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Association of Kidney Graft Long-term Outcome With Recipient Cystathionine Gamma-lyase Polymorphisms and Hydrogen Sulfide Levels: A Cohort Study

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Background. Hydrogen sulfide (H_2S) produced endogenously by the *CTH* gene-encoded cystathionine gamma-lyase protects from renal ischemia–reperfusion injury in preclinical models. Here, we hypothesized that *CTH* gene polymorphisms (single nucleotide polymorphism [SNP]) and recipient H_2S serum levels influence kidney graft outcomes after transplantation. **Methods.** We included all consecutive recipients of a first kidney transplant in the Swiss Transplant Cohort Study and with available genotyping. In addition, 192 deceased-donor kidney transplant recipients were randomly selected to measure baseline serum H_2S levels. The primary endpoint was graft loss during follow-up. **Results.** *CTH* SNPs were identified in up to 50% of the patients. During median follow-up (6.4 y, interquartile range: 3.9–9.8), graft loss was observed in 247 (9.8%) of 2518 patients. The incidence of graft loss was associated with the presence or absence of *CTH* SNPs. Specifically, rs672203 and rs10458561, increased the risk of graft loss (hazard ratio [HR]: 1.36, 95% confidence interval [CI]: 1.04-1.78, $P = 0.02$; and HR: 1.29, 95% CI: 1.0-1.66, $P = 0.05$; respectively), whereas rs113285275 was protective (HR: 0.78, 95% CI: 0.6-1.01, $P = 0.05$). Interestingly, rs672203 was associated with an increased risk of acute rejection ($P = 0.05$), whereas rs113285275 was associated with a lower risk of acute rejection ($P = 0.01$). Finally, in patients with delayed graft function, serum H_2S levels correlated with lower graft dysfunction (defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2) ($P = 0.05$). **Conclusions.** Graft outcome after kidney transplantation was associated with *CTH* genotype and, to some extent, H_2S serum levels. Further research is needed to define the underlying protective mechanisms.

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In patients with end-stage kidney disease, transplantation provides superior survival and better quality of life compared with dialysis, but is currently limited by the number of available organs.[1] To address the disparity between organ supply and demand, there has been a growing utilization of donation after cardiocirculatory death (DCD) and extended

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M.H., R.E., D.G., and A.L. contributed equally. M.H. collected and analyzed data, wrote the article. R.E. collected data and performed experiments (H_2S measurements). T.A. and A.Ly. performed and interpreted serum H_2S measurements. S.D., M.P., K.U., H.Y., L.V.R., and J.F.M. critically reviewed the article. P.-Y.B. provided and analyzed the genetic data, and critically reviewed the article. D.G. and A.L. designed the study, analyzed data, wrote, and reviewed the article.

The data underlying this article cannot be made publicly available because of the privacy of the study participants. The anonymized data are available upon reasonable request for a collaborative research project providing the agreement of the STCS scientific committee. Please contact the corresponding authors for all requests regarding data sharing.

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criteria donors (ECDs). However, DCD and ECD kidneys are more susceptible to ischemia–reperfusion injury (IRI), manifest clinically as delayed graft function (DGF), which is a risk factor for subsequent graft dysfunction and loss.[2] IRI is unavoidable during solid organ transplantation and occurs in 2 steps. First, during ischemia cells switch from an aerobic to an anaerobic metabolism, which results in a decrease in ATP production, intracellular acidosis, leakage of lysosomal enzymes, breakdown of the cytoskeleton, and inhibition of membrane-bound Na^+/K^+ ATPase activity.[3] It is, however, during reperfusion that most of the damage occurs, with production of large amounts of reactive oxygen species, together with a reduction in the antioxidant capacity.[4] Altogether, implementing strategies that can either predict or reduce IRI holds great promise in enhancing both graft and patient survival following kidney transplantation.

Hydrogen sulfide (H_2S) is a gas that is produced endogenously by the cystathionine gamma-lyase (CGL) enzyme, encoded on the *CTH* gene. H_2S has anti-inflammatory, antioxidant, and cytoprotective properties.[5,6] Mice lacking *CTH* were more prone to IRI, whereas systemic adenoviral overexpression of *CTH* was protective.[7] In preclinical models, exogenous H_2S protected from renal IRI[8] and improved graft survival after kidney transplantation,[9-11] possibly via the regulation of mitochondrial energy metabolism.[12] In humans, circulating H_2S levels correlate positively with vascular health (eg, blood pressure, limb ischemia) and postoperative survival.[13-16] Thus, CGL and H_2S have emerged as important regulators of ischemia and reperfusion.[12,13] In humans, mutations in the *CTH* gene leading to reduced enzymatic activity provided the genetic basis for cystathioninuria, an autosomal recessive metabolic disorder. Similarly, a common nonsynonymous single nucleotide polymorphism (SNP) 1364G>T (rs1021737) in exon 12 was associated with higher plasma homocysteine levels[17,18] and was more frequent in patients with cardiovascular diseases.[19]

Although mutations in *CTH* were associated with alterations in homocysteine levels and cardiovascular diseases, their specific role in patient and graft outcomes after kidney transplantation is unknown. Additionally, although H_2S emerged as a significant regulator of IRI in preclinical models, its relevance in humans has yet to be established. In this study, we hypothesized that recipient *CTH* polymorphisms and H_2S serum levels at the time of transplantation could impact kidney graft function.

MATERIALS AND METHODS

Study Design and Clinical Data Collection

The study followed the principles of the Declaration of Helsinki and was approved by the local Ethics committee (CER-VD, 2019-00457). 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." This study (project number FUP126) was nested in the Swiss Transplant Cohort Study (STCS), a prospective nationwide longitudinal cohort study in solid organ and hematopoietic stem cells transplantation in Switzerland, approved by all the participating centers' ethical committees (2018-02394).[20,21] All patients enrolled in the STCS signed an informed consent and agreed to the prospective collection of clinical and biological data. Patients were excluded if they were <18 y, had previous kidney or multiorgan transplantation. Patients were included if they were ≥18 y of age and underwent a first kidney transplantation between May 2008 and December 2021, and with available data regarding the following SNPs in the *CTH* gene: rs6677781 (NC_000001.11:70439718:C:A, NC_000001.11:70439718:C:G, NC_000001.11:70439718:C:T), rs1021737 (NC_000001.11:70439116:G:A, NC_000001.11:70439116:G:T); rs672203 (NC_000001.11:70421415:A:G), rs113285275 (NC_000001.11:70430635:G:A, NC_000001.11:70430635:G:C), and rs10458561 (NC_000001.11:70455489:G:A, NC_000001.11:70455489:G:T).

