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ORIGINAL ARTICLE

Propensity score-matched analysis of long-term outcomes for living kidney donation in alternative complement pathway diseases: a pilot study

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Abstract

Background Atypical hemolytic syndrome (aHUS) and C3 glomerulopathy (C3G) are complement-mediated rare diseases with excessive activation of the alternative pathway. Data to guide the evaluation of living-donor candidates for aHUS and C3G are very limited. The outcomes of living donors to recipients with aHUS and C3G (Complement disease-living donor group) were compared with a control group to improve our understanding of the clinical course and outcomes of living donation in this context.

Methods Complement disease-living donor group [$n=28$; aHUS(53.6%), C3G(46.4%)] and propensity score-matched control-living donor group ($n=28$) were retrospectively identified from 4 centers (2003–2021) and followed for major cardiac events (MACE), de novo hypertension, thrombotic microangiopathy (TMA), cancer, death, estimated glomerular filtration rate (eGFR) and proteinuria after donation.

Results None of the donors for recipients with complement-related kidney diseases experienced MACE or TMA whereas two donors in the control group developed MACE (7.1%) after 8 (IQR, 2.6–12.8) years ($p=0.15$). New-onset hypertension was similar between complement disease and control donor groups (21.4% vs 25%, respectively, $p=0.75$). There were no differences between study groups regarding last eGFR and proteinuria levels ($p=0.11$ and $p=0.70$, respectively). One related donor for a recipient with complement-related kidney disease developed gastric cancer and another related donor developed a brain tumor and died in the 4th year after donation (2, 7.1% vs none, $p=0.15$). No recipient had donor-specific human leukocyte antigen antibodies at the time of transplantation. Median follow-up period of transplant recipients was 5 years (IQR, 3–7). Eleven (39.3%) recipients [aHUS (n = 3) and C3G (n = 8)] lost their allografts during the follow-up period. Causes of

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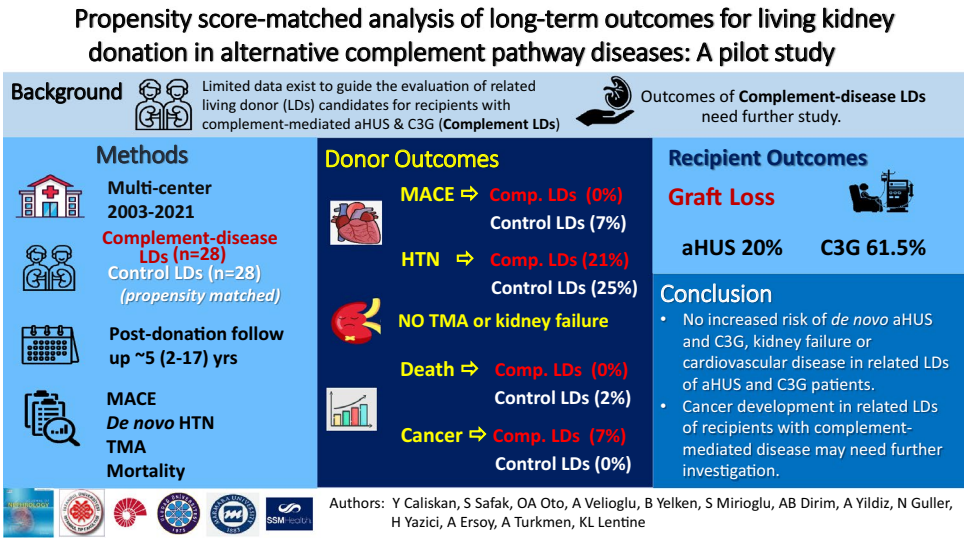
allograft loss were chronic antibody-mediated rejection in 6 recipients and recurrence of C3G in 5. Last serum creatinine and last eGFR of the remaining patients on follow up were 1.03 ± 038 mg/dL and 73.2 ± 19.9 m/min/1.73 m2 for aHUS patients and 1.30 ± 0.23 mg/dL and 56.4 ± 5.5 m/min/1.73 m2 for C3G patients.

Conclusion The present study highlights the importance and complexity of living related-donor kidney transplant for patients with complement-related kidney disorders and motivates the need for further research to determine the optimal risk-assessment for living donor candidates to recipients with aHUS and C3G.

