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# The outcome of thrombotic microangiopathy in kidney transplant recipients

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## Abstract

**Background** The outcome of kidney transplant recipients with a history of complement-mediated thrombotic microangiopathy (cTMA) and those who develop post-transplant de novo TMA (dnTMA) is largely unknown.

**Methods** We retrospectively studied all kidney transplant recipients with end-stage kidney disease secondary to cTMA and those who developed dnTMA, between Jan 2000 and Dec 2020 in our center.

**Results** We identified 134 patients, 22 with cTMA and 112 had dnTMA. Patients with cTMA were younger at the time of TMA diagnosis (age at diagnosis,  $28.9 \pm 16.3$ . vs  $46.5 \pm 16.0$  years;  $P < 0.001$ ). T-cell mediated rejection, borderline rejection, and calcineurin inhibitor toxicity were more prevalent in the first kidney transplant biopsy ( $P < 0.05$ ) in the dnTMA group, and antibody-mediated rejection was more prevalent in anytime-biopsy ( $P = 0.027$ ). After adjusting for potential confounders, cTMA was associated with a sixfold increase in the hazard of transplant failure during the first-year post-transplant (adjusted hazard ratio (aHR): 6.37 [95%CI: 2.17 to 18.68;  $P = 0.001$ ]; the aHR decreased by 0.87 (95% CI: 0.76 to 0.99;  $P = 0.033$ ) per year elapsed since transplantation. Long-term allograft survival was similar in both groups.

**Conclusion** Post kidney transplant TMA is an important cause of poor allograft survival. More studies are needed to enhance our understanding and management of this disorder.

**Keywords** Kidney, Transplant, Thrombotic Microangiopathy, Complement-mediated TMA, De novo TMA

## Background

Kidney transplantation is the treatment of choice for patients with end-stage kidney disease (ESKD) secondary to thrombotic microangiopathy (TMA) [1]. TMA is a clinical syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, organ ischemia, and dysfunction due to microvascular thrombosis [2]. Post-transplant TMA is a well-recognized complication that affects 0.8–15% of renal transplant recipients [3] [4] [5], and is associated with poor graft and patient outcomes [6]. TMA is caused by various factors, including infection, drug toxicity, and immunological factors [7].

Post-transplant TMA can occur at any time after kidney transplantation, but most commonly manifests in the first 6 months [8], and can be either de novo (dnTMA) with no evidence of the disease before transplant or

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recurrence of the native kidney TMA (cTMA) [9]. dnTMA accounts for most post-transplant cases [10] [11], with incidence ranges from 1%–15% in different reports [12]. The pathogenesis is multifactorial, and the most common causes include medications, such as calcineurin inhibitor (CNI) toxicity, ischemia–reperfusion injury, antibody-mediated rejection (ABMR), and infections, such as cytomegalovirus [13] [14–16]. The mechanism of CNI-related dnTMA includes arteriolar vasoconstriction due to the enhanced production of vasoconstrictive factors, particularly endothelin-1 and angiotensin II [17] [18]. Genetic abnormalities in complement regulation were the precipitating factors in some dnTMA cases [19].

Atypical hemolytic uremic syndrome (aHUS) is a rare cause of ESKD that manifests as TMA in the native kidneys and is caused by uninhibited activation of the complement alternative pathway [20] [21]. Genetic mutations in the regulatory complement system were identified in approximately 50–60% of the patients [22]. Recurrence rate of aHUS post kidney transplant has been reported in 50–60% of cases [23] [24] [25]. The risk of recurrence depends on the individual genetic mutation [26] [27] [28] [29].

The kidney transplant biopsy findings in acute TMA are similar to those of the native kidneys, including mucoid intimal edema, arteriolar or glomerular capillary loop fibrin thrombi, endothelial swelling with occlusion of capillary loops, and mesangiolysis [30].

Eculizumab use for post-transplant aHUS recurrence was first reported in 2009 [31], and it is effective in the treatment and prevention of recurrent cTMA [32] [33] [34] [35].

In this study, we present our center's comprehensive long-term outcome of adult kidney transplant recipients with cTMA and those who developed dnTMA post-transplant.

## Methods

### Study population and data collection

We conducted a retrospective study including all adult patients  $\geq 18$ -year-old kidney transplant recipients with cTMA and those who developed dnTMA post-transplant between January 2000 and December 2020 in our center. The study was approved by the Johns Hopkins Hospital's Institutional Review Board. The data were collected from the electronic medical records.

TMA before transplant, or cTMA, was defined as the disorder in the native kidneys that led to ESKD. While dnTMA was defined as any TMA disorder that occurred post kidney transplant in patients for whom the native

kidney disease was not caused by cTMA. All kidney biopsy obtained in the dnTMA were for clinical cause.

We sought to compare between TMA before and after a transplant to provide insights into the pathogenesis, risk factors, and outcomes associated with TMA in the context of transplantation.

We reviewed all available clinical data, including transplant-related variables, recipient and donor information, genetic testing, histological data, and treatment modalities including the use of eculizumab. We compared the baseline characteristics, clinical and histological characteristics at the time of post-transplant TMA diagnosis, and short and long-term transplant outcomes between the two groups.

