Immunosuppression/glucocorticoids, n (%)	27 (37)	19 (36)	8 (42)	0.78
Months since start of KRT, median (IQR)	15 (10-25)	14 (10-24)	17 (11-25)	0.68
Pre-emptive transplant, n (%)	2 (3)	1 (2)	1 (5)	0.46
ANCA status				
Positive, n (%)	15 (21)	13 (24)	2 (11)	0.20
Negative, n (%)	54 (75)	37 (70)	17 (89)	0.20
Not available	3 (4)	3 (6)	0	
Transplant induction therapy				
IL-2 receptor antagonist, n (%)	46 (64)	31 (58)	15 (80)	0.16
Anti-thymocyte globulins, n (%)	2 (3)	1 (2)	1 (5)	0.46
None, n (%)	19 (26)	17 (32)	2 (10)	0.07
Not available	4 (6)	3 (6)	1 (5)	
Transplant maintenance therapy				
GC-TAC-MMF, n (%)	43 (60)	33 (62)	10 (53)	0.58
GC-TAC-AZA, n (%)	13 (18)	7 (13)	6 (32)	0.09
GC-CsA-MMF, n (%)	5 (7)	4 (8)	1 (5)	1
GC-CsA-AZA, n (%)	3 (4)	2 (4)	1 (5)	1
Other, n (%)	8 (11)	7 (13)	1 (5)	0.67

Abbreviations: AAV: ANCA-associated vasculitis; AZA, azathioprine; C-ANCA, cytoplasmic ANCA pattern; CsA, cyclosporine A; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; IQR, interquartile range; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; MPA: microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA pattern; PR3, proteinase 3; PVAS: pediatric vasculitis activity score; TAC, tacrolimus

Table 2 Post-transplantation outcomes (last follow-up) of AAV recipients.

	Last follow-up N=72
Patient survival	
Alive, n (%)	70 (97)
Graft survival	
Patients with a functioning graft, n (%)	62 (86)
eGFR, median (IQR) – mL/min/1.73 m^2	66 (35-90)
Chronic graft dysfunction*, n (%)	28 (39)
AAV relapse	
Patients, n (%)	8 (11)
No. of episodes	10
Acute rejection	
Patients, n (%)	26 (36)
No. of episodes	32
Chronic rejection	
Patients, n (%)	8 (11)
Severe infections	
Patients, n (%)	42 (58)
No. of episodes	64
Cardiovascular events	
Patients, n (%)	0
Malignancy	
Patients, n (%)	0

*Permanent decrease in eGFR <60 mL/min/1.73 m^2

Table 3 Associations with graft failure and chronic graft dysfunction according to univariate and multivariate logistic regression models among AAV recipients. Results are shown as hazard ratios (HR) and 95% confidence intervals (95% CI).

	Graft failure				**Chronic graft dysfunction***			
	Univariate		**Multivariate**		**Univariate**		**Multivariate**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Male (Ref. Female)	No events	N.a.			0.48 (0.16-1.41)	0.18		
White (Ref. other ethnicity)	1.46 (0.30-7.04)	0.63			1.39 (0.58-3.29)	0.45		
MPA (Ref. GPA)	1.01 (0.20-4.91)	0.99			1.03 (0.41-2.61)	0.93		
MPO-/P-ANCA	0.66 (0.16-2.69)	0.57			1.05 (0.43-2.54)	0.89		
PR3-/C-ANCA	1.20 (0.24-5.86)	0.82			1.15 (0.44-2.95)	0.76		
ANCA-negative	1.90 (0.23-15.77)	0.50			0.43 (0.05-3.26)	0.42		
Cyclophosphamide	1.77 (0.22-14.11)	0.58			0.59 (0.23-1.48)	0.26		
Age at transplantation (years)**	1.04 (0.89-1.21)	0.58			**1.09 (1.00-1.18)**	**0.04**	1.09 (0.99-1.21)	0.07
ANCA+ at transplantation	1.47 (0.29-7.46)	0.63			**4.16 (1.71-10.13)**	**0.002**	2.54 (0.97-6.63)	0.05
Active disease at transplantation	No events	N.a.			No events	N.a.		
CRP at transplantation (mg/L)°	0.93 (0.62-1.38)	0.73			0.98 (0.84-1.14)	0.82		
Immunosuppressive therapy at transplantation	1.04 (0.18-5.85)	0.95			1.08 (0.45-2.57)	0.86		
Months since AAV induction therapy#	1.00 (0.98-1.03)	0.52			1.00 (0.98-1.02)	0.61		
Transplant after 2010	0.21 (0.02-1.85)	0.16			0.48 (0.20-1.16)	0.10		
Living donor (Ref. deceased)	0.14 (0.01-1.17)	0.07			1.34 (0.60-2.97)	0.46		
≥3 HLA mismatches	0.45 (0.07-2.74)	0.39			0.88 (0.36-2.14)	0.77		
Cold ischemia time (hours)^	**1.14 (1.02-1.27)**	**0.02**	1.06 (0.93-1.21)	0.34	1.00 (0.93-1.07)	0.96		
Transplant induction therapy	0.49 (0.13-1.88)	0.30			1.13 (0.46-2.73)	0.78		

GC-CNI-MMF	0.87 (0.25-3.03)	0.83			0.80 (0.37-1.81)	0.57		
Delayed graft function	1.06 (0.13-8.51)	0.95			**5.91 (2.29-15.26)**	**<0.001**	**4.33 (1.52-12.35)**	**0.006**
AAV relapse	1.30 (0.27-6.26)	0.74			1.06 (0.14-5.96)	0.95		
Acute rejection	**13.77 (1.73-109.35)**	**0.01**	**12.11 (1.19-122.49)**	**0.03**	1.91 (0.90-4.06)	0.09		
Severe infections	0.65 (0.17-2.36)	0.51			0.62 (0.28-1.35)	0.23		

*Permanent decrease in eGFR <60 mL/min/1.73 m^2

** per 1 year increment

°per 1 mg/L increment

^per 1 hour increment

#per 1 month increment

Abbreviations: AAV: ANCA-associated vasculitis; C-ANCA, cytoplasmic ANCA pattern; CI, confidence interval; CNI, calcineurin inhibitors; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; HLA, human leukocyte antigen; HR, hazard ratio; IQR, interquartile range; MMF, mycophenolate mofetil; MPA: microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA pattern; PR3, proteinase 3.

Table 4 Main features and outcomes of AAV recipients according to ANCA status at time of transplantation

	ANCA+^ N = 15	**ANCA-^ N = 54**	**P value**
Demographics			
Female, n (%)	12 (80)	37 (68)	0.52
Age at diagnosis, median (IQR) - years	12 (10-15)	12 (9-14)	0.32
AAV features			
MPA/GPA, n	13/2	37/17	0.20
P-ANCA/MPO-ANCA, n (%)	10 (66)	34 (63)	1
C-ANCA/PR3-ANCA, n (%)	5 (34)	15 (28)	0.75
Cyclophosphamide, n (%)	10 (66)	46 (85)	0.13
Rituximab, n (%)	4 (27)	13 (24)	1
Recipient features at transplantation			
Age, median (IQR) – years	15 (12-17)	14 (12-16)	0.31
Months from induction to transplant, median (IQR)	16 (11-32)	21 (13-35)	0.36
Active disease (PVAS ≥1), n (%)	0	1 (2)	1
CRP >5 mg/L, n (%)	5/11 (45)	5/30 (17)	0.09
Ongoing maintenance therapy, n (%)	8 (53)	18 (33)	0.22
Transplant features			
Before 2000, n (%)	1 (7)	5 (10)	1
2000-2009, n (%)	3 (20)	18 (33)	0.52
After 2009, n (%)	11 (73)	31 (57)	0.37
Living/deceased donor, n	5/10	18/36	1
Cold ischemia time, median (IQR) - hours	10 (3-16)	11 (4-13)	0.80
≥3 HLA mismatches, n (%)	5/10 (50)	24/38 (63)	0.49
Anti-IL2 receptor antagonist for induction, n (%)	10 (66)	35 (65)	1
GC-TAC-MMF, n (%)	12 (80)	31 (57)	0.13
Outcomes			
Delayed graft function, n (%)	4 (27)	2 (4)	**0.01**
eGFR at month 1, median (IQR) – mL/min/1.73 m^2	65 (58-75)	84 (65-96)	**0.03**
AAV relapse, n (%)	5 (33)	2 (4)	**0.004**
Acute rejection, n (%)	7 (47)	18 (33)	0.37
Chronic rejection, n (%)	3 (20)	4 (7)	0.17
eGFR at last follow-up, median (IQR) – mL/min/1.73 m^2	59 (33-68)	77 (51-93)	**0.003**
Chronic graft dysfunction at last follow-up, n (%)	9 (60)	17 (31)	0.06
Graft failure, n (%)	2 (13)	7 (13)	1
Death, n (%)	0	2 (4)	1

Abbreviations: AAV: ANCA-associated vasculitis; C-ANCA, cytoplasmic ANCA pattern; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; HLA, human leukocyte antigen; HR, hazard ratio; IQR, interquartile range; MMF, mycophenolate mofetil; MPA: microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA pattern; PR3, proteinase 3; PVAS, paediatric vasculitis activity score; TAC, tacrolimus.

^Three patients had no available results of ANCA testing at the time of transplantation and were excluded from the analysis.

Figure legends

Figure 1 Kaplan-Meier curves of time to graft failure and time to chronic graft dysfunction in all AAV recipients (plots on the left-hand side of the figure) and according to ANCA status at time of transplantation (plots on the right-hand side of the figure). Shaded areas represent 95% confidence intervals. P values of the log rank tests comparing survival probabilities of patients with positive ANCA (red) and negative ANCA (blue) are shown.

Figure 2 Kaplan-Meier curves of time to acute rejection and time to relapse in all AAV recipients (plots on the left-hand side of the figure) and according to ANCA status at time of transplantation (plots on the right-hand side of the figure). Shaded areas represent 95% confidence intervals. P values of the log rank test comparing survival probabilities of patients with positive ANCA (red) and negative ANCA (blue) are shown.

Figure 3 Kaplan-Meier curves of time to death, time to graft failure, time to chronic graft dysfunction and time to infection-related hospitalisation of AAV recipients and matched non-AAV recipients. Shaded areas represent 95% confidence intervals. P values of log-rank tests comparing survival probabilities of cases (black) and controls (green) are shown.

Kidney transplantation in childhood-onset ANCA-associated vasculitis: long-term outcomes and prognostic factors

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Abstract

Background. ANCA-associated vasculitis (AAV) is rare in children, and results in kidney failure in up to one third of cases. There is very limited knowledge on kidney transplantation in childhood-onset AAV. We assessed kidney transplantation outcomes and prognostic factors in a multicentre cohort of patients with childhood-onset AAV.

Methods Patients diagnosed with AAV during childhood (≤18 years) who received a kidney transplant were included in this retrospective study. We determined patient and graft survival, rates of chronic graft dysfunction (defined as eGFR<60 mL/min/1.73 m^2 for ≥3 months) and AAV relapse, and assessed determinants of outcome with logistic regression models. Patients were matched 1:2 for age, sex, and era of transplantation with non-AAV recipients from The Hospital for Sick Children in Toronto, Canada, and their graft survival was compared.

Results We included 72 patients, of whom 53 (74%) had microscopic polyangiitis and 19 (26%) granulomatosis with polyangiitis. Their median age (interquartile range, IQR) at the time of diagnosis and transplantation was 12 (9-14) and 14 (12-16) years, respectively. After a median post-transplant follow-up of 53 months (IQR 25-97), 70 patients (97%) were alive, 62 (86%) had a functioning graft, 28 (39%) had developed chronic graft dysfunction, and eight (11%) had experienced AAV relapse. Graft survival was comparable between AAV and non-AAV recipients. Acute rejection was the only independent predictor of graft failure (HR 12.11, 95% CI 1.19-122.49). Positive ANCA at the time of transplantation was significantly associated with a chronic graft dysfunction (HR 4.16, 95% CI 1.71-10.13) and AAV relapse (HR 23.1, 95% CI 2.67-200.28)

Conclusions Patients with childhood-onset AAV show good overall and graft survival after kidney transplantation and a low rate of post-transplant relapse. Further studies are warranted to confirm whether positive ANCA at the time of transplantation is associated with poorer graft outcomes.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses rare disorders including microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), characterised by pauci-immune small vessel vasculitis and positive ANCA, which usually targets myeloperoxidase (MPO) or proteinase 3 (PR3).[1] AAV has an annual incidence of 11-47 cases per million persons and mostly affects adults and elderly individuals.[2,3] However, both MPA and GPA also occur in childhood and adolescence, albeit with a significantly lower incidence, and their clinical phenotype is similar to that of adults, including a high frequency of kidney involvement.[4–11] In a previous study on children with ANCA-associated glomerulonephritis,[12] we observed a distribution of kidney histological classes and a rate of kidney failure comparable to those of adult cohorts.[13,14] Other studies reported that 28-40% of children with AAV required chronic kidney replacement therapy (KRT).[8,11,12,15]

Kidney transplantation is regarded as the preferred modality of KRT for patients with AAV. In adults, it has been consistently associated with good patient and graft survival, and a low post-transplant relapse.[16–29] Currently, it is recommended to defer transplantation until patients are in stable remission and have completed induction therapy for at least 6-12 months, while ANCA positivity should not preclude transplantation, although the role of ANCA status in relapse risk and graft outcomes is unclear.[22,30] However, data on kidney transplantation in children with AAV are lacking. Two single-centre case series (seven patients each) and one registry study reported excellent results, but little is known about long-term prognosis and baseline predictors of graft outcome, including ANCA.[31–33] To mitigate this gap, we assessed long-term outcomes and prognostic factors of kidney transplantation in a large, multicentre cohort of patients with childhood-onset AAV and compared their graft survival with that of matched non-AAV controls.

Methods

Patients

Physicians with expertise in childhood-onset AAV were contacted in order to identify patients who received a kidney transplant. To be included, patients had to: i) fulfil the European League Against Rheumatism

(EULAR) and Paediatric Rheumatology European Society (PRES) classification criteria for childhood MPA and GPA, the 2008 Ankara classification criteria endorsed by EULAR/PRES/Paediatric Rheumatology International Trials Organization (PRINTO) for GPA;[34,35] ii) be diagnosed at age ≤18 years; iii) have received a kidney transplant; iv) have a post-transplant follow-up period of at least six months. Cases with vasculitis secondary to drugs, infections, or other autoimmune diseases and cases with kidney failure not attributable to AAV were excluded.

