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Risk factors for transplant-associated thrombotic microangiopathy and mortality in a pediatric cohort

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Key Points

- A total of 36% of children met Jodele TA-TMA criteria after HCT, which was associated with significantly worse OS and increased TRM.
- TA-TMA features associated with increased TRM included need for ≥2 antihypertensive medications, acute kidney injury, and LDH ≥2 times ULN.

Transplant-associated thrombotic microangiopathy (TA-TMA) is a well-recognized complication of hematopoietic cell transplantation (HCT). Diagnosis is challenging and in the absence of a tissue biopsy, TA-TMA is provisionally diagnosed by meeting clinical criteria. In this study, we describe the prevalence, outcomes, and risk factors for meeting 2 different diagnostic criteria for TA-TMA and for increased transplant-related mortality (TRM). In this retrospective study of 307 pediatric HCT patients, records were reviewed for the first 100 days after HCT. Patients who were diagnosed with TA-TMA by a provider during this time were included. In addition, the Cho et al criteria (2010) and Jodele et al (2014) TA-TMA criteria were applied retrospectively. Eight patients (2.6%) were diagnosed with TA-TMA by their provider. However, on retrospective review, 20% and 36% met the Cho and Jodele criteria for TA-TMA, respectively. Overall survival was significantly worse ($P < .0001$) and TRM was significantly higher in patients who met criteria for TA-TMA (MC-TA-TMA) ($P < .0001$). After controlling for comorbid conditions, MC-TA-TMA (hazard ratio [HR], 10.9; $P = .0001$) and grade 3/4 acute graft-versus-host-disease (aGVHD) (HR 3.5; $P = .01$) remained independently associated with increased TRM. Among allogeneic HCT recipients, features associated with an increased risk for MC-TA-TMA included ≥2 HCT, concurrent grade 3/4 aGVHD and concurrent infections. Among patients who MC-TA-TMA, LDH ≥2 times the upper limit of normal ($P = .001$), the need for ≥2 antihypertensive medications ($P < .0001$), and acute kidney injury ($P = .003$) were associated with significantly increased TRM.

Introduction

Transplant-associated thrombotic microangiopathy (TA-TMA) is an increasingly described complication of allogeneic and autologous hematopoietic cell transplantation (HCT).[1-4] Although the historical reported prevalence of TA-TMA ranges from 0% to 70%,[5-9] more recent reports suggest that it occurs in 20% to 30% of HCT recipients.[10,11] A tissue biopsy is the gold standard for diagnosis[12]; however, this is often difficult to obtain in critically ill children. Therefore, clinical criteria are commonly used to operationally diagnose patients with TA-TMA.[13] This has become increasingly important since the advent of a potentially disease-modifying drug, eculizumab.[14-16] This approach to diagnosis is challenging, because clinical features of TA-TMA are common to multiple post-HCT complications, including acute graft-versus-host disease (aGVHD) and infections.[17] These complications are also risk factors for the subsequent development of TA-TMA.[11,14] Thus, it is difficult to interpret abnormal clinical and laboratory findings and make a definitive diagnosis of TA-TMA.

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Send data sharing requests via e-mail to corresponding author.

The full-text version of this article contains a data supplement.

Table 1. TA-TMA diagnostic criteria used

Category	Cho criteria (5/5)	Jodele criteria (4/7)
Presence of schistocytes	X	X
Increased LDH	X	X
Thrombocytopenia or need for platelet transfusions	X	X
Anemia or required RBC transfusions	X	X
Negative Coombs test	X	
Other	No coagulopathy	HTN >99th percentile for age (<18 y) or 140/90 mm Hg (>18 y) or needing ≥2 antihypertensive medications
Proteinuria		≥30 mg/dL on random UA*
Terminal complement activation		Plasma sC5b-9 above normal (≥244 ng/mL)*

RBC, red blood cell; UA, urinanalysis; X, required.
*Presence of proteinuria and elevated complement are described as high-risk features with OS <80% in a historic untreated cohort.[11]

There are several proposed diagnostic criteria for TA-TMA, with consumptive anemia and thrombocytopenia being universal features.[13] Jodele and colleagues suggest maintaining a high suspicion of TA-TMA if a patient meets ≥4 of the 7 following criteria: lactate dehydrogenase (LDH) above the upper limit of normal, proteinuria ≥30 mg/dL, hypertension (HTN), thrombocytopenia, anemia, schistocytes in the peripheral blood, and plasma concentration of serum sC5b-9 above the upper laboratory limit (Table 1).[10] Although expert consensus recommends the use of Jodele et al criteria (hereafter referred to as "Jodele criteria") to diagnose TA-TMA, a validation of these criteria has not been published.[13] "Probable TA-TMA criteria" have also been published by Cho et al, which require all 5 of the following features for diagnosis: elevated LDH, anemia, thrombocytopenia, schistocytes, and a negative Coombs test.[18] The use of Cho et al criteria (hereafter referred to as "Cho criteria") has been reported in other cohorts.[19,20]

Mortality in patients meeting criteria for TA-TMA (MC-TA-TMA) typically exceeds 50% within 6 months of MC-TA-TMA.[1,3,11,16] However, there are conflicting data on whether these poor outcomes are the result of bona fide TA-TMA or reflect the severity of illness in patients with these findings, regardless of etiology.[2,21] There is no consensus on how or when to start therapy for patients MC-TA-TMA; this is due, in part, to the difficulty of making a tissue diagnosis. Treating concurrent aGVHD, infections, or altering medications may ameliorate TA-TMA.[17] Eculizumab, a complement-blocking agent approved for atypical hemolytic uremic syndrome, has resulted in resolution of TA-TMA and improvement in overall survival (OS) in patients with evidence of complement activation (including elevation of sC5b-9) and MC-TA-TMA.[14,16,22]

In this article, we describe the prevalence of patients MC-TA-TMA in a large pediatric cohort of autologous and allogeneic HCT recipients, applying Cho and Jodele criteria. We identify risk factors for MC-TA-TMA, assess whether meeting diagnostic criteria for TA-TMA is independently associated with increased transplant-related mortality (TRM), and identify high-risk features associated with TRM in children with MC-TA-TMA.

Methods

The patients described in this article were enrolled on a retrospective single-center study that was conducted according to the principles set forth in the Declaration of Helsinki and approved by the Boston Children's Hospital Institutional Review Board. Data were extracted from the medical records of all children who received an HCT at Boston Children's Hospital from January 2014 through May 2018. All patients diagnosed with TA-TMA by the attending physician during the HCT course were captured. In addition, the Cho and Jodele criteria (Table 1) were retrospectively applied to all patients from day 0 until day 100 day after HCT. All patients who met Cho criteria (n = 62) also met Jodele criteria (n = 110), by virtue of the criteria. Patients who were both clinically diagnosed during HCT and who retrospectively met criteria were grouped together for analysis.

