



Kidney transplantation in Alport syndrome: A genotype-guided case series and literature review

Aleksandra Gavrilovska-Brzanov¹, Haris Sulejmani², Sasho Dohcev³, Goce Spasovski⁴, Nikola Georgievski⁴,
 Aleksandar Trifunovski³, Dimitar Trajkovski³, Marija Jovanovski Srceva¹, Nikola Brzanov¹

¹Department of Anesthesiology, Reanimation and Intensive Care Medicine and Emergency, Ss. Cyril and Methodius University in Skopje Faculty of Medicine, Skopje, Republic of North Macedonia

²Ss. Cyril and Methodius University in Skopje Faculty of Medicine, Skopje, Republic of North Macedonia

³Department of Urology, Ss. Cyril and Methodius University in Skopje Faculty of Medicine, Skopje, Republic of North Macedonia

⁴Department of Nephrology, Ss. Cyril and Methodius University in Skopje Faculty of Medicine, Skopje, Republic of North Macedonia

ABSTRACT

Alport syndrome (AS) is a hereditary nephropathy caused by pathogenic variants in COL4A3, COL4A4, or COL4A5, leading to type IV collagen defects and progressive glomerular basement membrane dysfunction. Kidney transplantation provides excellent long-term outcomes; however, donor eligibility, genotype-specific prognosis, and post-transplant complications continue to raise important clinical considerations in the era of precision medicine. We present a comparative case series of three genetically confirmed patients with AS who underwent kidney transplantation: Two with X-linked disease and one with autosomal-dominant inheritance. Genetic, clinical, and immunologic findings were analyzed and contextualized within current literature and recommendations. All patients initially achieved functioning grafts. The autosomal-dominant case demonstrated stable long-term function under cyclosporine-based immunosuppression. Among the X-linked cases, one experienced coronavirus disease-2019-associated arterial thrombosis requiring graft nephrectomy and subsequently underwent successful deceased-donor transplantation one year later; the other developed late antibody-mediated rejection six years post-transplant, with partial recovery following corticosteroid therapy. Kidney transplantation is an effective treatment for AS when guided by molecular confirmation and careful donor evaluation. In this national case series of three patients, outcomes were generally favorable across inheritance types; however, vascular events and late humoral immune complications affected the long-term course of the graft and underscored the need for individualized surveillance.

Keywords: Alport syndrome, antibody-mediated rejection, COL4A3, COL4A4, COL4A5 mutations, donor selection, kidney transplantation

INTRODUCTION

Alport syndrome (AS) is an inherited nephropathy caused by pathogenic variants in COL4A3, COL4A4, or COL4A5, which encode the $\alpha 3$ - $\alpha 5$ chains of type IV collagen, a key structural component of the glomerular basement membrane (GBM) (1-3). Clinically, AS manifests with progressive renal dysfunction, sensorineural hearing loss, and ocular abnormalities (4). Approximately 80% of affected individuals have X-linked disease due to COL4A5 variants, while autosomal dominant and autosomal recessive forms result from COL4A3 or COL4A4 mutations (5,6). Disease severity often correlates with the specific genotype and its impact on collagen stability (7,8).

Contemporary recommendations from the ERKNet-ERA-ESPN working group emphasize the importance of molecular diagnostics, standardized donor evaluation, and genotype-based clinical management (9,10). Most affected individuals ultimately progress to end-stage renal disease (ESRD), for which kidney transplantation remains the preferred treatment, with survival outcomes comparable to those seen in other causes of ESRD (11,12).

Although post-transplant prognosis is generally favorable, certain considerations remain essential. A subset of males with X-linked AS may develop *de novo* anti-GBM nephritis following exposure to donor-derived $\alpha 5$ (IV) collagen, a historically severe but rare complication (13). In addition, evaluating potential living donors, particularly heterozygous female carriers, requires careful clinical and molecular assessment due to their increased lifetime risk of renal decline (14,15).