Experts from 18 European centres, mostly belonging to the European Vasculitis Society (EUVAS) network, and from The Hospital for Sick Children (SickKids) of Toronto, Canada, and Tonji Hospital, Wuhan, China, contributed cases (**Table S1**). Eleven patients had previously been included in the paper by Calatroni *et al.*, which focused on ANCA-associated glomerulonephritis but did not report data on kidney transplantation.[12] Furthermore, seven patients had been described in the transplant series by Noone *et al.*; their post-transplant follow-up has been extended by a median of 11 months (range 0-46) in the current study.[31] The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Meyer Children's Hospital, Florence, Italy (protocol #l120/2019), and was shared with the participating centres.

Data collection and definitions

Patient data were retrieved from electronic records or archived medical charts. We collected demographic characteristics, features of AAV, information regarding donor, recipient, and transplant immunosuppressive therapy, and reviewed post-transplant follow-up, which was continued until graft failure, death, last available visit or December 2022. Data on second transplants were not collected.

Results of enzyme-linked immunosorbent assay (ELISA) were used to define ANCA status (positive or negative) and specificity (MPO or PR3). ANCA pattern on immunofluorescence, *i.e.* cytoplasmic (C-ANCA) or perinuclear (P-ANCA), was considered for those whose ELISA results were not available. For the purpose of the analysis, P-ANCA was grouped with MPO-ANCA and C-ANCA with PR3-ANCA, in view of their usual correspondence. ANCA status at transplantation was defined according to the results of the most recent ANCA test, provided this had been performed within three months prior to transplant.

Remission was defined as absence of clinical vasculitis activity, measured by the Paediatric Vasculitis Activity Score (PVAS), and relapse as new or recurrent manifestation of active disease.[36] The occurrence of new or worsening graft dysfunction and/or urinary abnormalities were considered as relapse with graft involvement if graft biopsy showed compatible histological changes (*e.g.,* pauci-immune crescentic glomerulonephritis not secondary to rejection), or, in the absence of histological confirmation, if extra-renal manifestations of AAV were present.

Delayed graft function (DGF) was defined as the temporary need for dialysis in the first post-transplant week and primary non-function (PNF) as being unable to discontinue dialysis for ≥3 months, or no sign of improvement in kidney function in case of pre-emptive transplantation. Graft failure was defined as the need to resume or start dialysis after a dialysis-free post-transplant period ≥3 months. The modified Schwartz formula and the chronic kidney disease (CKD) epidemiology (CKD-EPI) equation were used to calculate estimated glomerular filtration rate (eGFR) in patients aged <18 and ≥18 years, respectively.[37,38] Chronic graft dysfunction was defined as an eGFR <60 mL/min/1.73 m^2 for ≥3 months, and the day of the first test showing eGFR <60 mL/min/1.73 m^2 was considered as the incidence date.

Biopsy reports were reviewed and findings scored according to the 2022 Banff Meeting for Allograft Pathology.[39] For the purpose of the analysis, borderline and acute T-cell mediated rejection (TCMR) and active antibody-mediated rejection (ABMR) were grouped together as acute rejection, while chronic active TCMR, chronic active ABMR and chronic ABMR were grouped as chronic rejection.

Infections were defined as severe when they required hospitalization, administration of intravenous antimicrobial therapy, change in the regimen of anti-rejection therapy, or resulted in death. Cytomegalovirus (CMV), Epstein-Bar virus (EBV) or BK Polyoma virus (BKV) infections were all considered severe. Malignancy was defined as any malignant neoplastic diseases, including post-transplant lymphoproliferative disorder (PTLD), while cardiovascular events as any acute coronary syndrome, cerebrovascular accident, or peripheral artery disease complication.

Controls

Propensity score matching was used to match AAV patients with recipients who were transplanted for causes other than AAV in a 1:2 ratio, for age, sex and era of the transplant. All non-AAV recipients were followed at SickKids. We retrieved the date of transplant, death, graft failure or last follow-up and analysed longitudinal eGFR values to identify those who developed chronic graft dysfunction. Data on severe infections were also collected, while ~~S~~since protocol biopsy was standard of care at SickKids but not in most other centres, rates of rejection were not considered for comparison.

Statistical analysis

Continuous variables are presented as median (range or interquartile range, IQR), and differences between groups were assessed using the Mann-Whitney or Kruskal-Wallis tests, as appropriate. Categorical variables are presented as numbers (%) and were compared using Fisher's exact test or Chi Square test. Death-censored graft survival and time to chronic graft dysfunction, acute rejection and relapse were assessed using the Kaplan-Meier method. The log-rank test was used to compare survival between groups, *e.g.*, patients with positive vs negative ANCA at transplantation and AAV vs non-AAV recipients.

Univariate Cox proportional logistic regression models were used to estimate the effect of demographic, AAV-related and transplant-related covariates on time to graft failure, chronic graft dysfunction, relapse, acute rejection and severe infections. Post-transplant covariates, such as relapse, were fitted into the models as time-dependent variables. Only variables significantly associated with the outcome were included into the multivariate Cox regression models. Results were reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Statistical analyses were performed using STATA software version 14 (StataCorp). Two-sided P values <0.05 were considered statistically significant.

Results

Patients

We included 72 patients, of whom 53 (74%) had MPA and 19 (26%) GPA; 52 (72%) were female, and the median age at diagnosis was 12 years (IQR 9-14) (**Table 1**). Six patients had negative ANCA or no available

ANCA test results, but all had kidney biopsy or extra-renal features consistent with AAV. As expected, patients with MPA had a significantly higher frequency of positive P-ANCA/MPO-ANCA than those with GPA, who conversely were more frequently C-ANCA/PR3-ANCA positive. Sex, age at diagnosis, and type of induction therapy, *e.g.*, cyclophosphamide or rituximab, did not differ significantly between MPA and GPA, while patients with GPA more frequently had extra-renal involvement (**Table S2**).

Characteristics at transplantation

Transplantation was performed between 1985 and 2021, with 43 patients (60%) transplanted between 2010 and 2021 (**Table 1**). The median age at the time of transplantation was 14 years (IQR 11-16) and five patients (7%) were >18 years old. Two patients (3%) underwent pre-emptive transplantation while the remainder were transplanted a median of 15 months (IQR 10-25) after starting dialysis. Twenty-five transplants were from living donors (34%) with the remainder from deceased donors (donation after brain death).

All patients were in vasculitis remission (PVAS=0) at the time of transplantation and the median time since completion of the most recent induction regimen was 19 months (IQR 12-35). Of 69 patients with available results at the time of transplantation, 15 (22%) had positive ANCA. The frequency of positive ANCA did not differ significantly between patients with P-ANCA/MPO-ANCA and C-ANCA/PR3-ANCA.

Forty-nine patients (72%) received IL2-receptor antagonists or anti-thymocyte globulins as transplant induction therapy (**Table 1**). Maintenance regimen was based on a calcineurin inhibitor (CNI) plus an anti-metabolite and glucocorticoids in 64 patients (89%). Six patients (8%) had DGF but their grafts eventually gained independent function and none had PNF. eGFR at 1 month was >60 mL/min/1.73 m^2 in all but two patients.

Transplant outcomes

The median post-transplant follow-up was 53 months (IQR 25-97). **Table 2** presents outcomes while **Figures 1** and **2** show survival curves. At last follow-up, all but two patients (97%) were alive. These two patients died of infectious complications 106 and 200 months after transplantation, respectively, and the graft had already

failed in one of them. Ten patients (14%) lost their graft a median of 45 months (IQR 28-95) after transplantation due to acute rejection (5/10), chronic rejection (2/10), relapse (1/10) while two had no established cause. Twenty-eight patients (39%) developed chronic graft dysfunction a median of 19 months (IQR 6-67) after transplantation. There was a trend towards better graft survival and a lower incidence of chronic graft dysfunction among patients transplanted after 2010 (**Figure S1**).

Twenty-six patients (36%) experienced 32 episodes of acute rejection, of which 28 (87%) were classified as TCMR (**Table S3**). All received standard-of-care treatment according to centre policy. Eight patients (11%) were diagnosed with chronic rejection, which in 6/8 (75%) was due to ABMR. The frequencies of acute and chronic rejection and those of TCMR and ABMR were comparable between patients that were treated with or without rituximab for induction therapy of AAV (**Figure S2**).

Forty-two patients (59%) experienced 64 severe infections, with urinary tract infections accounting for almost 40% of the episodes (**Table S3**). Three patients developed CMV disease, while there were no cases of *Pneumocystis jirovecii* pneumonia and BKV nephropathy. Excluding the two fatal infections, all episodes resolved with no permanent complications. Neither malignancy nor cardiovascular events were reported.

AAV relapse

Eight patients (11%) experienced a relapse, and one of them suffered from three episodes (**Table S4**). The median time from transplantation to first relapse was 71 months (range 7-182) and the relapse rate was 0.02 per patient-year. All patients had positive ANCA at the time of relapse (MPO-ANCA in 5/8 and PR3-ANCA in 3/8) and were taking a CNI and an antimetabolite as transplant immunosuppression therapy, while 5/8 had previously discontinued glucocorticoids. Two patients experienced a graft-limited relapse, three only had extra-renal manifestations, while three had both graft and extra-renal involvement. Four patients presented with acute graft dysfunction (median eGFR 33 mL/min/1.73 m^2). All were treated with intravenous pulses of methylprednisolone and three additionally received rituximab, one cyclophosphamide and two plasma exchange. All but one patient achieved remission and graft function recovery, while one developed graft failure.

Prognostic factors

In the univariate analysis, only cold ischemia time (HR 1.14, 95% CI 1.02-1.27, p=0.02) and acute rejection (HR 13.77, 95% CI 1.73-109.35, p=0.01) were significantly associated with a higher risk of graft failure (**Table 3**). The association with acute rejection remained significant in the multivariate analysis (HR 12.11, 95% CI 1.19-122.49, p=0.03).

The univariate analysis for chronic graft dysfunction showed significant associations with age at transplantation (HR 1.09, 95% CI 1.00-1.18, p=0.04), positive ANCA at transplantation (HR 4.16, 95% CI 1.71-10.13, p=0.002) and DGF (HR 5.91, 95% CI 2.29-15.26, p<0.001; **Table 3**). The association between acute rejection and chronic graft dysfunction was of borderline significance (HR 1.91, 95% CI 0.90-4.06, p=0.09), while there was no association between this outcome and relapse. However, 7/8 patients had already developed chronic graft dysfunction at time of relapse and only one was considered exposed. In the multivariate analysis, the association between DGF and chronic graft dysfunction remained significant (HR 4.33, 95% CI 1.52-12.35, p=0.006), while that of positive ANCA status fell short (HR 2.54, 95% CI 0.97-6.63, p=0.065).

Positive ANCA at time of transplantation was also significantly associated with a higher risk of relapse in the univariate analysis (HR 23.1, 95% CI 2.67-200.28, p=0.004), while having MPA compared to GPA with a lower risk (HR 0.23, 95% CI 0.05-0.96, p=0.044; **Table S5**). Furthermore, glucocorticoid withdrawal showed a non-significant association with relapse (HR 3.85, 95% CI 0.91-16.29, p=0.06). Neither AAV-related features nor the type of immunosuppressive therapy or time elapsed since the completion of the previous remission induction regimen were associated with acute rejection and severe infection (**Tables S6-7**).

Associations with ANCA status at transplantation

Since ANCA status emerged as a possible prognostic factor, we compared patients with positive and negative ANCA at transplantation (**Table 4**). Age at transplantation, use of cyclophosphamide or rituximab, era of transplantation, type of donor, and cold ischemia time were comparable in the two groups, while patients with

positive ANCA had a significantly higher frequency of DGF and a lower eGFR at month 1 after transplant. Furthermore, when we compared patients who developed DGF with those who did not, the only significant difference we detected was a higher frequency of ANCA positivity at transplantation among DGF patients, while other factors, such as cold ischemia time, were comparable (**Table S8**).

In keeping with the results of the logistic regression analysis, time to chronic graft dysfunction and time to relapse were significantly shorter in patients with positive ANCA, while graft survival did not differ significantly according to ANCA status (**Figures 1-2**). Patients with positive ANCA had also a non-significantly shorter time to acute rejection compared to those with negative ANCA (**Figure 2**).

We also analysed ANCA status of 39 patients who had available results during follow-up. ANCA remained persistently positive in 8/11 (73%) with positive ANCA at the time of transplantation and persistently negative in 26/28 (93%) who already were ANCA negative at the time of transplantation. As expected, survival curves of patients with persistently positive and persistently negative ANCA were comparable to those of patients with positive and negative ANCA status at the time of transplantation, respectively (**Figure S3**).

Comparison with matched non-AAV recipients

Kaplan-Meier analysis showed that AAV recipients had a comparable patient and graft survival and a longer time to chronic graft dysfunction compared to non-AAV recipients (**Figure 3**). It must be acknowledged that the non-AAV recipients had a significantly shorter follow-up due to the local policy of discharging patients older than 18 years from paediatric to adult care (**Table S9**). Furthermore, we compared severe infections in the two groups. AAV recipients had a non-significantly better survival free from infection-related hospitalisation (**Figure 3**) and a lower frequency of EBV viraemia than non-AAV recipients, while the incidence of CMV viraemia was similar in the two groups (**Table S10**). It should be noted that a substantial proportion of individuals of the control group had vescico-ureteral reflux or congenital anomalies of the kidneys and the urinary tract, which are known to be associated with urinary tract infections, while more patients of the AAV group received rituximab that reduces the risk of EBV reactivation.

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Discussion

Since mortality due to vasculitis has dramatically decreased but the rate of kidney failure remains high, KRT has become key to the care of patients with AAV.[14] Despite concerns about high cumulative burden of immunosuppression and persisting risk of disease relapse, kidney transplantation has shown favourable outcomes and appears to be the best modality of KRT in this population.[16,17] However, no study has assessed long-term outcomes of kidney transplantation and prognostic factors in large cohorts of children with AAV, for whom a transplant is a high priority, given the benefits on length and quality of life and on neuro-physical development.

Here, we present the results of an international, multicentre cohort of 72 patients with childhood-onset AAV that received kidney transplantation. Most children were treated with cyclophosphamide for induction of remission of AAV and received a standard transplant immunosuppressive regimen based on basiliximab, glucocorticoids, CNI and antimetabolites. After a median follow-up of almost five years, cumulative patient and graft survival were 97% and 86%, respectively, and were comparable to a matched control population. Furthermore, disease relapse occurred in a small number of patients and in most cases years after transplantation. Relapses were successfully managed with immunosuppressive treatment and only one patient developed graft failure. ~~Severe i~~Infections were frequent and were fatal in two cases, but AAV recipients did not appear to be at higher risk of severe infections as compared to non-AAV recipients~~other episodes resolved with no major consequences~~. Importantly, neither malignancies nor cardiovascular events were reported.