Medical records were reviewed, and clinical data were extracted manually. Data related to alive/dead status, relapse, and cause of death were confirmed through comparison with data submitted to the Center for International Bone Marrow Transplant Registry. Additional quality control included independent adjudication of MC-TA-TMA in 10% of randomly selected patients. There was >98% agreement in this analysis, with minor discrepancies around the exact date on which patients met criteria. The maximum aGVHD stage and grade, as documented by an attending provider, were also collected. All patients with grade 3/4 aGVHD were independently reviewed and confirmed. The maximum aGVHD stage and grade were adjudicated in 10% of the remaining patients.

Per institutional policy, all HCT patients from admission to discharge had the following screening: daily complete blood count, schistocyte review by hematology laboratory technician, serum electrolytes, and macroscopic urinalysis, as well as multiple blood pressure measurements daily. LDH was obtained twice weekly. After discharge and until day 100, the majority of allogeneic HCT recipients had weekly blood pressure assessments, complete blood count with differential, schistocyte review by laboratory technician, and serum chemistry, including creatinine measurement. Autologous HCT recipients had laboratory evaluations as clinically indicated. Blood pressure was considered persistently elevated if ≥99th percentile for age in children younger than 18 years or ≥140/90 mm Hg in children aged ≥18 years and required as-needed or standing medication for management. Complement levels, quantitative urine studies, and hematopathologist review of the peripheral blood smear were ordered at the providers' discretion. CH50 levels were considered elevated if above the institutional reference range of 144 complement activity, total EIA, and sC5b-9 was considered elevated at ≥244 ng/mL. Acute kidney

Table 2. Patient and transplant characteristics by transplant type

	Total cohort (N = 307)	Autologous HCT (n = 102; 33%)	Allogeneic HCT (n = 205; 67%)
Age at HCT, median (range), y	8.5 (0.1-27.3)		
Sex			
Male	195 (64)	73 (72)	122 (60)
Female	112 (36)	29 (28)	83 (40)
Race			
White	182/206 (88.4)	65/75 (87)	117/131 (89.3)
African American	13/206 (6.3)	7/75 (9)	6/131 (4.6)
Asian	8/206 (3.8)	3/75 (4)	5/131 (3.8)
Middle Eastern	2/206 (1)	0/75 (0)	2/131 (1.5)
Native American/Alaskan Native	1/206 (0.5)	0/75 (0)	1/131 (0.8)
No data	101	27	74
HCT			
1	266 (87)	75 (73.5)	191 (93)
2	32 (10)	20 (19.6)	12 (6)
3	9 (3)	7 (6.9)	2 (1)
Transplant indication			
Hematologic malignancy	104 (34)	18 (17.6)	86 (42)
Immunodeficiency	67 (22)	4 (3.9)	63 (31)
Heme (SCD, Thal, aAA, BMF)	46 (15)	0 (0)	46 (22)
Solid tumor	73 (24)	73 (71.6)	0 (0)
Metabolic/neurodegenerative	17 (6)	7 (6.9)	10 (5)
TA-TMA			
Provider diagnosed	8 (2.6)	6 (6)	2 (1)
Cho criteria	62 (20)	13 (13)	49 (24)
Jodele criteria	110 (36)	21 (21)	89 (43)
Time to TA-TMA diagnosis, median (range), d			
Cho criteria	29 (5-97)	20 (5-71)	30 (11-97)
Jodele criteria	30 (1-97)	19 (3-71)	31 (1-97)
Allogeneic HCT recipients only			
Donor			
Related			82 (40)
Unrelated			123 (60)
HLA match*			
10/10			140 (74)
>9/10			48 (26)
Cell source			
Bone marrow			181 (88.3)
Peripheral blood			7 (3.4)
Umbilical cord			17 (8.3)
Conditioning intensity			
Myeloablative			137 (66.8)
Reduced intensity			53 (25.9)
Nonmyeloablative			15 (7.3)

Unless otherwise noted, data are n (%) or n/N (%).

aAA, aquired aplastic anemia; BMF, bone marrow failure; Heme, benign hematology (including sickle cell disease, beta-thalassemia, aquired aplastic anemia, and inherited bone marrow failure syndromes); SCD sickle cell disease; Thal, beta thalassemia.

*Bone marrow transplant and peripheral blood stem cell source only.

Table 3. Univariate analysis of risk factors associated with MC-TA-TMA using Cho and Jodele criteria in patients receiving allogeneic or autologous HCT

	Cho criteria		Jodele criteria	
Factors	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age at transplant, y	1.01 (0.97-1.1)	.5	1.006 (0.97-1.04)	.7
Sex				
Female	1		1	
Male	1.3 (0.7-2.3)	.4	0.7 (0.5-1.2)	.2
Number of HCTs				
None or 1 HCT	1		1	
≥2 HCTs	3.5 (1.7-7.0)	**.0005**	2.1 (1.1-4.1)	**.03**
HCT indication		.1		**.02**
Solid tumor	1		1	
Hematologic malignancy	2.4 (1.1-5.2)	.03	2.5 (1.3-4.8)	.008
Immunodeficiency	1.8 (0.7-4.3)	.2	2.3 (1.1-4.8)	.02
Heme	1.3 (0.5-3.6)	.6	2.1 (0.9-4.7)	.07
Metabolic/neurodegenerative	0.2 (0.009-3.4)	.2	0.5 (0.1-2.3)	.4
Transplant type				
Autologous	1		1	
Allogeneic	2.2 (1.1-4.2)	**.02**	3.0 (1.7-5.1)	**.0001**
Cell source†		.1		**.003**
Bone marrow	1		1	
Peripheral blood	2.7 (0.6-12.7)	.2	1.1 (0.2-5.1)	.9
Umbilical cord	2.5 (0.9-7.1)	.07	4.8 (1.5-15.3)	.08
Related donor†				
Yes	1		1	
No	1.7 (0.9-3.4)	.1	2.1 (1.2-3.7)	**.01**
HLA match†,‡		**.03**		**.004**
10/10	1		1	
9/10	2.2 (0.97-4.9)	.06	1.4 (0.6-2.8)	.4
≤8/10	2.7 (1.1-6.3)	**.03**	4.4 (1.8-10.7)	**.0009**
Conditioning†		.3		.4
Nonmyeloablative	1		1	
Myeloablative	1.5 (0.4-5.5)	.6	0.5 (0.2-1.4)	.2
Reduced intensity	0.8 (0.2-3.5)	.8	0.5 (0.2-1.6)	.3
Active aGVHD†				
Grade 1/2, no aGVHD, or nonactive grade 3/4 aGVHD	1		1	
Active grade 3/4 aGVHD	6.9 (2.1-22.2)	**.001**	19.7 (2.5-154.9)	**.005**
VOD				
No	1		1	
Yes	2.0 (0.6-7.0)	.3	2.6 (0.8-8.4)	.1
Any active infection*,§				
No	1		1	
Yes	137 (33.8-559.4)	**<.0001**	50 (9.3-271.1)	**<.0001**

Variables were analyzed using a univariate logistic regression model, age was analyzed as a continuous variable, and risk reported is for every year older at HCT. Bold *P* values denote characteristics significantly associated with MC-TA-TMA. For HCT indication, cell source, HLA match, conditioning, and aGVHD, odds ratios (OR) were compared to the reference group (OR = 1); the *P* value denotes characteristics significantly associated with MC-TA-TMA compared to the reference group.