This report aims to distill practical, case-based lessons relevant to contemporary Alport transplant care: (i) how molecular diagnosis shapes donor eligibility and

Cite this article as: Gavrilovska-Brzanov A, Sulejmani H, Dohcev S, Spasovski G, Georgievski N, Trifunovski A, et al. Kidney transplantation in Alport syndrome: a genotype-guided case series and literature review. *Turk J Surg*. [Epub Ahead of Print]

Corresponding Author

Haris Sulejmani

E-mail: Sulejmani.haris@hotmail.com

ORCID ID: orcid.org/0009-0002-5583-5489

Received: 04.12.2025

Accepted: 17.03.2026

Epub: 04.05.2026

DOI: [10.47717/turkjsurg.2026.2025-12-4](https://doi.org/10.47717/turkjsurg.2026.2025-12-4)

Available at www.turkjsurg.com



counseling, (ii) how late immune-mediated graft dysfunction may emerge despite long-term stability, and (iii) how major systemic infections such as coronavirus disease-2019 (COVID-19) may precipitate catastrophic vascular complications in selected recipients.

MATERIAL and METHODS

Patient selection – the three cases represent the complete national experience of genetically confirmed AS recipients who have undergone kidney transplantation in North Macedonia to date, reflecting the rarity of the condition and the centralized transplant referral pathway. Each patient reached ESRD and received a kidney transplant. For every recipient, we recorded age, sex, mode of inheritance (X-linked, autosomal dominant, or autosomal recessive) and baseline renal function (serum creatinine, estimated glomerular filtration rate). For each recipient, available baseline phenotypic data were extracted from records and included age at ESRD, dialysis history (when applicable), and documented extrarenal manifestations (hearing impairment and ocular findings) when present.

DNA extraction and quality control – genomic DNA was isolated from peripheral blood leukocytes using a silica column-based extraction kit. Purity was assessed by spectrophotometry ($A_{260}/A_{280} \approx 1.8-2.0$) and concentration by Qubit fluorometry, requiring $> 30 \text{ ng}/\mu\text{L}$ for downstream analysis. Samples failing these thresholds were reextracted.

Targeted gene panel sequencing – a custom capture panel covering the full coding regions and exon-intron boundaries of COL4A3, COL4A4, and COL4A5 was employed. Library preparation followed the Illumina TruSeq protocol, and paired-end sequencing ($2 \times 150 \text{ bp}$) was performed on a MiSeq instrument, achieving a minimum mean coverage of $100\times$.

Bioinformatic pipeline – reads were aligned to the human reference genome (hg38) with BWAMEM. Variant calling was performed using GATK HaplotypeCaller and variants were annotated using ClinVar, gnomAD, and ACMG guidelines. Variants were classified as pathogenic/likely pathogenic, variants of uncertain significance or benign.

Donor evaluation – all potential living donors underwent the same targeted panel. Individuals harboring pathogenic COL4A3/A4/A5 variants or exhibiting abnormal urinalysis (hematuria, proteinuria) were excluded. Standard immunologic workup (HLA crossmatch and ABO compatibility) was documented for each donor-recipient pair.

CASE SERIES

Three patients with genetically confirmed AS underwent kidney transplantation. Two procedures were performed using living-related donors, while one patient first underwent living donation and, due to complications and graft nephrectomy, later received a deceased-donor graft. All living donors underwent standard immunological evaluation, including cross-match and HLA typing, with negative results in all cases. Preoperative imaging confirmed suitable iliac vasculature and single-vessel donor anatomy. All donor nephrectomies were performed laparoscopically, with uneventful postoperative recoveries. The evaluation was conducted in accordance with institutional ethical standards; Institutional Review Board approval was obtained, and all patients provided written informed consent. The clinical courses and corresponding genetic findings are summarized below.

Case 1

A 26-year-old male with ESRD secondary to X-linked AS underwent an elective living-related kidney transplantation from his father. His mother confirmed by genetic testing to be heterozygous for COL4A5 and was therefore not considered for donation based on the donor eligibility criteria recommended at that time. Molecular testing identified a hemizygous COL4A5 non-sense variant (c.1117C>T; p.Arg373Ter) and an additional heterozygous CDC5L variant of uncertain significance (Table 1). The CDC5L finding was interpreted as an incidental variant of uncertain significance without an established link to type IV collagen nephropathy and was not considered contributory to the renal phenotype.