Within the STCS, patient and transplantation-specific data are collected at baseline (day 0 before transplantation), then prospectively at months 6 and 12, and yearly using standardized case-report forms. The following baseline donor and recipient data were extracted for our study: sex, age, body mass index, type of donation (living or deceased donor), preemptive or not, cause of end-stage kidney disease, type of dialysis, and cardiovascular comorbidities (hypertension, peripheral artery disease [PAD], cerebrovascular disease, coronary heart disease). Transplantation-related data further included were: cold ischemia time, HLA mismatches, immunosuppressive induction and maintenance regimen. Follow-up data included: graft function (serum creatinine [μmol/L]), graft loss, cause of graft loss, patient's death, cause of death, cardiovascular complications, and the occurrence of DGF defined as the need for dialysis in the first 7 d posttransplantation.[20,21]

The primary endpoint was death-censored graft loss during follow-up, according to the presence of *CTH* SNPs or based on recipient serum H_2S levels measured on the day of transplantation. Secondary endpoints included, acute rejection episodes, patient's survival, occurrence of major adverse cardiovascular events (MACE) and graft function, during follow-up posttransplantation. Graft function (estimated glomerular filtration rate [eGFR]) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and graft loss defined as return to dialysis or preemptive retransplantation. For rejection episodes, only biopsy-proven acute rejection (BPAR) episodes were analyzed and included T-cell and antibody-mediated rejection. We excluded biopsies with findings of "borderline changes" and, per patient, considered only the first episode of BPAR for the analysis. MACE was defined as a composite endpoint of coronary heart disease, cerebrovascular disease, or cardiovascular death.

DNA Sequencing

For all STCS recipients, DNA samples were collected and stored on the day of transplantation, prior surgery (day 0). DNA was extracted from frozen blood samples, as previously described.[22] A whole genome sequencing was performed with ~1 000 000 SNPs by the genomics platform of the National Center of Competence in Research "Frontiers in Genetics" at the University of Geneva (Geneva, Switzerland) using Illumina human 1M-Duo BeadChips.[23] Genotype calling and quality control filters were applied. Genotype calling was performed with the default settings of the BeadStudio software (Illumina). For genetic markers, we discarded SNPs with: (1) a genotype clustering score,[23] (2) a call rate <90%, (3) a minor allele frequency < 1%, and (4) a Hardy-Weinberg value $<10^{-7}$. Quality control filtering led to a total of 912 765 high-quality SNPs. In this cohort, we identified the following

SNPs for the *CTH* gene encoding the H_2S producing enzyme (chr 1): rs6677781, rs1021737, rs672203, rs113285275, and rs10458561.

H_2S Measurements

To evaluate circulating H_2S levels in kidney transplant recipients, we randomly selected 192 recipients of deceased donors from Lausanne University Hospital included in the STCS. This subcohort is thereafter referred to as the "serum cohort." Similar to DNA samples, peripheral venous blood was collected into ethylenediaminetetraacetic acid collection tubes and stored on the day of transplantation, prior surgery (day 0). Samples were centrifuged at room temperature for 15 minutes at 2000g and the plasma was stored at −80 °C for future analysis. All samples were then thawed and processed at once to ensure uniformity. H_2S levels were measured using the lead acetate method as described previously.[12,24] In brief, plasma was mixed with 80 µL freshly prepared reaction mixture, containing 100 mM L-cysteine and 0.5 mM pyridoxal 5′-phosphate (PLP, also known as vitamin B6) in phosphate-buffered saline in a plastic 384-well plate. The plate was then incubated at 37 °C with lead acetate embedded filter paper on top. Upon the reaction of H_2S with the lead acetate paper, a dark lead sulfide precipitate is produced. The paper was then incubated for 6 h, until a detectable, but nonsaturated signal was seen. The amount of lead sulfide captured on the paper was quantitated using the IntDen measurement function in ImageJ software and normalized after subtracting the background. An empty well without plasma was used as blank value for background measurement. These measurements were assessed by 2 independent investigators blinded to group assignment and serum H_2S levels were expressed in arbitrary units (a.u.). High and low H_2S levels/free sulfide groups were divided by median split, which was arbitrary (**Figure S1, SDC,** http://links.lww.com/TXD/A749).

Statistical Analysis

Descriptive statistics were used to report demographic and baseline data, with results expressed as medians and interquartile ranges (IQRs) or means and SDs, as appropriate. Categorical variables were summarized as numbers and percentages. The Kaplan-Meier method was used to estimate survival in recipient with wild type (WT) and *CTH* SNPs, as well as in high and low H_2S levels/free sulfide groups. Groups were compared using the log-rank test. A logistic regression analysis was used to analyze the association of H_2S levels with kidney function (eGFR) at various timepoints after kidney transplantation. Cox proportional hazard models were fit to estimate hazard ratios (HRs) for graft loss and acute rejection, between WT and SNP groups, corrected for potentially confounding variables at the time of transplantation (donor type, recipient H_2S levels, recipient sex, hypertension, coronary artery disease (CAD), PAD, donor/recipient HLA mismatches, and the use of antithymocyte globulin [ATG] at induction), and after transplantation (calcineurin inhibitor [CNI]-based maintenance regimen). Both unadjusted and adjusted Cox proportional hazard models met assumptions of proportional hazard. Analysis was performed with SPSS statistics version 29. All reported *P* values are based on 2-sided tests and *P* values of <0.05 were considered statistically significant.

RESULTS

Study Population

We included 2518 patients who underwent kidney transplantation between May 2008 and December 2021 in Switzerland. In the list of variants reported for the *CTH* gene, we identified several *CTH* SNPs: rs6677781, rs1021737, rs672203, rs113285275, and rs10458561. Baseline patient characteristics are presented in Table 1. The median age of recipients was 55 (range 44–64) y, 64.5% of the patients were male, and 41.7% of the cohort had a living-donor kidney transplant. The majority of patients were on dialysis before transplantation. Patients were given induction and maintenance immunosuppression according to their immunological risk status. The majority received basiliximab as induction therapy, ATG was used in 23% of the recipients. The majority of patients received a CNI-based maintenance regimen (Table 1). Considering the investigated SNPs, 339 patients (13%) had none, 185 (7%) had only 1, 798 (32%) had 2, 643 (25%) had 3, 246 (10%) had 4, and 307 (12%) had 5 SNPs.

Graft Outcome in Carriers of the *CTH* Polymorphisms

During the median follow-up of 6.4 (IQR: 3.9–9.8) y, graft loss was observed in 247 (9.8%) patients.

The main causes of graft loss were rejection for 54 (22%) patients, chronic allograft nephropathy/CNI toxicity for 42 (17%), recurrence of disease for 31 (13%), vascular causes (graft arterial or venous stenosis/thrombosis) for 28 (11%), infections for 22 (9%), urologic or postrenal causes for 3 (1%), and other/miscellaneous causes for 67 (27%) patients.

