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Long-Term Outcomes of Living-Related Kidney Donation for Alport Syndrome Spectrum: A Propensity Score-Matched Analysis

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Keywords
Alport syndrome · Cardiovascular outcomes · Collagen · Genetics · Kidney transplantation · Living donors

Abstract
Introduction: Data to guide the evaluation of living-related donor candidates for kidney transplant recipients with Alport syndrome (AS) spectrum are limited. We aimed to examine a cohort of living-related donors to recipients with AS and compare their outcomes with a control group to improve understanding of the clinical course and outcomes of living donation in this context. ***Methods:*** Living donors (LDs) of AS recipients and propensity score-matched control LDs without any family history of AS (control group) were followed for major cardiac events, death, post-donation estimated glomerular filtration rate (eGFR), and proteinuria. ***Results:*** There were 31 LDs (48.4% male), in whom relationship to AS recipient included mother (45.2%), father (32.3%), sibling (16.1%), grandparent (3.2%), and uncle (3.2%). Long-term outcomes over 10.0 (IQR, 3.0–15.0) years were evaluated in 25 and 25 LDs from study and control groups, respectively. During follow-up, 5 LDs (20.0%) in study group developed major cardiac event (acute coronary ischemia [$n = 4$] and severe congestive heart failure [$n = 1$]) after 5.5 (IQR, 4.5–10.3) years, whereas only 2 (8.0%) LDs in control group developed major cardiac events ($p = 0.221$). New-onset hypertension was higher in study group (56.0%) compared to the control group (16.0%) ($p = 0.003$). Three donors in study and 2 donors in control group who developed new-onset hypertension died during follow-up ($p = 0.297$). Major cardiac event rate was significantly higher in donors who developed hypertension after donation (0 vs. 28.0%, $p < 0.001$). There were no differences between study groups regarding last eGFR and proteinuria levels ($p = 0.558$ and $p = 0.120$, respectively). ***Discussion/Conclusion:*** Although the risk of kidney disease can be minimized by careful donor evaluation, our findings suggest that hypertension risk after the donation is higher than expected in related donors of recipients with AS.

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Introduction

Alport syndrome (AS) spectrum includes genetic diseases related to basement membrane major collagen type IV network genes *COL4A3*, *COL4A4*, or *COL4A5* in various organs including kidney, ear, and eye [1–3]. Type of inheritance is essential for prognosis. In the X-linked disease form, about 50% of males require dialysis or kidney transplantation (KT) by age of 30 and female patients have a better prognosis with approximately 12% developing end-stage kidney disease (ESKD) by age of 40 [4]. In comparison, autosomal-recessive (AR) form of AS can cause kidney failure by age of 20 while autosomal-dominant form of the disease typically does not progress to ESKD until middle age [5]. KT improves outcomes for patients with AS reaching ESKD compared to chronic dialysis. Living donor KT (LDKT) in particular is the preferred therapy, offering lower risk of rejection, better allograft function, and longer life expectancy compared to deceased donor KT [6]. However, ESKD from hereditary diseases raises special considerations for the practice of living-related donation and LDKT. Possible occurrence of the same disease in the related potential donors due to an underlying genetic predisposition should be excluded prior to donor candidate approval [7–9].

Advances and reduced costs in various sequencing methods led to a significant improvement in the genetic diagnosis of AS [2, 10]. Currently, comprehensive kidney disease gene panels and exome sequencing have become readily available. These tools are increasingly used to evaluate genetic risk in living kidney donor candidates and have the potential to improve risk assessment and optimize the safety of living donation. To date, available guidance [11] on the evaluation of genetic kidney disease in prospective living kidney donors to potential recipients with AS is scarce due to the lack of outcome studies. Already available studies on LDKT for AS mainly focused on recipient outcomes and showed varying results [12–18]. Data to guide the evaluation of living-related donor candidates for KT recipients with AS are limited.

To address these knowledge gaps, we examined a cohort of living-related donors for recipients with AS in comparison with a propensity-matched control LD group. Our goals were to better understand the clinical course and outcomes of living donation and LDKT in this context.