Initial recovery was satisfactory, although the decline in serum creatinine was slower than anticipated. Standard

Case	Gene	Variant (cDNA/protein)	Zygoty	Inheritance	Testing summary
1	COL4A5	c.1117C>T (p.Arg373Ter)	Hemizygous	X-linked (maternal carrier)	Pathogenic variant inherited from heterozygous mother.
	CDC5L	c.2014C>T (p.Pro672Ser)	Heterozygous	Autosomal (paternal)	Variant of uncertain significance, likely benign.
2	COL4A4	c.755G>A (p.Gly252Asp)	Heterozygous	Autosomal-dominant (likely familial)	Likely pathogenic variant; family testing ongoing.
3	COL4A5	c.81G>T	Hemizygous	X-linked (maternal testing pending)	Genetic confirmation of COL4A5 mutation; family testing recommended.

immunosuppression consisted of cyclosporine, mycophenolate mofetil, and prednisone. Four weeks post-transplant, shortly after a confirmed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, the patient developed abdominal pain and graft-site tenderness. Imaging demonstrated a large peritransplant hematoma and thrombosis of the renal and external iliac arteries. Due to the extent of vascular compromise, urgent surgical revision was performed, resulting in graft nephrectomy.

Baseline extrarenal manifestations were assessed based on available specialist documentation. An ophthalmologic evaluation performed in 2021 demonstrated myopic astigmatism with preserved visual acuity and no Alport-specific ocular abnormalities, such as anterior lenticonus or retinal flecks. No documented sensorineural hearing loss was identified in the available medical records, and no audiometric abnormalities were reported. He subsequently resumed hemodialysis and maintained clinical stability. One year later, he successfully underwent deceased-donor kidney transplantation, with a functioning graft at the most recent follow-up.

Case 2

A 15-year-old boy with autosomal-dominant AS caused by a heterozygous COL4A4 missense variant (c.755G>A; p.Gly252Asp) underwent a pre-emptive living-related kidney transplantation from his paternal aunt (Table 1). At the time of surgery, he was the youngest transplant recipient at our center to undergo the procedure after transitioning from pediatric nephrology care.

Postoperative recovery was uncomplicated, and graft function stabilized early under maintenance immunosuppression

with cyclosporine, mycophenolate, and prednisone. At the two-year follow-up, graft function remained stable based on routine biochemical parameters, including renal function tests and immunosuppressive drug-level monitoring; there were no biopsy-proven rejections or clinically significant infectious events.

Baseline extrarenal symptoms were comprehensively recorded in Case 2. The otolaryngologic assessment indicated bilateral hearing impairment, with audiometric testing showing a mixed sensorineural hearing loss of 50-60 dB, which was corroborated by subsequent evaluations. Ophthalmologic evaluations conducted during childhood and adolescence revealed preserved visual acuity and normal retinal and anterior segment findings, without Alport-specific ocular anomalies.

Case 3

A 22-year-old male with X-linked AS due to a hemizygous COL4A5 variant, c.81G>T (Table 1), underwent living-donor kidney transplantation from his father after a period of hemodialysis. The graft was implanted into the left iliac fossa. Early postoperative recovery was complicated by a small peritransplant hematoma requiring surgical evacuation, after which renal function stabilized (Table 2). He was maintained on tacrolimus, mycophenolate mofetil, and prednisone. Six years post-transplant, he developed a progressive increase in serum creatinine accompanied by newly detected class II HLA antibodies, consistent with antibody-mediated rejection. Treatment with pulse methylprednisolone and anticoagulation resulted in improved graft function. He remains clinically stable, with preserved graft function and no further rejection events reported during follow-up.

System	Parameter	Reference range	Day 1 (C1/C2/C3)	Day 7 (C1/C2/C3)	Month 1 (C1/C2/C3)	Month 12 (C1/C2/C3)
Renal function	Creatinine (μmol/L)	45-109	725/308/166	490/63/130	381/60/188	629/55/152
	Urea (mmol/L)	2.7-7.8	25.6/9.3/8.3	21.8/6.7/7.1	18.2/6.6/6.9	16.4/5.5/7.5
Inflammatory markers	CRP (mg/L)	≤6	180/39.6/<1.0	97/3.0/2.5	55/2.9/1.8	35/<1.0/<1.0
	LDH (U/L)	≤250	950/178/198	700/241/220	486/316/304	320/300/245
Protein status	Albumin (g/L)	35-50	28/27/43	34/31/41	36/36/44	40/43/45
Immunosuppression monitoring	Calcineurin inhibitor level (ng/mL)	100-400	CSA 380/CSA 405/TAC 7.8	CSA 310/CSA 753/TAC 8.5	CSA 250/CSA 405/TAC 7.1	CSA 185/CSA 320/TAC 6.9
Hematologic	Hemoglobin (g/L)	120-180	70/104/130	98/75/122	92/97/128	110/118/135
Electrolytes	Sodium (mmol/L)	135-145	130/140/138	138/143/140	140/142/139	142/141/140
	Potassium (mmol/L)	3.5-5.1	5.2/3.5/3.5	4.8/4.8/4.1	4.5/4.3/4.0	4.4/4.2/4.1
	Calcium (mmol/L)	2.1-2.6	2.34/2.0/2.2	2.27/2.3/2.3	2.30/2.34/2.35	2.38/2.41/2.36