All kidney biopsies were reviewed by our internal renal pathologists, employing the contemporary Banff Classification during the initial biopsy assessment.

For the purpose of our study, “highly sensitized” patients refer to those who have a pre-formed HLA antibodies define by a calculated panel reactive antibody (CPRA) level of  $\geq 80\%$ .

### Statistical analysis

We compared between the cTMA and dnTMA groups. The demographic and clinical characteristics were described using descriptive statistics. We used the Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables. Patients were followed from the time of transplantation until graft failure or death, whichever came first. We estimated the crude survival probability using the Kaplan–Meier estimator. We estimated the adjusted hazard ratio (aHR) associated with cTMA using multiple Cox regression models. We fitted non-linear continuous variables with fractional polynomials and tested proportional hazard based on Schoenfeld residuals. We included biopsy diagnoses as time-varying cumulative sum (i.e. cumulative sum of each diagnosis that is updated every time the patient undergoes a new biopsy). Because the non-proportional hazard assumption did not hold, we allowed the HR associated with cTMA to vary over follow-up by including an interaction term with time. We performed an additional analysis in which the Cox regression model was modified so that 1) dnTMA were classified as such from the time of recurrence (i.e., it was included as a time-varying variable from the time of recurrence onward), and 2) we included a time-varying indicator variable for recurrent cTMA. Therefore, in the modified model, we had three virtual groups namely, dnTMA as a time-varying indicator variable (patients were classified as dnTMA only from the time on recurrence onward), cTMA, and cTMA that recurred (time-varying indicator variable from the time of recurrence onward). The time-varying indicator

variables (i.e., patients classified as recurrent only from the time of recurrence onward) was required to avoid fallacies in the Cox-regression model. We considered two-sided P values of less than 0.05 as statistically significant.

**Results**

**Patients’ characteristics**

We identified 134 kidney transplant recipients in our center who met the inclusion criteria. All patients had the histological diagnosis of TMA before or after kidney transplant. Out of the 134 patients, 22 (16.4%) had cTMA and 112 (83.6%) developed dnTMA post-transplant. The demographic characteristics of all patients are shown in Table 1.

The causes of ESKD in the dnTMA patients were diabetic nephropathy in 24 (21%), glomerular diseases in 33 (29%), lupus nephritis in 8 (7%), polycystic kidney disease

and other congenital kidney diseases in 22 (20%), hypertension in 11 (10%), and other causes or unknown etiology in 14 (13%) patients.

Compared with dnTMA, patients with cTMA were younger at TMA diagnosis, mean (SD) of 28.9 ± 16.3. vs 46.5 ± 16.0 years, *p* < 0.001, and at transplantation, mean (SD) of 38.5 ± 10.6 vs 46.1 ± 14.8, *p* = 0.022, respectively. There were no statistical differences in race or gender between the two groups. The majority of the dnTMA group received deceased donor kidney transplantation (DDKT), 69 (61.6%), compared to 9 (40.9%) in the cTMA group; however, the difference was not statistically significant. Thirteen patients (59.1%) had previous kidney transplants in the cTMA and 63 (56.2%) in the dnTMA. Donors were significantly younger in the cTMA group with a mean (SD) of 37.0 (13.7) years, compared to 43.5 (14.9) years in the dnTMA group, *p* = 0.038.

**Table 1** Baseline Patients Characteristic

	dnTMA	cTMA	<i>p</i> -value
N	112 (83.6%)	22 (16.4%)	
† Mean (SD) Age at TMA diagnosis, years	46.5 ± 16.0	28.9 ± 16.3	< 0.001
Mean (SD) Age at transplant, years	46.1 ± 14.8	38.5 ± 10.6	0.022
Ethnicity			
White	66 (58.9%)	17 (77.3%)	0.287
Black	42 (37.5%)	5 (22.7%)	
Other	4 (3.6%)	0 (0.0%)	
Gender, Female	56 (50.0%)	15 (68.2%)	0.161
Donor type			
Deceased donor	69 (61.6%)	9 (40.9%)	0.185
Living unrelated	20 (17.9%)	6 (27.3%)	
Living related	23 (20.5%)	7 (31.8%)	
Donor’s age, years	43.5 ± 14.9	37.0 ± 13.7	0.038
Donor’s terminal Creatinine, mg/dL	1.1 (0.4–4.0)	1.4 (0.5–6.5)	0.540
Highly sensitized	47 (67.1%)	15 (75.0%)	0.592
‡ HLAi or ABOi transplant (required desensitization)	46 (51.1%)	6 (30.0%)	0.136
§ Pre-transplant DSA	50 (66.7%)	8 (40.0%)	0.04
Re-transplantation	63 (56.2%)	13 (59.1%)	1
Warm ischemic time, minutes	47.2 ± 24.8	42.5 ± 11.8	0.641
Cold ischemic time, hours	19.7 ± 17.2	10.3 ± 10.8	0.023
Delayed graft function	45 (40.9%)	4 (18.2%)	0.054
Reason for previous graft loss			
TMA	4 (5.3%)	15 (93.8%)	< 0.001
¶ Acute ABMR	9 (11.8%)	0 (0.0%)	
Chronic ABMR	30 (39.5%)	0 (0.0%)	
BK nephropathy	3 (3.9%)	0 (0.0%)	

† SD standard deviation, TMA thrombotic microangiopathy

‡ HLAi Human leukocyte antigens incompatible, ABOi ABO-incompatible

§ DSA donor specific antibody

¶ ABMR antibody mediated rejection

There was no statistical difference in the number of patients who were highly sensitized in the two groups, however, preformed donor specific antibody (DSA) was more prevalent in the dnTMA group compared to the cTMA group, 50 (66.7%) vs 8 (40.0%),  $p=0.04$ .