Analysis of *CTH* SNPs revealed that patients with rs672203 and rs10458561 had a significantly higher incidence risk of graft loss during follow-up ($P = 0.02$ and 0.04, respectively) (Figure 1A and B). Conversely, in patients with rs113285275, the rate of graft loss was reduced ($P = 0.05$) as compared with WT *CTH* patients (Figure 1C). No significant difference was observed in the presence or absence of rs6677781 and rs1021737 (Figure 1D and E). In our cohort of kidney transplant recipients, HR of graft loss was 0.78 (95% CI: 0.61-1.01, $P = 0.06$) for rs6677781, 0.88 (95% CI: 0.60-1.0, $P = 0.14$) for rs1021737, 0.78 (95% CI: 0.6-1.01, $P = 0.05$) for rs113285275, 1.36 (95% CI: 1.04-1.78, $P = 0.02$) for rs672203, and 1.29 (95% CI: 1.0-1.66, $P = 0.05$) for rs10458561 (**Table S1, SDC,** http://links.lww.com/TXD/A749).

To assess whether there was a synergistic effect of the SNPs on graft loss, we calculated the cumulative risk of graft loss among patients carrying both rs672203 and rs10458561. We compared this group to patients carrying either rs672203 or rs10458561, as well as to patients with neither of them. There was a trend toward an increased risk of graft loss for patients carrying both SNPs compared with other groups ($P = 0.06$) (**Figure S2, SDC,** http://links.lww.com/TXD/A749). There was no significant difference in the risk of graft loss between patients carrying both rs672203 and rs113285275 compared with those carrying either rs672203 or rs113285275 or compared with patients without either SNPs ($P = 0.7$). Similarly, no significant difference in graft loss was observed between patients carrying both rs10458561 and rs113285275 compared with those carrying either rs10458561 or rs113285275, or patients without either of them ($P = 0.9$). Finally, considering patient survival and the occurrence of MACE, there was no difference

TABLE 1.

Characteristics of the study population (n = 2518) at the time of transplantation stratified by *CTH* SNPs

	rs6677781			rs1021737			rs672203			rs113285275			rs10458561		
	Yes, n = 1184	No, n = 1334	*P*	Yes, n = 1188	No, n = 1330	*P*	Yes, n = 1497	No, n = 1021	*P*	Yes, n = 1080	No, n = 1448	*P*	Yes, n = 1280	No, n = 1238	*P*
Recipient sex															
Male	769 (65%)	856 (64%)		773 (65%)	852 (64%)		975 (65%)	650 (64%)		702 (65%)	923 (64%)		834 (65%)	791 (64%)	
Female	415 (35%)	478 (36%)	0.6	415 (35%)	478 (36%)	0.6	522 (35%)	371 (36%)	0.4	378 (35%)	515 (36%)	0.7	446 (35%)	447 (36%)	0.5
Donor age (y)															
Median (Q1–Q3)	56 (46–64)	55 (45–64)	0.3	56 (46–64)	54 (45–63)	0.2	55 (45–63)	56 (46–64)	0.18	56 (47–64)	54 (45–63)	0.25	55 (46–64)	55 (46–63)	0.9
Donor type															
DBD	578 (49%)	654 (49%)	0.9	586 (49%)	646 (49%)	0.8	714 (48%)	518 (51%)	0.06	526 (49%)	706 (49%)	0.9	617 (48%)	615 (50%)	0.6
DCD	114 (10%)	122 (9%)		114 (9%)	122 (9%)		156 (10%)	80 (8%)		101 (9%)	135 (9%)		127 (10%)	109 (9%)	
Living	492 (41%)	558 (42%)		488 (41%)	562 (42%)		627 (42%)	423 (41%)		453 (42%)	597 (41%)		536 (42%)	514 (41%)	
Cold ischemia time[a] (min)															
Median [Q1, Q3]	550 (428-720)	562 (433-730)	0.14	552 (428-728)	559 (433-725)	0.27	560 (436-738)	551 (418-716)	0.17	551 (428-720)	560 (432-732)	0.15	554 (441-725)	555 (420-729)	0.7
Delayed graft function[b]															
Yes	168 (14%)	184 (14%)	0.7	185 (15%)	167 (12%)	0.97	209 (14%)	143 (14%)	0.3	204 (19%)	148 (10%)	0.9	168 (13%)	184 (15%)	0.15
No	927 (78%)	1059 (79%)		935 (79%)	1051 (79%)		1191 (79%)	795 (78%)		852 (79%)	1134 (78%)		1029 (80%)	957 (77%)	
Recipient age (y)															
Median (Q1–Q3)	56 (44–63)	55 (56–64)	0.6	56 (44–64)	55 (44–63)	0.8	56 (45–64)	54 (43–63)	0.05	55 (44–64)	55 (45–63)	0.5	55 (46–64)	54 (43–63)	0.006
BMI[c] (kg/m^2)															
Median (Q1–Q3)	26 (23–29)	26 (23–29)	0.6	26 (23–29)	26 (23–29)	0.6	26 (23–29)	26 (23–29)	0.13	26 (23–29)	26 (23–29)	0.3	26 (23–29)	26 (23–29)	0.5
Hypertension															
No	218 (18%)	224 (17%)	0.3	215 (18%)	227 (17%)	0.5	228 (15%)	174 (17%)	0.6	185 (17%)	257 (18%)	0.6	227 (18%)	215 (17%)	0.8
Yes	966 (82%)	1110 (83%)		973 (82%)	1103 (83%)		1129 (85%)	847 (83%)		895 (83%)	1181 (82%)		1023 (82%)	1053 (83%)	
Coronary artery disease															
No	956 (80%)	1087 (81%)	0.6	961 (81%)	1082 (81%)	0.8	1201 (80%)	842 (82%)	0.15	882 (82%)	1161 (80%)	0.5	1032 (80%)	1011 (82%)	0.5
Yes	228 (20%)	247 (19%)		227 (19%)	248 (19%)		296 (20%)	179 (18%)		198 (18%)	277 (20%)		248 (20%)	277 (18%)	
Peripheral artery disease															
No	1032 (87%)	1172 (88%)	0.6	1034 (87%)	1170 (88%)	0.5	1307 (87%)	897 (88%)	0.7	943 (87%)	1261 (87%)	0.8	1125 (88%)	1079 (87%)	0.6
Yes	152 (13%)	162 (12%)		154 (13%)	160 (12%)		190 (13%)	124 (12%)		137 (13%)	177 (13%)		155 (12%)	159 (13%)	
Dialysis type															
HD	815 (68%)	894 (67%)	0.5	816 (68%)	893 (67%)	0.7	1002 (67%)	707 (69%)	0.3	741 (69%)	968 (67%)	0.4	850 (66%)	859 (69%)	0.2
PD	157 (13%)	196 (15%)		161 (14%)	192 (14%)		223 (15%)	130 (13%)		139 (13%)	214 (14%)		193 (15%)	160 (13%)	
Preemptive transplantation	212 (18%)	244 (18%)		211 (18%)	245 (18%)		272 (18%)	184 (18%)		200 (18%)	256 (18%)		237 (18%)	219 (18%)	

(Continued)

TABLE 1.

