

Changing Diagnostic and Treatment Landscape of HSCT-TMA

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1R01HL153723-01

Conflicts of interest and Disclosures

MIDAS (**M**icroangiopathy, Endothelial **D**amage in **A**adults undergoing **S**tem cell transplantation) Consortium is fully supported by the National Heart, Lung and Blood Institute of the National Institutes of Health.

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Consultancy: Omeros, Alexion.



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Learning objectives

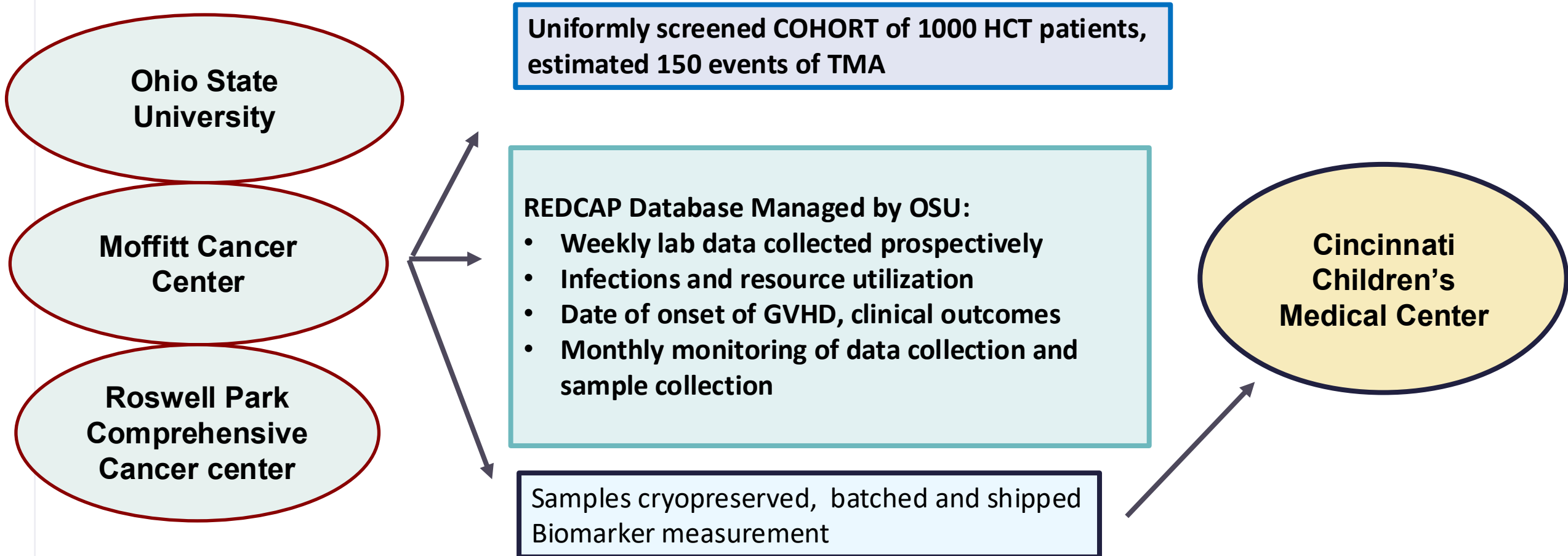
- Understand real world evidence of diagnostic and prognostic criteria of transplant associated thrombotic microangiopathy (TA-TMA).
- Understand influence of concomitant TA-TMA and other comorbidities occurring post-transplant.
- Understand biomarkers and risk factors of TA-TMA.
- Understand management of TA-TMA.

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Harmonization of Definitions criteria for TA-TMA

Criteria	Definitions
1) Biopsy proven disease (kidney or GI) or	
2) Clinical criteria: must meet ≥4/7 of the following within 14 days at two consecutive time points	
Anemia*	Defined as one of the following: 1. Failure to achieve transfusion independence for pRBCS despite evidence of neutrophil engraftment 2. Hemoglobin decline from patient's baseline by 1 gm/dL 3. New onset of transfusion dependence Rule out other causes as sole cause of anemia such as AIHA and PRCA
Thrombocytopenia*	Defined as one of the following: 1. Failure to achieve platelet engraftment 2. Higher than expected platelet transfusions needs 3. Refractoriness to platelet transfusions 4. 50% reduction in baseline platelet count after full platelet engraftment
Elevated LDH	Above upper limit of normal for age
Schistocytes	Present
Hypertension	>99th percentile for age (<18 years old), or systolic BP ≥140 or diastolic BP ≥90 (≥ 18 years old)
Elevated sC5b-9	≥ upper limit of normal
Proteinuria	≥ 1mg/mg rUPCR