Cold ischemia time was significantly shorter in the cTMA group with a mean (SD) of  $10.3 \pm 10.8$  h compared with  $19.7 \pm 17.2$  in the dnTMA group,  $p=0.023$ ; this translated into a trend toward a higher rate of delayed graft function (DGF) in the dnTMA group 45 (40.9%) vs 4 (18.2%) in the cTMA group,  $p=0.054$ .

Since 2000, our center has been using mostly the same immunosuppression protocol including induction therapy with a T-cell depleting agent (mostly thymoglobulin), and maintenance therapy with calcineurin inhibitor (tacrolimus and less likely cyclosporine), steroids, and anti-metabolites mycophenolate mofetil. Most patients in our cohort received induction therapy with thymoglobulin and maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and steroids. There were no statistical differences in induction and maintenance therapies between the two groups.

Treatment of post-transplant TMA, before the utilization of eculizumab for this disorder, was consistent of plasmapheresis and in some cases high doses of steroids. In our cohort, treatment with plasmapheresis was implemented in 19 patients (86.4%) of the cTMA group compared to 41 patients (36.9%) of the dnTMA group,  $p<0.001$ .

Eculizumab was first used off-label in our center in 2010, since then it has become the treatment of choice for prevention and treatment of recurrent cTMA post-transplant. In our cohort, Eculizumab was used in 13 patients (59.1%) for recurrent or prevention of cTMA post-transplant, compared to 6 patients (5.4%) in the treatment of dnTMA group,  $p<0.001$ .

#### Diagnostic findings of post-transplant TMA

The median time (interquartile range (IQR)) to biopsy-proven TMA post-transplant was 16.4 (3.6 -79.7) months. There were 543 biopsies in the cohort, median (IQR) number per patient: of 4 (2 -5) biopsies.

Twelve patients (60%) with cTMA experienced recurrence after kidney transplantation, confirmed by kidney transplant biopsy. Pathogenic mutations were identified in 10 patients (45.5%) while 12 (54.5%) patients had either no identified 7 (31.8%) mutation or testing was not done 5 (22.7%).

Laboratories results including hemoglobin, platelets, and kidney function were not statistically significant on the day of discharge post hospitalization for kidney transplant between the two groups. At the time of TMA diagnosis post-transplant, which was confirmed by kidney

transplant biopsy, the laboratory parameters did not differ significantly except for serum creatinine, Table 2. Median serum creatinine (IQR) was much higher at the time of dnTMA diagnosis compared with cTMA recurrence post-transplant, 3.6 (0.4–24.0) vs 2.0 (0.7–15.6) mg/dL,  $p=0.043$ .

Patients with dnTMA had a much higher rate of rejection confirmed by kidney transplant biopsy at the time of TMA diagnosis compared with cTMA, 49 (43.8%) vs 2 (10%),  $p=0.005$ , Table 1. Similarly, CNI toxicity in the diagnostic biopsy was more frequent in the dnTMA group compared to the cTMA group, 80 (71.4%) vs 5 (22.7%),  $p<0.001$ . In anytime kidney transplant biopsy, ABMR was more prevalent in the dnTMA group compared to the cTMA group, 29 (25.9%) vs 1 (4.5%) patients,  $p=0.027$ . Otherwise, there was no difference in the other Banff scores of the first kidney biopsy, including g, I, ti, t, v, ptc, C4d, cg, ci, ct, cv, mm, ah, IFTA, Table 2.

#### Allograft and patient outcome

The survival analysis was performed in the 129 patients with available follow-up (109 with dnTMA, and 20 with cTMA), Fig. 1. The mean follow-up was 4.5 years during which 73 (54%) had allograft failure and 22 (16%) died. Black race was associated with a higher risk of allograft failure. Pathological changes of any type of acute rejection, including borderline rejection, and tacrolimus toxicity in the kidney transplant biopsy at the time of TMA diagnosis post kidney transplant were associated with a significantly higher risk of allograft failure, Table 3.

After adjusting for age, gender, ethnicity, donor type, lymphodepleting agent induction and DGF patients with cTMA had a significant increase in the hazard risk of allograft failure in the first-year post-transplant, aHR: 6.37 (95% CI: 2.17 to 18.68,  $P=0.001$ ). However, the aHR decreased by 0.87 (95% CI: 0.76 to 0.99,  $P=0.033$ ) per year elapsed since transplantation, Table 3. By the end of the study's time, there were no statistical differences in the allograft survival between the two groups, Fig. 2. Among the 132 patients who contributed to the survival analyses, 97 (87%) in the dnTMA and 13 (65%) in the cTMA receive a TMA diagnosis in the post-transplant biopsy report ( $P=0.044$ ).