CI, confidence interval; VOD, veno-occlusive disease.

*Firth's penalized maximum likelihood estimation was performed for active infection variables.

†Allogeneic HCT only.

‡Bone marrow transplant and peripheral blood stem cell source only.

§Multiple infections can occur simultaneously.

Table 3. (continued)

Factors	Cho criteria		Jodele criteria	
	OR (95% CI)	P	OR (95% CI)	P
Active bacterial infection*,§				
No	1		1	
Yes	168.5 (9.1 to >999.9)	**.0006**	56.3 (3.1 to >999.9)	**.007**
Active viral infection*,§				
No	1		1	
Yes	105.3 (26.1-424.3)	**<.0001**	43.5 (8.0-236.4)	**<.0001**
Active fungal infection*,§				
No	1		1	
Yes	38.7 (1.6-939.9)	**.02**	15.2 (0.6-366.8)	.09

Variables were analyzed using a univariate logistic regression model, age was analyzed as a continuous variable, and risk reported is for every year older at HCT. Bold *P* values denote characteristics significantly associated with MC-TA-TMA. For HCT indication, cell source, HLA match, conditioning, and aGVHD, odds ratios (OR) were compared to the reference group (OR = 1); the *P* value denotes characteristics significantly associated with MC-TA-TMA compared to the reference group.

CI, confidence interval; VOD, veno-occlusive disease.

*Firth's penalized maximum likelihood estimation was performed for active infection variables.

†Allogeneic HCT only.

‡Bone marrow transplant and peripheral blood stem cell source only.

§Multiple infections can occur simultaneously.

injury (AKI) after HCT was defined as a doubling of the serum creatinine or a decrease ≥50% in estimated or measured glomerular filtration rate (GFR).[23] Neurologic involvement was defined as altered mental status or seizures. Center for International Bone Marrow Transplant Registry definitions were used to assign intensity categories for myeloablative conditioning, reduced intensity conditioning, and nonmyeloablative conditioning among allogeneic HCT recipients.[24] Bacterial infections were confirmed by culture, viral infections were confirmed by culture or polymerase chain reaction (PCR), and fungal infections were confirmed by culture, fungal markers, and/or imaging findings.

Descriptive statistics were used to summarize patient characteristics. Fisher's exact test and the Wilcoxon rank-sum test were used for between-group comparisons for continuous and categorical variables, respectively. Univariate logistic regression was used to determine risk factors for MC-TA-TMA. Statistically significant ($P < .05$) factors were entered into a multivariable logistic regression model for a subset of patients receiving allogeneic HCT only. OS was measured from initial transplant time to death, or to last follow-up if censored. Kaplan-Meier curves were generated for OS, and the log-rank test was used to compare OS between groups. All deaths not related to relapse were considered to be transplant related. Cumulative incidence curves were generated for TRM, and the Gray's test was used to compare TRM between groups, accounting for the competing risk of relapse-related death. Univariate proportional subdistributional hazards models with competing risks were used to identify risk factors for TRM. For this analysis, graft-versus-host disease was considered concurrent if the patient had ongoing symptoms meeting grade 3/4 criteria within 30 days of MC-TA-TMA. Infections were considered concurrent if culture and/or serum PCR studies were positive within 30 days of MC-TA-TMA. Patients with aGVHD and/or infections that did not temporally occur with MC-TA-TMA were excluded from this analysis. Statistically significant ($P < .05$) factors were entered into a multivariable model.

To create a prediction model for MC-TA-TMA, a patient's total risk score was calculated as the sum of the β coefficients (eg, log odds ratio) from the final multivariable logistic regression model for each of the patient's risk factors. From this model, 3 risk factors were identified: need for ≥2 HCTs, concurrent grade 3/4 aGVHD, and concurrent infection (bacterial, viral, and/or fungal). Patients were then categorized into 2 risk categories as follows: low risk (0 factors) or high risk (≥1 factors). A univariate logistic regression was performed to determine the odds of predicting the development of MC-TA-TMA between risk categories. The estimated probability for the development of MC-TA-TMA was calculated in each risk category using logistic regression

Table 4. Adjusted multivariable analysis of risk factors for MC-TA-TMA among recipients of allogeneic HCT (n = 198)

Factors	Cho criteria		Jodele criteria	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
≥2 HCT	8.5 (1.4-50.3)	.02	10.3 (1.4-74.3)	.02
Active grade 3/4 aGVHD	9.8 (2.1-45.9)	.004	14.1 (2.1-92.7)	.006
Active infection	140.2 (32.3-608.6)	<.0001	44.4 (8.0-245.5)	<.0001

Seven patients with graft failure were excluded from the analysis. Active infection included bacterial, viral, and/or fungal infection within 30 days of MC-TA-TMA. Firth's penalized maximum likelihood estimation was performed for the model.

Table 5. Predicted probability of MC-TA-TMA by risk category among recipients of allogeneic HCT (N = 198)

	Cho criteria	Jodele criteria
Low risk (n = 153)	5.2 (2.64-10.11)	25.5 (19.2-33)
High risk (n = 45)	77.8 (63.4-87.6)	95.6 (83.9-98.9)

Seven patients with graft failure were excluded from the analysis. Risk factors included ≥2 HCTs, active grade 3/4 aGVHD, or active bacterial, viral, or fungal infection. Data are predicted probability % (95% CI).