Materials and Methods

Study Cohort and Design

In this retrospective multicenter study, medical records related to LDKT for AS and non-AS kidney diseases, including donor and recipient information on demographic features, extrarenal symptoms, kidney function test results of both donors and recipients, cardiovascular diseases, and hospitalizations, were reviewed. LDs and their recipients between 1987 and 2021 were retrospectively identified from data of 4 transplant centers. Recipients with AS diagnosed by kidney biopsy, genetic testing, family history evaluation, hearing and visual tests, and their living-related donors were included [19].

Baseline demographic and clinical information and follow-up outcomes were collected from medical records, which included both hard copy and electronic files. The investigator team collected and reviewed all available data from the annual medical records that included donor survival, medical treatment for cardiovascular, kidney, or lung diseases at other clinics, and regular checkups. Our examination of the patients conformed to good medical and laboratory practices and the recommendations of the Declaration of Helsinki on Biomedical Research Involving Human Subjects or its later amendments. This study was approved by the Ethical Committee of Istanbul School of Medicine (approval No.: 727087). 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. All LDs who could be reached during routine follow-up visit were included in the study with written informed consent. Living donors who were not on clinic follow-up were reached by telephone and verbal informed consent was obtained.

Propensity Matching

To assemble matched LD controls without family history of AS, transplant centers' LD database was used. Propensity scores were calculated using a multivariable logistic regression model based on potentially confounding differences including donor sex, donor age at donation, and follow-up duration between two study groups.

Study Outcomes

LDs were followed for post-donation kidney function measured by estimated glomerular filtration rate (eGFR), proteinuria, new-onset hypertension (HTN), major cardiac events (MACEs), and death. MACE and death were considered primary outcomes. MACE was defined as the composite of total death, myocardial infarction, stroke, hospitalization because of heart failure, and revascularization, including percutaneous coronary intervention and coronary artery bypass graft [20]. Secondary outcomes included post-donation new-onset HTN during follow-up, eGFR, and proteinuria level at the last visit. HTN was defined as blood pressure is consistently 140/90 mm Hg or higher or if they are on any anti-hypertensive treatment. eGFRs of patients were calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [21]. Urinary protein-to-creatinine ratio in the first-morning urine specimen was used to measure the level of proteinuria.

Molecular Analyses

Genomic DNA stored in −80°C which was previously extracted from peripheral blood of LDs after research consent was used. Stored

Table 1. Various characteristics of living donors of recipients

Characteristics	ASLD group (n = 25)	Non-ASLD group (n = 25)	p value
Age at donation, mean±SD, years	50.9±10.3	48.6±8.3	0.383
Sex (male/female), *n* (%)	11 (44.0)/14 (56.0)	11 (44.0)/14 (56.0)	1.000
HLA mismatch, mean±SD	2.8±1.0	2.4±1.1	0.342
Donor's relationship to recipients, *n* (%)			
Mother	12 (48)	8 (32.0)	0.005
Father	8 (32)	4 (16.0)	
Sibling	4 (16)	2 (8.0)	
Grandparent	1 (4)	0 (0)	
Uncle	0 (0)	0 (0)	
LURD (spouse)	0 (0)	11 (44.0)	
Recipients' causal genes and inheritance pattern in the family, *n* (%)			
COL4A5 (XLAS)	4 (16)	NA	NA
COL4A4 (AR)	3 (12)	NA	
COL4A4 (AD)	2 (8)	NA	
COL4A3 (AR)	5 (20)	NA	
COL4A3 (AD)	1 (4)	NA	
Genetic test not performed	10 (40)	NA	

AD, autosomal dominant; AR, autosomal recessive; AS, Alport syndrome spectrum; ASLD, living donor of recipient with Alport syndrome; HLA, human leukocyte antigen; LURD, living unrelated donor; SD, standard deviation; XLAS, X-linked Alport syndrome.

genomic DNAs were sent for targeted exome capture using the NimbleGen/Roche SeqCap EZ Exome v2 reagent, or MedExome reagent, followed by 75-bp paired-end sequencing using Illumina HiSeq 2000. Sequence reads were aligned to the GRCh37/hg19 human reference genome using the Burrows Wheeler Aligner algorithm BWA-MEM. Variants were called using the Genome Analysis Toolkit Haplotype Caller. The analysis pipeline has been validated and makes use of SAMtools and Genome Analysis Toolkit utilities and ANNOVAR software. Variants were included if minor allele frequency <0.01 (recessive) or <0.001 (dominant) or identified in previous AS cases; loss of function mutation or missense with CADD score ≥15; not seen as homozygotes in any control databases; amino acid residue conserved through evolution in multicellular organisms. Synonymous and intronic variants that were not located within splice site regions were excluded. Identified variants were classified by ACMG criteria [22, 23]. Sanger sequencing also confirmed all variants called by next-generation sequencing.