Continued

	rs6677781			rs1021737			rs672203			rs113285275			rs10458561		
	Yes, n = 1184	**No, n = 1334**	***P***	**Yes, n = 1188**	**No, n = 1330**	***P***	**Yes, n = 1497**	**No, n = 1021**	***P***	**Yes, n = 1080**	**No, n = 1448**	***P***	**Yes, n = 1280**	**No, n = 1238**	***P***
Cause of end-stage kidney disease															
ADPKD	248 (21%)	274 (21%)	0.8	252 (21%)	270 (20%)	0.7	310 (21%)	212 (21%)	0.5	225 (21%)	297 (21%)	0.9	274 (21%)	248 (20%)	0.6
Diabetic nephropathy	117 (10%)	141 (11%)		118 (10%)	140 (10%)		165 (11%)	93 (9%)		107 (10%)	151 (10%)		140 (11%)	118 (9%)	
Glomerulonephritis	328 (25%)	347 (26%)		326 (27%)	349 (26%)		398 (26%)	277 (27%)		291 (27%)	384 (27%)		335 (26%)	340 (27%)	
Other	491 (41%)	572 (43%)		492 (41%)	571 (43%)		623 (42%)	439 (43%)		457 (42%)	606 (42%)		532 (42%)	531 (43%)	
HLA mismatch[d]															
Median (Q1–Q3)	4 (3–5)	4 (3–5)	0.06	4 (3–5)	4 (3–5)	0.06	4 (3–5)	4(3–5)	0.2	4 (3–5)	4(3–5)	0.25	4 (3–5)	4 (3–5)	0.3
Antithymocyte globulin induction therapy															
Yes	264 (22%)	316 (24%)	0.4	270 (23%)	310 (23%)	0.7	367 (24%)	213 (21%)	0.03	238 (22%)	342 (24%)	0.3	299 (23%)	281 (23%)	0.7
No	920 (78%	1018 (76%)		918 (77%)	1020 (77%)		1130 (74%)	808 (79%)		842 (78%)	1096 (76%)		981(77%)	957 (77%)	
CNI for maintenance therapy															
Yes	1182 (99%)	1325 (99%)	0.06	1185 (99%)	1322 (99%)	0.2	1492 (99%)	1015 (99%)	0.7	1077 (99%)	1440 (99%)	0.3	1274 (99%)	1233 (99%)	0.8
No	2 (1%)	9 (1%)		3 (1%)	8 (1%)		5 (1%)	6 (1%)		3 (1%)	8 (1%)		6 (1%)	5 (1%)	
mTOR inhibitor for maintenance therapy															
Yes	100 (8%)	101 (8%)	0.6	85 (8%)	100 (8%)	0.7	104 (7%)	81 (8%)	0.3	82 (8%)	103 (8%)	0.7	92 (7%)	93 (8%)	0.8
No	1180 (92%)	1233 (92%)		1103 (92%)	1230 (92%)		1393 (93)	940 (92%)		998 (92%)	1335 (92%)		1188 (93%)	1145 (92%)	
H_2S levels															
Not measured	1092 (92%)	1237 (92%)	0.8	1092 (92%)	1237 (92%)	0.8	1391 (92%)	938 (92%)	0.4	992 (92%)	1337 (92%)	0.6	1186 (92%)	1143 (92%)	0.4
High	47 (4%)	48 (4%)		47 (4%)	48 (4%)		50 (4%)	45 (4%)		45 (4%)	50 (4%)		43 (4%)	52 (4%)	
Low	45 (4%)	49 (4%)		45 (4%)	4 (4%)		56 (4%)	38 (4%)		43 (4%)	51 (4%)		51 (4%)	43 (4%)	

[a]Missing value for 1 patient.
[b]Missing values for 180 patients.
[c]Missing values for 153 patients.
[d]Missing values for 5 patients.
Fisher test or *t*-test were used when appropriate.
ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CNI, calcineurin inhibitor; DBD, donation after brain death; DCD, donation after cardiocirculatory death; HD, hemodialysis; H_2S, hydrogen sulfide; mTOR, mammalian target of rapamycin; PD, peritoneal dialysis; SNP, single nucleotide polymorphism.

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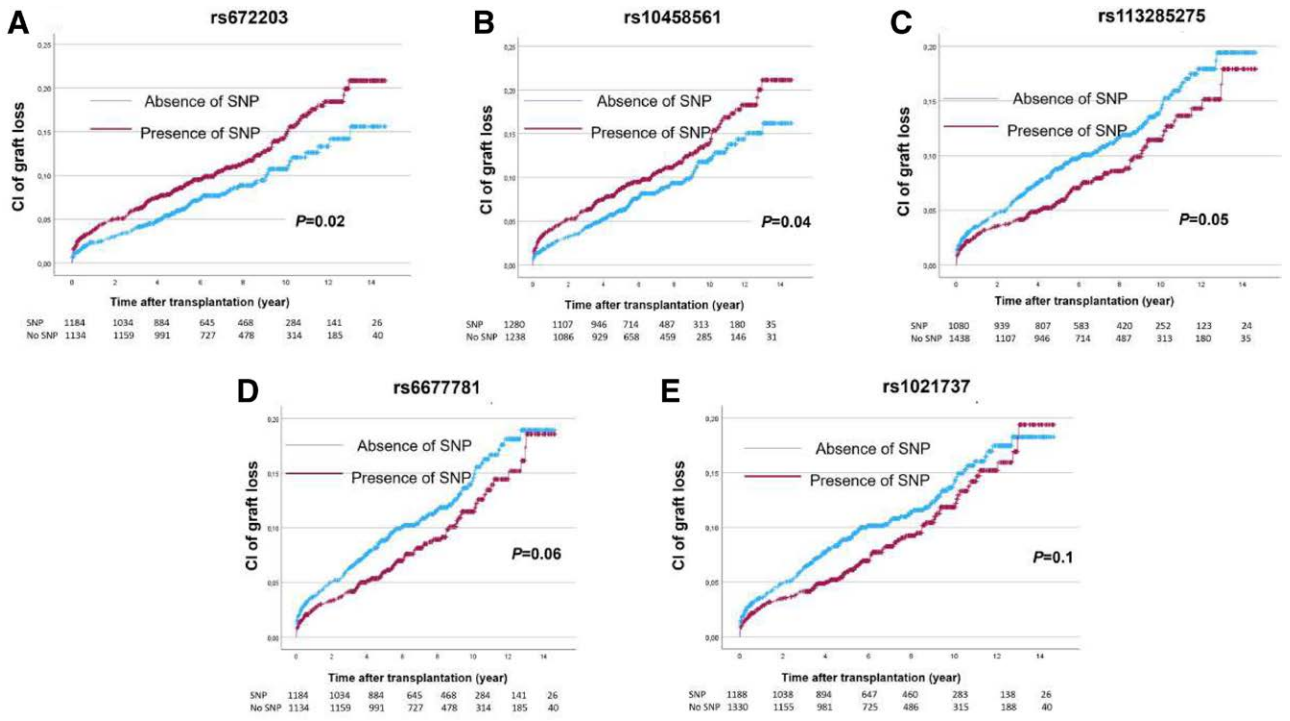

FIGURE 1. Long-term risk of graft loss according to recipient *CTH* polymorphisms in 2518 kidney transplant recipients. A, rs672203, rs10458561 (B), rs113285275 (C), rs6677781 (D), and rs1021737 (E), according to the presence (red line) or absence (blue line) of *CTH* polymorphism. Death censored. *P* values were calculated from log-rank test. CI, confidence interval; SNP, single nucleotide polymorphism.

between recipients with WT *CTH* and any of the SNPs (**Figures S3 and S4, SDC,** http://links.lww.com/TXD/A749).