High risk, ≥1 risk factor; low risk, no risk factors.

modeling. Firth's penalization was performed in the multivariable analysis to reduce bias in the parameter estimates.[25] Two-sided $P < .05$ was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

A total of 307 patients underwent HCT during the study period; 205 (67%) received an allogeneic HCT, and 102 (33%) received an autologous HCT. Patient and transplant characteristics are shown in Table 2. Eight patients (2.6%) were diagnosed with TA-TMA. In 7 of these 8 patients, Cho criteria were used for TA-TMA diagnosis. One patient met only Jodele criteria. Seven of 8 patients with provider-diagnosed TMA were treated with eculizumab; 3 of them died. The remaining 4 patients responded to eculizumab, with resolution of hemolysis and/or nephrotic range proteinuria, if present. The median number of eculizumab doses given in this cohort was 23 (range, 3-63). One patient with provider-diagnosed TA-TMA had aGVHD prophylaxis switched from cyclosporine to tacrolimus, with resolution of TA-TMA. The remaining patients described below were not diagnosed by providers as having TA-TMA; instead, they met criteria for TA-TMA retrospectively. Patients who retrospectively MC-TA-TMA received therapy for conditions that occurred at the time patient's MC-TA-TMA with the most common diagnoses including, aGVHD (n = 16), infections including bacteremia (n = 10) and viruses (n = 18), acute respiratory failure of unknown etiology (n = 5), and engraftment failure (n = 5) (of note, some patients had multiple diagnoses). These patients were not treated with eculizumab.

Table 6. Outcomes of patients MC-TA-TMA using Jodele criteria vs those who did not meet criteria

		Allogeneic HCT (n = 205)			Autologous HCT (n = 102)		
Outcome	**Total cohort (N = 307)**	**MC-TA-TMA (n = 92; 45%)**	**Not MC-TA-TMA (n = 113; 55%)**	***P***	**MC-TA-TMA (n = 21; 21%)**	**Not MC-TA-TMA (n = 81; 79%)**	***P***
ICU admission after HCT*	55 (18)	33 (36)	9 (8)	<.0001†	9 (43)	4 (5)	<.0001†
Stay in ICU, median (range), d*	12 (1-162)	19 (1-162)	4.5 (1-36)	.03‡	13 (3-42)	2.5 (1-12)	.1‡
Interventions needed in ICU							
Intubation	25 (8)	19 (58)	3 (33)	.3†	3 (33)	0 (0)	.5†
Noninvasive ventilation	10 (3)	5 (15)	1 (11)	1.0†	3 (33)	1 (25)	1.0†
Dialysis	8 (3)	7 (21)	0 (0)	.3†	1 (11)	0 (0)	1.0†
ECMO	2 (4)	1 (3)	1 (11)	.4†	0 (0)	0 (0)	N/A
Engraftment failure	7 (2)	7 (8)	0 (0)	.003†			N/A
Length of stay, median (range), d*	33 (0-100)	52 (18-100)	34 (18-100)	<.0001‡	36 (18-100)	19 (0-57)	<.0001‡
Readmissions, median (range), n*	1 (1-7)	1 (1-6)	1 (1-7)	.5‡	1 (1-4)	1 (1-3)	.9‡
cGVHD	30/155 (19)	14/49 (29)	16/57 (28)	1.0†			N/A
Organ dysfunction at last follow-up							
Cardiac	105 (34)	37 (40)	28 (25)	.02†	10 (48)	30 (37)	.5†
Renal	40 (13)	15 (16)	13 (12)	.4†	6 (29)	6 (7)	.02†
GI	25 (8)	16 (17)	7 (6)	.01†	0 (0)	2 (3)	1.0†
Pulmonary	32 (10)	18 (20)	13 (12)	.1†	0 (0)	1 (1)	1.0†
OS, % (95% CI)				<.0001§			.07§
100 d	96.6 (94.6-98.7)	94.6 (89.9-99.2)	99.1 (97.4-100)		83.9 (67.1-100)	98.6 (96.0-100)	
1 y	88.8 (84.9-92.7)	78.6 (69.7-87.5)	96.7 (93.0-100)		75.5 (53.8-97.2)	93.1 (86.6-99.7)	
2 y	80.1 (74.5-85.7)	59.9 (47.6-72.1)	94.5 (88.9-100)		75.5 (53.8-97.2)	85.6 (75.3-95.7)	
TRM, % (95% CI)				<.0001¶			.0004¶
100 d	2.7 (1.3-5.0)	5.4 (2.0-11.4)	0 (0-0)		16.1 (3.8-36.2)	0 (0-0)	
1 y	5.8 (3.4-9.0)	15.2 (8.4-23.8)	0 (0-0)		16.1 (3.8-36.2)	0 (0-0)	
2 y	10.8 (7.0-15.6)	28.4 (17.9-39.9)	2.2 (0.2-10.2)		16.1 (3.8-36.2)	0 (0-0)	

Unless otherwise noted, data are n (%) or n/N (%).

cGVHD, chronic graft-versus-host disease; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; N/A, not applicable.

*Within first 100 days post-HCT.

†Fisher's exact test

‡Wilcoxon rank-sum test.

§Log-rank test.

¶Gray's test.