Our findings are reassuring about efficacy and safety of kidney transplantation in childhood-onset AAV and in line with results of adult studies.[19,20,40] Furthermore, they compare well with results of the one study on children with AAV based on a US registry, which reported better patient and graft survival among AAV recipients compared to non-AAV recipients.[33] Consistent with previous studies is also the fact that relapse is an uncommon cause of graft failure in these patients.[21–25,28]

We did not find an association between graft failure and AAV-related factors. Only acute rejection was identified as a negative independent predictor of graft survival. Rejection is indeed a main contributor to adverse transplant outcomes in adolescence and young adulthood, likely due to several factors, such as a lower

therapeutic adherence and a more robust immune system.[41–44] Our patients were transplanted at a median age of 14 years and largely fell into this "high-risk window".

Since the low number of events might have hampered our ability to detect associations with graft failure, we applied the regression model to chronic graft dysfunction (permanent eGFR <60 mL/min/1.73 m^2), which occurred in almost 40% of patients. This condition may precede graft failure, albeit by variable time, and is clinically significant for a child or young adult. Recipient age at transplantation, positive ANCA status at transplantation and DGF were significantly associated with a higher risk of chronic graft dysfunction in the univariate model and the association with DGF remained significant in the multivariate analysis, while that of positive ANCA status fell short in the multivariate model (p=0.065). Furthermore, being ANCA positive at the time of transplantation was significantly associated with a higher probability of relapse, as reported by previous studies.[23,24,26,27] However, relapse was not associated with chronic graft dysfunction in the univariate analysis, likely because it occurred after chronic graft dysfunction had been detected in almost all relapsing patients. Patients with positive and negative ANCA at the time of transplantation did not differ significantly in baseline features, including type of donor and cold ischemia time. However, those with a positive ANCA status developed DGF more frequently.

The association between positive ANCA and worse graft function is novel but difficult to explain since relapse does not appear to be involved. It is possible that it is entirely coincidental due to a random imbalance in the rate of DGF, facilitated by the low numbers. However, the fact that the association between chronic graft dysfunction and ANCA status remained almost significant after adjustment for DGF might suggest a true effect. Since ANCA positivity has been associated with a higher risk of relapse in this and other cohorts,[23,24,26,27,45–47] one could speculate that disease activity was not fully controlled in recipients with positive ANCA, resulting in subclinical graft function deterioration. Of note, chronic graft dysfunction is established before relapse in almost all relapsing patients, suggesting that subclinical involvement precedes apparent active disease. Furthermore, subclinically active disease might have exacerbated ischemia-reperfusion injury, leading to DGF.[48,49] Intriguingly, a previous study reported an association between positive ANCA status at the time of transplantation and chronic vascular changes in the graft biopsy, *i.e.* transplant vasculopathy.[22] We were unable to assess transplant vasculopathy in our cohort but are mindful that ANCA may contribute in various ways to kidney damage. Finally, patients with positive ANCA showed a non-significantly higher tendency to

develop acute rejection, which could have contributed to chronic graft dysfunction. Whether the increased rate of acute rejection in those with positive ANCA was coincidental or due to a more intense immune response remains unknown.

ANCA status did not change in most patients with available longitudinal post-transplant results. Current guidelines do not recommend deferring transplantation until ANCA becomes negative, and we believe that our findings do not yet warrant a change in this practice, since positive ANCA was not associated with graft failure and the rate of relapse remained low.[30] However, our results suggest that in the absence of more accurate biomarkers, ANCA status helps identify patients at higher risk of adverse graft outcomes, who may benefit from closer monitoring, including surveillance graft biopsies. Such an association has not been previously reported in adult studies and may represent a true difference with children. Notwithstanding, we believe that these findings are also of interest to adults as it is plausible that we were able to detect an effect in children due to fewer confounding factors, such as donor and recipient comorbidity, and ANCA plays a role also in older recipients.

Our study has limitations, including its retrospective nature and the fact that patients were transplanted over a span of almost 30 years and followed at various centres, with potential heterogeneity in practice and ANCA test assays, while controls were selected from only one centre. We acknowledge that the management of AAV has changed significantly during this time and only a minority of our patients were treated with rituximab, which is now increasingly used compared to cyclophosphamide. Hence, our cohort may not be representative of patients from the most recent era. Furthermore, several data were missing or were not analysed, such as donor age and sex, and details of histological lesions, *e.g.* transplant vasculopathy. Finally, the subgroups, such as ANCA positive patients, and the number of events of interest, including graft failure, were small, preventing firm conclusions. However, it must be acknowledged that in the context of childhood-onset AAV being a rare condition, our cohort is of considerable size.

In conclusion, this is the first study to assess outcomes of kidney transplantation and prognostic factors in a large, multicentre cohort of patients with childhood-onset AAV. We observed good patient and graft survival and low rates of disease relapse. Positive ANCA at the time of transplantation was not associated with graft failure but was significantly associated with a higher risk of DGF, chronic graft dysfunction, and relapse,

highlighting the need for increased vigilance. Our findings support kidney transplantation as a safe and effective modality of KRT in AAV and encourage further study on the role of ANCA in transplant outcomes.

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Conflicts of interest

None of the authors has conflicts to disclose.

Table 1 Main patient and transplant features of AAV recipients.

	All N=72	MPA N=53	GPA N=19	P value
Before transplantation				
Demographics				
Female, n (%)	52 (72)	40 (75)	12 (63)	0.37
White, n (%)	50 (69)	34 (64)	16 (84)	0.14
Age at diagnosis, median (IQR) - years	12 (9-14)	12 (9-14)	12 (10-14)	0.77
Type of ANCA				
P-ANCA/MPO ANCA, n (%)	48 (66)	45 (84)	3 (16)	**<0.001**
C-ANCA/PR3 ANCA, n (%)	18 (25)	4 (8)	14 (74)	**<0.001**
Negative, n (%)	4 (6)	3 (6)	1 (5)	1
Not available, n (%)	2 (3)	1 (2)	1 (5)	
Remission induction therapy for AAV				
Cyclophosphamide, n (%)	59 (82)	43 (81)	16 (84)	1
Rituximab, n (%)	17 (24)	10 (19)	7 (39)	0.12
Other immunosuppressive therapies, n (%)	4 (6)	3 (6)	1 (5)	1
None/glucocorticoids only, n (%)	3 (4)	3 (6)	0	0.56
At the time of transplantation				
Era of transplantation				
Before 2000, n (%)	8 (11)	6 (11)	2 (11)	1
2000-2009, n (%)	21 (29)	17 (32)	4 (21)	0.55
After 2009, n (%)	43 (60)	30 (57)	13 (68)	0.42
Donor				
Living, n (%)	25 (35)	17 (32)	8 (42)	0.57
Deceased, n (%)	47 (65)	36 (68)	11 (58)	0.57
Recipient				
Age, median (IQR) – years	14 (11-16)	14 (11-16)	14 (13-16)	0.56
Months since completion of remission induction therapy for vasculitis, median (IQR)	19 (12-35)	18 (11-36)	22 (16-35)	0.30
Complete AAV remission (PVAS=0), n (%)	71 (99)	53 (100)	18 (95)	0.26
Immunosuppression/glucocorticoids, n (%)	27 (37)	19 (36)	8 (42)	0.78
Months since start of KRT, median (IQR)	15 (10-25)	14 (10-24)	17 (11-25)	0.68
Pre-emptive transplant, n (%)	2 (3)	1 (2)	1 (5)	0.46
ANCA status				
Positive, n (%)	15 (21)	13 (24)	2 (11)	0.20
Negative, n (%)	54 (75)	37 (70)	17 (89)	0.20
Not available	3 (4)	3 (6)	0	
Transplant induction therapy				
IL-2 receptor antagonist, n (%)	46 (64)	31 (58)	15 (80)	0.16
Anti-thymocyte globulins, n (%)	2 (3)	1 (2)	1 (5)	0.46
None, n (%)	19 (26)	17 (32)	2 (10)	0.07
Not available	4 (6)	3 (6)	1 (5)	
Transplant maintenance therapy				
GC-TAC-MMF, n (%)	43 (60)	33 (62)	10 (53)	0.58
GC-TAC-AZA, n (%)	13 (18)	7 (13)	6 (32)	0.09
GC-CsA-MMF, n (%)	5 (7)	4 (8)	1 (5)	1
GC-CsA-AZA, n (%)	3 (4)	2 (4)	1 (5)	1
Other, n (%)	8 (11)	7 (13)	1 (5)	0.67

Abbreviations: AAV: ANCA-associated vasculitis; AZA, azathioprine; C-ANCA, cytoplasmic ANCA pattern; CsA, cyclosporine A; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; IQR, interquartile range; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; MPA: microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA pattern; PR3, proteinase 3; PVAS: pediatric vasculitis activity score; TAC, tacrolimus

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Table 2 Post-transplantation outcomes (last follow-up) of AAV recipients.

	Last follow-up N=72
Patient survival	
Alive, n (%)	70 (97)
Graft survival	
Patients with a functioning graft, n (%)	62 (86)
eGFR, median (IQR) – mL/min/1.73 m^2	66 (35-90)
Chronic graft dysfunction*, n (%)	28 (39)
AAV relapse	
Patients, n (%)	8 (11)
No. of episodes	10
Acute rejection	
Patients, n (%)	26 (36)
No. of episodes	32
Chronic rejection	
Patients, n (%)	8 (11)
Severe infections	
Patients, n (%)	42 (58)
No. of episodes	64
Cardiovascular events	
Patients, n (%)	0
Malignancy	
Patients, n (%)	0

*Permanent decrease in eGFR <60 mL/min/1.73 m^2

Table 3 Associations with graft failure and chronic graft dysfunction according to univariate and multivariate logistic regression models among AAV recipients. Results are shown as hazard ratios (HR) and 95% confidence intervals (95% CI).

	Graft failure				Chronic graft dysfunction*			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Male (Ref. Female)	No events	N.a.			0.48 (0.16-1.41)	0.18		
White (Ref. other ethnicity)	1.46 (0.30-7.04)	0.63			1.39 (0.58-3.29)	0.45		
MPA (Ref. GPA)	1.01 (0.20-4.91)	0.99			1.03 (0.41-2.61)	0.93		
MPO-/P-ANCA	0.66 (0.16-2.69)	0.57			1.05 (0.43-2.54)	0.89		
PR3-/C-ANCA	1.20 (0.24-5.86)	0.82			1.15 (0.44-2.95)	0.76		
ANCA-negative	1.90 (0.23-15.77)	0.50			0.43 (0.05-3.26)	0.42		
Cyclophosphamide	1.77 (0.22-14.11)	0.58			0.59 (0.23-1.48)	0.26		
Age at transplantation (years)**	1.04 (0.89-1.21)	0.58			**1.09 (1.00-1.18)**	**0.04**	1.09 (0.99-1.21)	0.07
ANCA+ at transplantation	1.47 (0.29-7.46)	0.63			**4.16 (1.71-10.13)**	**0.002**	2.54 (0.97-6.63)	0.05
Active disease at transplantation	No events	N.a.			No events	N.a.		
CRP at transplantation (mg/L)°	0.93 (0.62-1.38)	0.73			0.98 (0.84-1.14)	0.82		
Immunosuppressive therapy at transplantation	1.04 (0.18-5.85)	0.95			1.08 (0.45-2.57)	0.86		
Months since AAV induction therapy#	1.00 (0.98-1.03)	0.52			1.00 (0.98-1.02)	0.61		
Transplant after 2010	0.21 (0.02-1.85)	0.16			0.48 (0.20-1.16)	0.10		
Living donor (Ref. deceased)	0.14 (0.01-1.17)	0.07			1.34 (0.60-2.97)	0.46		
≥3 HLA mismatches	0.45 (0.07-2.74)	0.39			0.88 (0.36-2.14)	0.77		
Cold ischemia time (hours)^	**1.14 (1.02-1.27)**	**0.02**	1.06 (0.93-1.21)	0.34	1.00 (0.93-1.07)	0.96		
Transplant induction therapy	0.49 (0.13-1.88)	0.30			1.13 (0.46-2.73)	0.78		

GC-CNI-MMF	0.87 (0.25-3.03)	0.83			0.80 (0.37-1.81)	0.57		
Delayed graft function	1.06 (0.13-8.51)	0.95			**5.91 (2.29-15.26)**	**<0.001**	**4.33 (1.52-12.35)**	**0.006**
AAV relapse	1.30 (0.27-6.26)	0.74			1.06 (0.14-5.96)	0.95		
Acute rejection	**13.77 (1.73-109.35)**	**0.01**	**12.11 (1.19-122.49)**	**0.03**	1.91 (0.90-4.06)	0.09		
Severe infections	0.65 (0.17-2.36)	0.51			0.62 (0.28-1.35)	0.23		

*Permanent decrease in eGFR <60 mL/min/1.73 m^2

** per 1 year increment

°per 1 mg/L increment

^per 1 hour increment

#per 1 month increment

Abbreviations: AAV: ANCA-associated vasculitis; C-ANCA, cytoplasmic ANCA pattern; CI, confidence interval; CNI, calcineurin inhibitors; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; HLA, human leukocyte antigen; HR, hazard ratio; IQR, interquartile range; MMF, mycophenolate mofetil; MPA: microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA pattern; PR3, proteinase 3.