DGF was previously shown to reduce both short- and long-term graft survival after kidney transplantation. Thus, we then investigated the influence of *CTH* polymorphisms on the occurrence of DGF and its subsequent impact on graft outcome. Among patients without DGF, harboring rs6677781 ($P = 0.03$), rs1021737 ($P = 0.04$), and rs113285275 ($P = 0.03$) was associated with improved graft survival compared with the WT genotype. Conversely, patients with rs672203 ($P = 0.01$) and rs10458561 ($P = 0.01$) demonstrated lower graft survival compared with those without these SNPs, in the absence of DGF (Figure 2A–E). Interestingly, in patients with DGF, the presence or absence of *CTH* polymorphisms did not influence graft outcome (**Figure S5A–E, SDC,** http://links.lww.com/TXD/A749). This suggests that the effects of *CTH* SNPs on graft survival may be independent of IRI.

Next, we examined the potential impact of *CTH* SNPs on acute rejection episodes. During follow-up, 727 (29%) patients experienced at least 1 episode of BPAR. Remarkably, the same SNPs associated with an increased risk of graft loss were also linked to a higher risk of acute rejection. Consistently, SNPs previously identified to reduce the risk of graft loss were also associated with a lower risk of acute rejection (Figure 3A–E). Considering the risk of acute rejection, to assess possible synergistic effects of these SNPs, we calculated the cumulative risk of rejection by comparing patients carrying the 3 SNPs rs6677781, rs1021737, and rs113285275 to those without these SNPs. We found a significant decreased risk of acute rejection among patients carrying all 3 SNPs ($P = 0.01$) (**Figure S6 and Table S2, SDC,** http://links.lww.com/TXD/A749).

We constructed Cox proportional hazard models to assess the contribution of each SNP to graft loss and adjust for potential confounding factors. We included in the model donor type, recipient sex, hypertension, CAD, PAD, the use of ATG, CNI-based maintenance immunosuppressive regimen and all the SNPs. In the final model, CNI-based immunosuppression (HR: 0.07, 95% CI: 0.03-0.17, $P = 0.001$), ATG-based induction (HR: 1.42, 95% CI: 1.07-20.0, $P = 0.01$), CAD at baseline (HR: 1.38, 95% CI:1.02-1.86, $P = 0.03$), living donation (HR: 0.50, 95% CI: 0.39-0.52, $P = 0.01$), and rs672203 (HR: 1.31, 95% CI: 1.05-1.79, $P = 0.02$) remained independently associated with graft loss (**Table S3, SDC,** http://links.lww.com/TXD/A749). Finally, we constructed a cox proportional hazard model to assess the contribution of each SNP to the risk of acute rejection. We included in the model CNI-based maintenance regimen, the use of ATG, donor/recipient HLA mismatches, and all the SNPs. In the final model, ATG use (HR: 0.76, 95% CI: 0.63-0.91, $P = 0.04$), HLA mismatches (HR: 1.12, 95% CI: 1.06-1.81, $P = 0.001$), and rs113285275 (HR: 0.82, 95% CI: 0.71-0.95, $P = 0.01$) remained independently associated with the risk of acute rejection (**Table S4, SDC,** http://links.lww.com/TXD/A749).

Serum H_2S Levels Do Not Correlate With *CTH* Polymorphisms

To assess the association between recipient baseline serum H_2S levels with *CTH* polymorphisms, 192 recipients were randomly extracted from the whole cohort (see Materials and Methods) and referred thereafter as the "serum cohort." Baseline patient characteristics are shown in **Table S5** (**SDC,** http://links.lww.com/TXD/A749). Median H_2S levels were 5599.2 a.u. (IQR: 4786.5-6585.7) (**Figure S1, SDC,** http://links.lww.com/TXD/A749). None