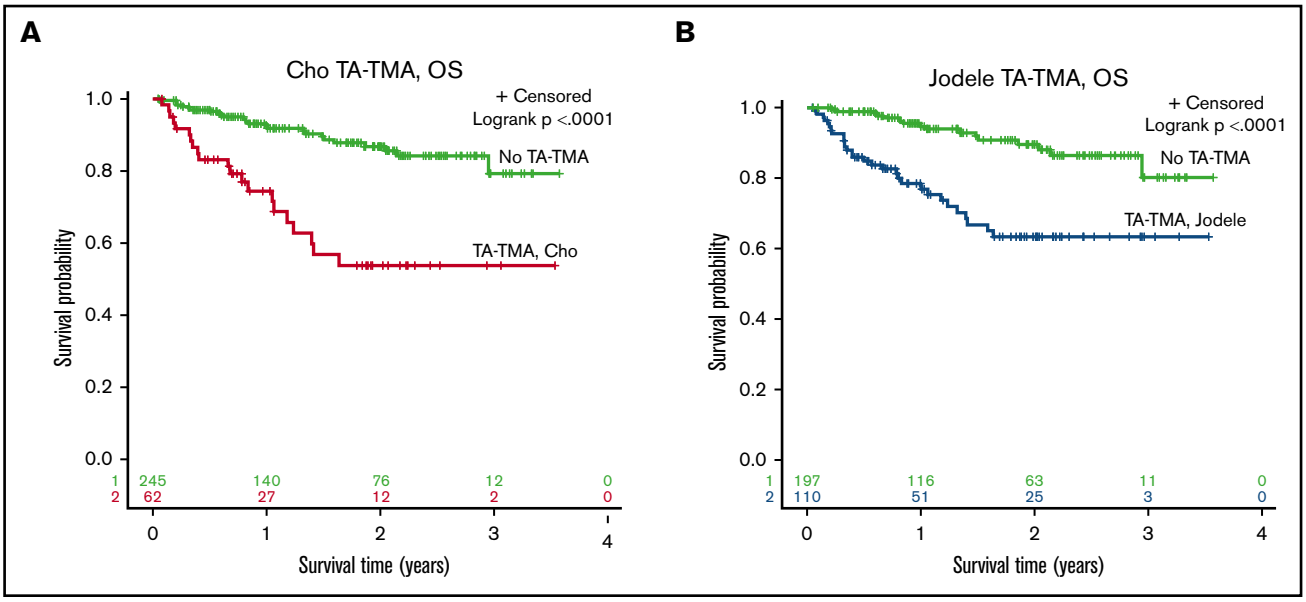

Figure 1. Overall survival, MC-TA-TMA vs no MC-TA-TMA by Cho and Jodele criteria. OS of patients MC-TA-TMA vs those not meeting Cho criteria (A) and Jodele criteria (B). OS was significantly worse in patients MC-TA-TMA using Cho criteria (A) or Jodele criteria (B) ($P < .0001$, log-rank test). Estimated survival at 100 days.

Of the 110 patients who retrospectively met criteria for TA-TMA, 62 patients (20% of the total cohort) met Cho TA-TMA criteria at a median of 29 days (range, 5-97). A total of 110 patients (36% of the cohort) met Jodele TA-TMA criteria at a median of 30 days (range, 1-97) (Table 2). Among the 48 patients who met Jodele TA-TMA criteria, but not Cho criteria, HTN and proteinuria were the most common contributing features. Of the 19 patients who had complement testing sent, only 8 had evidence of abnormal complement activation (supplemental Figure 1).

In a univariate analysis including all patients, risk factors for MC-TA-TMA using either criteria included ≥2 HCTs, an HLA match of ≤8 of 10 in peripheral blood stem cells or bone marrow transplant graft sources, an allogeneic HCT, active grade 3/4 aGVHD, and active bacterial, viral, or fungal infection (Table 3). Of all patients MC-TA-TMA and having grade 3/4 aGVHD (n = 17), 4 were excluded from this analysis, because aGVHD did not occur contemporaneously with MC-TA-TMA. Conditioning regimen intensity, age, and sex were not associated with MC-TA-TMA.

Risk factors for MC-TA-TMA among allogeneic recipients

Among allogeneic HCT recipients only, an adjusted multivariable logistic regression model identified the following 3 common significant risk factors for MC-TA-TMA using Cho or Jodele criteria:

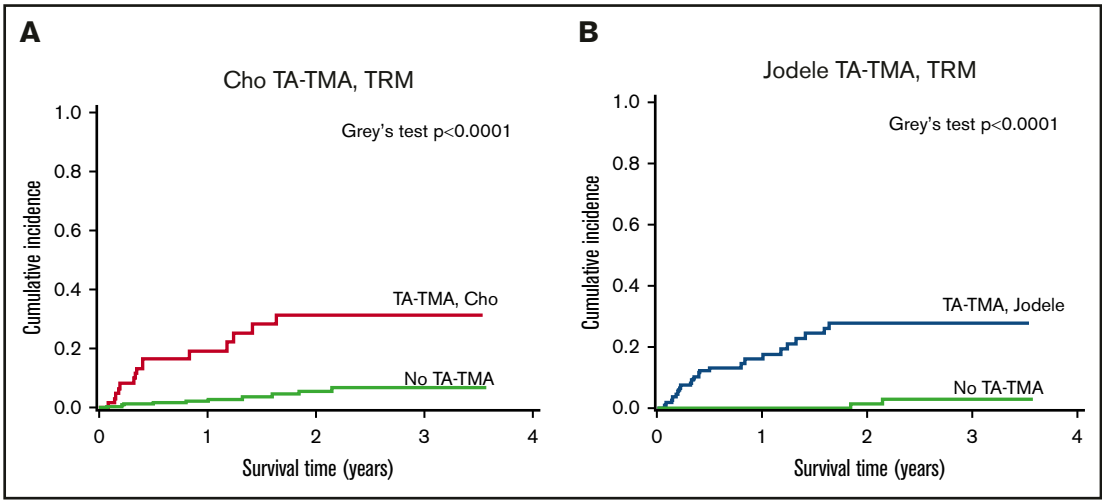

Figure 2. Transplant related mortality, MC-TA-TMA vs no MC-TA-TMA by Cho and Jodele criteria. TRM of patients MC-TA-TMA vs those not MC-TA-TMA using Cho criteria (A) and Jodele criteria (B). TRM was significantly higher in patients MC-TA-TMA using Cho criteria or Jodele criteria vs those who did not meet criteria ($P < .0001$, Gray's test).

Table 7. Multivariable proportional subdistribution hazards model with competing risks for TRM for allogeneic and autologous HCT recipients with TA-TMA using Cho criteria or Jodele criteria

	Cho criteria		Jodele criteria	
Factor	**Adjusted HR (95% CI)**	**Adjusted *P***	**Adjusted HR (95% CI)**	**Adjusted *P***
TMA	3.0 (1.1-8.2)	**.003**	10.9 (2.6-46.1)	**.001**
Grade 3/4 aGVHD*	2.9 (1.0-8.0)	**.04**	3.5 (1.3-9.1)	**.01**
Infection	2.7 (0.9-8.3)	.09	2.2 (0.7-7.1)	.2

Bold *P* values denote association of the factor (TA-TMA, grade 3/4 aGVHD, and infection) with TRM in a multivariable model.
*Allogeneic recipients only; 7 patients with graft failure were excluded from the analysis.

≥2 HCTs, concurrent grade 3/4 aGVHD, and concurrent infection (bacterial, viral, and/or fungal) (Table 4). Infection was most strongly associated with MC-TA-TMA ($P < .0001$). In our prediction model for MC-TA-TMA, patients with none of these risk factors were categorized as having low risk for MC-TA-TMA, whereas patients with ≥1 factor were categorized as having high risk (Table 5). The presence of ≥1 risk factor increased the predicted probability of MC-TA-TMA from 5.2% (low risk) to 77.8% (high risk) using Cho criteria and from 25.5% to 95.6% using Jodele criteria (Table 5).

Outcomes

In the first 100 days after HCT, patients who met Cho or Jodele criteria had a higher risk for engraftment failure ($P = .0003$ and $P = .0007$, respectively), a longer hospital stay ($P < .0001$), and more intensive care unit (ICU) admissions ($P < .0001$) compared with patients not MC-TA-TMA (Table 6). There were no significant differences in the number of hospital readmissions or the diagnosis of chronic graft-versus-host disease.