HR associated with dnTMA as time-varying variable biopsy diagnosis showed a relative 87% increase in rate of transplant failure which was, however, only of borderline statistical significance (aHR: 1.87 [95%CI: 0.83 to 4.23;  $P=0.134$ ). On the contrary, cTMA was associated with a striking increase in early transplant failure. The increase in the rate of early transplant failure associated with cTMA did not depend on whether or not there was a biopsy diagnosis of TMA recurrence in cTMA patients. In fact, the HR associated with biopsy-proven recurrence

**Table 2** Clinical and pathological findings at the time of post-transplant TMA diagnosis

	dnTMA (N = 112)	cTMA (N = 22)	p-value
Number of graft biopsies	4.0 (1.0–12.0)	3.5 (0.0–10.0)	0.134
Time from first to last biopsy, months	18.8 (0.0–296.2)	45.2 (0.6–1290.0)	0.197
<sup>†</sup> Median (IQR) of SCr at time of diagnostic biopsy, mg/dL	3.6 (0.4–24.0)	2.0 (0.7–15.6)	0.043
<sup>‡</sup> Mean (SD) of Hg at time of diagnostic biopsy, g/dL	9.4 ± 2.0	9.6 ± 1.5	0.449
Median (IQR) of platelets count at time of diagnostic biopsy, × 1000/dL	167 (21.0–459)	176 (47.0–396)	0.855
Median (IQR) of LDH at time of diagnostic biopsy, U/L [Ref. 100–200]	312 (91–1547)	286 (200–1183)	0.753
Median (IQR) of last SCr, mg/dL	3.1 (0.3–17.8)	2.3 (0.4–5.0)	0.025
<sup>§</sup> Mean (SD) of last eGFR, mL/min/1.73 m <sup>2</sup>	23.5 ± 22.1	42.2 ± 27.3	0.003
Mean (SD) of last Hemoglobin, g/dL	10.6 ± 2.2	9.5 ± 2.7	0.212
Rejection in the diagnostic biopsy	49 (43.8%)	2 (10.0%)	0.005
<sup>¶</sup> TCMR in diagnostic biopsy	26 (23.2%)	0 (0.0%)	0.007
<sup>#</sup> CNi toxicity in diagnostic biopsy	34 (30.4%)	1 (5.0%)	0.025
Rejection, at least in one biopsy	90 (80.4%)	11 (50.0%)	0.005
<sup>††</sup> ABMR, at least in one biopsy	29 (25.9%)	1 (4.5%)	0.027
<sup>†††</sup> CTG, at least in one biopsy	11 (9.8%)	3 (13.6%)	0.701
CNi toxicity, at least in one biopsy	80 (71.4%)	5 (22.7%)	< 0.001

<sup>†</sup> SCr serum creatinine<sup>‡</sup> Hg Hemoglobin<sup>§</sup> eGFR estimated glomerular filtration rate<sup>¶</sup> TCMR T cell mediated rejection, antibody-mediated rejection<sup>#</sup> CNi calcineurin inhibitor<sup>††</sup> ABMR antibody mediated rejection<sup>†††</sup> CTG chronic transplant glomerulopathy

in the cTMA did not differ between cTMA that had biopsy-proven recurrence and those who did not have biopsy-proven recurrence: HR in cTMA with no biopsy-proven recurrence: 8.18 [95%CI: 1.69 to 39.66;  $P=0.009$ ]; HR in cTMA with biopsy-proven recurrence: 5.56 [95%CI: 1.77 to 17.52;  $P=0.003$ ]; difference between the two HRs (test for interaction):  $P=0.629$ . The reason why biopsy-proven recurrence did not apparently affect the transplant failure rate within the cTMA group is likely related to the fact that, within the cTMA group, there were recurrences that occurred shortly post-transplantation and that we did not record as such because they were non documented by a biopsy.

In the most recent follow-up, allograft function as measured by mean (SD) eGFR ( $23.5 \pm 22.1$  vs  $42.2 \pm 27.3$  ml/min/m<sup>2</sup>,  $p=0.003$ ), was significantly worse in the dnTMA group comparing with cTMA group. The difference in serum creatinine (SCr) at the time of diagnosis between the dnTMA and cTMA groups does not appear to be directly related to the time elapsed between the timing of biopsies for each group. The study provided data on the serum creatinine levels at the time of diagnostic biopsy, showing a significant difference between the two groups (median SCr of 3.6 mg/dL in dnTMA vs. 2.0 mg/dL in cTMA,  $p=0.043$ ). However, the time from