Graphical abstract



Keywords Atypical hemolytic uremic syndrome · Complement · C3 glomerulopathy · Kidney · Living donation · Transplantation

Introduction

Complement activation plays a main role in various kidney diseases, and atypical hemolytic-uremic syndrome (aHUS) and C3 glomerulopathy (C3G) are the major complement-mediated rare diseases with excessive alternative pathway activation [1–3]. Kidney transplantation, especially living donor related, is the best treatment for end-stage kidney disease (ESKD) [4]. However, there is debate in the literature over whether living related-donor transplants should be offered for patients with aHUS and C3G [5]. It is absolutely crucial if a living related donor is considered, to protect the living donors and outcomes of the allograft in the recipient [6, 7].

Data to guide living donor candidate evaluation for aHUS and C3G are very limited. Living related-donor kidney transplantation presents a risk of recurrence in the recipient and de novo disease in the donor if the donor carries a predisposing genetic variant [8], although living donor transplant alone was not found to be a risk factor for recurrence [9]. We examined the clinical course of living donors to recipients with aHUS and C3G and compared their outcomes with a control group to improve our understanding of the clinical course and outcomes of living donation in this context.

Materials and methods

Study cohort and design

In this retrospective multicenter study, medical records from 4 transplant centers related to living-donor kidney transplant for aHUS/C3G recipients between 2003 and 2021 were reviewed by the investigator team. The medical records include donor and recipient information on demographic features, extrarenal symptoms, kidney function test results, cardiovascular diseases and hospitalizations. Recipients with aHUS/C3G diagnosed by kidney biopsy, genetic testing and laboratory findings and their living donors were included.

Baseline demographic and clinical information, as well as 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 donor medical records including donor survival, medical treatment for cardiovascular, kidney or lung diseases at other clinics, and regular check-ups.

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. 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. This study was approved by the Ethical Committee of Istanbul School of Medicine (approval number: 727087). All living donors who could be reached during routine follow up visit were included in the study with written informed consent. For donors deceased during follow up, next of kin provided written informed consent for the study.

Diagnostic criteria for aHUS and C3G

The diagnosis of aHUS was based on the presence of acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia after excluding antecedent Shiga toxin-producing *Escherichia coli* (STEC) infection, malignant hypertension and thrombotic thrombocytopenic purpura with normal ADAMTS13 activity, if available. The diagnosis of biopsy-proven C3G was defined by standard criteria, including predominant deposition of C3 (dominant C3 staining: C3 intensity ≥ 2 of magnitude more than any other immune reactants) based on the 2013 C3G consensus report [10]. Each renal biopsy was reviewed and reevaluated by the local pathologists in accordance with the criteria suggested in the 2013 C3G consensus report [10].

Matching process

Living donors to recipients with aHUS and C3G (complement-disease living donor group) were matched with living-donor controls without family history of aHUS/C3G (control-living donor group) which were assembled from the transplant centers' living donor database including 118 donors. Propensity scores were calculated using a multivariable logistic regression model based on potentially confounding differences including donor sex, donor age at donation, and year of donation between the two study groups. Ninety living donors were excluded following the matching procedure (Tables S1 and S2).

Molecular analyses

Genomic DNA stored at −80 °C which was previously extracted from peripheral blood of living donors after research consent was used. Stored 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 aHUS/C3G 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 [11]. Sanger sequencing also confirmed all variants called by next generation sequencing.

Study outcomes

Living donors were followed-up for post-donation kidney function measured by estimated glomerular filtration rate (eGFR), proteinuria, de novo hypertension, diabetes mellitus, thrombotic microangiopathy (TMA), acute kidney injury, cancer, major cardiac events (MACE) and death. MACE and death were considered as 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 [12]. Secondary outcomes included post-donation new onset hypertension, TMA, acute kidney injury during follow-up, eGFR and proteinuria level at the last visit. Hypertension was defined as blood pressure consistently 140/90 mmHg or higher or if on anti-hypertensive treatment. eGFRs of patients were calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [13]. Urinary protein-to-creatinine ratio in the first-morning urine specimen was used to measure the level of proteinuria.