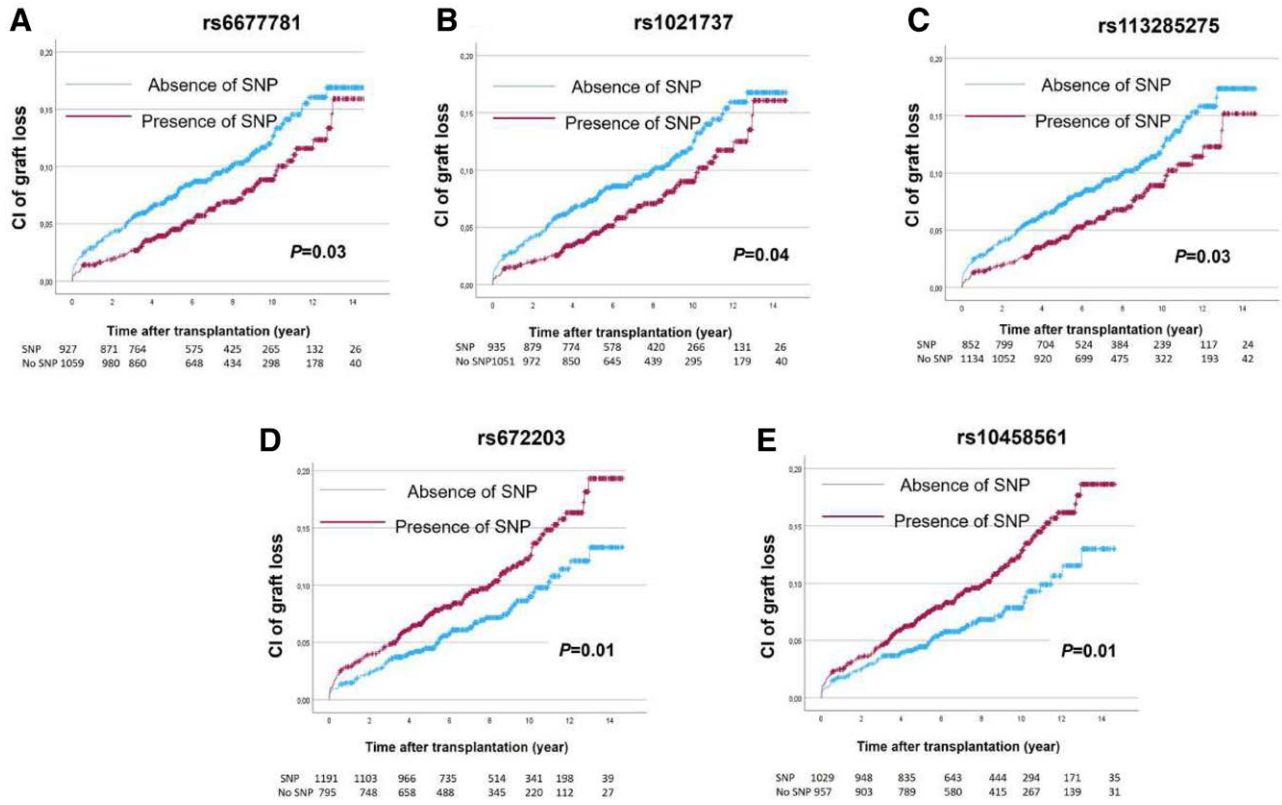

FIGURE 2. Long-term risk of graft loss according to recipient *CTH* polymorphisms in 1986 kidney transplant recipients without delayed graft function. A, rs6677781, rs1021737 (B), rs113285275 (C), rs672203 (D), and rs10458561 (E), according to the presence (red line) or absence (blue line) of *CTH* polymorphism. Death censored. *P* values were calculated from log-rank test. CI, confidence interval; SNP, single nucleotide polymorphism.

of the *CTH* polymorphisms impacted recipient serum H_2S levels prior to transplantation (**Figure S7, SDC**, http://links.lww.com/TXD/A749). When patients were divided into high versus low serum H_2S groups (using a median split), there was no difference in the risk of graft loss ($P = 0.4$), and patient survival ($P = 0.08$) during follow-up (Figure 4A and B). Similarly, we did not find any correlation between recipient baseline H_2S serum levels and eGFR posttransplantation (**Figure S8, SDC,** http://links.lww.com/TXD/A749). In preclinical models, H_2S administration limits renal IRI that manifests clinically as early DGF after transplantation. Thus, we hypothesized that higher serum levels of H_2S could improve recovery in patients with initial DGF. Consistent with our hypothesis, we observed a trend toward better graft outcomes for patients with DGF and high baseline serum H_2S levels compared with lower serum H_2S levels ($P = 0.25$) (Figure 5A and B). Given the relatively low overall number of graft losses during follow-up, we sought to enhance the power of the analysis by investigating whether baseline serum H_2S levels (ie, at the time of transplantation) could predict severe graft dysfunction (eGFR < 30 mL/min/1.73 m^2) during follow-up (Figure 5C and D). In patients with DGF, a high serum level of H_2S was associated with a longer time to reach eGFR <30 mL/min/1.73 m^2 compared with patients with low serum level of H_2S at baseline (HR: 5.5, 95% CI: 0.80-38.1, $P = 0.05$). However, baseline serum H_2S levels did not influence graft outcome in the absence of DGF (HR: 0.83, 95% CI: 0.58-1.22, $P = 0.3$).

DISCUSSION

In a prospective cohort of kidney transplant recipients, *CTH* polymorphisms were associated with graft outcome. Interestingly, the same polymorphisms did not influence patient survival or MACE during follow-up. Surprisingly, in a subgroup of patients, baseline recipient serum H_2S levels did not correlate with *CTH* polymorphisms. However, in patients with DGF, higher serum H_2S levels were associated with a better graft function during follow-up.

To date, a few recipient and donor-related factors are known to have an impact on graft and patient outcome after kidney transplantation. Among them, recipient age was associated with 1-y graft survival.[25,26] Other recipient-related factors include, among others, the cause of the initial renal disease, as patients with glomerulonephritis or diabetic nephropathy experience worst outcomes.[26,27] In recent years, several prognostic scores have been developed to assess both short- and long-term graft and patient outcomes, mainly based on donor and recipient demographic, clinical, and immunological data on the day of transplantation.[28-30] For example, the recipient risk score used at allocation of deceased-donor kidneys effectively predicts recipient mortality after transplantation but is limited by relying solely on recipient baseline demographic and clinical characteristics.[31] Other scores, such as the kidney transplant failure score or the 1-y recipient risk score, can be computed only after the first year of transplantation to assesses the risk of graft and patient loss, respectively. Consequently, they fail to capture the early risk of graft dysfunction (including DGF) or

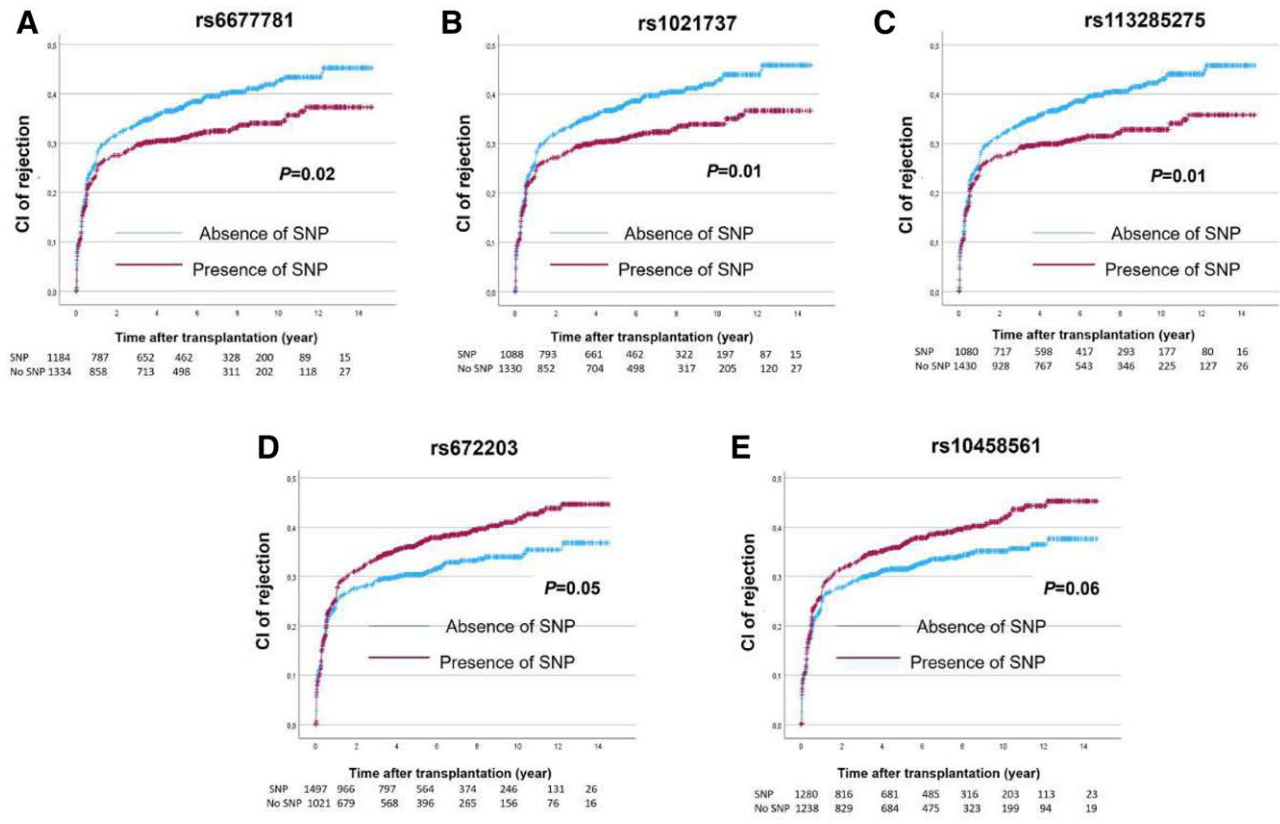

FIGURE 3. Long-term risk of acute graft rejection according to recipient *CTH* polymorphisms in 2518 kidney transplant recipients. A, rs6677781, rs1021737 (B), rs113285275 (C), rs672203 (D), and rs10458561 (E), according to the presence (red line) or absence (blue line) of *CTH* polymorphism. Death censored. *P* values were calculated from log-rank test. CI, confidence interval; SNP, single nucleotide polymorphism.