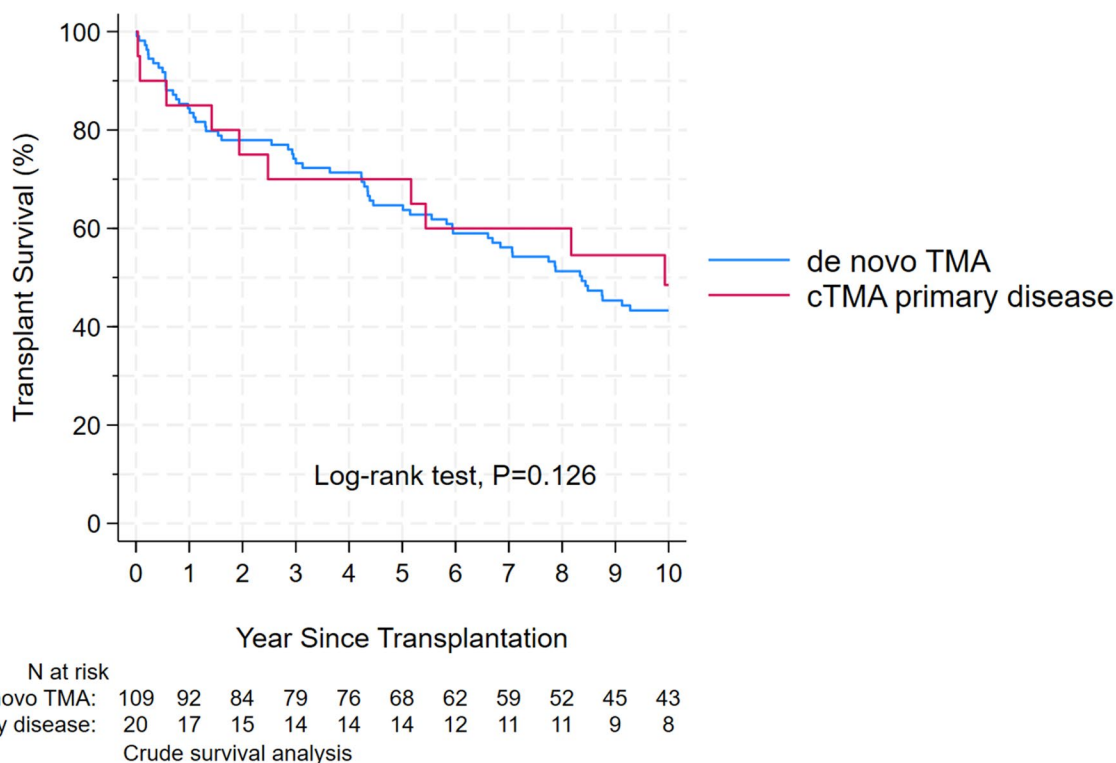
the first to the last biopsy, which might reflect the timing of biopsy, was not significantly different between the two groups (median time of 18.8 months for dnTMA vs. 45.2 months for cTMA,  $p=0.197$ ). While not statistically significant, this may have influenced the results given larger sample size and more power.

Therefore, while there is a noted difference in serum creatinine at diagnosis, this difference does not seem to be explained by the timing of the biopsies. Instead, it could be related to other factors, such as underlying pathology or clinical management differences between the two groups.

There was a trend toward worse patients' survival in the dnTMA group, which did not reach a statistical difference,  $p=0.087$ , Fig. 3. The Hazard Ratio (HR) for graft failure for living unrelated donors compared to deceased donors was 1.22 (95% CI: 0.65 to 2.29,  $p=0.526$ ). For living related donors compared to deceased donors, the HR was 0.47 (95% CI: 0.22 to 1.00,  $p=0.051$ ).

#### Ecilizumab effect on the allograft outcome

We performed a sub-group analysis of patients who received Ecilizumab; mostly cTMA. There was no difference in allograft survival between those who received ecilizumab and those who did not, Fig. 4. However, the



**Fig. 1** Kaplan–Meier plot of transplant survival (death or end-stage kidney disease, ESKD) of primary cTMA vs dnTMA. Time at risk starts from transplantation and includes patients with available follow-up. The population is divided into those who had known cTMA before transplantation (red) and those who had dnTMA (blue). There was a sudden drop by 10% in cTMA patients shortly after follow-up, but survival was similar between the groups in the long term; cTMA

**Table 3** Hazard ratio of transplant failure from Cox proportional hazards regression model

	HR	95% CI	P value
Male gender	1.70	(1.06 to 2.75)	0.029
Ethnicity (vs White)			
Black	1.76	(1.06 to 2.93)	0.029
Other	0.37	(0.09 to 1.57)	0.176
Donor type (vs Deceased donor)			
Living unrelated	1.22	(0.65 to 2.29)	0.526
Living related	0.47	(0.22 to 1.00)	0.051
Delayed graft function	1.38	(0.78 to 2.42)	0.267
Recurrent cTMA, first year	6.37	(2.17 to 18.68)	0.001
† ABMR	1.23	(0.90 to 1.67)	0.188
‡ TCMR grade 1	1.37	(1.12 to 1.67)	0.002
TCMR grade 2	1.55	(1.22 to 1.98)	<0.001
Borderline rejection	1.47	(1.08 to 2.00)	0.013
§ CNI toxicity	1.65	(1.28 to 2.12)	<0.001
Yearly change of the HR associated with cTMA	0.87	(0.76 to 0.99)	0.033