Median follow-up was 1.3 years (range, 0.04-3.6) for the 261 patients who were alive at last follow-up. OS was significantly lower ($P < .0001$, log-rank test; Figure 1) and TRM was significantly higher ($P < .0001$, Gray's test; Figure 2) in patients who met Cho or Jodele criteria for TA-TMA. The median time to TRM after HCT was 0.8 years (range, 0.08-3.5) and 0.9 years (range, 0.07-3.5) using Cho and Jodele criteria, respectively (Table 6). In a multivariable model, MC-TA-TMA was significantly associated with increased TRM (Cho criteria: hazard ratio [HR], 3.0; 95% CI, 1.1-8.2; $P = .003$ and Jodele criteria: HR, 10.9; 95% CI, 2.6-46.1; $P = .001$) after adjusting for grade 3/4 aGVHD, engraftment failure, and bacterial, viral, or fungal infection (Table 7). Grade 3/4 aGVHD also remained significantly associated with TRM in the multivariable model (Cho criteria: HR, 2.9; 95% CI, 1-8; $P = .04$ and Jodele criteria: HR, 3.5; 95% CI, 1.3-9.1; $P = .01$).

Of the 110 patients MC-TA-TMA, 48 met Jodele criteria but did not meet Cho criteria. We hypothesized that patients who met Jodele criteria (n = 48), but not Cho criteria (n = 62) may represent a different severity of MC-TA-TMA. However, there was no significant difference in OS ($P = .21$) or TRM ($P = .2$) between the groups. Because the Cho and Jodele criteria identified patients with significantly increased TRM, all patients who met Jodele criteria also met Cho criteria, and the use of Jodele criteria for TA-TMA is recommended by expert consensus.[13] The remaining analyses focus on patients who met Jodele criteria.

High-risk features of TA-TMA

The following features were assessed for an association with TRM among the 110 patients who met Jodele criteria for TA-TMA: individual TA-TMA features (anemia, thrombocytopenia, presence of schistocytes, proteinuria, HTN, elevated serum complement), a maximum LDH ≥ 2 times the upper limit of normal (ULN), need for ≥2 antihypertensive medications, AKI, neurologic symptoms, estimated or measured GFR <90 mL/min/1.73 m^2 prior to HCT, and meeting 4 of 7, 5 of 7, or ≥6 of 7 Jodele criteria for TA-TMA. Two measures of AKI (creatinine and estimated GFR) were chosen because of the evidence showing that elevated creatinine is not sensitive for renal injury in children given differences in muscle mass.[23] We evaluated patients with severe HTN requiring ≥2 antihypertensive medications, because we suspected that this was an indication of more severe disease and may be more predictive of outcomes than HTN alone. Finally, we hypothesized that meeting more criteria would be a marker of severity and be associated with TRM.

Features univariately associated with significantly increased TRM among patients MC-TA-TMA included the need for ≥2 antihypertensive medications ($P < .001$, Gray's test), an LDH ≥ 2 times the ULN ($P = .0011$), and AKI ($P = .0034$; Figure 3). Proteinuria, a feature previously described as high risk was not associated with increased TRM. The number of patients with elevated serum complement levels was too small to analyze appropriately in this cohort.

Allogeneic vs autologous HCT: Jodele criteria for TA-TMA

Of the 205 patients who underwent an allogeneic HCT, 89 (43%) met Jodele criteria for TA-TMA; OS and TRM were significantly worse among patients who met these criteria (Figure 4; $P < .001$). Among 102 autologous HCT recipients, 21% (n = 21) met Jodele criteria for TA-TMA. Of autologous patients MC-TA-TMA, 15 (71%) underwent HCT for neuroblastoma. The prevalence of MC-TA-TMA among all neuroblastoma HCT recipients was 32% (15/47). All 15 patients developed TA-TMA after a planned tandem approach: 7 patients after the first HCT conditioned with cyclophosphamide and thiotepa, and 8 patients after the second HCT conditioned with carboplatin, etoposide, and melphalan. Of the 7 patients who developed TA-TMA after the first HCT, 1 died from TA-TMA–related complications, but the remaining 6 patients proceeded to second HCT.

Transplant indications in the remaining autologous recipients MC-TA-TMA included Hodgkin lymphoma (n = 3/17; 18%), Wilms

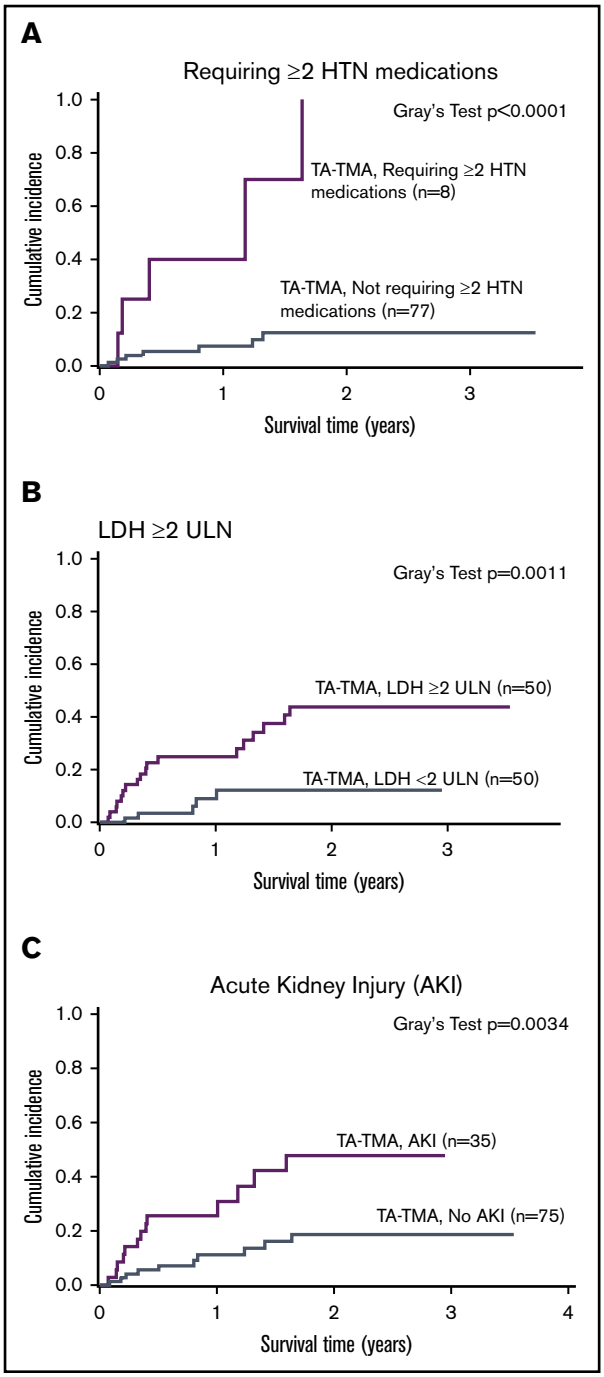

Figure 3. Risk stratification: characteristics associated with increased TRM in patients MC-TA-TMA. Among the 110 patients MC-TA-TMA, the factors associated with increased TRM included the need for >2 antihypertensive medications ($P = .0001$, Gray's test) (A), LDH >2 times the ULN ($P = .0011$, Gray's test) (B), and AKI ($P = .0034$, Gray's test) (C).