TA-TMA Prognosis and risk stratification – define a clinically meaningful phenotype

High-risk TMA (Harmonization of definitions criteria)	Severe TA-TMA
Peak LDH > 2x ULN*	Peak LDH > 2x ULN*
Spot random urine protein to creatinine $\geq$ 1 mg/mg	Spot random urine protein to creatinine $\geq$ 1 mg/mg
Any organ dysfunction that develops in the setting of TMA except KDIGO stage I acute kidney injury	Any organ dysfunction that develops in the setting of TMA except KDIGO stage I acute kidney injury
Elevated soluble C5b-9 (> ULN)	Elevated soluble C5b-9 (> ULN)
Concurrent acute GVHD grade II-IV *	Concurrent acute GVHD grade II-IV*
Concurrent systemic infection (bacterial or viral)*	Concurrent systemic infection (bacterial or viral)*

Schoettler, M....Vasu, S TCT 2023

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MIDAS- Initial analysis of patients with 1 year follow-up

- First study in adults applying Harmonization of definitions criteria for TA-TMA in a prospective cohort (n=239 patients).
- TA-TMA was adjudicated by a 3-member panel who were blinded to each other and to the HCT center's reporting of TA-TMA.
- Panel consisting of: Sumi Vasu, Theresa Hahn, Nelli Bejanyan
- Significant heterogeneity in conditioning regimens and donor sources reflecting real world data.

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Severe TA TMA – Example of an adjudication dataset

Event Name	baseline	Day +7	Day +14	Day +21	Day +28	Week 5	Week 6
hemoglobin (HGB)	9.3	7.3	6.6	5.7	5.7	6.3	6.8
Was there RBC transfusion during this period?		No	Yes	Yes	Yes	Yes	Yes
platelet count	290	5	6	5	6	5	8
date of last platelet transfusion during this period		Yes	Yes	Yes	Yes	Yes	Yes
LDH	171	388	304	227	322	452	458
Were schistocytes identified on a manual differential count since last report?		Yes	No	Yes	Yes	Yes	Yes
schistocytes		Occasional		Occasional	Occasional	Occasional	Occasional
haptoglobin		236	54	30	30	30	30
creatinine, serum	1.07	1.09	1.49	1.73	2.22	2.31	2.42
protein, urine		30	100	30	100		
direct antibody test		negative	negative	negative	negative	negative	negative

- Weekly until day 100
- 5,6,9, 12 months

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Example adjudication dataset of No TA-TMA

Event Name	baseline	Day +7	Day +14	Day +21	Day +28	Week 5	Week 6	Week 7
Patient Diagnosed with Hypertension	No							
Number of hypertensive meds								
hemoglobin (HGB) (13.4-16.8)	11.9	8.8	7.7	6.3	9.8	9	8.9	9.1
Was there RBC transfusion during this period?		No	No	Yes	No	No	No	No
platelet count (145-337)	206	47	7	11	60	78	111 *	220
date of last platelet transfusion during this period		No	Yes	Yes	No	No	No	No
LDH (100-190)		147	101	189	183	256	347	161
Were schistocytes identified on a manual differential count since last report?		No	No	No	No	No	No	Yes
schistocytes								Occasional
protein, urine		Negative	Negative		Negative	Negative	Negative	Negative