† ABMR antibody mediated rejection

‡ TCMR T cell mediated rejection

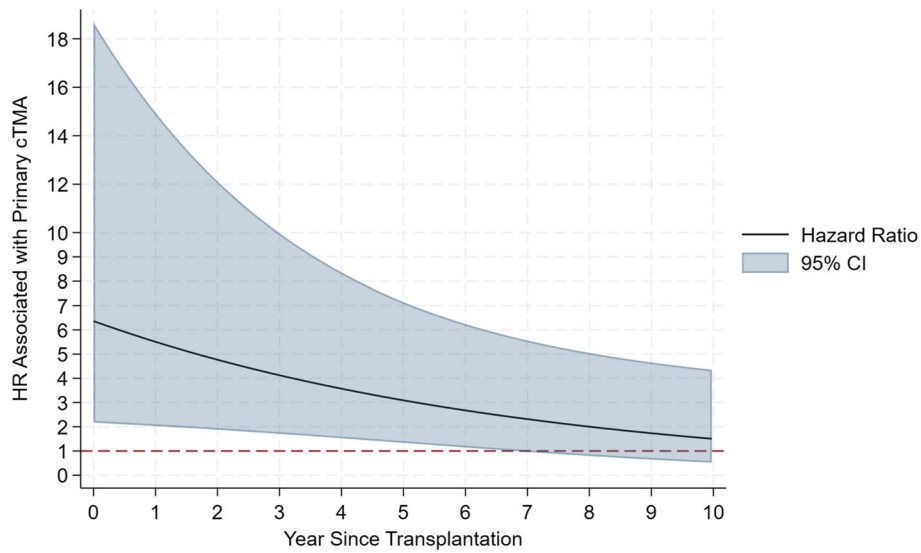
§ CNI calcineurin inhibitor

treatment of eculizumab has been utilized only since 2010, and in many cases, it was used late in the course of post-transplant TMA.

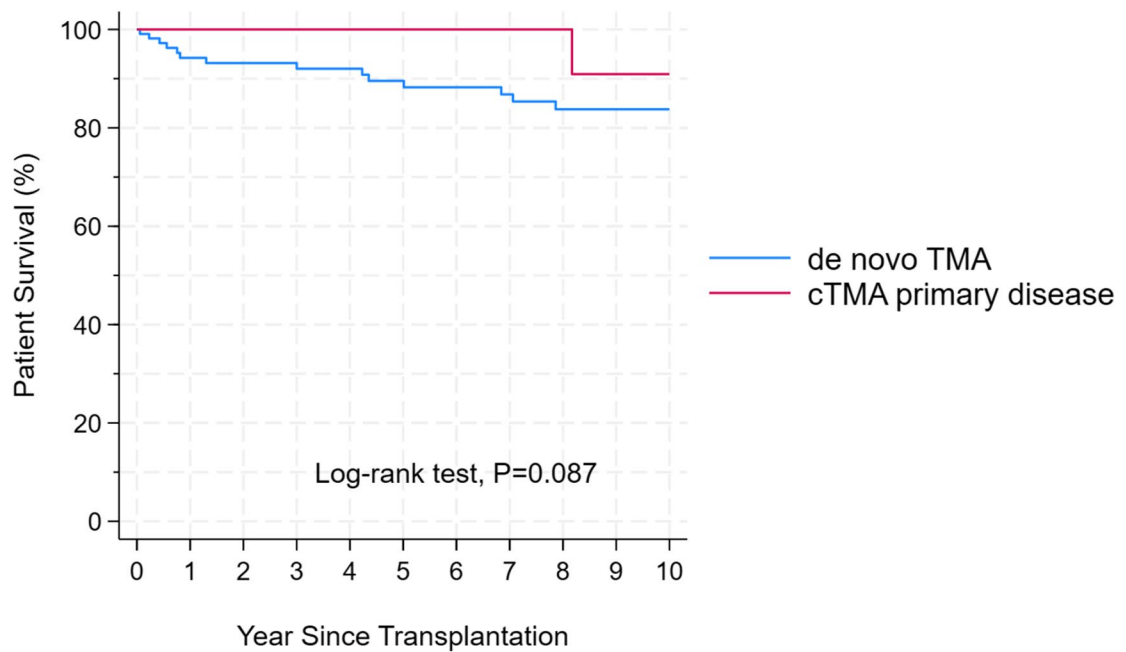
**Discussion**

In this single-center study, we identified a total of 134 patients with TMA, 22 patients with cTMA, and 112 developed dnTMA post-transplant. Patients with cTMA were younger both at transplantation and at the time of TMA diagnosis. We found that biopsy-proven acute TCMR and ABMR rejections and biopsy-proven CNI toxicity were much more common in the dnTMA group. Rejection and CNI toxicity were most likely the causes of dnTMA post kidney transplantation.