Table 4 Main features and outcomes of ~~patients~~ AAV recipients according to ANCA status at time of transplantation

	ANCA+^ N = 15	ANCA-^ N = 54	P value
Demographics			
Female, n (%)	12 (80)	37 (68)	0.52
Age at diagnosis, median (IQR) - years	12 (10-15)	12 (9-14)	0.32
AAV features			
MPA/GPA, n	13/2	37/17	0.20
P-ANCA/MPO-ANCA, n (%)	10 (66)	34 (63)	1
C-ANCA/PR3-ANCA, n (%)	5 (34)	15 (28)	0.75
Cyclophosphamide, n (%)	10 (66)	46 (85)	0.13
Rituximab, n (%)	4 (27)	13 (24)	1
Recipient features at transplantation			
Age, median (IQR) – years	15 (12-17)	14 (12-16)	0.31
Months from induction to transplant, median (IQR)	16 (11-32)	21 (13-35)	0.36
Active disease (PVAS ≥1), n (%)	0	1 (2)	1
CRP >5 mg/L, n (%)	5/11 (45)	5/30 (17)	0.09
Ongoing maintenance therapy, n (%)	8 (53)	18 (33)	0.22
Transplant features			
Before 2000, n (%)	1 (7)	5 (10)	1
2000-2009, n (%)	3 (20)	18 (33)	0.52
After 2009, n (%)	11 (73)	31 (57)	0.37
Living/deceased donor, n	5/10	18/36	1
Cold ischemia time, median (IQR) - hours	10 (3-16)	11 (4-13)	0.80
≥3 HLA mismatches, n (%)	5/10 (50)	24/38 (63)	0.49
Anti-IL2 receptor antagonist for induction, n (%)	10 (66)	35 (65)	1
GC-TAC-MMF, n (%)	12 (80)	31 (57)	0.13
Outcomes			
Delayed graft function, n (%)	4 (27)	2 (4)	**0.01**
eGFR at month 1, median (IQR) – mL/min/1.73 m^2	65 (58-75)	84 (65-96)	**0.03**
AAV relapse, n (%)	5 (33)	2 (4)	**0.004**
Acute rejection, n (%)	7 (47)	18 (33)	0.37
Chronic rejection, n (%)	3 (20)	4 (7)	0.17
eGFR at last follow-up, median (IQR) – mL/min/1.73 m^2	59 (33-68)	77 (51-93)	**0.003**
Chronic graft dysfunction at last follow-up, n (%)	9 (60)	17 (31)	0.06
Graft failure, n (%)	2 (13)	7 (13)	1
Death, n (%)	0	2 (4)	1

Abbreviations: AAV: ANCA-associated vasculitis; C-ANCA, cytoplasmic ANCA pattern; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; HLA, human leukocyte antigen; HR, hazard ratio; IQR, interquartile range; MMF, mycophenolate mofetil; MPA: microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA pattern; PR3, proteinase 3; PVAS, paediatric vasculitis activity score; TAC, tacrolimus.

^Three patients had no available results of ANCA testing at the time of transplantation and were excluded from the analysis.

Figure legends

Figure 1 Kaplan-Meier curves of time to graft failure and time to chronic graft dysfunction in all ~~patients~~ AAV recipients (plots on the left-hand side of the figure) and according to ANCA status at time of transplantation (plots on the right-hand side of the figure). Shaded areas represent 95% confidence intervals. P values of the log rank tests comparing survival probabilities of patients with positive ANCA (red) and negative ANCA (blue) are shown.

Figure 2 Kaplan-Meier curves of time to acute rejection and time to relapse in all ~~patients~~ AAV recipients (plots on the left-hand side of the figure) and according to ANCA status at time of transplantation (plots on the right-hand side of the figure). Shaded areas represent 95% confidence intervals. P values of the log rank test comparing survival probabilities of patients with positive ANCA (red) and negative ANCA (blue) are shown.

Figure 3 Kaplan-Meier curves of time to death, time to graft failure, ~~and~~ time to chronic graft dysfunction and time to infection-related hospitalisation of AAV recipients and matched non-AAV recipients. Shaded areas represent 95% confidence intervals. P values of log-rank tests comparing survival probabilities of cases (black) and controls (green) are shown.

Figure 1

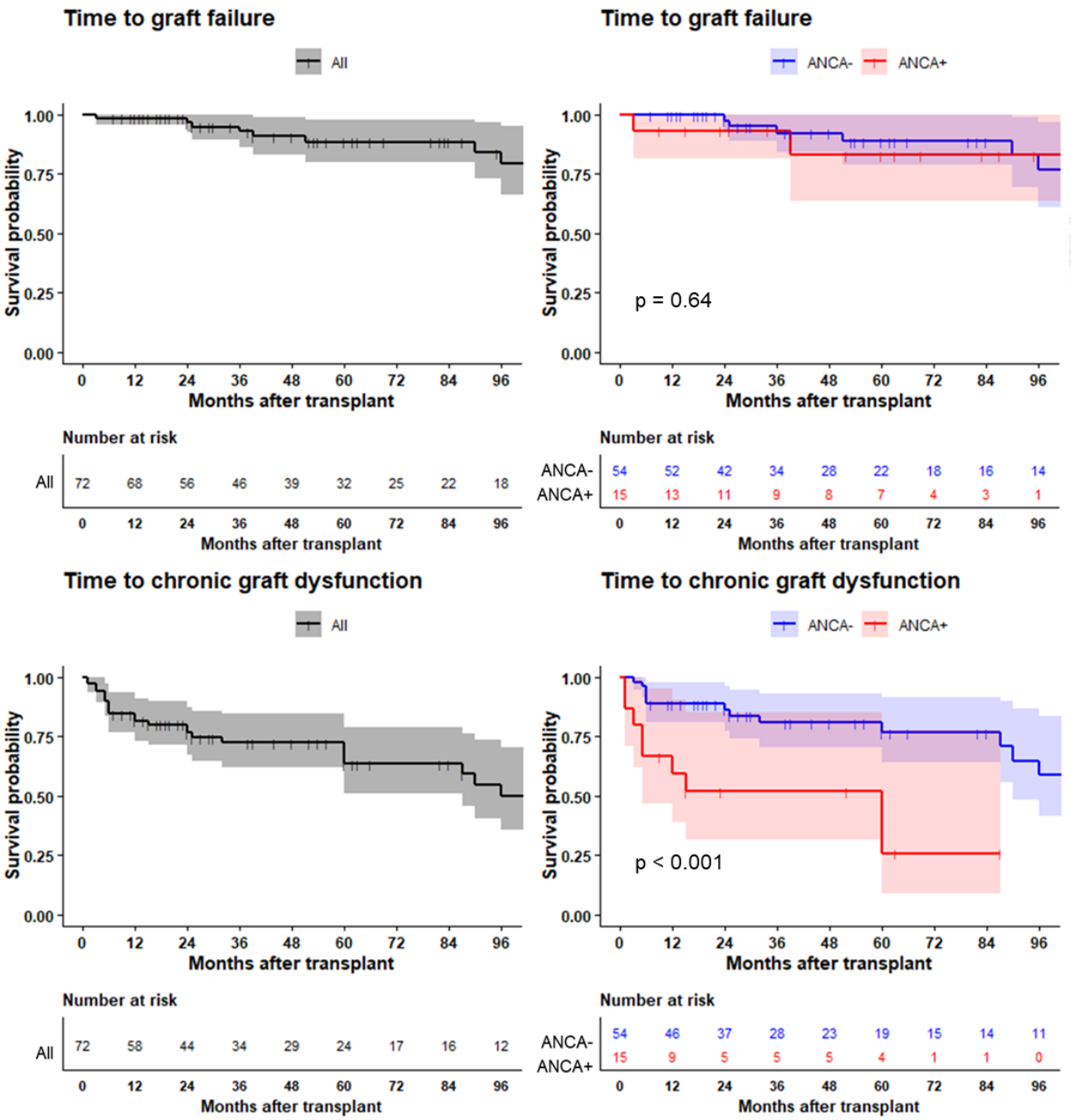
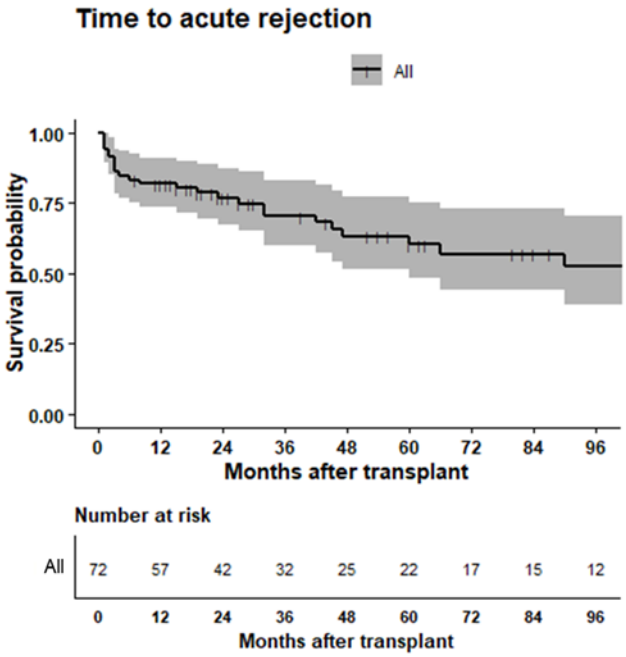
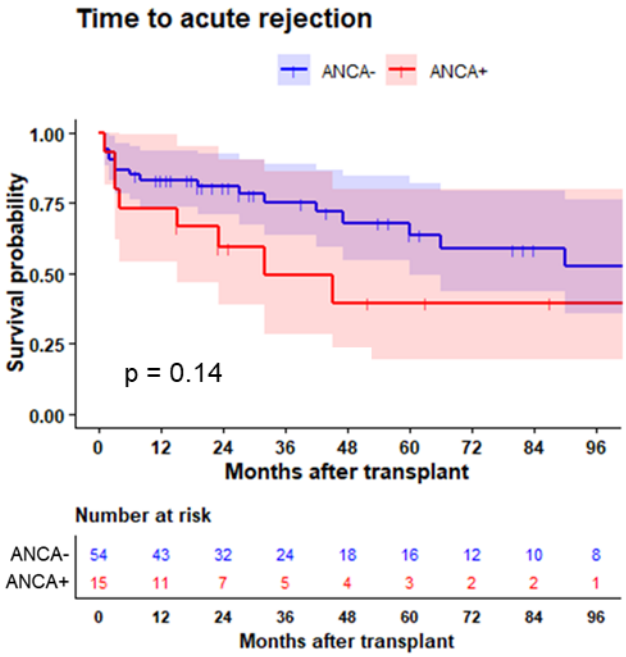
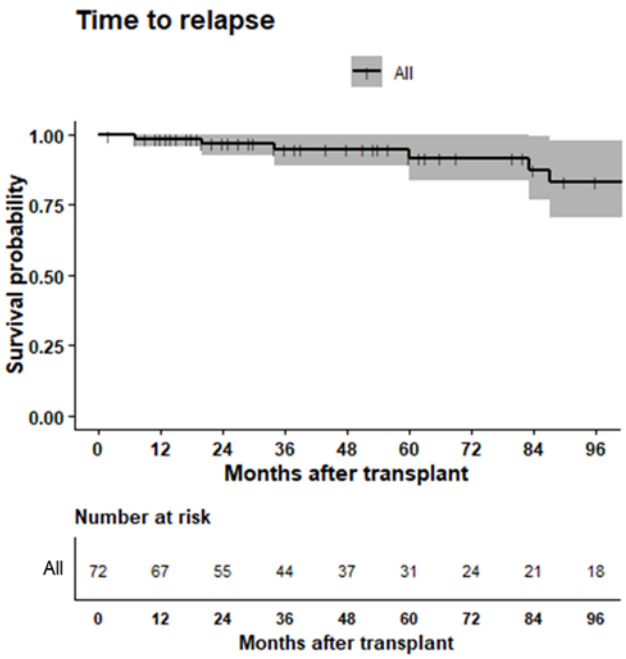