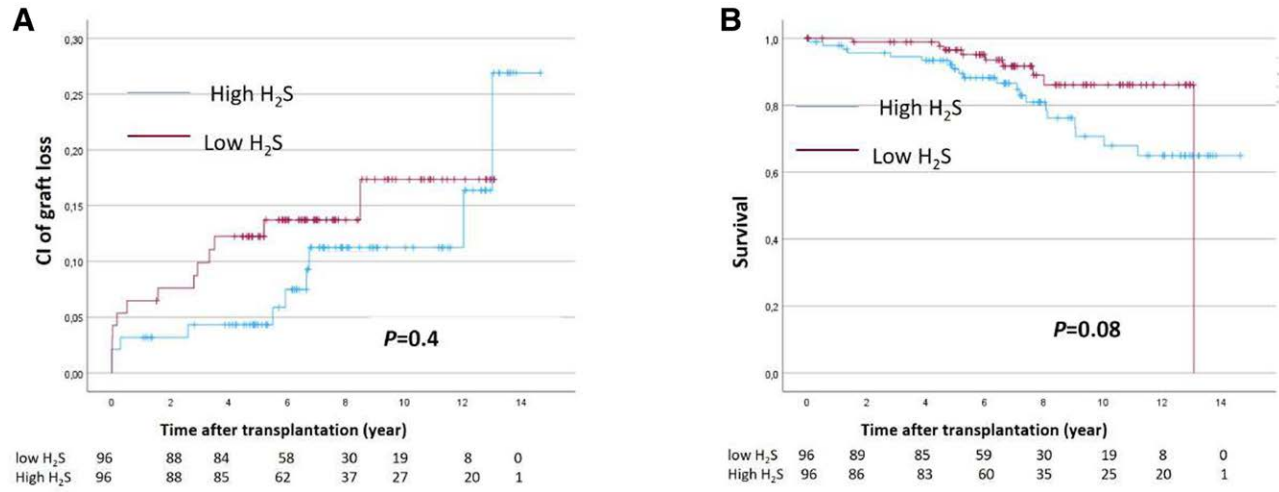

FIGURE 4. Long-term risk of graft loss (A) and patient survival (B) in 192 kidney transplant recipients according to pretransplantation H_2S serum level. A, Probability of graft loss. B, Patient survival in recipients with low (red line) or high (blue line) serum H_2S level. Death censored. *P* values were calculated from log-rank test. CI, confidence interval; H_2S, hydrogen sulfide.

patient death.[28,30] Finally, some donor-based scores, such as the kidney donor profile index may not be suitable for implementation in all countries, as they were validated in populations with different prevalent comorbidities and mixed ethnicities.[32] Therefore, there is a need to improve prediction models for graft and patient outcomes in kidney transplantation.[33] Our findings are clinically relevant, at least for a similar ethnical population (majority of Caucasian patients), as recipient *CTH* polymorphisms were a frequent trait in the STCS cohort. This could constitute a novel measurable prognostic biomarker that could be utilized for organ allocation and posttransplant management strategies. Additionally, it might lead to personalized and more effective strategies to improve long-term graft survival and overall patient outcome. However, before *CTH* SNPs can be implemented as biomarkers in clinical practice, further studies are needed to