tumor (n = 1/3; 33%), peripheral T-cell lymphoma (n = 1/1), and a rhabdoid tumor (n = 1/1). Notably, of the 11 patients who received genetically corrected autologous cells, none met the criteria for TA-TMA. OS was not significantly different in autologous HCT recipients MC-TA-TMA, although TRM was increased significantly ($P < .0001$) (Figure 4C-D).

Discussion

TA-TMA is an increasingly recognized complication of allogeneic and autologous HCT. Here, we describe the application of 2 accepted TA-TMA diagnostic criteria in a large pediatric cohort: Cho criteria, validated in other cohorts,[26] and Jodele criteria, a more recent diagnostic paradigm that has been recommended by expert consensus.[13] Although the prevalence of provider-diagnosed TA-TMA was very low in this retrospective analysis, many more patients retrospectively met TA-TMA criteria. In fact, because complement and urine protein testing were not standardly sent on patients who may have met other Jodele criteria, it is possible that the prevalence of patients MC-TA-TMA using Jodele criteria is underestimated in this cohort. This study highlights that, although diagnosing TA-TMA is challenging, MC-TA-TMA after HCT in children and young adults can be much more common. A similar finding was recently reported in an adult cohort at Dana-Farber Cancer Institute, underscoring the commonality of this finding.[19]

In our cohort, MC-TA-TMA occurred after allogeneic and autologous HCT. MC-TA-TMA occurred most frequently after autologous HCT in children with neuroblastoma (n = 15/21) and did not occur in any patients with genetically corrected autologous transplantation (n = 11). Including gene-corrected patients may have obscured the risk for MC-TA-TMA in the autologous cohort; however, allogeneic HCT recipients had a greater risk for MC-TA-TMA (odds ratio, 3; $P = .0001$, using Jodele criteria). Among allogeneic patients, common risk factors for MC-TA-TMA included receiving ≥2 transplants, active grade 3/4 aGVHD, and an active bacterial, viral, and/or fungal infection. Patients who met ≥1 of these features had a 95.6% predicted probably of meeting Jodele criteria for TA-TMA. Although this model must be validated in another cohort, suspicion for TA-TMA should remain very high in patients with these features. Importantly, many patients MC-TA-TMA also had other documented posttransplant complications, including severe aGVHD or infections. It has been demonstrated that TA-TMA can occur concurrently with these conditions, and patients may not improve if treatment is only directed at the underlying illness.[27] Thus, it may be important to independently screen for features of TA-TMA and remain highly vigilant for patients MC-TA-TMA, particularly those with high-risk features.

Our study showed that patients MC-TA-TMA had a significantly worse OS ($P < .0001$) and increased TRM ($P < .0001$) compared with patients who did not meet the criteria. Of note, although more patients met Jodele criteria (110/307) vs Cho criteria (62/307) for TA-TMA, outcomes remained significantly worse among patients who met either set of criteria. Thus, this study validates previous work; we propose that Jodele criteria can be used to identify patients with increased TRM.[11]

Conflicting results have been found in previous adjusted multivariable analyses studying the relationship between TA-TMA and TRM.[2,21] In 1 study, TA-TMA was independently associated with worse survival, with an adjusted HR of 2.8 (95% CI, 1.3-5.9).[21] In another adjusted analysis, grade 3/4 aGVHD, but not TA-TMA, was associated with TRM (HR, 12.5; $P < .001$).[2] A key objective of this study was to determine whether MC-TA-TMA was independently associated with increased TRM. In this cohort, we found that, even after adjusting for severe aGVHD and infections, meeting Cho or Jodele criteria for TA-TMA (HR, 3.0; $P = .003$ and HR, 10.9; $P = .001$, respectively) was significantly associated with increased