Values represent serial laboratory measurements obtained at standardized postoperative intervals (Day 1, Day 7, Month 1, and Month 12). Data are presented in the format Case 1 (C1), Case 2 (C2), and Case 3 (C3).
For Case 1, Month 12 laboratory values (serum creatinine and urea) reflect the interval following graft loss and return to dialysis prior to re-transplantation, rather than post-second transplantation graft function.
CSA: Cyclosporine, TAC: Tacrolimus, CRP: C-reactive protein, LDH: Lactate dehydrogenase.

The relative timing and sequence of key clinical events for each recipient are summarized in Table 3 to facilitate comparison across cases.

In Case 3, extrarenal involvement was prominent and evolved over time. Audiologic follow-up revealed an early-onset bilateral sensorineural hearing impairment, documented since adolescence, with progressive deterioration during serial otolaryngologic assessments. The severity of hearing loss necessitated bilateral hearing amplification and ongoing auditory rehabilitation. Initial ophthalmologic evaluations demonstrated myopic astigmatism, preserved visual acuity, and unremarkable anterior segment findings. During later follow-up, additional ocular abnormalities were identified, including incipient posterior subcapsular cataract and recurrent episodes of herpetic keratitis, both occurring in the setting of long-term immunosuppressive therapy after kidney transplantation. Retinal imaging showed peripapillary and pigmentary alterations, with no evidence of anterior lenticonus. Genetic testing confirmed the molecular basis and inheritance pattern of AS in all three recipients. The main variants identified and their clinical relevance are summarized in Table 1.

Patient Perspective

Due to the retrospective nature of this case series, formal patient-reported outcome measures were not systematically collected. Nevertheless, all patients were informed about their diagnosis, treatment options, and genetic implications and provided written informed consent for transplantation and the publication of anonymized clinical data. At the last follow-up, patients with functioning grafts reported satisfactory overall clinical status and improved quality of life compared with the pre-transplant period, which is consistent with routine post-transplant clinical assessments.

DISCUSSION

The three presented cases illustrate the genetic and clinical heterogeneity of AS and demonstrate how inheritance patterns

may shape post-transplant outcomes. Cases 1 and 3, both with X-linked disease, and Case 2, with autosomal-dominant inheritance, align with current evidence showing that genotype correlates with clinical severity and renal progression (1-4).

Kidney transplantation remains the treatment of choice for patients with AS, with long-term graft survival frequently exceeding 80% (3,7-9). Gillion et al. (3) reported no significant differences in graft outcomes between X-linked and autosomal forms, supporting the view that transplantation is safe and effective across genotypes when donor selection and immunologic risk are appropriately addressed (7). In our series, all three recipients achieved functioning grafts following transplantation, further reinforcing the favorable overall prognosis in AS.

Donor and Recipient Evaluation in Genotype-guided Alport Transplantation

Molecular confirmation of COL4A3-COL4A5-related disease is central to transplant planning in AS and informs both recipient assessment and living-donor eligibility. In clinical practice, first-line molecular testing for transplant candidates should employ targeted next-generation sequencing panels covering the full coding regions and exon-intron boundaries of COL4A3, COL4A4, and COL4A5, which collectively account for the majority of AS cases. Broader approaches such as whole-exome or whole-genome sequencing should be reserved for unresolved cases or atypical phenotypes, in accordance with contemporary ERKNet-ERA-ESPN recommendations (10,16).

Living-donor selection must account for the inheritance pattern. In X-linked AS, affected males are not suitable donors, and heterozygous COL4A5 females should be considered as donors only after careful evaluation and counseling because of their increased renal risk. In autosomal recessive AS, both parents are obligate heterozygotes; therefore, related donors require careful molecular testing and clinical evaluation; donation should be considered only for asymptomatic carriers with preserved