Statistical analyses

Statistical analyses were performed by using SPSS for Windows (SPSS version 25.0, IBM Corp., Armonk, NY). Data were expressed as mean ± standard deviation (SD) 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 the complement-disease living donor group and the control 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 chi-squared 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

The cohort comprised 28 living donors to recipients with aHUS ($n = 15$, 53.6%) and C3G ($n = 13$, 46.4%) including 21 related living donors, where relationship to recipient included father (9, 32%), mother (6, 21%), sibling (3, 11%), son (1, 4%), aunt (1, 4%), cousin (1, 4%) and unrelated spouses and friends (7, 25%). Long-term outcomes were compared with a propensity score-matched control group over 5 years (IQR, 2.1–10.8) of follow up. Living donors for recipients with complement-related kidney diseases had a mean age of 46.4 ± 11.6 years at donation and were matched with 28 control living donors. Baseline demographic characteristics of complement-disease living donor and control-living donor groups 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, thrombocytopenia or history of diabetes mellitus, hypertension, 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 their medical records at the time of donation.

Genetic testing was performed in 7 living donors of aHUS patients and 2 living donors of C3G patients, and heterozygous variants were found in 4 of them including 3 benign variants in 3 donors of aHUS patients and a likely pathogenic variant in a donor of a C3G patient according to the ACMG criteria (Table 2) [11].

Donor follow up and outcomes

Long-term outcomes were evaluated in 28 living donors for recipients with complement-related kidney diseases [17 (60.7%) female, mean age 46.4 ± 11.6 years] and control-living donors [17 (60.7%) female, mean age 49.8 ± 8.1 years] during a median follow-up of 5 (IQR, 2.1–10.8) years. During follow-up, none of the donors for recipients with complement-related kidney diseases developed MACE, whereas 2 donors in the control group did (7.1%) after 8 (IQR, 2.6–12.8) years ($p = 0.15$). New-onset hypertension was similar between the donors for recipients with complement-related kidney diseases and the control-living donor group (21.4% vs 25%, respectively, $p = 0.75$) (Table 3). There were no differences between study groups regarding last eGFR and proteinuria levels ($p = 0.58$ and $p = 0.70$, respectively). Although de novo diabetes mellitus was higher in the control group, the difference was not significant (none vs 10.7%, $p = 0.08$). None of the donors developed TMA or kidney failure (eGFR < 15 ml/min/1.73 m^2 or dialysis). In the group of donors for recipients with complement-related kidney diseases, one related donor developed gastric cancer and another related donor developed a brain cancer (family

Table 1 Demographic characteristics of living donors of recipients with complement-related kidney diseases and propensity score matched control donor group

Characteristics	Complement-disease living donor Group ($n = 28$)	Control-living donor Group ($n = 28$)	*P* value
Age at donation (years), mean ± SD	46.4 ± 11.6	49.8 ± 8.1	0.19
Sex, male/female, *n* (%)	17 (61)/11 (39)	17 (61)/11 (39)	1
HLA mismatch, mean ± SD	3.4 ± 1.2	3.3 ± 1.3	0.84
Donor's relationship to recipients, *n* (%)			
Mother	6 (21.4)	5 (17.9)	
Father	9 (32.1)	11 (39.3)	
Sibling	3 (10.7)	3 (10.7)	
Aunt/uncle	1 (3.6)	2 (7.1)	0.85
Son	1 (3.6)	0 (0.0)	
Cousin	1 (3.6)	0 (0.0)	
LURD (spouse/friend)	7 (25.0)	7 (25.0)	

HLA human leukocyte antigen, *LURD* living unrelated donor, *SD* standard deviation

Table 2 Genetic test results of recipients with atypical hemolytic uremic syndrome and C3 glomerulopathy and their living donors and outcomes