Statistical Analyses

Statistical analyses were performed by using SPSS for Windows (SPSS version 25.0; IBM Corp., Armonk, NY, USA). Data were expressed as mean ± standard deviation when normally distributed or as the median (interquartile range [IQR]) otherwise. Parametric and nonparametric tests were used according to the distribution pattern of the data. Propensity scores were generated by multivariable logistic regression model as described above for living donor to recipient with AS (ASLD) group and non-ASLD group, and matching process using the nearest neighboring method in 1:1 ratio was performed. Comparisons of continuous variables were assessed by t tests or the Mann-Whitney U test, where appropriate. Differences in the proportions were compared by the χ^2 or Fisher's exact test. All statistical tests were two sided and the level of statistical significance was set at $p < 0.05$.

Results

Donor Characteristics and Outcomes

ASLDs cohort comprised 31 living-related donors, with a mean age of 49.7 ± 10.8 years at donation. Six of 31 ASLD donors were lost to follow-up. Remaining 25 ASLD were matched with 25 control LDs without any family history of AS (non-ASLD) using a propensity score. Baseline genetic and demographic characteristics of ASLDs and recipients with AS are presented in Table 1. None of the donors had low 24-h creatinine clearance (<80 mL/min/1.73 m^2), microscopic hematuria, proteinuria (≥0.15 mg/day), albuminuria (≥30 mg/day) or history of diabetes mellitus, HTN, valvular heart disease, previous coronary intervention, congestive heart failure (New York Heart Association class II or greater), cardiac arrhythmia, cerebral infarction or transient ischemic attack, active infection or noninfectious overt inflammation defined as elevated acute-phase reactant levels in medical records at the time of donation. The donor's relationship to recipient included mother (12, 48.0%), father (8, 32.0%), sibling (4, 16.0%), and grandparent (1, 4.0%). Genetic testing was performed in 9 related donors, and heterozygous pathogenic variants were found in 6 of them after donation (Table 2).

Long-term outcomes were evaluated in 25 ASLD and 25 non-ASLD during a median follow-up of 10.3 (IQR, 3.5–15.0) years. Five AS donors (20.0%) suffered from

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Table 2. Genetic test results and donor outcomes