Case	Diagnosis/ESRD	Transplant (donor type)	Early course (0-3 months)	Major complication(s)	Key interventions	Latest follow-up status
1	XLAS → ESRD (age 26)	Living-related (father)	Slow creatinine decline	Post-COVID vascular thrombosis, graft loss	Surgical revision + graft nephrectomy; dialysis; re-transplant at 12 months	Functioning deceased-donor graft at last follow-up
2	ADAS → ESRD (age 15)	Pre-emptive living-related (aunt)	Uncomplicated recovery	None reported	Standard maintenance immunosuppression	Stable graft function at 2 years
3	XLAS → ESRD (age 22)	Living-related (father)	Hematoma → evacuation	Late ABMR (year 6)	Pulse methylprednisolone (+ supportive therapy)	Stable graft function at last follow-up

COVID: Coronavirus, ESRD: End-stage renal disease.

renal function and normal urinalysis. In autosomal dominant diseases, related donors may carry pathogenic variants with age-dependent penetrance, making cascade genetic testing, combined with renal assessment, essential before donation.

In the present series, molecular testing directly guided donor selection: A COL4A5-carrier mother was excluded in Case 1, while donors in Cases 2 and 3 were genetically unaffected relatives, consistent with contemporary guideline-based practice. Extrarenal manifestations were inconsistently observed across the three cases, illustrating the recognized phenotypic variability of AS. In the autosomal-dominant case, extrarenal involvement was minimal, whereas both X-linked cases exhibited more pronounced and progressive features, particularly sensorineural hearing loss. This pattern aligns with published data demonstrating earlier onset and greater severity of extrarenal manifestations in X-linked forms than in autosomal-dominant forms. Ocular findings were absent or non-specific during early evaluations but evolved over time in one X-linked recipient, with subsequent changes occurring in the context of prolonged immunosuppression after transplantation. These observations suggest that extrarenal features may be incomplete at baseline and emerge longitudinally, underscoring the importance of careful documentation during long-term follow-up rather than relying on a single time-point assessment.

Post-transplant Anti-GBM Nephritis in AS

De novo anti-GBM nephritis is a rare but potentially severe complication after kidney transplantation in AS, and it is reported mainly in males with X-linked disease and, less frequently, in autosomal forms, affecting fewer than 3-5% of recipients. It is thought to result from alloimmune responses against donor-derived type IV collagen epitopes—particularly the $\alpha 5$ (IV) chain—leading to anti-GBM antibody formation in recipients previously unexposed to these antigens. Clinically, the condition typically presents early after transplantation with rapidly progressive graft dysfunction and carries a substantial risk of graft loss.

Prevention relies on appropriate candidate selection, optimized immunosuppression, and close post-transplant surveillance. When suspected, establishing the diagnosis requires prompt serologic testing and graft biopsy, and treatment strategies include intensified immunosuppression and antibody-removal therapies, although outcomes remain variable. In the present series, no recipient developed clinical or serologic evidence of *de novo* anti-GBM nephritis during follow-up. Across the three cases, immunosuppressive regimens were selected according to institutional protocols at the time of transplantation and were subsequently adjusted in response to clinical course and complications, rather than according to predefined genotype-based strategies. Donor evaluation remains a cornerstone of

clinical decision-making, particularly when considering living-related donation. Traditional recommendations discouraged the use of heterozygous COL4A5 female carriers as donors due to their lifelong risk of proteinuria and progressive renal impairment (7,11,12). Updated ERKNet-ERA-ESPN guidelines now advise that such carriers be considered only as a last resort, and that individuals carrying COL4A3 or COL4A4 variants should generally be excluded unless comprehensive evaluation demonstrates minimal future risk (15,16). Several mother-to-son transplant reports demonstrate acceptable short- and medium-term outcomes yet also emphasize the potential for long-term renal decline in carriers (8,14). These data highlight the need for individualized donor assessment, multidisciplinary review, and sustained long-term monitoring of living donors.

In our series, all living donors were genetically unaffected relatives, consistent with contemporary recommendations. In Case 1, the patient's mother, a COL4A5 carrier, was appropriately excluded from donation. Donors for Cases 2 and 3 exhibited no pathogenic variants and experienced uneventful postoperative recovery.

Immunologic complications in AS remain relatively uncommon. *De novo* anti-GBM nephritis affects fewer than 5% of males with X-linked disease (13). None of our patients developed this condition, in agreement with recent observations suggesting that optimized immunosuppression and close monitoring reduce occurrence (7,13,15). Case 3 developed late antibody-mediated rejection six years post-transplant, an increasingly recognized contributor to late graft dysfunction (9,15). His favorable response to corticosteroid therapy highlights the importance of long-term immunologic surveillance even in otherwise stable recipients.