Additionally, we found that cTMA was associated with a sixfold increase in the hazard risk of allograft failure in the first year after transplant but the aHR decreased as time elapsed after transplant. This finding may be explained by the high recurrence rate of cTMA early post-transplant triggered by several factors that lead to the activation of the alternative complement pathway, e.g., ischemia–reperfusion injury, infections, and the use of immunosuppressive drugs, especially before the



**Fig. 2** Time-varying adjusted hazard ratio (HR) of transplant failure (death or end-stage kidney disease, ESKD) of patients with cTMA compared to dnTMA. The hazard ratio is highest shortly after transplantation, and then decreases with time. The model is adjusted for age, gender, ethnicity, donor type, induction with lymphodepleting agents, DGF, eculizumab use (any time), and biopsy diagnosis (time-varying cumulative sum). The line represents the hazard ratio estimates, the blue shaded area represents the 95 percent confidence interval; cTMA, complement-mediated thrombotic microangiopathy

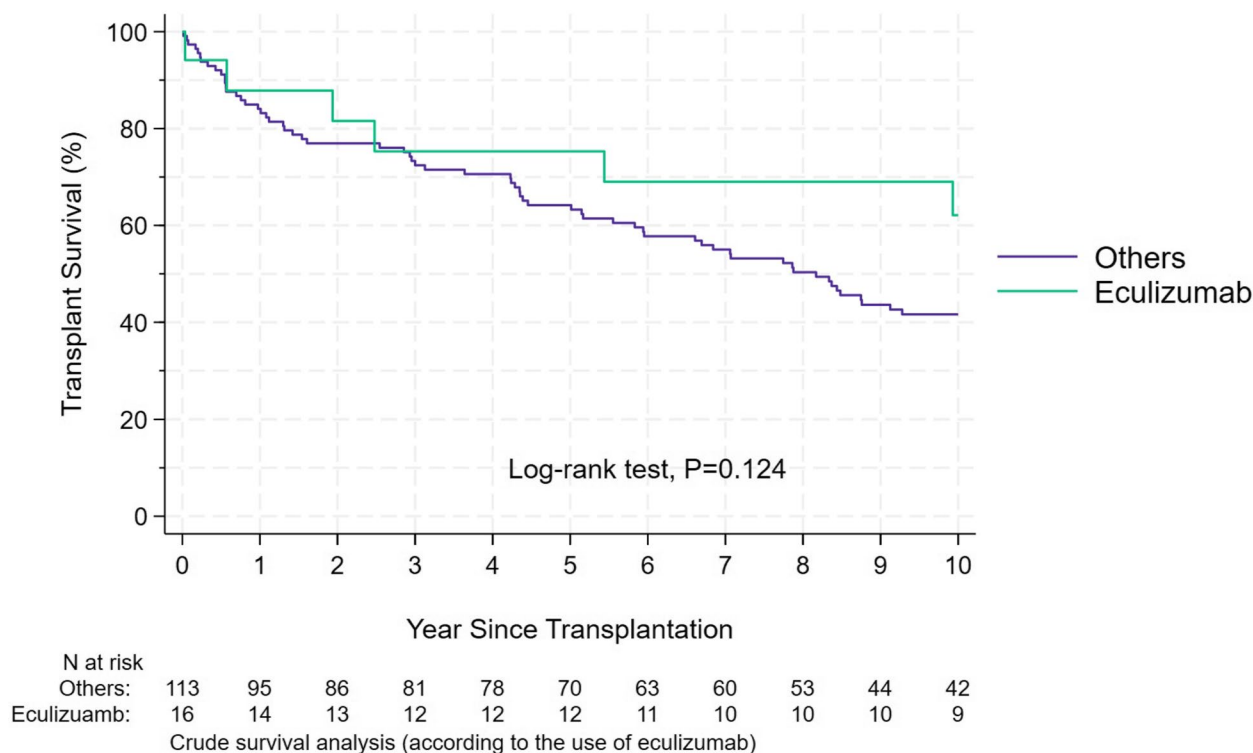


N at risk

de novo TMA:	111	93	85	81	77	69	63	60	52	45	43
cTMA primary disease:	20	17	15	14	14	14	12	11	11	9	8

Crude survival analysis

**Fig. 3** Kaplan–Meier patient survival estimates in cTMA and dnTMA. Time at risk started from transplantation and included patients with available follow-up. Patients starting dialysis were censored



**Fig. 4** Kaplan–Meier allograft survival estimates according to the use of eculizumab

utilization of anti-C5 antibodies. However, the long-term allograft survival of the two groups was similar.

Before the utilization of eculizumab in the treatment of post-transplant TMA in our center, plasma exchange was the main treatment of choice for recurrent cTMA and in some cases of dnTMA. Although eculizumab improved the allograft survival in published case reports, our study did not capture this benefit. This can be explained by the underpowered sample size and the fact that the utilization of eculizumab was delayed in some cases.

cTMA is a systemic disorder caused by uncontrolled activation of the alternative complement pathway and can lead to ESKD. A variety of genetic defects in complement-related factors have been identified and recurrence rate post-transplant largely depends on the pathogenetic mutations involved [33]. Before the utilization of anti-C5 antibodies in cTMA, kidney transplant outcome of recurrent cTMA was dire [36].

Although acute rejection episodes commonly occur in the first year post-transplant, mostly in the first 6 months, successful rejection treatment and allograft functional recovery may not have a negative long-term impact on the allograft survival [37]. However, the detection of dnTMA in the early post-transplant period holds significant implications for the long-term allograft outcome.