Family	Age at KT/sex	Gene variant	Zygosity	ACMG classification	Donor HTN	Donor DM	Donor MACE	Donor death
Family 1								
Recipient	25/M	*COL4A5* (NM_000495.5):c.142-1G>A	Hem	P (PVS1, PM2, PP3)				
Donor (mother)	49/F	*COL4A5* (NM_000495.5):c.142-1G>A	Het	P (PVS1, PM2, PP3)	No	No	No	No
Family 2								
Recipient	24/F	*COL4A5* (NM_033380.3):c.546+6T>G	Hem	VUS (BP4)				
Donor (father)	46/M	No pathogenic variant			Yes	No	No	No
Family 3								
Recipient	50/M	*COL4A4* (NM_000092.5):c.2438del	Het	P (PVS1, PM2, PP3)				
Donor (sibling)	59/F	No pathogenic variant			Yes	No	No	No
Family 4								
Recipient	20/M	*COL4A4* (NM_000092.5):c.2320G>C	Compound	LP (PP5, PM2, PP3)				
		COL4A4 (NM_000092.5):c.4394G>A	Het	VUS (PM2, PP3)				
Donor (mother)	40/F	*COL4A4* (NM_000092.5):c.4394G>A	Het	VUS (PM2, PP3)	Yes	No	Yes	Yes
Family 5								
Recipient	24/M	*COL4A4* (NM_000092.5):c.81_86del	Hom	VUS (PM2, PM4, PP3)				
Donor (mother)	56/F	*COL4A4* (NM_000092.5):c.81_86del	Het	VUS (PM2, PM4, PP3)	No	No	No	No
Family 6								
Recipient	35/F	*COL4A3* (NM_000091.5):c.1408+1G>C	Hom	P (PVS1, PM2, PP3)				
Donor (father)	67/M	*COL4A3* (NM_000091.5):c.1408+1G>C	Het	P (PVS1, PM2, PP3)	Yes	No	Yes	Yes
Family 7								
Recipient	24/F	*COL4A3* (NM_000091.5):c.4887_4888del	Hom	P (PVS1, PM2, PP3)				
Donor (father)	48/M	*COL4A3* (NM_000091.5):c.4887_4888del	Het	P (PVS1, PM2, PP3)	No	No	No	No
Family 8								
Recipient	42/F	*COL4A3* (NM_000091.5):c.2584G>A	Het	P (PM1, PM2, PP2, PP3, PP5)				
Donor (mother)	65/F	No pathogenic variant			Yes	No	No	No
Family 9								
Recipient	16/F	*COL4A3* (NM_000091.5):c.3646G>A	Hom	P (PM2, PS1, PM1, PP2)				
Donor	38/F	*COL4A3* (NM_000091.5):c.3646G>A	Het	P (PM2, PS1, PM1, PP2)	No	No	No	No

ACMG, American College of Medical Genetics and Genomics; DM, diabetes mellitus; F, female; Hem, hemizygous; Het, heterozygous; Hom, homozygous; HTN, hypertension; KT, kidney transplantation; LP, likely pathogenic; M, male; MACE, major adverse cardiac event; P, pathogenic; VUS, variant of unknown significance.

Table 3. Demographic characteristics and long-term outcomes of AS donors and control group

Follow-up data	ASLD group (n = 25)	Non-ASLD group (n = 25)	p value
Duration of follow-up, median (IQR), years	13.0 (5.0–16.5)	10.0 (5.0–14.0)	0.107
Serum creatinine at last follow-up, mean±SD, mg/dL	1.1±0.3	1.0±0.3	0.420
Pre-donation eGFR, median (IQR), mL/min/1.73 m^2	99.0±10.3	98.2±11.9	0.834
COL4A5 (X-linked)	97.5±12.0	–	
COL4A3/COL4A4 (AR, AD)	96.0±13.9	–	
ASLD without genetic testing	100.3±10.0	–	
eGFR at last follow-up, median (IQR), mL/min/1.73 m^2	67.8±17.0	70.6±17.1	0.558
COL4A5 (X-linked)	58.5±7.8	–	
COL4A3/COL4A4 (AR, AD)	69.8±22.7	–	
ASLD without genetic testing	68.0±15.4	–	
Proteinuria at last follow-up, median (IQR), g/g	0.1 (0.09–0.2)	0.1 (0.04–0.1)	0.120
COL4A5 (X-linked)	0.1±0.01	–	
COL4A3/COL4A4 (AR, AD)	0.41±0.66	–	
HTN after donation, *n* (%)	14 (56.0)	4 (16.0)	0.003
DM after donation, *n* (%)	6 (24.0)	3 (12.0)	0.269
MACE, *n* (%)	5 (20.0)	2 (8.0)	0.221
Acute coronary ischemia	4 (16.0)	2 (8.0)	
Congestive heart failure	1 (4.0)	0 (0)	
Death, *n* (%)	3 (12.0)	1 (4.0)	0.297

AD, autosomal dominant; AR, autosomal recessive; AS, Alport syndrome spectrum; ASLD, living donor of recipient with Alport syndrome; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

MACE (acute coronary ischemia [n = 4, 16.0%] and severe congestive heart failure [n = 1, 4.0%]) after a median 5.5 (IQR, 4.5–10.3) years post-donation, whereas only two LDs in non-ASLD group developed MACE (acute coronary ischemia [n = 2]). Although MACE rate trended higher in ASLD group compared with non-ASLD group, the difference did not reach statistical significance (20.0 vs. 8.0%; p = 0.221). Death rates were similar between ASLD and non-ASLD groups (12.0 vs. 4.0%, p = 0.297) (Table 3). Three ASLDs (12.0%) died (1 myocardial infarction and 2 sudden deaths) 14.4 (10.0–14.9) years after donation, as compared to 1 (4.0%) death (1 sepsis and 1 sudden death) in control group after a median of 13.7 (11.5–15.9) years. All ASLD and non-ASLDs who died during follow-up had developed HTN in the post-donation follow-up period.