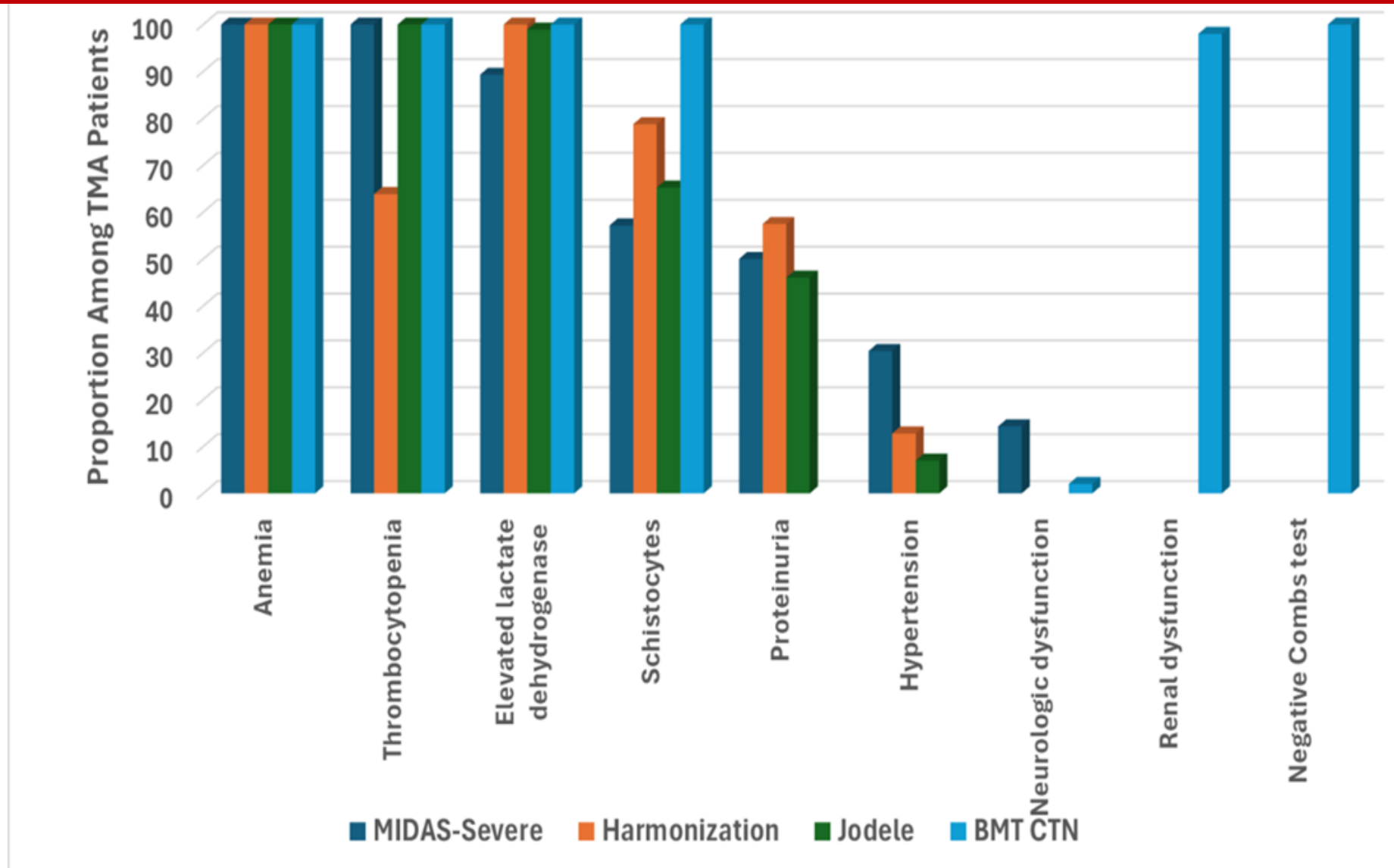
Additional Data :

- Hypertension – number of anti hypertensive medications
- Neurologic dysfunction
- GVHD diagnosis
- Infections, resource utilization
- Laboratory data- coagulation, transaminases.
- Comorbidities