Figure 2







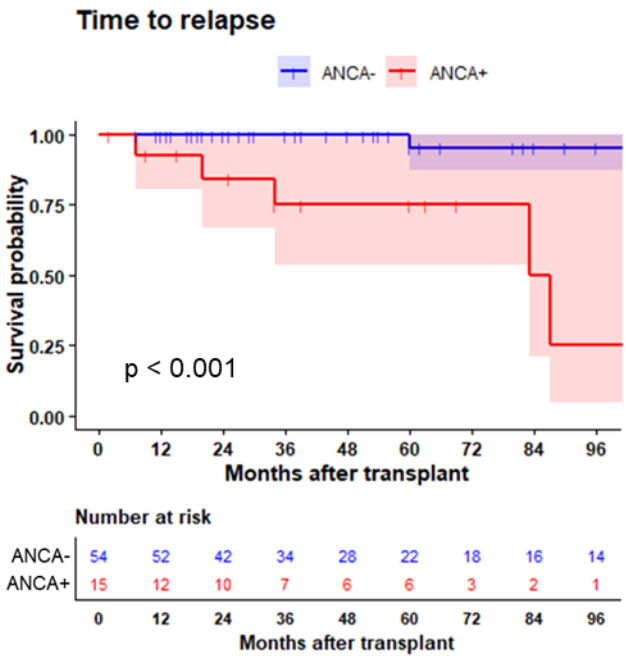


Figure 3

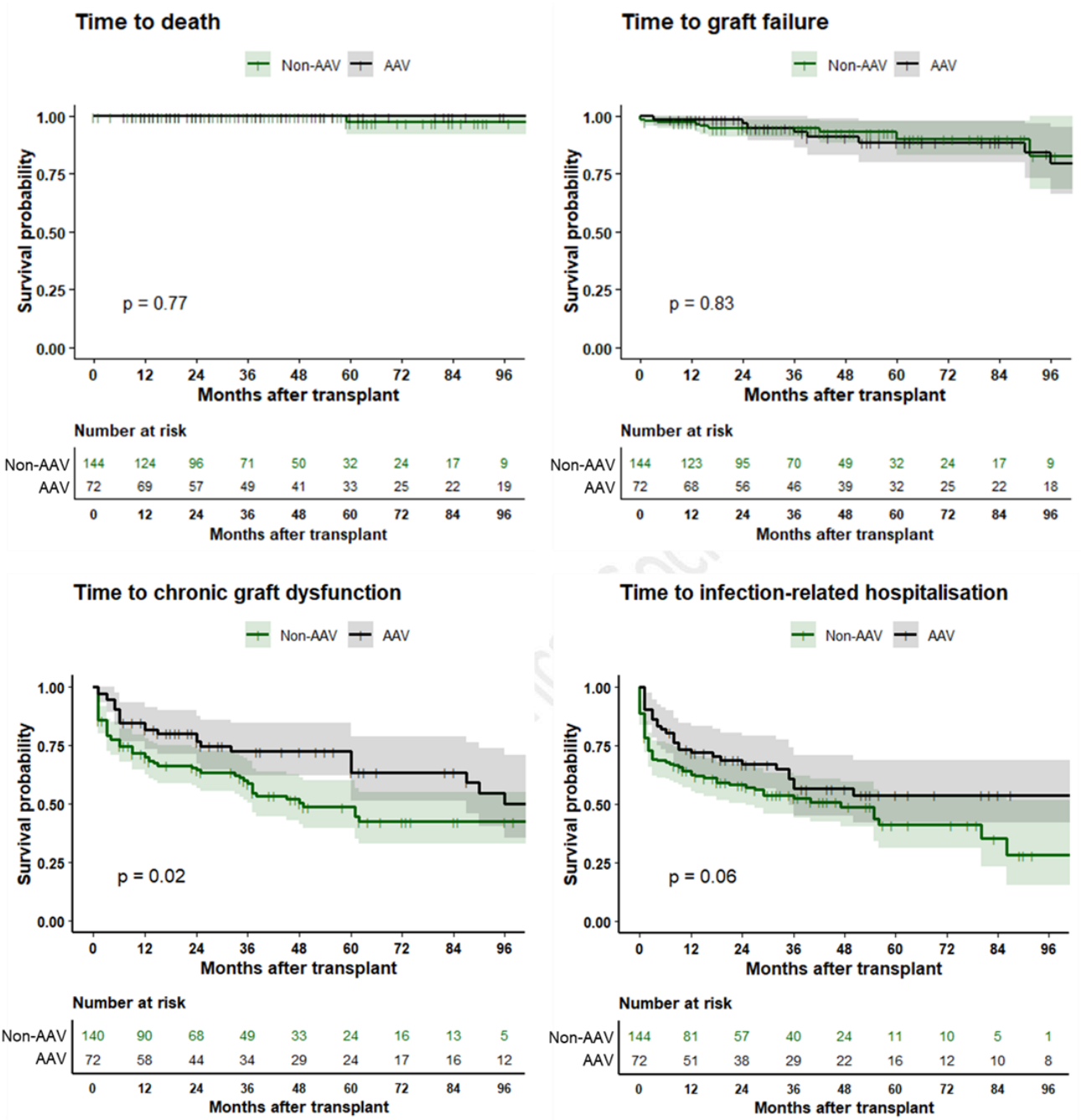


Table S1 Main investigators and number of cases per participating centre

Hospital	City	Country	Principal investigator	No. of cases
IRCCS "G. Gaslini"	Genoa	Italy	Dr Ghiggeri	7
Careggi University Hospital	Florence	Italy	Dr Allinovi	1
Meyer Children's Hospital	Florence	Italy	Dr Vaglio	2
Ospedale Maggiore Policlinico	Milan	Italy	Dr Moroni/Testa	4
Bambino Gesù	Rome	Italy	Dr Guzzo	1
Policlinco Sant'Orsola-Malpighi	Bologna	Italy	Dr Pasini	1
Bristol Children's Hospital	Bristol	UK	Dr Saleem	4
Great Ormond Street Hospital	London	UK	Dr Marks	2
Evelina Children's Hospital	London	UK	Dr Ware	6
Alder Hey Children's Hospital	Liverpool	UK	Dr Oni	1
Hopital Cochin	Paris	France	Dr Puéchal	1
Robert Debré Hospital	Paris	France	Dr Dossier	4
Hospices Civils de Lyon	Lyon	France	Dr Laurent	2
Hopital Pellegrin-Enfants	Bordeaux	France	Dr Harambat	1
Krakow University Hospital	Krakow	Poland	Dr Kosałka-Węgiel	1
Children's Memoral Health Institute	Warsaw	Poland	Dr Grenda	3
Erciyes University Hospital	Kayseri	Turkey	Dr Dursun	1
Hacettepe University Hospital	Ankara	Turkey	Dr Ozen/Topaloglu/Gülhan	2
Saint-Petersburg State Pediatric Medical University	Saint Petersburg	Russian Federation	Dr Kostik	1
SickKids	Toronto	Canada	Dr Noone/Teoh	8
Helsinki University Hospital	Helsinki	Finland	Dr Jahnukainen	4
Karolinska Institutet	Stockholm	Sweden	Dr Bruchfeld	3
Skane University Hospital	Lund	Sweden	Dr Mohammad	3
Tonji Hospital	Wuhan	China	Dr Zhou	9

Table S2 Main patient and disease features before kidney transplantation of AAV recipients.

	All N=72	**MPA N=53**	**GPA N=19**	**P value** (MPA vs GPA)
Demographics				
Female, n (%)	52 (72)	40 (75)	12 (63)	0.37
White, n (%)	50 (69)	34 (64)	16 (84)	0.14
Age at diagnosis, median (IQR) - years	12 (9-14)	12 (9-14)	12 (10-14)	0.77
ANCA pattern by immunofluorescence	N=58	N=44	N=14	
P-ANCA, n (%)	42 (72)	40 (90)	2 (14)	**<0.001**
C-ANCA, n (%)	13 (22)	2 (5)	11 (79)	**<0.001**
Double positive/other, n (%)	1 (2)	0	1 (7)	0.24
Negative, n (%)	2 (4)	2 (5)	0	1
ANCA specificity by ELISA	N=62	N=45	N=17	
MPO, n (%)	38 (61)	37 (82)	1 (6)	**<0.001**
PR3, n (%)	15 (24)	3 (7)	12 (70)	**<0.001**
Double positive, n (%)	1 (2)	0	1 (6)	0.27
Negative, n (%)	8 (13)	5 (11)	3 (18)	0.67
Serum complement factors at diagnosis	N=51	N=39	N=12	
C3, median (IQR) – mg/L	103 (81-121)	102 (80-120)	111 (99-125)	0.23
C4, median (IQR) – mg/L	29 (24-39)	29 (24-39)	34 (25-41)	0.58
Low C3 (<80 mg/L), n (%)	16 (31)	14 (36)	2 (17)	0.29
Extra-renal organ involvement	N=61	N=44	N=17	
ENT, n (%)	17 (28)	8 (18)	9 (53)	**0.01**
Lung, n (%)	30 (49)	15 (34)	15 (88)	**<0.001**
Skin, n (%)	10 (16)	7 (16)	3 (18)	1
Peripheral nervous system, n (%)	2 (3)	2 (4)	0	1
Central nervous system, n (%)	14 (23)	13 (29)	1 (6)	0.05
Gastro-intestinal tract, n (%)	13 (21)	10 (23)	3 (18)	0.74
Musculo-skeletal, n (%)	13 (21)	7 (16)	6 (35)	0.16
Eye, n (%)	4 (7)	0	4 (24)	**0.004**
Other, n (%)	3 (5)	3 (7)	0	0.55
None (renal-limited), n (%)	14 (23)	14 (32)	0	**0.01**
Kidney involvement at AAV diagnosis	N=61	N=44	N=17	
eGFR, median (IQR)–ml/min/1.73m^2	9 (5-18)	6 (5-18)	12 (7-21)	0.10
Renal replacement therapy, n (%)	34 (56)	29 (66)	5 (29)	**0.01**
Haematuria, n (%)	48/53 (91)	34/37 (92)	14/16 (87)	0.63
Proteinuria, median (IQR) – g/day	1.8 (1.2-3.0)	1.7 (1.2-2.9)	2.0 (1.1-2.8)	0.92
Nephrotic-range proteinuria, n (%)	21/50 (42)	15/35 (43)	6/15 (40)	1
Hypertension, n (%)	43 (70)	31 (70)	12 (71)	1
Biopsy, n (%)	59 (97)	43 (98)	16 (94)	0.48
PVAS, median (IQR)	17 (14-21)	15 (14-19)	21 (18-23)	**0.005**
Treatment and outcome				
Cyclophosphamide, n (%)	59 (82)	43 (81)	16 (84)	1
Rituximab, n (%)	17 (24)	10 (19)	7 (39)	0.12
Other immunosuppressants, n (%)	4 (6)	3 (6)	1 (5)	1
None/glucocorticoids only, n (%)	3 (4)	3 (6)	0	0.56
Remission, n (%)	25 (35)	18 (34)	7 (37)	1
Relapse, n (%)	9/25 (36)	6/18 (33)	3/7 (43)	0.67
Time to kidney failure, median (IQR) – months	5 (0-17)	4 (0-13)	14 (0-25)	0.28

Abbreviations: AAV: ANCA-associated vasculitis; C-ANCA, cytoplasmic ANCA pattern; CI, confidence interval; CNI, calcineurin inhibitors; ELISA, enzyme-linked immunosorbent assay; ENT, ear-nose-throat; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; HLA, human leukocyte antigen; HR, hazard ratio; IQR,

interquartile range; IS, immunosuppressant; MMF, mycophenolate mofetil; MPA: microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA pattern; PR3, proteinase 3; PVAS, paediatric vasculitis activity score

Table S3 Types of rejection and severe infections among AAV recipients during the first year post-transplant and the whole follow-up

	First year		Whole follow-up		
	Patients, n (%) N=72	**No. of episodes**	**Patients, n (%) N=72**	**No. of episodes**	**Months after transplant, median (IQR)**
Acute rejection					
All	13 (18)	13	26 (36)	32	17 (3-34)
TCMR	13 (18)	13	23 (32)	28	15 (3-35)
ABMR	1 (1)	1	4 (5)	4	20 (6-39)
Chronic rejection					
All	0	0	8 (11)	8	60 (44-100)
TCMR	0	0	2 (3)	2/8 (25)	36-69
ABMR (chronic-active and chronic)	0	0	6 (8)	6/8 (75)	75 (48-103)
Severe infections					
All	31 (43)	46	42 (58)	67	8 (3-27)
Febrile UTI	11 (15)	15	17 (24)	22	9 (4-33)
Pharyngitis/tonsillitis	6 (8)	7	9 (12)	10	8 (3-28)
Pneumonia	3 (4)	3	4 (5)	4	9 (5-15)
PJP	0	0	0	0	/
Sepsis	1 (1)	1	2 (3)	2	1-6
CMV infection	10 (14)	10	11 (15)	11	4 (2-6)
CMV disease	2 (3)	2	3 (4)	3	6 (6-35)
EBV viremia	3 (4)	3	5 (7)	5	16 (16-19)
EBV-associated PTLD	0	0	0	0	/
BKV viremia	3 (4)	3	4 (5)	4	4 (2-25)
BKV-associated nephropathy	0	0	0	0	/
Other	2 (3)	2	6 (8)	6	21 (13-105)

Abbreviations: ABMR, antibody-mediated rejection; BKV; BK virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PJP, Pneumocystis jirovecii pneumonia; PTLD, post-transplant lymphoproliferative disorders; TCMR, T cell-mediated rejection; URTI, upper respiratory tract infections; UTI, urinary tract infections

Figure S4 Features of relapses of AAV after kidney transplantation

Sex, age^	Months after transplant	Pre-relapse immuno-suppression	Manifestations	Creatinine (% change°)	Biopsy results	ANCA titre at the time of relapse (normal range)	Treatment	Outcome (creatinine)
Female, 23 y.o.	87	TAC, MMF, PDN	Graft involvement	1.26 mg/dL (+30%)	Focal necrotising GN	MPO ANCA 1429 U/mL (<20)	IV MPL, PLEX, Rituximab	Remission (0.99 mg/dL)
Female, 14 y.o.*	20	NA	Constitutional symptoms, lung infiltrates	NA	NA	NA	PDN	Partial remission
Female, 16 y.o.*	32	NA	Constitutional symptoms and arthralgia	NA	NA	NA	PDN	Partial remission
Female, 17 y.o.*	41	NA	Constitutional symptoms, arthralgia, skin purpura	NA	NA	NA	PDN and cyclophospha mide	Remission
Female, 19 y.o.	34	TAC, MMF, PDN	Graft involvement, pericarditis	1.8 (mg/dL) (+42%)	Not performed	MPO ANCA 39 (<5)	IV MPL; PDN (20 mg/d) and MMF	Graft failure
Female, 14 y.o.	7	TAC, AZA, PDN	Constitutional symptoms	0.6 mg/dL (0%)	Not performed	PR3 ANCA positive (titre NA)	Rituximab	Remission (0.7 mg/dL)
Female, 23 y.o.	60	TAC, MMF	Graft involvement	2.7 mg/dL (+110%)	Necrotising crescentic GN	MPO ANCA positive (titre NA)	IV MPL, PLEX, Rituximab	Remission (2.4 mg/dL)
Female, 17 y.o.	83	TAC, MMF	Graft involvement, constitutional symtoms	3.3 mg/dL (+20%)	Not performed	MPO ANCA positive (titre NA)	IV MPL	Remission (2.3 mg/dL)
Male, 30 y.o.	182	CyA, PDN	Rhinosinutis	1.9 mg/dL (+12%)	Not performed	PR3 ANCA 12 U/mL (<3)	Increased PDN (40 mg/d), MMF started	Remission (1.7 mg/dL)

Female, 27 y.o.	140	CyA, AZA, PDN	Skin, ENT, graft involvement	2.6 mg/dL (+70%)	Not performed	MPO ANCA 70 U/mL (<3)	Increased PDN (40 mg/d), MMF started	Remission (2.0 mg/dL)

Abbreviations: AZA, azathioprine; CyA, cyclosporine A; ENT, ear-nose-throat; IV, intravenous; GN, glomerulonephritis; MPL, methylprednisolone; MMF, mycophenolate mofetil; PDN, prednisolone; PLEX, plasma exchange; TAC, tacrolimus; UPCR, urine proteinuria:creatinine ratio

^Age refers to the time of relapse.

*These relapses occurred in the same patient.

°% change in serum creatinine is calculated from the result three months before the relapse.

Table S5 Risk factors for AAV relapse according to univariate and multivariate Cox regression model among AAV recipients. The model for the multivariate analysis has been fitted using Firth's penalised likelihood.

	AAV relapse			
	Univariate		**Multivariate**	
	Crude HR (95% CI)	**P value**	**Crude HR (95% CI)**	**P value**
Gender				
Female	Ref.			
Male	0.42 (0.05-3.45)	0.42		
Ethnicity (White)	2.86 (0.35-23.53)	0.32		
Diagnosis				
GPA	Ref.			
MPA	**0.23 (0.05-0.96)**	**0.04**	**0.01 (0.00-0.16)**	**<0.001**
Type of ANCA				
MPO-ANCA	0.48 (0.11-2.07)	0.33		
PR3-ANCA	2.85 (0.66-12.24)	0.15		
ANCA-negative	No events	N. a.		
Cyclophosphamide	0.45 (0.09-2.27)	0.33		
Age at transplantation (years)*	1.06 (0.90-1.24)	0.46		
ANCA+ at transplantation	**23.12 (2.67-200.28)**	**0.004**	**188.15 (14.84-28390.11)**	**<0.001**
PVAS >0 at transplantation	No events	N.a.		
CRP at transplantation (mg/L)°	0.97 (0.66-1.43)	0.88		
Immunosuppression at transplantation	1.72 (0.27-10.75)	0.56		
Months since completion of induction therapy#	1.02 (0.99-1.05)	0.13		
Transplant after 2010	2.92 (0.38-13.93)	0.35		
Type of donor				
Deceased	Ref.			
Living	0.91 (0.21-3.97)	0.90		
No. of HLA mismatches				
0-2	Ref.			
≥3	0.23 (0.02-2.24)	0.20		
Cold ischemia time (hours)^	0.96 (0.84-1.10)	0.59		
Anti-rejection induction therapy	1.83 (0.21-15.69)	0.58		
Anti-rejection maintenance therapy	Ref.			
Other	1.30 (0.29-5.87)	0.72		
GC-CNI-MMF				
Glucocorticoid withdrawal	3.85 (0.91-16.29)	0.66		
Delayed graft function	2.85 (0.58-14.86)	0.18		
Acute rejection	1.53 (0.38-6.16)	0.54		
Severe infections	0.76 (0.17-3.34)	0.71		

*per 1 year increment

°per 1 mg/L increment

^per 1 hour increment

#per 1 month increment

Abbreviations: CI, confidence interval; CNI, calcineurine inhibitors; GC, glucocorticoids; HLA, human leukocyte antigen; HR, hazard ratio; MMF, mycophenolate mofetil; PVAS, paediatric vasculitis activity score

Table S6 Risk factors for acute rejection according to univariate Cox regression model among AAV recipients.