Development of HTN was significantly higher in the ASLD group compared to the non-ASLD group (14, 56.0 vs. 5, 16.0%; p = 0.003). In all donors (n = 50), MACE rate was significantly higher in LDs who already developed new-onset HTN (n = 7) than LDs without HTN (n = 0) after donation (28.0 vs. 0%, p < 0.001). No donors in either group developed kidney failure (eGFR <15 mL/min/1.73 m^2 or dialysis) during follow-up. Last serum creatinine, eGFR, and proteinuria levels in ASLD group were 1.1 ± 0.3 mg/dL, 67.8 ± 17.0 mL/min/1.73 m^2, and 0.1 (IQR, 0.09–0.2) g/g, respectively, which were similar with the control group (p = 0.420, p = 0.558, p = 0.120, respectively) (Table 3). Post-transplant diabetes mellitus rate was also similar between study groups (24.0 vs. 12.0%; p = 0.269). When long-term outcomes of donors with *COL4A3-5* variants were evaluated, of 6 ASLDs with variants only a donor with *COL4A3* and another donor with *COL4A4* heterozygous variant developed HTN and MACE (Table 2).

Characteristics and Outcomes of Recipients with AS Spectrum

The cohort included 31 recipients (21 [66.7%] male, mean age 27.5 ± 10.4 years) with ESKD due to AS. The inheritance pattern of AS in recipients was as follows: X-linked AS (XLAS) (n = 15), AR (n = 11), and autosomal dominant (n = 5). None of the recipients had previous KT or had additional organ transplantation during the follow-up period. No recipients had donor-specific human leukocyte antigen antibodies at the time of KT. Median

follow-up period of AS recipients was 12 years (IQR, 5–19). Eight (21.2%) recipients lost their allografts during the follow-up period. A male recipient with XLAS died with a functioning graft due to intracranial arterial dissection. Causes of allograft loss were chronic antibody-mediated rejection in 6 (19%) recipients and chronic allograft nephropathy in 1 (3%) recipient.

Discussion

Although the risk of kidney failure can be minimized by careful donor evaluation, our findings suggest that the development of HTN after kidney donation is significantly higher in ASLD recipients compared with a propensity-matched non-ASLD control group. All deaths in the ASLD group were observed in donors who develop post-donation HTN, suggesting that cardiovascular risk might be higher than expected in this group.

Even though outcomes of LDKT studies are superior than deceased donor KT in AS, there are challenges related to the difficulty of predicting risks for both the donor and the recipient [8, 14, 16]. Despite all advantages for the recipient, a living donation does not come without risk. Previous studies showed that living kidney donation may be associated with an increased risk of HTN; however, they did not identify increased risks of cardiovascular disease or death [24, 25]. Most of these studies report relatively short durations with a median follow-up period of 6–8 years, meaning that increased long-term cardiovascular risk cannot be excluded. In the present study, we followed our ASLDs for a median of 13 years, which is longer but may still be short to detect the adverse cardiovascular effects of donation that may take decades to develop. The high incidence of HTN and observed MACE supports the rigorous evaluation the LD candidates should undergo, including detailed physical examination, blood pressure and proteinuria measurement, kidney function tests, and assessment of other comorbidities to optimize donor safety [26, 27].

In our study, the cause of high HTN incidence in ASLD remains unclear. However, this high incidence may point out the importance of blood pressure control in living-related donors of AS recipients. Angiotensin-converting enzyme inhibitors (ACEi) have been the most well-studied treatment in AS over the past 20 years. Gross et al. [28, 29] showed a benefit of ramipril treatment in an AS mouse model almost two decades ago and recently the results of EARLY PROTECT study provided strong supportive evidence for both long-term safety and a clinical benefit of early treatment with ACEi in slowing the progression of kidney disease in children with AS. Cardiovascular effects of this benefit is still not known. The increased incidence of HTN in related LDs of AS may require specific antihypertensive treatments and ACEi may stand as a potential candidate for future trials in ASLDs.