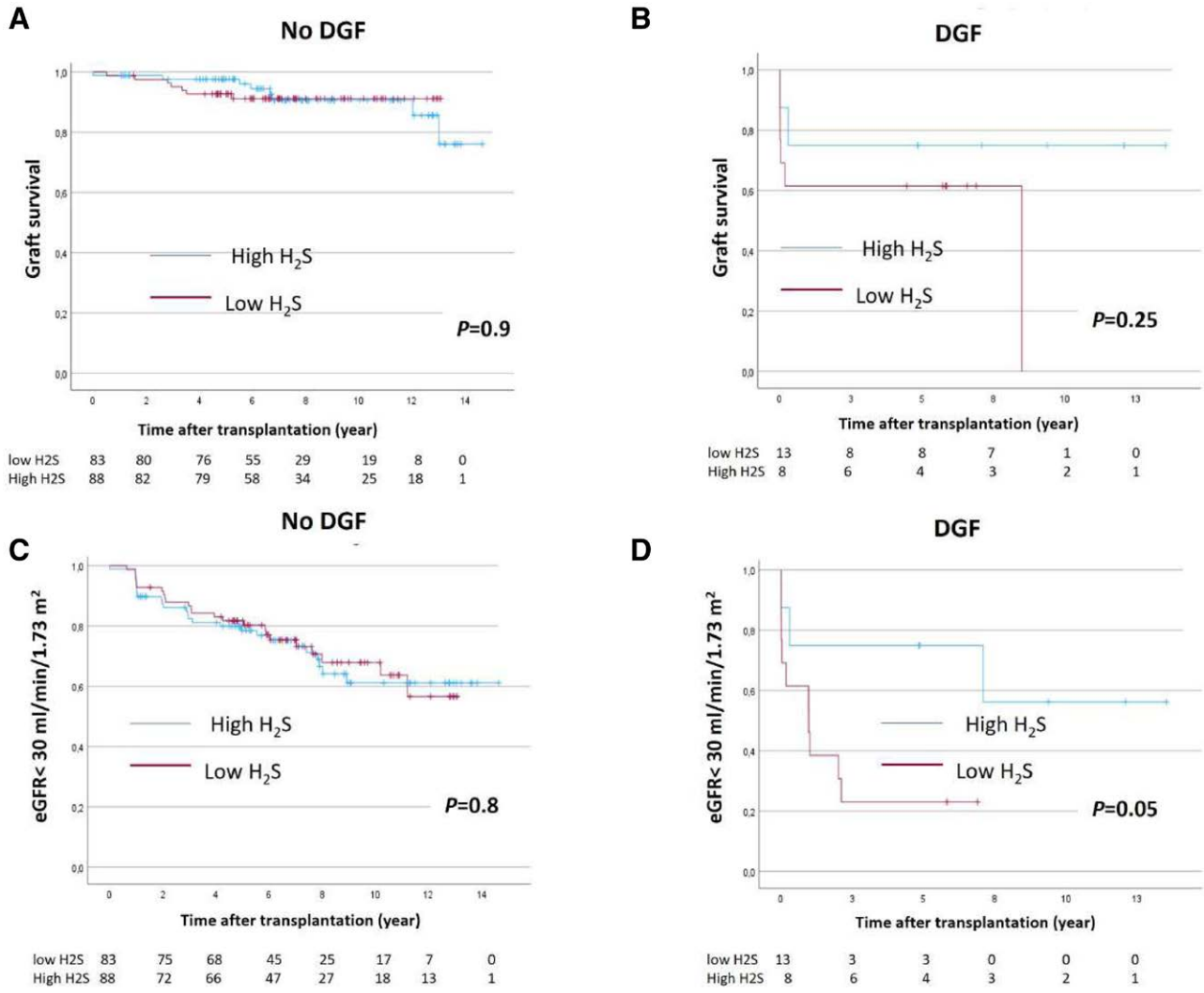

FIGURE 5. Long-term risk of graft loss or graft dysfunction according to H_2S serum levels and presence of delayed graft function in 192 kidney transplant recipients. Graft survival in patients without (A) and with DGF (B). eGFR <30 mL/min/1.73 m^2 in recipients without (C) and with DGF (D). Red and blue lines represent low and high serum H_2S levels, respectively. Death censored. *P* values were calculated from log-rank test. DGF, delayed graft function; eGFR, estimated glomerular filtration rate; H_2S, hydrogen sulfide.

investigate their impact on CGL function and downstream pathways. Of note, there are only limited data on the relevance of these SNPs in biological functions and in the field of transplantation. The most studied SNP so far is rs1021737, which was associated with elevated levels of homocysteine and cardiovascular risks.[18,19]

Although the presence or absence of *CTH* polymorphisms is not modifiable per se, further work should identify their functional consequences, that could be amenable to interventions (eg, H_2S or glutathione supplementation). Our results provide the first evidence in humans that *CTH* polymorphisms can impact kidney graft function and survival, independent of serum H_2S levels. Although the underlying functional pathways that could be impacted by the presence of various *CTH* polymorphisms are unknown, our data suggest that the protective effect on graft survival might be linked to the prevention of acute rejection episodes. CGL is the key enzyme of the transsulfuration pathway, notably metabolizing cysteine into H_2S and glutathione.[5] Cysteine and glutathione are molecules involved in effective T-cell activation,[34] regulating intracellular activation-dependent signaling pathways in immune cells, in particular the expression of costimulatory molecules on dendritic cells. Indeed, glutathione depletion was shown to impair effective priming of alloreactive T cells.[35] Accordingly, Vuillefroy de Silly et al[36] have shown that blocking CGL activity with propargylglycine reduced the risk of T cell–mediated rejection in a murine model of heart transplantation. Interestingly, they also demonstrated that the immunomodulatory effect of CGL was H_2S-independent. Additionally, CGL expression was downregulated in their model of induced transplantation tolerance.

In our study, *CTH* polymorphisms did not correlate with serum H_2S levels, as measured by the lead acetate assay.[7,12] Thus, the observed effect of *CTH* polymorphisms on graft outcome in our cohort may be independent of H_2S pretransplantation baseline levels, as *CTH*/CGL also impact cellular redox balance during glutathione, cysteine, and homocysteine metabolism.[18] Moreover, the lead acetate method quantifies only relative differences in H_2S between individuals and groups. Likewise, it primarily serves as a surrogate for the actual amount of H_2S produced from available substrates in plasma.[13] Consistently, although most tests assess sulfide

release from bound sulfide reserves, more specific assays might better capture distinct biological phenomena with clinical relevance. Important questions remain about which specific plasma components determine and regulate H_2S levels. One theory revolves around the sulfur-containing amino acid homocysteine, which in itself has been long associated with the risk of cardiovascular diseases, but the underlying physiologic mechanisms remain not well understood.[37] Considering the risk of MACE, we did not observe a significant effect of *CTH* polymorphisms compared with WT patients in our cohort. However, rs1021737 was described to be more prevalent in patients with cardiovascular diseases in a study by Rajpal et al.[19] It should be noted that this later study was rather small (n = 113 patients in the cardiovascular disease group), and included a general population admitted for cardiac catheterization and not kidney transplant recipients.

Regarding patient mortality, we had observed that lower serum H_2S levels were associated with decreased survival in a study following nontransplanted patients undergoing surgical revascularization.[13] This observation was not confirmed in the present study following kidney transplant patients. Although kidney transplant recipients are considered a high-risk group for cardiovascular diseases, our patients were younger and with fewer overall cardiovascular comorbidities, including less diabetes, compared with the above-mentioned patients studied by Longchamp et al. Furthermore, although the cause of death was not reported in the former study, it could be speculated that cardiovascular causes were important contributors based on the demographic profile of the included patients.[38] However, although cardiovascular diseases are also frequent causes of death following kidney transplantation, other complications such as cancer and infections are also very frequent[39] and could explain the lesser role of H_2S on overall mortality.[19]

In a subgroup of patients with DGF, higher preoperative levels of H_2S were associated with improved kidney graft outcome. This is relevant in an era where DCD and ECD are increasingly used.[1] Thus, organs that are at great risk of DGF could be preferentially allocated to recipients with high baseline serum H_2S levels. On the other hand, patients with low preoperative serum H_2S and DGF might benefit from H_2S administration (eg, clinically available H_2S donors such as zofenopril, sodium thiosulfate).[40,41] Alternatively, H_2S-based therapeutic strategies could also be envisaged during organ preservation and ex vivo organ perfusion,[2] limiting systemic side effects.

The limitations of our study need to be acknowledged. The STCS is a relatively small cohort for genetic-association studies. Future work is therefore needed to validate these findings in independent and larger cohorts. Additionally, the quantification of H_2S using the lead acetate method does not capture absolute levels. We previously demonstrated that dietary restriction and the hypothalamic-pituitary axis were important regulators of endogenous H_2S levels and downstream signaling.[7,42,43] Thus, specific dietary interventions could be envisaged in a future study of patients undergoing deceased-donor kidney transplantation to boost endogenous H_2S. Of note, homocysteine or glutathione levels were not available in the STCS cohort, which would have been of great interest as it is linked to *CTH* polymorphism, cardiovascular health and kidney function.[18,44] Finally, additional studies distinguishing specific inorganic and organic per/polysulfide such as cysteine or glutathione-related sulfur species are needed to better understand the relationship of these metabolites with *CTH* polymorphisms and their role in kidney transplantation.

In conclusion, in a cohort of 2518 patients who underwent kidney transplantation, *CTH* polymorphisms were associated with graft outcome. This finding may enable improved risk stratification, which ultimately should improve the overall success of kidney transplantation.

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