	Acute rejection	
	Crude HR (95% CI)	**P value**
Gender		
Female	Ref.	
Male	0.47 (0.16-1.36)	0.16
Ethnicity (White)	0.76 (0.33-1.73)	0.52
Diagnosis		
GPA	Ref.	
MPA	0.89 (0.37-2.14)	0.81
Type of ANCA		
MPO-ANCA	1.06 (0.44-2.53)	0.89
PR3-ANCA	1.09 (0.43-2.74)	0.85
ANCA-negative	0.48 (0.06-3.59)	0.47
Cyclophosphamide	0.62 (0.24-1.54)	0.30
Age at transplantation (years)*	1.01 (0.92-1.10)	0.78
ANCA+ at transplantation	1.86 (0,80-4.29)	0.14
PVAS >0 disease at transplantation	No events	N.a.
CRP at transplantation (mg/L)°	**1.17 (1.06-1.29)**	**0.001**
Immunosuppression at transplantation	0.65 (0.27-1.58)	0.34
Months since completion of induction therapy#	0.99 (0.97-1.01)	0.65
Induction therapy <18 months	0.40 (0.14-1.08)	0.07
Transplant after 2010	0.79 (0.35-1.79)	0.58
Type of donor		
Deceased	Ref.	
Living	0.42 (0.15-1.12)	0.08
No. of HLA mismatches		
0-2	Ref.	
≥3	0.82 (0.32-2.09)	0.68
Cold ischemia time (hours)^	**1.08 (1.02-1.15)**	**0.006**
Transplant induction therapy	0.94 (0.41-2.20)	0.91
Transplant maintenance therapy		
Other	Ref.	
GC-TAC-MMF	0.47 (0.21-1.04)	0.06
Delayed graft function	2.05 (0.70-5.97)	0.18
AAV relapse	0.57 (0.07-4.28)	0.58
Severe infections	0.59 (0.27-1.29)	0.18

*per 1 year increment

°per 1 mg/L increment

^per 1 hour increment

#per 1 month incrementAbbreviations: CI, confidence interval; CNI, calcineurine inhibitors; GC, glucocorticoids; HLA, human leukocyte antigen; HR, hazard ratio; MMF, mycophenolate mofetil; PVAS, paediatric vasculitis activity score

Table S7 Risk factors for severe infections according to univariate Cox regression models among AAV recipients.

	Severe infections	
	Crude HR (95% CI)	**P value**
Gender		
Female	Ref.	
Male	0.74 (0.36-1.51)	0.41
Ethnicity (White)	0.68 (0.36-1.29)	0.24
Diagnosis		
GPA	Ref.	
MPA	0.62 (0.33-1.17)	0.14
Type of ANCA		
Anti-MPO	1.24 (0.64-2.42)	0.51
Anti-PR3	1.23 (0.63-2.40)	0.54
ANCA-negative	0.21 (0.02-1.63)	0.13
Cyclophosphamide	0.81 (0.38-1.71)	0.58
Age at transplantation (years)*	0.97 (0.90-1.04)	0.44
PVAS >0 at transplantation	**8.25 (1.03-65.96)**	**0.04**
ANCA+ at transplantation	1.08 (0.51-2.28)	0.82
Immunosuppression at transplantation	1.00 (0.53-1.87)	0.98
CRP at transplantation (mg/L)°	1.06 (0.99-1.13)	0.09
Months since completion of induction therapy#	0.98 (0.96-1.01)	0.30
Induction therapy <18 months	0.60 (0.23-1.52)	0.28
Transplant after 2010	1.00 (0.55-1.82)	0.99
Type of donor		
Deceased	Ref.	
Living	0.89 (0.49-1.77)	0.72
No. of HLA mismatches		
0-2	Ref.	
≥3	0.48 (0.22-1.02)	0.05
Cold ischemia time (hours)^	1.02 (0.97-1.06)	0.35
Anti-rejection induction therapy	0.93 (0.47-1.84)	0.84
Anti-rejection maintenance therapy		
Other	Ref.	
GC-CNI-MMF	0.92 (0.50-1.66)	0.78
Delayed graft function	1.44 (0.51-4.06)	0.48
eGFR at month 6	0.99 (0.98-1.01)	0.80
AAV relapse	1.08 (0.26-4.48)	0.91
Acute rejection	0.62 (0.29-1.36)	0.23
Chronic graft dysfunction	0.47 (0.19-1.11)	0.08

*per 1 year increment

°per 1 mg/L increment

^per 1 hour increment

#per 1 month increment

Abbreviations: CI, confidence interval; CNI, calcineurine inhibitors; GC, glucocorticoids; HLA, human leukocyte antigen; HR, hazard ratio; MMF, mycophenolate mofetil; PVAS, paediatric vasculitis activity score

Table S8 Comparison of patient characteristics according to the occurrence of DGF among AAV recipients.

	DGF N=6	**Non-DGF N=66**	**P value**
Female, n (%)	4 (66)	48 (73)	0.66
MPA, n (%)	5 (83)	48 (73)	1
Age at transplantation	14 (14-16)	14 (11-16)	1
Positive ANCA at transplantation	4 (66)	11/63 (17)	**0.01**
C-reactive protein at transplantation, median (IQR) – mg/L	2 (1-4)	2 (1-3)	0.98
Immunosuppression at transplantation, n (%)	4 (66)	23 (35)	0.18
Transplant after 2010, n (%)	3 (50)	40 (61)	0.67
Cold ischemia time, median (IQR) - hours	9 (5-13)	11 (3-13)	0.21
Living donor, n (%)	3 (50)	22 (34)	0.41
Transplant induction therapy, n (%)	6 (100)	42 (64)	0.16
CNI, n (%)	6 (100)	64 (97)	1

Abbreviations: CNI: calcineurin inhibitor; DGF, delayed graft function; IQR, interquartile range

Table S9 Main features of AAV recipients and non-AAV recipients of the Sick Kids Hospital matched for age, decade of transplantation and type of donor.

	cAAV N=72	**Sick Kids N=144**	**P value**
Age at transplantation, median (IQR), years	14 (11-16)	14 (11-16)	0.72
Female, n (%)	52 (72)	88 (61)	0.13
Cause of kidney disease			
AAV, n (%)	72 (100)	0	
Glomerular diseases, n (%)	0	44 (30)	
Tubulo-interstitial diseases, n (%)	0	20 (14)	
Cystic diseases, n (%)	0	8 (5)	
CAKUT, n (%)	0	45 (31)	
Other, n (%)	0	26 (18)	
Date of transplantation			
Before 2000, n (%)	8 (11)	12 (8)	0.61
2000-2009, (%)	21 (29)	55 (38)	0.22
2010-2020, n (%)	43 (60)	77 (53)	0.46
Type of donor			
Living, n (%)	25 (35)	66 (46)	0.14
Deceased, n (%)	47 (65)	78 (54)	0.14
Post-transplant follow-up, median (IQR), months	53 (25-97)	35 (18-58)	**<0.001**

Abbreviations: CAKUT, congenital anomalies of the kidneys and the urinary tract.

Table S10 Frequency of post-transplant viral reactivations and infection-related hospitalisations among AAV and non-AAV recipients.

	AAV recipients		**Non-AAV recipients**	
	N=72	**No. of episodes**	**N =144**	**No. of episodes**
Post-transplant viral reactivations				
CMV, n (%)	11 (15)	13	18 (12)	20
EBV, n (%)	5 (7)	6	37 (26)	52
BKV, n (%)	4 (5)	4	22 (15)	22
Infection-related hospitalisations				
All, n (%)	31 (43)	45	71 (49)	219
Bacterial infection, n (%)	22 (30)	29	60 (42)	172
Viral infection, n (%)	12 (17)	13	20 (14)	30
Other causes, n (%)	3 (4)	3	12 (12)	17

Abbreviations: BKV, BK virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus

Supplementary figure

Figure S1 Kaplan-Meier curves of time to graft failure (left) and time to chronic graft dysfunction (right) in AAV recipients according to the era of transplantation. Shaded areas represent 95% confidence intervals. Survival probabilities of transplants before 2010 (pink) and after 2010 (cyan) are compared using the log-rank test and P values are shown.

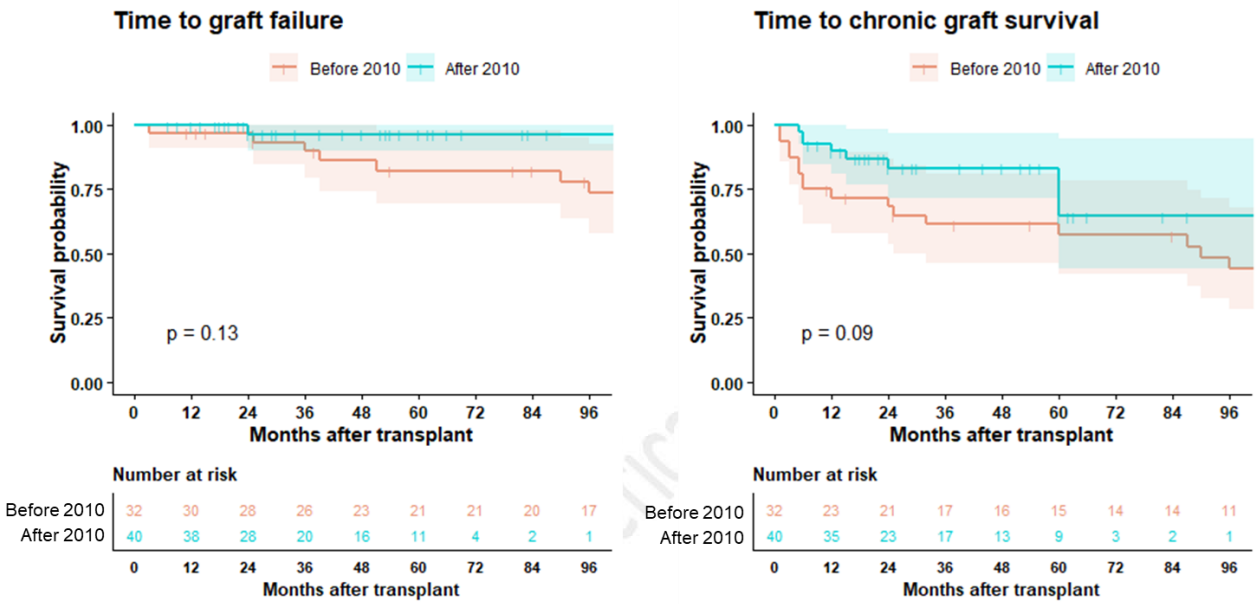


Figure S2 Kaplan-Meier curves of time to acute rejection (left) and time to chronic rejection (right) according to treatment with rituximab for remission induction of AAV. Shaded areas represent 95% confidence intervals. Survival probabilities of patients who received rituximab (orange) or not (grey) are compared using the log-rank test and P values are shown.

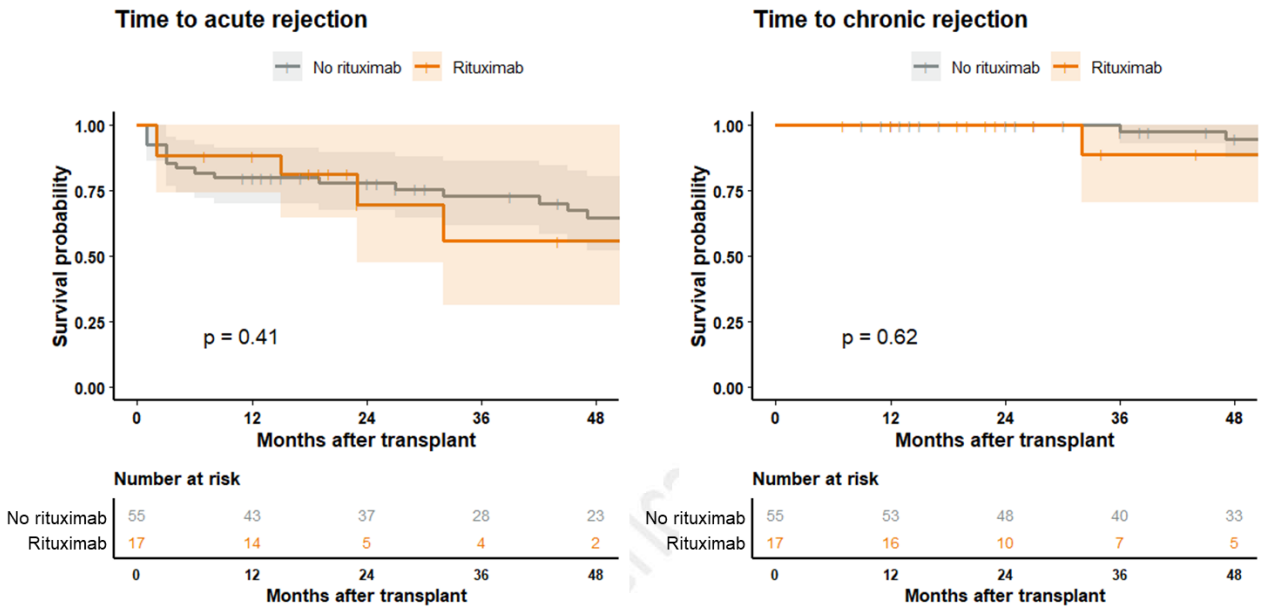


Figure S3 Kaplan-Meier curves of time to graft failure (top left), time to chronic graft dysfunction (top right), time to acute rejection (bottom left) and time to relapse (bottom right) among AAV recipients according to ANCA status during follow-up. ANCA+/+ indicates persistently ANCA positive status, ANCA-/- persistently ANCA negative status, ANCA+/- disappearance of ANCA and ANCA-/+ reappearance of ANCA. Shaded areas represent 95% confidence intervals. Survival probabilities of patients are compared using the log-rank test and P values are shown.