Data on long-term outcomes of donors accepted for living donation to recipients with AS are limited. Gross et al. [30] evaluated the course of 6 heterozygous mothers with AS after donating their kidneys to their children with AS. Although all donors had creatinine clearance above 40 mL/min/1.73 m^2, they found a 25–60% reduction in kidney functions in 4 within an average of 6.7 years after donation. Three donors developed new-onset HTN and 2 new-onset proteinuria. In the present study, 6 living-related kidney donors were found to have heterozygous *COL4A3/A4/A5* variants without any abnormal clinical and laboratory findings and none of them developed kidney failure after donation. Unfortunately, none of these donors with *COL4A3/A4/A5* variants were known to have these variants and underwent a kidney biopsy during the donor evaluation period. The present study may reveal that ASLDs do not have a significant disadvantage in terms of kidney survival compared to other donors. However, they have a significantly higher risk of HTN. Therefore, the risks and benefits of LDKT in AS should be discussed in detail with the recipient and donor candidates.

The guidelines and expert opinions on related LD candidates for AS is changing over time. In 2013 consensus-based guideline, Savige et al. [11] opined that after exclusion of kidney damage and coincidental kidney disease by kidney biopsy, blood pressure monitoring, and kidney function tests, if XLAS also excluded by sequencing, donor candidates with family history of AR AS who are heterozygous for the causal variant may be accepted as kidney donors. Another expert suggested that as the disease course in heterozygous females is not predictable, it does not seem appropriate for younger women (age <45 years) who have heterozygous variants of AS to donate a kidney [4]. A recent guideline recommended not to consider candidates with pathogenic *COL4A3* or *COL4A4* heterozygotes as kidney donors [31]. In the present study, none of the donors from AR AS families carrying heterozygous *COL4A3* or *COL4A4* variants developed kidney dysfunction during follow-up. This may support the thought that in the evaluation of potential kidney donors with heterozygous *COL4A3* and *COL4A4* mutations, attention should be paid to the genotype-phenotype correlation in the family and/or database. With the use of NGS now, we

also understood that predicted heterozygous pathogenic *COL4A3* or *COL4A4* variants occurred in about 1 in 106 of the population and are not rare in the general population [32].

Our study had two main limitations. First was the lack of genetic analysis for all donors and recipients. Second, although patient ages and follow-up times were statistically similar in both groups, the ASLD group was on average 5.3 years older at the end of follow-up. It was not possible to clearly assess this condition as a contributing factor to HTN. On the other hand, the study has several strengths, including the multicenter design. To the best of our knowledge, this series is the largest ASLD series in the literature. Moreover, ASLD was compared with a propensity score-matched control group composed of non-ASLD.

In conclusion, we recommend that all ASLD candidates undergo detailed cardiac evaluations with routine analysis and further genetic studies. Increased risk of HTN and consequently cardiac events should be considered in long-term follow-up.

Statement of Ethics

This study was approved by the Ethical Committee of Istanbul School of Medicine (approval No.: 727087). All living donors on clinic follow-up have given written informed consent for using their data for research purposes. As this is a retrospective study, some of the donors are no longer being followed from transplant clinics. The Ethics Committee waived the need for additional written informed consent for the donors who could not be reached in clinics.

Conflict of Interest Statement

The authors declare no conflict of interest.

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There is no funding source for any research relevant to our study.

Author Contributions

Oto O.A. and Caliskan Y. conceived the study; Lentine K.L., Turkmen A., Mirioglu S., Guller N., and Safak S. contributed to study concept and design and acquisition of data; Yelken B., Velioglu A., Yildiz A., and Ersoy A. contributed to interpretation of data and performed the data collection; Oto O.A., Caliskan Y., Mirioglu S., Yazici H., and Lentine K.L. contributed to drafting of the manuscript; and all authors critically reviewed the manuscript and approved it.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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