Family		Age at KT/sex	Gene variant	Zygosity	ACMG classification	Donor HTN	Donor MACE	Donor Malignancy
Atypical hemolytic uremic syndrome								
Family 1	Recipient	26 / F	*CFH* (NM_000186.4):c.1204C > T	Het	B (BA1, BP6, BP4, PP5)			
			CFI (NM_000204.5):c.804G > A	Hom	B (BA1, BP6, BP4, BP7)			
	Donor (mother)	49/F	*CFI* (NM_000204.5):c.804G > A	Hom	B (BA1, BP6, BP4, BP7)	Yes	No	No
Family 2	Recipient	39/M	*CFH* (NM_000186.4):c.1204C > T	Het	B (BA1, BP6, BP4, PP5)			
			CFH (NM_000186.4):c.823G > A	Het	VUS (PM2, PP3)			
			CFH (NM_000186.4):c.1792A > G	Het	VUS (PM2, BP4)			
	Donor (cousin)	47/M	No pathogenic variant			No	No	Yes
Family 3	Recipient	27/F	*CFH* (NM_000186.4):c.1204C > T	Het	B (BA1, BP6, BP4, PP5)			
			PLG (NM_000301.5):c.1646G > T	Het	VUS (PM2, BP4)			
	Donor (mother)	49/F	No pathogenic variant			Yes	No	No
Family 4	Recipient	31/F	*CFH* (NM_000186.4):c.1204C > T	Hom	B (BA1, BP6, BP4, PP5)			
	Donor (father)	62/M	*CFH* (NM_000186.4):c.1204C > T	Het	B (BA1, BP6, BP4, PP5)	No	No	No
Family 5	Recipient	32/F	*CFH* (NM_000186.4):c.2808G > T	Het	B (BA1, BP6, BP4)			
	Donor (father)	61/M	No pathogenic variant			Yes	No	No
Family 6	Recipient	26/F	*CFH* (NM_000186.4):c.1204C > T	Hom	B (BA1, BP6, BP4, PP5)			
			CFH (NM_000186.4):c.2850G > T	Het	P (PP5, PS3, BP4)			
	Donor (father)	55/M	*CFH* (NM_000186.4):c.1204C > T	Het	B (BA1, BP6, BP4, PP5)	No	Yes	No
Family 7	Recipient	35/M	*CFH* (NM_000186.4):c.1218 T > A	Het	VUS (PM2, BP4)			
	Donor (LURD)	36/M	No genetic testing			No	No	No
Family 8	Recipient	43/F	*C3* (NM_000064):c.2852G > T	Het	VUS (PM2, PM5, BP4)			
			CFI (NM_000204.5):c.148C > G	Hom	LP (PP5, PM2, PP3)			
	Donor (spouse)	45/M	No genetic testing			No	No	No
Family 9	Recipient*	31/M	*CFH* (NM_000186.4):c.1204C > T	Het	B (BA1, BP6, BP4, PP5)			
			CFH (NM_000186.4):c.312 T > G	Het	VUS (PM2)			
			CFH (NM_000186.4):c.2029G > A	Het	VUS (PM2, BP4)			
			CFH (NM_000186.4):c.2410 T > C	Het	VUS (PM2, BP4)			
	Donor 1 (mother)	55/F	*CFH* (NM_000186.4):c.1204C > T	Het	B (BA1, BP6, BP4, PP5)	Yes	No	No
	Donor 2 (spouse)	29/F	No genetic testing			No	No	No
Family 10	Recipient	28/F	*CFH* (NM_000186.4):c.3134-5 T > C	Het	VUS (PM2, BP4)			
	Donor (father)	57/M	No pathogenic variant			No	No	No
C3 glomerulopathy								
Family 11	Recipient	31/F	*CFHR5* (NM_030787):c.1558C > T	Het	VUS (PM2, BP4)			
	Donor (aunt)	43/F	No pathogenic variant			Yes	No	No
Family 12	Recipient	20/M	*CFH* (NM_000186.4):c.1204C > T	Hom	B (BA1, BP6, BP4, PP5)			
	Donor (LURD)	31/M	No genetic testing			No	No	Yes
Family 13	Recipient	49/F	*CFHR5* (NM_030787):c.1558C > T	Het	VUS (PM2, BP4)			
	Donor (spouse)	55/M	No genetic testing			Yes	No	No
Family 14	Recipient	34/F	*C5* (NM_001735):c.130delT	Hom	LP (PVS1, PM2)			
	Donor (father)	62/M	*C5* (NM_001735):c.130delT	Het	LP (PVS1, PM2)	No	No	No

ACMG American College of Medical Genetics and Genomics, *B* Benign, *F* female, *Het* heterozygous, *Hom* homozygous, *HTN* hypertension, *LP* likely pathogenic, *LURD* living unrelated donor, *M* male, *MACE* major adverse cardiac events, *P* pathogenic, *VUS* variant of unknown significance

*Two kidney transplants

Table 3 Long-term outcomes of living donors of recipients with complement-related kidney diseases and propensity score-matched control group