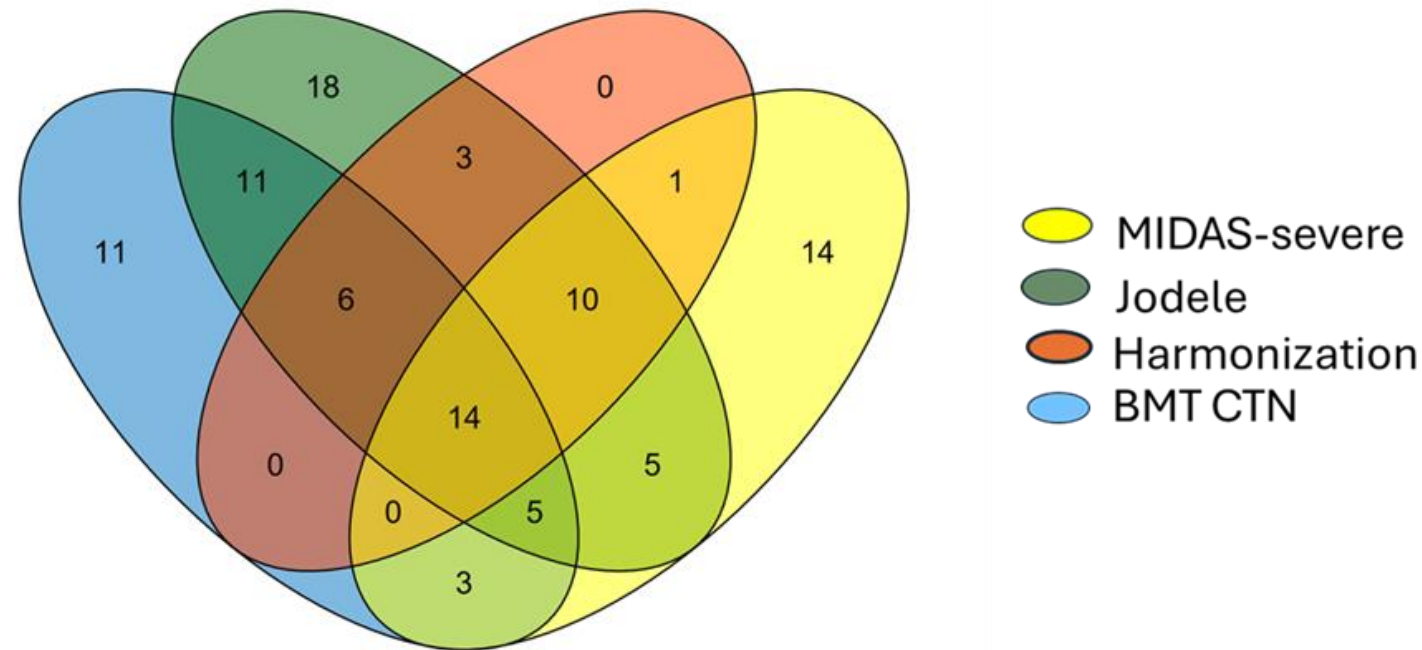
Diagnostic TA-TMA criteria

	Cho <i>et al</i> 2010	BMT-CTN 2005	IWG 2007	City of Hope 2013	Li <i>et al</i> 2019	Jodele <i>et al</i> 2014
Criteria	All features present at least 2 time points	All features present	All features present	4 criteria, definite TMA, 3 criteria probable TMA	All occurring within 24 hours, overall TA-TMA microangiopathy, definite MAHA + organ dysfunction	Renal biopsy consistent with TA-TMA OR clinical diagnosis ≥4/7 features at least 2 time points in 14d
Anemia	X	X	X	X	X	X
Thrombocytopenia	X	X	X	X	X	X
Elevated LDH	X	X	X	X ≥ 2X ULN	≥ 2X ULN	X
Schistocytes	X (≥ 2 per HPF)	X (≥ 2 HPF)	X (>4%)	X (present) or nRBCS	X (>2 HPF)	X (Present)
Negative Coombs	X				X	
Renal dysfunction		X			X (definite)	
Low haptoglobin	X		X			
Normal coagulation	X				X	
sC5b-9 > ULN						X
Hypertension, ≥ 140/90 in patients ≥ 18 years						X
Random spot (rUPCR)						X
Renal biopsy						X
Neurologic dysfunction			X		X (definite)	
Schoettler <i>et al</i> TCT 2023						