Our study demonstrates that dnTMA may serve as a pivotal early pathological marker associated with poor long-term allograft survival.

The incidence of recurrent cTMA or dnTMA is not very well defined, likely because most of the transplant centers do not do protocol biopsies. In a small retrospective study of 57 renal transplant recipients with early allograft dysfunction, post-transplant biopsy-proven TMA was detected in 10.5% of cases [38].

The significant advances in our understanding of the cTMA disorder and the approval of anti-C5 antibodies have resulted in a major improvement in the outcome of kidney transplants in patients with cTMA [39] [40]. Eculizumab has been used for the treatment of recurrent cTMA and as a preventive measurement that decreases or prevents recurrent cTMA post-transplant [41]. On the other hand, limited options are available for dnTMA that mostly depend on the cause. In cases of CNI toxicity, many providers switch to mTOR inhibitors or belatacept with some success [42] [43].

Furthermore, there is limited data on the long-term outcome of renal transplantation in patients with post-transplant TMA. In a study from Brazil, 17 (1.1%) out of 1549 kidney transplant recipients developed dnTMA that occurred at a median of 25 (1–1755) days after transplantation. CNI withdrawal or reduction was the



first step in the management of 10/15 (66%) patients, and 6 (35%) received fresh frozen plasma (FFP) and/or plasmapheresis. Eight (47%) patients needed dialysis after TMA diagnosis and 75% remained on dialysis. At 4 years of follow-up, death-censored graft survival was worse for the dnTMA group (43.0% versus 85.6%, log-rank = 0.001; hazard ratio = 3.74), with no difference in patient survival (53.1% versus 82.2%, log-rank = 0.24) [9].

In most published data the two types of post-transplant TMA were grouped. In a retrospective study of 89 patients with post-transplant TMA, underlying precipitating factors were infection (54%), acute rejection (34%), CNI toxicity (13%), and pregnancy (3%). The 1-year patient survival was 97% and graft survival was 66%. Allograft survival was inferior when ABMR occurred (with 41%; without 70%,  $p = 0.01$ ) [44].

Despite the significant novel findings of our study, it has several limitations, primarily stemming from its retrospective nature. Additionally, the absence of protocol biopsy might have led to the oversight of numerous other patients with post-transplant TMA. Furthermore, our understanding of cTMA, primarily attributed to its association with genetic disorders within the complement alternative pathway, remains relatively new. Consequently, treatment modalities for both cTMA and dnTMA were notably limited in the first ten years of our study. Other limitation of our study is the limited available data on eculizumab use in TMA. However, despite these limitations, our study represents one of the largest cohorts of kidney transplant recipients with TMA. Moreover, the outcomes derived from our study carry substantial implications for advancing comprehension of this disorder and elucidating its ramifications on allograft outcomes. The fact that we only classified recurrence based on biopsy report is a limitation of the study that we acknowledged. Nonetheless, we contend that the study shows clear evidence that cTMA and dnTMA are, in fact different and that by no means they can be regarded the same disease. Additionally, the possibility that cTMA led to heightened awareness and potentially earlier biopsying/diagnosis is indeed a valid concern. It is possible that clinicians, being more vigilant with patients who had a history of cTMA, might have detected TMA earlier, particularly when prompted by subtler signs like a lower rise in creatinine. This could, in turn, contribute to an earlier diagnosis in the cTMA group compared to dnTMA, where the suspicion of TMA might not be as immediately high. Future studies could aim to control for this bias by standardizing biopsy protocols or using additional biomarkers to guide the timing of

biopsy across all patient groups, regardless of their pre-transplant history.

## Conclusion

Post-transplant recurrent cTMA is an important cause of poor allograft survival in the first-year post kidney transplant. On the other hand, dnTMA is associated strongly with poor long-term allograft survival.

## Abbreviations

cTMA	Complement-mediated thrombotic microangiopathy
dnTMA	De novo thrombotic microangiopathy
aHR	Adjusted hazard ratio
ESKD	End-stage kidney disease
CNI	Calcineurin inhibitor toxicity
ABMR	Antibody-mediated rejection
TCMR	T cell-mediated rejection
aHUS	Atypical hemolytic uremic syndrome
MCP	Membrane cofactor protein
DDKT	Deceased donor kidney transplant
LURT	Living unrelated kidney transplant
LRT	Living-related kidney transplant
GN	Glomerulonephritis
DSA	Donor-specific antibodies
IFTA	INTERSTITIAL Fibrosis Tubular Atrophy
eGFR	Estimated glomerular filtration rate
rATG	Rabbit anti-thymocyte globulins
MMF	Mycophenolate mofetil
mTOR	Mammalian target of rapamycin

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## Authors' contributions

All authors reviewed the manuscript.

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## Data availability

Data is provided within the manuscript.

## Declarations

### Ethics approval and consent to participate

The ethics committee is the Johns Hopkins Hospital's Institutional Review Board. This is a retrospective study, data were collected from the electronic medical records, consents were waived by Johns Hopkins Hospital's Institutional Review Board.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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