Follow-up data	Complement-living donor group ($n=28$)	Control-living donor group ($n=28$)	*P* value
Duration of follow-up (years), median (IQR)	5 (2.25–10.75)	5.5 (2.13–10.75)	0.80
Serum creatinine at last follow-up (mg/dL), mean ± SD	1.1 ± 0.2	1.0 ± 0.3	0.38
eGFR at last follow-up (mL/min/1.73 m^2), median (IQR)	72.0 (66.8–87.5)	67.0 (60.0–84.8)	0.11
Proteinuria at last follow-up (g/g), median (IQR)	0.1 (0.05–0.1)	0.1 (0.04–0.1)	0.70
Hypertension after donation, *n* (%)	6 (21.4)	7 (25.0)	0.75
Diabetes mellitus after donation, *n* (%)	0 (0)	3 (10.7)	0.08
Malignancy, *n* (%)	2 (7.1)	0 (0)	0.15
Major cardiac event, *n* (%)	0 (0)	2 (7.1)	0.15
Acute coronary ischemia	0 (0)	2 (7.1)	0.15
Death, *n* (%)	1 (3.6)	2 (7.1)	0.55

eGFR estimated glomerular filtration rate, *IQR* interquartile range, *SD* standard deviation

2), whereas no living donors from the control group developed malignancy (2, 7.1% vs none, $p=0.15$). Two control living donors (7.1%) died (1 myocardial infarction and 1 sudden death) at 9 and 16 years after donation and one donor for a recipient with complement-related kidney disease (3.6%) died of a gastric cancer in the 4th year after donation ($p=0.55$).

Characteristics and outcomes of recipients with aHUS and C3G

The cohort included 28 recipients [15 (53.6%) female, mean age 30.6 ± 11.5 years] with ESKD due to aHUS ($n=15$, 53.6%) and C3G ($n=13$, 46.4%). The mean age of recipients with aHUS [10 (66.7%) female] was 30.9 ± 12.5 years at the time of transplantation, whereas it was 30.8 ± 10.8 years for C3G recipients [5 (38.5%) female]. None of the recipients underwent additional organ transplantation during the follow-up period. No recipients had donor-specific human leukocyte antigen antibodies at the time of transplantation. Median follow-up period of transplant recipients was 5 years (IQR, 3–7). Eleven (39.3%) recipients [aHUS ($n=3$, 20%) and C3G ($n=8$, 61.5%)] lost their allografts during the follow-up period. Causes of allograft loss were chronic antibody-mediated rejection in 6 recipients [(aHUS; $n=3$, 20%) and (C3G; $n=3$, 23%)] and recurrence of C3G in 5 (38.5%) recipients. Last serum creatinine and last eGFR of the remaining patients on follow up were 1.03 ± 038 mg/dL and 73.2 ± 19.9 m/min/1.73 m^2 for aHUS patients and 1.30 ± 0.23 mg/dL and 56.4 ± 5.5 m/min/1.73 m^2 for C3G patients, respectively.

Discussion

Recurrence of complement-related kidney diseases was a major issue in the post-transplant follow up of recipients, and the data to guide the evaluation of living related-donor candidates for these diseases are very limited. Our study highlights the role of living kidney transplant for recipients with complement-related kidney disorders with particular focus on donor safety and outcomes. The present study did not show any increased risk of de novo aHUS and C3G, kidney failure and cardiovascular disease in related living donors to recipients with aHUS and C3G during a follow up of over 5 years.

Recipient risk factors for recurrence of complement-related kidney diseases include genetic variants of regulatory complement factors and a previous history of recurrence in the prior transplant [14]. However, eculizumab and the recently approved long-acting complement inhibitor ravulizumab have shown favorable outcomes in aHUS of both native and transplanted kidneys [15]. With the use of complement inhibitor treatment, kidney transplant without need for liver transplant became an option for patients with aHUS. However, there still remains debate in the literature over whether living related-donor transplants should be offered for these patients [16]. As the clinical availability improved, genetic testing started to bear great importance on the decision of living donor candidate evaluation. Although the type of variants in complement-associated genes is still not very informative for the phenotype, de novo complement system-related disease can develop in the related donor if the donor possesses a predisposing genetic variant, particularly the same variant as the recipient [8]. There is awareness regarding incomplete penetrance of aHUS in mutation carriers, which complicates the living related-donor candidate evaluation for recipients with aHUS [3, 10, 17, 18]. Although

living donor transplant alone was not found to be a risk factor for recurrence [9], genetic screening is advised in the pre-transplant period in patients with aHUS-related ESKD [19]. The role of genetic testing in C3G is still not clear.