The vascular complications observed in Case 1 following SARS-CoV-2 infection reflect the growing body of evidence linking COVID-19 with endothelial injury and heightened thrombotic risk in transplant recipients. Reports describe graft infarction, intrarenal arterial thrombosis, and rapid allograft loss associated with COVID-19-mediated hypercoagulability (17-20). The clear temporal association in this case underscores the need for heightened vigilance regarding post-infectious vascular complications in this population. Although causality cannot be definitively established in a single case, the close temporal association, the vascular distribution of thrombosis, and published transplant reports are consistent with the contribution of COVID-19-associated endothelial injury and hypercoagulability to allograft-threatening events.

Our findings correspond with previously published experiences, including cases summarized in Table 4, which integrate both hereditary nephropathies and COVID-19-associated vascular events (8,14,19,20-23). These parallels reinforce the importance

Table 4. Published cases and series of kidney transplantation in Alport syndrome and related conditions						
Study (year)	Inheritance/gene	Age/sex	Donor type	Main issue/complication	Outcome/follow-up	Relevance to present series
Katayama et al. (8)	X-linked (COL4A5)	39 M, 36 M	Living-related (mothers)	Calcineurin inhibitor toxicity (1 case); no rejection	Stable grafts at 5 and 10 years	Highlights importance of genetic testing before maternal donation
Girimaji et al. (14)	Autosomal recessive (COL4A3)	22 M	Living-related (mother)	None reported	Excellent graft function	Demonstrates acceptable outcomes with maternal donation when heterozygous and asymptomatic
Webb et al. (17)	Not specified (post-transplant complication)	49 M	Deceased donor	COVID-19–related renal infarction	Graft loss with return to dialysis	Supports COVID-19–associated vascular injury as a mechanism of graft loss
Oto et al. (19)	Alport syndrome spectrum	31 donors (mean age 40 years)	Living-related	Hypertension (56%); cardiac events (20%)	Preserved renal function at 10 years	Highlights long-term cardiovascular risk in related living donors
Present series (2025)	Mixed inheritance (two X-linked, one autosomal-dominant)	15-26 years (3 male recipients)	Two living-related; one deceased donor	Late antibody-mediated rejection; COVID-related vascular thrombosis	Two functioning grafts; one graft loss	Case-based illustration of genotype-guided donor selection, late immune complications, and post-COVID vascular risk

of precise molecular diagnosis, thorough donor evaluation, and comprehensive long-term follow-up in AS transplant recipients.

Although emerging disease-modifying therapies may delay progression to ESRD in selected patients, kidney transplantation remains the definitive treatment once ESRD is reached, as illustrated by the present cases (10,21). Nonetheless, post-transplant management remains grounded in established immunosuppressive protocols and coordinated multidisciplinary care, as demonstrated by the variable clinical courses, immunologic complications, and long-term outcomes observed across the three recipients in this series.

This case series highlights key principles in the management of AS transplant recipients. Genetic confirmation remains essential for safe donor selection and accurate risk stratification. Sustained immunologic monitoring enables the early detection of late rejection episodes. Finally, awareness of COVID-19–related vascular risks is crucial for long-term graft preservation. As precision medicine evolves, genotype-guided decision-making and improved surveillance strategies are expected to enhance post-transplant outcomes in this rare hereditary nephropathy.

CONCLUSION

Kidney transplantation is an effective treatment option for patients with AS. In our series, favorable graft outcomes were achievable across different inheritance patterns when donor selection was guided by molecular testing and clinical risk assessment. Nevertheless, the heterogeneity of post-

transplant trajectories observed—including late antibody-mediated dysfunction and severe vascular complications temporally associated with COVID-19—highlights the need for individualized long-term surveillance and cautious interpretation of generalizability.

Ethics

Informed Consent: Written informed consent was obtained from all participants and/or their legal guardians for participation and publication of anonymized clinical data.

Acknowledgments

We thank the clinical genetics and transplant teams involved in the evaluation and management of included patients.

Footnotes

Author Contributions

Surgical and Medical Practices - A.G-B., N.G., A.T.; Concept - A.G-B., H.S., N.B.; Design - A.G-B., H.S., S.D., G.S., M.J.S., N.B.; Data Collection or Processing - A.G-B., H.S., S.D., G.S., N.G., A.T., D.T.; Analysis or Interpretation - A.G-B., H.S., S.D., G.S., M.J.S.; Literature Search - A.G-B., H.S., S.D., G.S., M.J.S., N.B.; Writing - A.G-B., H.S., G.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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