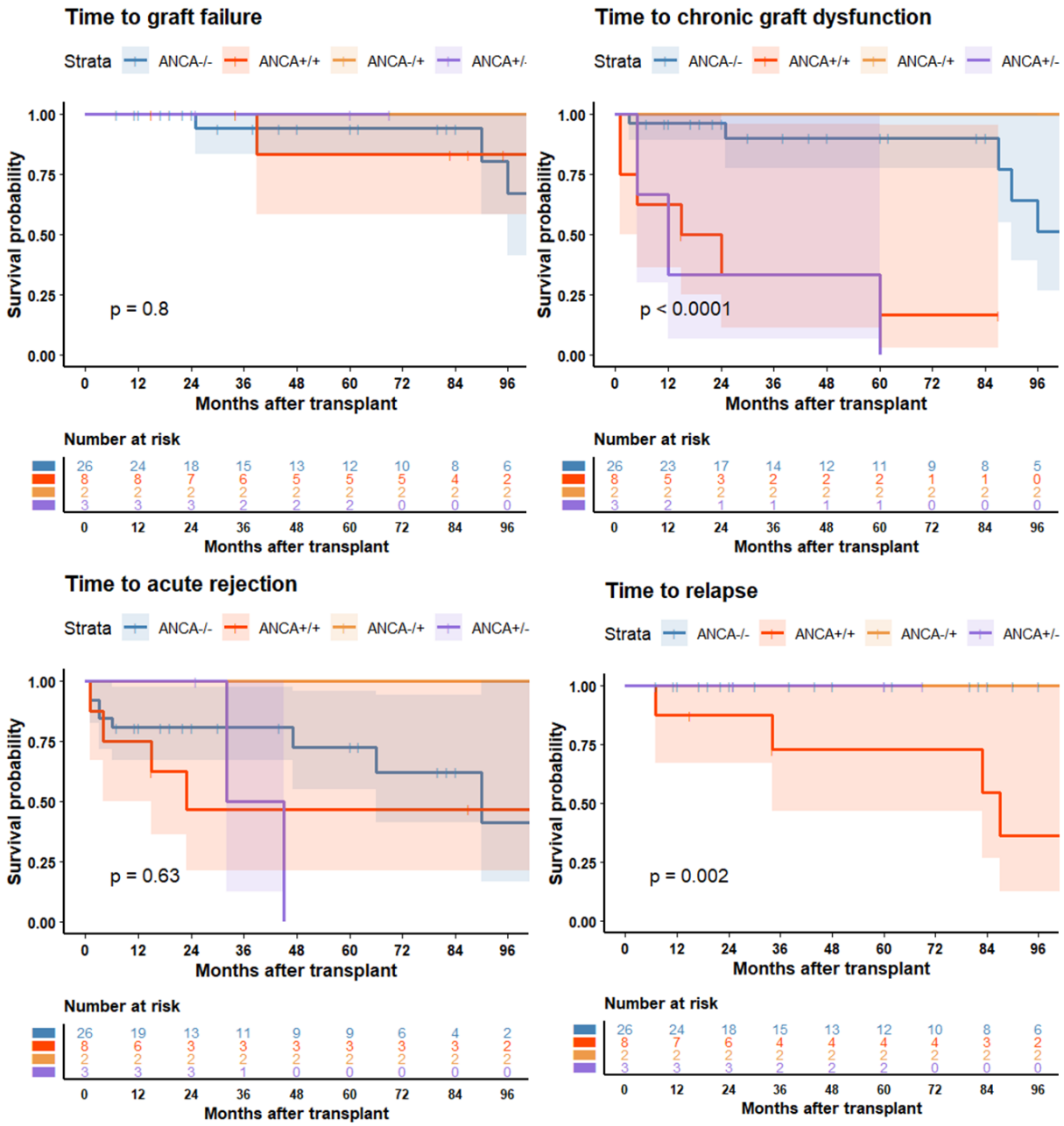


Table S1 Main investigators and number of cases per participating centre

Hospital	City	Country	Principal investigator	No. of cases
IRCCS "G. Gaslini"	Genoa	Italy	Dr Ghiggeri	7
Careggi University Hospital	Florence	Italy	Dr Allinovi	1
Meyer Children's Hospital	Florence	Italy	Dr Vaglio	2
Ospedale Maggiore Policlinico	Milan	Italy	Dr Moroni/Testa	4
Bambino Gesù	Rome	Italy	Dr Guzzo	1
Policlinco Sant'Orsola-Malpighi	Bologna	Italy	Dr Pasini	1
Bristol Children's Hospital	Bristol	UK	Dr Saleem	4
Great Ormond Street Hospital	London	UK	Dr Marks	2
Evelina Children's Hospital	London	UK	Dr Ware	6
Alder Hey Children's Hospital	Liverpool	UK	Dr Oni	1
Hopital Cochin	Paris	France	Dr Puéchal	1
Robert Debré Hospital	Paris	France	Dr Dossier	4
Hospices Civils de Lyon	Lyon	France	Dr Laurent	2
Hopital Pellegrin-Enfants	Bordeaux	France	Dr Harambat	1
Krakow University Hospital	Krakow	Poland	Dr Kosałka-Węgiel	1
Children's Memoral Health Institute	Warsaw	Poland	Dr Grenda	3
Erciyes University Hospital	Kayseri	Turkey	Dr Dursun	1
Hacettepe University Hospital	Ankara	Turkey	Dr Ozen/Topaloglu/Gülhan	2
Saint-Petersburg State Pediatric Medical University	Saint Petersburg	Russian Federation	Dr Kostik	1
SickKids	Toronto	Canada	Dr Noone/Teoh	8
Helsinki University Hospital	Helsinki	Finland	Dr Jahnukainen	4
Karolinska Institutet	Stockholm	Sweden	Dr Bruchfeld	3
Skane University Hospital	Lund	Sweden	Dr Mohammad	3
Tonji Hospital	Wuhan	China	Dr Zhou	9

Table S2 Main patient and disease features before kidney transplantation of AAV recipients.

	All N=72	**MPA N=53**	**GPA N=19**	**P value** (MPA vs GPA)
Demographics				
Female, n (%)	52 (72)	40 (75)	12 (63)	0.37
White, n (%)	50 (69)	34 (64)	16 (84)	0.14
Age at diagnosis, median (IQR) - years	12 (9-14)	12 (9-14)	12 (10-14)	0.77
ANCA pattern by immunofluorescence	N=58	N=44	N=14	
P-ANCA, n (%)	42 (72)	40 (90)	2 (14)	**<0.001**
C-ANCA, n (%)	13 (22)	2 (5)	11 (79)	**<0.001**
Double positive/other, n (%)	1 (2)	0	1 (7)	0.24
Negative, n (%)	2 (4)	2 (5)	0	1
ANCA specificity by ELISA	N=62	N=45	N=17	
MPO, n (%)	38 (61)	37 (82)	1 (6)	**<0.001**
PR3, n (%)	15 (24)	3 (7)	12 (70)	**<0.001**
Double positive, n (%)	1 (2)	0	1 (6)	0.27
Negative, n (%)	8 (13)	5 (11)	3 (18)	0.67
Serum complement factors at diagnosis	N=51	N=39	N=12	
C3, median (IQR) – mg/L	103 (81-121)	102 (80-120)	111 (99-125)	0.23
C4, median (IQR) – mg/L	29 (24-39)	29 (24-39)	34 (25-41)	0.58
Low C3 (<80 mg/L), n (%)	16 (31)	14 (36)	2 (17)	0.29
Extra-renal organ involvement	N=61	N=44	N=17	
ENT, n (%)	17 (28)	8 (18)	9 (53)	**0.01**
Lung, n (%)	30 (49)	15 (34)	15 (88)	**<0.001**
Skin, n (%)	10 (16)	7 (16)	3 (18)	1
Peripheral nervous system, n (%)	2 (3)	2 (4)	0	1
Central nervous system, n (%)	14 (23)	13 (29)	1 (6)	0.05
Gastro-intestinal tract, n (%)	13 (21)	10 (23)	3 (18)	0.74
Musculo-skeletal, n (%)	13 (21)	7 (16)	6 (35)	0.16
Eye, n (%)	4 (7)	0	4 (24)	**0.004**
Other, n (%)	3 (5)	3 (7)	0	0.55
None (renal-limited), n (%)	14 (23)	14 (32)	0	**0.01**
Kidney involvement at AAV diagnosis	N=61	N=44	N=17	
eGFR, median (IQR)–ml/min/1.73m^2	9 (5-18)	6 (5-18)	12 (7-21)	0.10
Renal replacement therapy, n (%)	34 (56)	29 (66)	5 (29)	**0.01**
Haematuria, n (%)	48/53 (91)	34/37 (92)	14/16 (87)	0.63
Proteinuria, median (IQR) – g/day	1.8 (1.2-3.0)	1.7 (1.2-2.9)	2.0 (1.1-2.8)	0.92
Nephrotic-range proteinuria, n (%)	21/50 (42)	15/35 (43)	6/15 (40)	1
Hypertension, n (%)	43 (70)	31 (70)	12 (71)	1
Biopsy, n (%)	59 (97)	43 (98)	16 (94)	0.48
PVAS, median (IQR)	17 (14-21)	15 (14-19)	21 (18-23)	**0.005**
Treatment and outcome				
Cyclophosphamide, n (%)	59 (82)	43 (81)	16 (84)	1
Rituximab, n (%)	17 (24)	10 (19)	7 (39)	0.12
Other immunosuppressants, n (%)	4 (6)	3 (6)	1 (5)	1
None/glucocorticoids only, n (%)	3 (4)	3 (6)	0	0.56
Remission, n (%)	25 (35)	18 (34)	7 (37)	1
Relapse, n (%)	9/25 (36)	6/18 (33)	3/7 (43)	0.67
Time to kidney failure, median (IQR) – months	5 (0-17)	4 (0-13)	14 (0-25)	0.28

Abbreviations: AAV: ANCA-associated vasculitis; C-ANCA, cytoplasmic ANCA pattern; CI, confidence interval; CNI, calcineurin inhibitors; ELISA, enzyme-linked immunosorbent assay; ENT, ear-nose-throat; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; HLA, human leukocyte antigen; HR, hazard ratio; IQR,

interquartile range; IS, immunosuppressant; MMF, mycophenolate mofetil; MPA: microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA pattern; PR3, proteinase 3; PVAS, paediatric vasculitis activity score

Table S3 Types of rejection and severe infections among AAV recipients ~~after transplantation~~during the first year post-transplant and the whole follow-up

	First year		Whole follow-up		
	Patients, n (%) N=72	No. of episodes	Patients, n (%) N=72	No. of episodes	Months after transplant, median (IQR)
Acute rejection					
All	13 (18)	13	26 (36)	32	17 (3-34)
TCMR	13 (18)	13	23 (32)	28	15 (3-35)
ABMR	1 (1)	1	4 (5)	4	20 (6-39)
Chronic rejection					
All	0	0	8 (11)	8	60 (44-100)
TCMR	0	0	2 (3)	2/8 (25)	36-69
ABMR (chronic-active and chronic)	0	0	6 (8)	6/8 (75)	75 (48-103)
Severe infections					
All	31 (43)	46	42 (58)	67	8 (3-27)
Febrile UTI	11 (15)	15	17 (24)	22	9 (4-33)
Pharyngitis/tonsillitis	6 (8)	7	9 (12)	10	8 (3-28)
Pneumonia	3 (4)	3	4 (5)	4	9 (5-15)
PJP	0	0	0	0	/
Sepsis	1 (1)	1	2 (3)	2	1-6
CMV infection	10 (14)	10	11 (15)	11	4 (2-6)
CMV disease	2 (3)	2	3 (4)	3	6 (6-35)
EBV viremia	3 (4)	3	5 (7)	5	16 (16-19)
EBV-associated PTLD	0	0	0	0	/
BKV viremia	3 (4)	3	4 (5)	4	4 (2-25)
BKV-associated nephropathy	0	0	0	0	/
Other	2 (3)	2	6 (8)	6	21 (13-105)

Abbreviations: ABMR, antibody-mediated rejection; BKV; BK virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PJP, Pneumocystis jirovecii pneumonia; PTLD, post-transplant lymphoproliferative disorders; TCMR, T cell-mediated rejection; URTI, upper respiratory tract infections; UTI, urinary tract infections

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Figure S4 Features of ~~patients who experiences~~ relapses of AAV after kidney transplantation

Sex, age^	Months after transplant	Pre-relapse immuno-suppression	Manifestations	Creatinine (% change°)	Biopsy results	ANCA titre at the time of relapse (normal range)	Treatment	Outcome (creatinine)
Female, 23 y.o.	87	TAC, MMF, PDN	Graft involvement	1.26 mg/dL (+30%)	Focal necrotising GN	MPO ANCA 1429 U/mL (<20)	IV MPL, PLEX, Rituximab	Remission (0.99 mg/dL)
Female, 14 y.o.*	20	NA	Constitutional symptoms, lung infiltrates	NA	NA	NA	PDN ~~and cyclophospha mide~~	Partial remission ~~(relapses at 32 and 41months)~~
Female, 16 y.o.*	32	NA	Constitutional symptoms and arthralgia	NA	NA	NA	PDN	Partial remission
Female, 17 y.o.*	41	NA	Constitutional symptoms, arthralgia, skin purpura	NA	NA	NA	PDN and cyclophospha mide	Remission
Female, 19 y.o.	34	TAC, MMF, PDN	Graft involvement, pericarditis	1.8 (mg/dL) (+42%)	Not performed	MPO ANCA 39 (<5)	IV MPL; PDN (20 mg/d) and MMF	Graft failure
Female, 14 y.o.	7	TAC, AZA, PDN	Constitutional symptoms	0.6 mg/dL (0%)	Not performed	PR3 ANCA positive (titre NA)	Rituximab	Remission (0.7 mg/dL)
Female, 23 y.o.	60	TAC, MMF	Graft involvement	2.7 mg/dL (+110%)	Necrotising crescentic GN	MPO ANCA positive (titre NA)	IV MPL, PLEX, Rituximab	Remission (2.4 mg/dL)
Female, 17 y.o.	83	TAC, MMF	Graft involvement, constitutional symtoms	3.3 mg/dL (+20%)	Not performed	MPO ANCA positive (titre NA)	IV MPL	Remission (2.3 mg/dL)
Male, 30 y.o.	182	CyA, PDN	Rhinosinutis	1.9 mg/dL (+12%)	Not performed	PR3 ANCA 12 U/mL (<3)	Increased PDN (40	Remission (1.7 mg/dL)

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							mg/d), MMF started	
Female, 27 y.o.	140	CyA, AZA, PDN	Skin, ENT, graft involvement	2.6 mg/dL (+70%)	Not performed	MPO ANCA 70 U/mL (<3)	Increased PDN (40 mg/d), MMF started	Remission (2.0 mg/dL)

Abbreviations: AZA, azathioprine; CyA, cyclosporine A; ENT, ear-nose-throat; IV, intravenous; GN, glomerulonephritis; MPL, methylprednisolone; MMF, mycophenolate mofetil; PDN, prednisolone; PLEX, plasma exchange; TAC, tacrolimus; UPCR, urine proteinuria:creatinine ratio

^Age refers to the time of relapse.