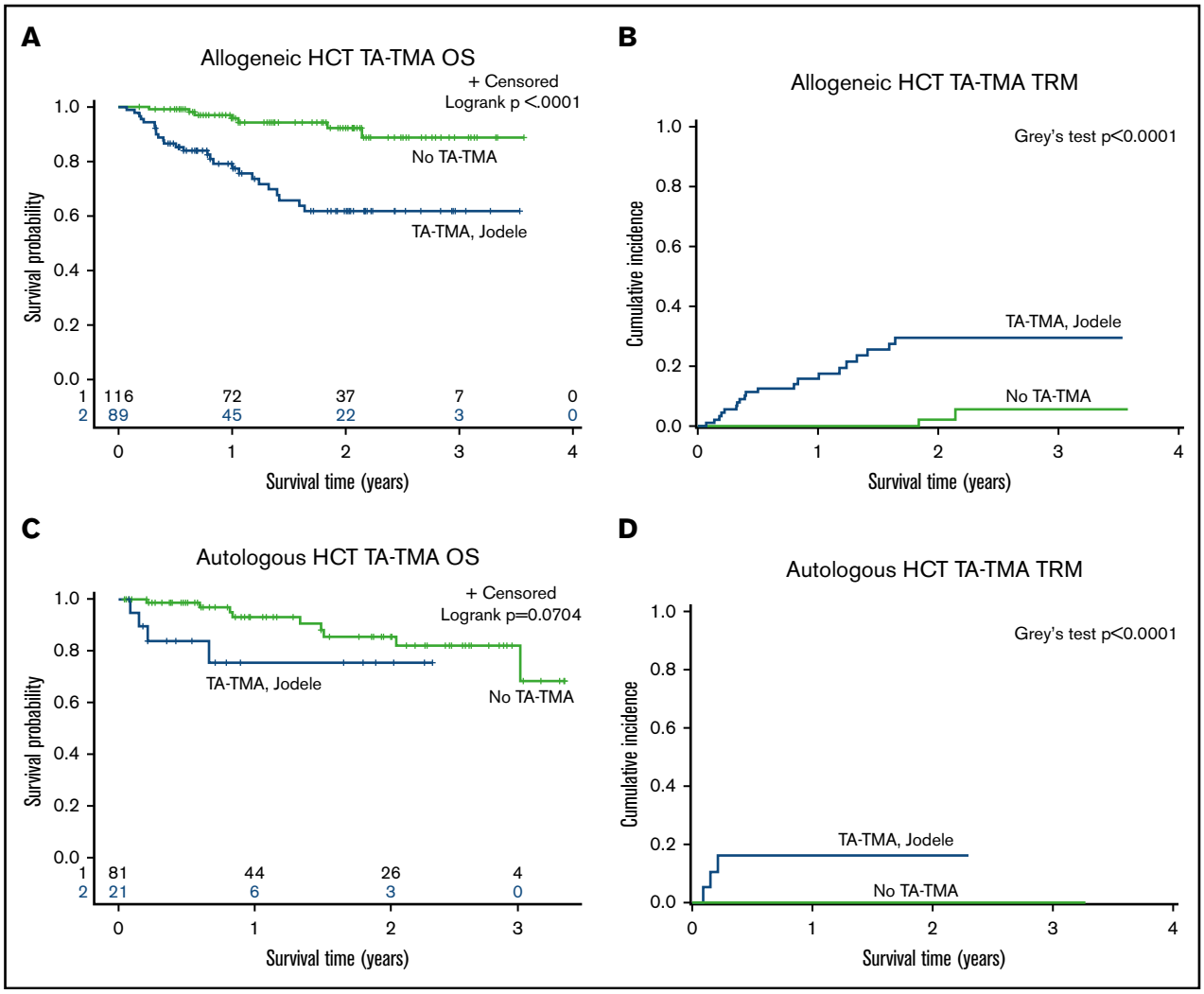

Figure 4. OS and TRM among allogeneic and autologous HCT reciepients, MC-TA-TMA vs no MC-TA-TMA. OS (A,C) and TRM (B,D) of allogeneic and autologous MC-TA-TMA among recipients of allogeneic HCT (n = 205). OS was significantly lower (A) ($P < .0001$, log-rank test) and TRM was significantly higher (B) ($P < .0001$, Gray's test) in allogeneic recipients (n = 205) who met Jodele criteria for TA-TMA. (C) Among recipients of autologous HCT (n = 102), there was no significant difference in OS among patients MC-TA-TMA vs those who did not ($P = .0704$, log-rank test). (D) However, TRM was significantly higher in patients MC-TA-TMA ($P < .0001$, Gray's test).

TRM. Grade 3/4 aGVHD also remained a predictor for TRM (Cho criteria: HR, 2.9; $P = .04$ and Jodele criteria: HR, 3.5; $P = .01$).

If all HCT recipients are carefully screened for TA-TMA, our study and others suggest that nearly one third of patients will meet diagnostic criteria,[11] making risk stratification critical when considering when and in whom to intervene with directed therapy. The 2 markers previously identified as conferring high risk for mortality are elevated sC5b-9 and proteinuria,[11] with Jodele recommending treatment with eculizumab when these markers are elevated.[28] In this cohort, the association between elevated serum complement markers (CH50 or sC5b-9) and TRM could not be determined, because only a small number of patients (19/307) underwent this testing. This retrospective study also was not able to confidently interrogate the role of proteinuria in identifying high-risk patients given a lack of uniformity in urine testing, especially after hospital discharge. The current study identified 3 characteristics associated with increased TRM in patients MC-TA-TMA: the need for ≥2 antihypertensive medications, a maximum LDH ≥2 times the ULN, and AKI (a doubling of serum creatinine from baseline or a decrease in GFR ≥50% from baseline). These features may further identify high-risk patients, even in the absence of complement testing.

The landscape of treatment in TA-TMA has changed with the availability of eculizumab, a C5 monoclonal antibody that inhibits the formation of the membrane activating complex in the complement system. We cannot comment on the use of eculizumab in children MC-TA-TMA, because very few patients in our cohort received this therapy. However, multiple retrospective and pilot prospective studies have demonstrated that treatment with eculizumab in patients MC-TA-TMA may be associated with improved OS.[16,22,29] In patients MC-TA-TMA and with high-risk features, as defined by proteinuria and elevated sc5b-9 at TA-TMA diagnosis, the use of eculizumab improved 1-year OS from a historic rate of 9% in untreated patients to 56% ($P = .003$).[30] It is also reported that

outcomes with eculizumab are better when treatment is initiated quickly after diagnosis; thus, expert consensus recommends prompt treatment in high-risk patients MC-TA-TMA.[4,30,31] There are no prospective trials of this intervention, and these are needed to confirm the efficacy of this therapy and the importance of early treatment of patients MC-TA-TMA.

Our conclusions must be interpreted within the limits of this study design. Given the retrospective nature, many patients did not have complement testing. Thus, previously reported risk stratification using complement levels could not be validated in this cohort. Although this is a large report of pediatric and young adult patients, it is a single-center study. In the future, it is important to design multi-institutional studies that include children and adults. Only 1 of the significant risk factors for MC-TA-TMA in allogeneic HCT patients, $\geq$2 HCTs, is a pre-HCT characteristic. Thus, this model could not be used in a future prophylaxis trial. Furthermore, understanding risk factors for MC-TA-TMA among autologous HCT patients, who were not included in this model, would be useful. Lastly, all patients identified in this study, by the provider at the time of HCT and retrospectively, were done so using clinical criteria. No patient had a biopsy-confirmed diagnosis of TA-TMA. As previously discussed, this is a common limitation of TA-TMA studies.

In conclusion, MC-TA-TMA occurs commonly after allogeneic and autologous HCT. In this large retrospective analysis, patients meeting Cho and Jodele criteria exhibited decreased OS and increased TRM, MC-TA-TMA was independently associated with increased TRM in multivariable analysis. Risk factors for the development of MC-TA-TMA among allogeneic HCT recipients included $\geq$2 HCTs, active grade 3/4 aGVHD, and active infections. This study suggests that pediatric transplant providers should maintain a high level of suspicion for patients MC-TA-TMA. Further, risk stratification may help to identify patients who should be treated with eculizumab, although prospective studies are needed to fully evaluate treatment success. Finally, sC5b-9 is a previously described prognostic marker for high-risk TA-TMA,[11] but an abnormality in this value alone is not sufficient to diagnose TA-TMA. Additional biomarker studies may be helpful in improving the specificity of diagnosing patients MC-TA-TMA and in predicting the development of this disease.

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Authorship

Contribution: M.S. designed the study and analysis and wrote the manuscript; C.D. and L.E.L. contributed to the study design and edited the manuscript; C.M. and P.-C.K. performed statistical analyses and edited the manuscript; and S.M., L.S.K., and M.L. edited the manuscript.

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