Overall, there is no clear guidance for the genetic screening of family members who are potential living related donors of patients with complement-related kidney diseases, particularly aHUS and C3G. One of the important features of these diseases is that individuals with variants of complement genes may not develop aHUS or C3G until adulthood [16]. This incomplete penetrance indicates that a genetic mutation alone is insufficient to cause aHUS or C3G; instead, carriers of complement gene variants require a second or third trigger, such as viral infection, cancer, pregnancy, or medications, to progress to clinically significant aHUS or C3G [20, 21].

Current genetic testing is not 100% sufficient to exclude any risk of de novo alternative pathway activation in related donor candidates, even when the complement gene related causal variant is known in the recipient. In cases of negative genetic result for complement-associated variants in the recipient candidate, the genetic evaluation of the living related donor candidates becomes more challenging. Therefore, previous reports recommended to evaluate related living kidney donor candidates for recipients with complement associated kidney diseases cautiously [19, 22]. A detailed team evaluation, experienced in genetics including kidney geneticists and genetic counselors, is recommended with a low threshold for not approving for donation [19, 22]. This excessive caution originates from the unfortunate outcomes reported for living related-donor cases for aHUS patients [23]. The meta-analysis of Ducloux et al. [23] showed that those recipients who developed recurrent aHUS after transplant received significantly higher rates of living related-donor kidney transplants (52%) compared with recipients without post-transplant recurrence (22%). They also reported living related donors presented with aHUS later after donation. Donne et al. [24] reported de novo aHUS within a year after donation in 2 related living donors of recipients who suffered recurrent aHUS in the allograft. This was also described twice before, once in a 21-year-old woman with aHUS onset 3 weeks after nephrectomy [24] and the other in a 24-year-old man who had aHUS onset 6 months after surgery [25].

It is very important to acknowledge the paucity of data in the literature to support or refute the safety and reliability of living related-donor transplant for complement-related kidney diseases. In this context, the results of our study are very important. None of these donors developed TMA during follow-up and living donors did not have any significant disadvantage in terms of kidney survival and cardiovascular diseases compared to other donors. The living donors included in our study were on follow up for a median of 5 years, none of them developed TMA, over a longer follow-up as compared to donors previously reported. Additionally, the follow up time may be too short to detect the adverse cardiovascular effects of donation that may take decades to develop. Interestingly, the relatively higher incidence of malignancy observed in living donors for recipients with complement-related kidney diseases may need to be studied further. Recent studies revealed that depending on the cancer type, the complement system can have pro or anti-tumor effects and, even for the same type of cancer, different models presented opposite effects [26]. A secondary finding of this study is that despite living (mostly related) donor kidney transplants performed for recipients with aHUS and C3G, allograft survival was poor for both aHUS and C3G recipients after a median of 5 years of follow up. There is a clear need for a better understanding of the pathogenesis of recurrent C3G, as well as for novel strategies to prevent recurrence after transplantation.

There are limitations to the present study. First, genetic analysis was not available for all donors and recipients. Second, the small sample size and shorter follow up time limits our ability to draw strong conclusions. However, the study has several strengths, including its multicenter design. To the best of our knowledge, this series is the largest living related-donor series for complement-related kidney diseases in the literature. Moreover, living donors for recipients with complement-related kidney diseases were compared with a propensity score-matched control living donor group.

In conclusion, the present study highlights the importance and complexity of living related-donor kidney transplant for patients with complement-related kidney disorders and motivates the need for further research to determine the optimal risk-assessment for living donor candidates to recipients with aHUS and C3G. Our study findings are novel but still not sufficient to rule out the risk of ESKD in the related donors of the recipients with complement-related kidney diseases, while confirming the high risk of allograft failure in these recipients. We recommend that all living-donor candidates for complement-related kidney disease should undergo detailed evaluation with routine analysis and genetic studies. Cancer development in related living donors of recipients with complement-mediated disease may need further investigation.

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Data availability Data discussed in the study will be made available upon reasonable request.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This study was approved by the Ethical Committee of Istanbul School of Medicine (approval number: 727087).

Informed consent All living donors who could be reached during routine follow up visit were included in the study with written informed consent. For donors deceased during follow up, next of kin provided written informed consent for the study.

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