*These relapses occurred in the same patient.

°% change in serum creatinine is calculated from the result three months before the relapse.

Table S5 Risk factors for AAV relapse according to univariate and multivariate Cox regression model among AAV recipients. The model for the multivariate analysis has been fitted using Firth's penalised likelihood.

	AAV relapse			
	Univariate		**Multivariate**	
	Crude HR (95% CI)	**P value**	**Crude HR (95% CI)**	**P value**
Gender				
Female	Ref.			
Male	0.42 (0.05-3.45)	0.42		
Ethnicity (White)	2.86 (0.35-23.53)	0.32		
Diagnosis				
GPA	Ref.			
MPA	**0.23 (0.05-0.96)**	**0.04**	**0.01 (0.00-0.16)**	**<0.001**
Type of ANCA				
MPO-ANCA	0.48 (0.11-2.07)	0.33		
PR3-ANCA	2.85 (0.66-12.24)	0.15		
ANCA-negative	No events	N. a.		
Cyclophosphamide	0.45 (0.09-2.27)	0.33		
Age at transplantation (years)*	1.06 (0.90-1.24)	0.46		
ANCA+ at transplantation	**23.12 (2.67-200.28)**	**0.004**	**188.15 (14.84-28390.11)**	**<0.001**
PVAS >0 at transplantation	No events	N.a.		
CRP at transplantation (mg/L)°	0.97 (0.66-1.43)	0.88		
Immunosuppression at transplantation	1.72 (0.27-10.75)	0.56		
Months since completion of induction therapy#	1.02 (0.99-1.05)	0.13		
Transplant after 2010	2.92 (0.38-13.93)	0.35		
Type of donor				
Deceased	Ref.			
Living	0.91 (0.21-3.97)	0.90		
No. of HLA mismatches				
0-2	Ref.			
≥3	0.23 (0.02-2.24)	0.20		
Cold ischemia time (hours)^	0.96 (0.84-1.10)	0.59		
Anti-rejection induction therapy	1.83 (0.21-15.69)	0.58		
Anti-rejection maintenance therapy				
Other	Ref.			
GC-CNI-MMF	1.30 (0.29-5.87)	0.72		
Glucocorticoid withdrawal	3.85 (0.91-16.29)	0.66		
Delayed graft function	2.85 (0.58-14.86)	0.18		
Acute rejection	1.53 (0.38-6.16)	0.54		
Severe infections	0.76 (0.17-3.34)	0.71		

*per 1 year increment

°per 1 mg/L increment

^per 1 hour increment

#per 1 month increment

Abbreviations: CI, confidence interval; CNI, calcineurine inhibitors; GC, glucocorticoids; HLA, human leukocyte antigen; HR, hazard ratio; MMF, mycophenolate mofetil; PVAS, paediatric vasculitis activity score

Table S6 Risk factors for acute rejection according to univariate Cox regression model among AAV recipients.

	Acute rejection Crude HR (95% CI)	P value
Gender		
Female	Ref.	
Male	0.47 (0.16-1.36)	0.16
Ethnicity (White)	0.76 (0.33-1.73)	0.52
Diagnosis		
GPA	Ref.	
MPA	0.89 (0.37-2.14)	0.81
Type of ANCA		
MPO-ANCA	1.06 (0.44-2.53)	0.89
PR3-ANCA	1.09 (0.43-2.74)	0.85
ANCA-negative	0.48 (0.06-3.59)	0.47
Cyclophosphamide	0.62 (0.24-1.54)	0.30
Age at transplantation (years)*	1.01 (0.92-1.10)	0.78
ANCA+ at transplantation	1.86 (0,80-4.29)	0.14
PVAS >0 disease at transplantation	No events	N.a.
CRP at transplantation (mg/L)°	**1.17 (1.06-1.29)**	**0.001**
Immunosuppression at transplantation	0.65 (0.27-1.58)	0.34
Months since completion of induction therapy#	0.99 (0.97-1.01)	0.65
Induction therapy <18 months	0.40 (0.14-1.08)	0.07
Transplant after 2010	0.79 (0.35-1.79)	0.58
Type of donor		
Deceased	Ref.	
Living	0.42 (0.15-1.12)	0.08
No. of HLA mismatches		
0-2	Ref.	
≥3	0.82 (0.32-2.09)	0.68
Cold ischemia time (hours)^	**1.08 (1.02-1.15)**	**0.006**
Transplant induction therapy	0.94 (0.41-2.20)	0.91
Transplant maintenance therapy		
Other	Ref.	
GC-TAC-MMF	0.47 (0.21-1.04)	0.06
Delayed graft function	2.05 (0.70-5.97)	0.18
AAV relapse	0.57 (0.07-4.28)	0.58
Severe infections	0.59 (0.27-1.29)	0.18

*per 1 year increment

°per 1 mg/L increment

^per 1 hour increment

#per 1 month incrementAbbreviations: CI, confidence interval; CNI, calcineurine inhibitors; GC, glucocorticoids; HLA, human leukocyte antigen; HR, hazard ratio; MMF, mycophenolate mofetil; PVAS, paediatric vasculitis activity score

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Table S7 Risk factors for severe infections according to univariate Cox regression models among AAV recipients.

	Severe infections Crude HR (95% CI)	P value
Gender		
Female	Ref.	
Male	0.74 (0.36-1.51)	0.41
Ethnicity (White)	0.68 (0.36-1.29)	0.24
Diagnosis		
GPA	Ref.	
MPA	0.62 (0.33-1.17)	0.14
Type of ANCA		
Anti-MPO	1.24 (0.64-2.42)	0.51
Anti-PR3	1.23 (0.63-2.40)	0.54
ANCA-negative	0.21 (0.02-1.63)	0.13
Cyclophosphamide	0.81 (0.38-1.71)	0.58
Age at transplantation (years)*	0.97 (0.90-1.04)	0.44
PVAS >0 at transplantation	**8.25 (1.03-65.96)**	**0.04**
ANCA+ at transplantation	1.08 (0.51-2.28)	0.82
Immunosuppression at transplantation	1.00 (0.53-1.87)	0.98
CRP at transplantation (mg/L)°	1.06 (0.99-1.13)	0.09
Months since completion of induction therapy#	0.98 (0.96-1.01)	0.30
Induction therapy <18 months	0.60 (0.23-1.52)	0.28
Transplant after 2010	1.00 (0.55-1.82)	0.99
Type of donor		
Deceased	Ref.	
Living	0.89 (0.49-1.77)	0.72
No. of HLA mismatches		
0-2	Ref.	
≥3	0.48 (0.22-1.02)	0.05
Cold ischemia time (hours)^	1.02 (0.97-1.06)	0.35
Anti-rejection induction therapy	0.93 (0.47-1.84)	0.84
Anti-rejection maintenance therapy		
Other	Ref.	
GC-CNI-MMF	0.92 (0.50-1.66)	0.78
Delayed graft function	1.44 (0.51-4.06)	0.48
eGFR at month 6	0.99 (0.98-1.01)	0.80
AAV relapse	1.08 (0.26-4.48)	0.91
Acute rejection	0.62 (0.29-1.36)	0.23
Chronic graft dysfunction	0.47 (0.19-1.11)	0.08

*per 1 year increment

°per 1 mg/L increment

^per 1 hour increment

#per 1 month increment

Abbreviations: CI, confidence interval; CNI, calcineurine inhibitors; GC, glucocorticoids; HLA, human leukocyte antigen; HR, hazard ratio; MMF, mycophenolate mofetil; PVAS, paediatric vasculitis activity score

Table S8 Comparison of patient characteristics according to the occurrence of DGF among AAV recipients.

	DGF N=6	**Non-DGF N=66**	**P value**
Female, n (%)	4 (66)	48 (73)	0.66
MPA, n (%)	5 (83)	48 (73)	1
Age at transplantation	14 (14-16)	14 (11-16)	1
Positive ANCA at transplantation	4 (66)	11/63 (17)	**0.01**
C-reactive protein at transplantation, median (IQR) – mg/L	2 (1-4)	2 (1-3)	0.98
Immunosuppression at transplantation, n (%)	4 (66)	23 (35)	0.18
Transplant after 2010, n (%)	3 (50)	40 (61)	0.67
Cold ischemia time, median (IQR) - hours	9 (5-13)	11 (3-13)	0.21
Living donor, n (%)	3 (50)	22 (34)	0.41
Transplant induction therapy, n (%)	6 (100)	42 (64)	0.16
CNI, n (%)	6 (100)	64 (97)	1

Abbreviations: CNI: calcineurin inhibitor; DGF, delayed graft function; IQR, interquartile range

Table S9 Main features of AAV recipients and non-AAV recipients of the Sick Kids Hospital matched for age, decade of transplantation and type of donor.

	cAAV N=72	**Sick Kids N=144**	**P value**
Age at transplantation, median (IQR), years	14 (11-16)	14 (11-16)	0.72
Female, n (%)	52 (72)	88 (61)	0.13
Cause of kidney disease			
AAV, n (%)	72 (100)	0	
Glomerular diseases, n (%)	0	44 (30)	
Tubulo-interstitial diseases, n (%)	0	20 (14)	
Cystic diseases, n (%)	0	8 (5)	
CAKUT, n (%)	0	45 (31)	
Other, n (%)	0	26 (18)	
Date of transplantation			
Before 2000, n (%)	8 (11)	12 (8)	0.61
2000-2009, (%)	21 (29)	55 (38)	0.22
2010-2020, n (%)	43 (60)	77 (53)	0.46
Type of donor			
Living, n (%)	25 (35)	66 (46)	0.14
Deceased, n (%)	47 (65)	78 (54)	0.14
Post-transplant follow-up, median (IQR), months	53 (25-97)	35 (18-58)	**<0.001**

Abbreviations: CAKUT, congenital anomalies of the kidneys and the urinary tract.

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Table S10 Frequency of post-transplant viral reactivations and infection-related hospitalisations among AAV and non-AAV recipients.

	AAV recipients		Non-AAV recipients	
	N=72	No. of episodes	N =144	No. of episodes
Post-transplant viral reactivations				
CMV, n (%)	11 (15)	13	18 (12)	20
EBV, n (%)	5 (7)	6	37 (26)	52
BKV, n (%)	4 (5)	4	22 (15)	22
Infection-related hospitalisations				
All, n (%)	31 (43)	45	71 (49)	219
Bacterial infection, n (%)	22 (30)	29	60 (42)	172
Viral infection, n (%)	12 (17)	13	20 (14)	30
Other causes, n (%)	3 (4)	3	12 (12)	17

Abbreviations: BKV, BK virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus

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Supplementary figure

Figure S1 Kaplan-Meier curves of time to graft failure (left) and time to chronic graft dysfunction (right) in AAV recipients according to the era of transplantation. Shaded areas represent 95% confidence intervals. Survival probabilities of transplants before 2010 (pink) and after 2010 (cyan) are compared using the log-rank test and P values are shown.

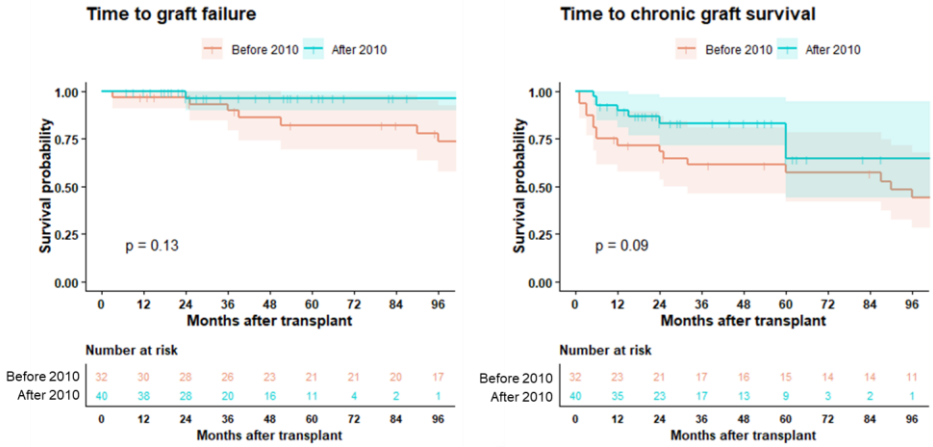

Figure S2 Kaplan-Meier curves of time to acute rejection (left) and time to chronic rejection (right) according to treatment with rituximab for remission induction of AAV. Shaded areas represent 95% confidence intervals. Survival probabilities of patients who received rituximab (orange) or not (grey) are compared using the log-rank test and P values are shown.

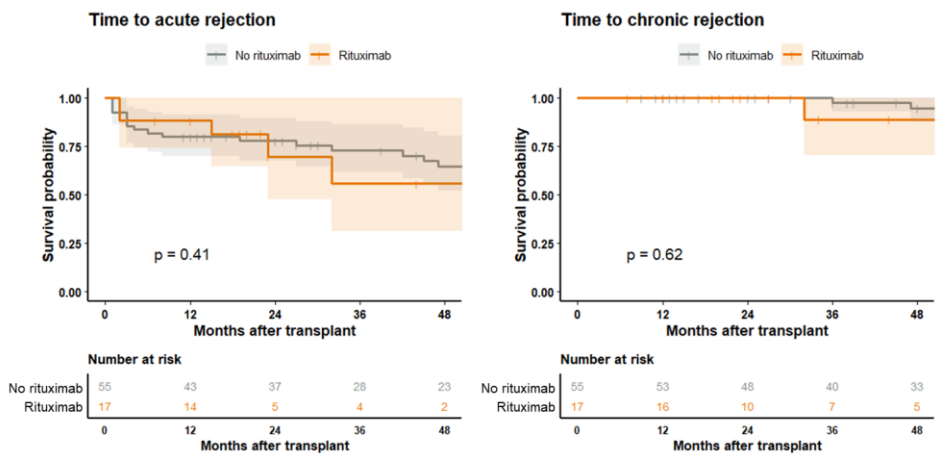

Figure S3 Kaplan-Meier curves of time to graft failure (top left), time to chronic graft dysfunction (top right), time to acute rejection (bottom left) and time to relapse (bottom right) among AAV recipients according to ANCA status during follow-up. ANCA+/+ indicates persistently ANCA positive status, ANCA-/- persistently ANCA negative status, ANCA+/- disappearance of ANCA and ANCA-/+ reappearance of ANCA. Shaded areas represent 95% confidence intervals. Survival probabilities of patients are compared using the log-rank test and P values are shown.