Prevalence of each individual criteria among the different diagnostic systems



TA-TMA is difficult to diagnose- varied criteria, confounding factors



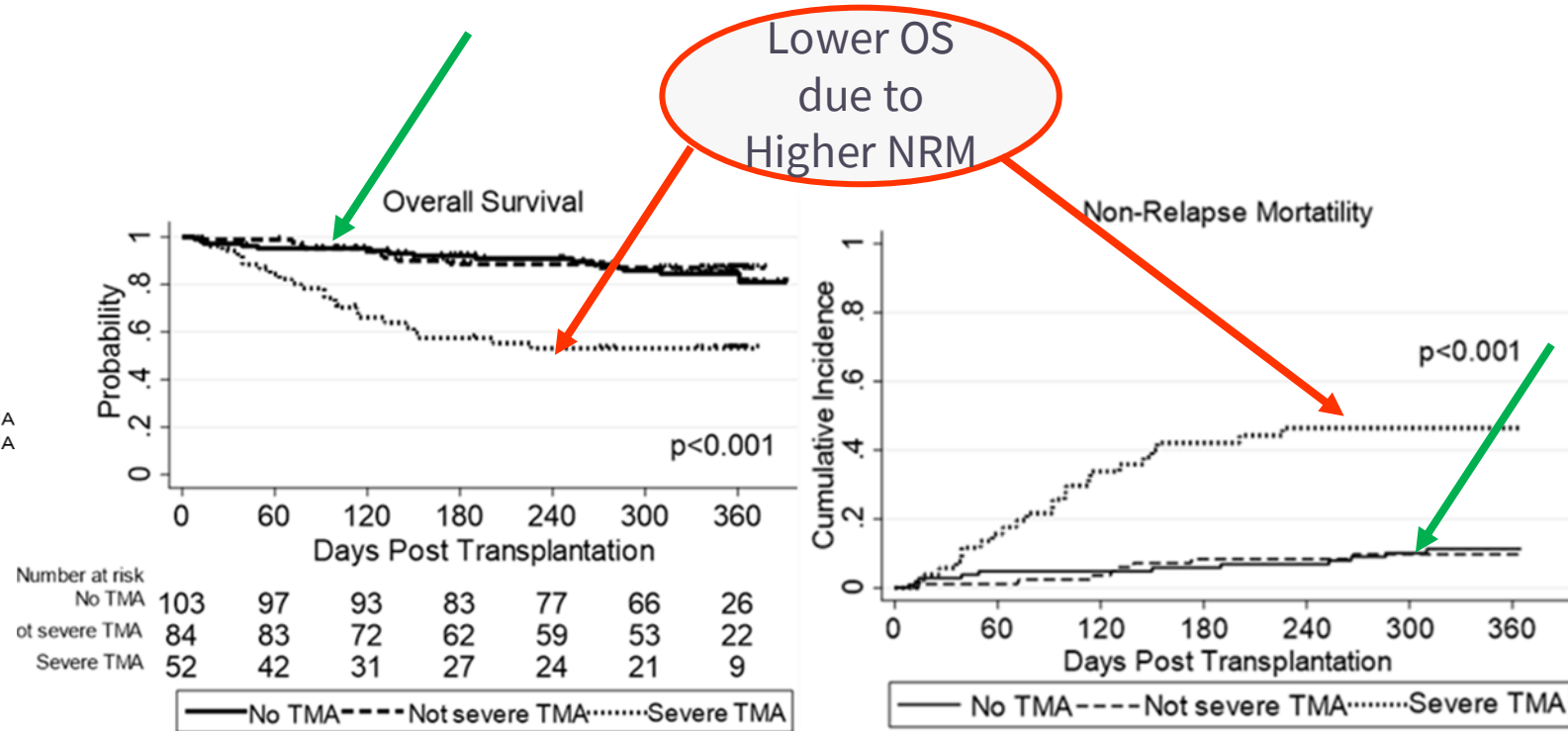
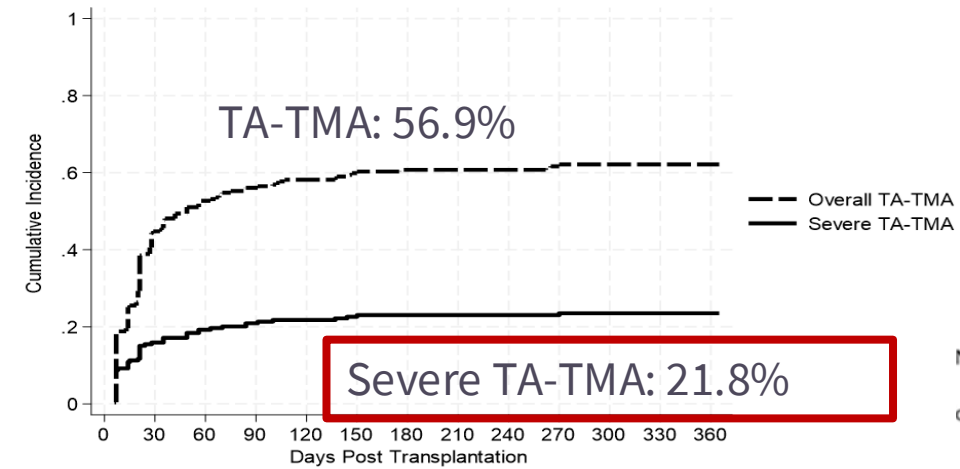
Crude proportion of patients who are classified with TA-TMA by day +100 post-HCT according to 7 different diagnostic criteria and the reporting center.							
Jodele ⁷	BMT-CTN ¹⁴	MIDAS Severe	Harmonization ¹²	IWG ¹⁵	Cho ¹³	Li ¹⁶	Center-reported
30%	21%	22%	14%	10%	4%	8%	8%

Legend: Jodele criteria were applied using only clinical criteria and did not consider sC5b-9 which is not routinely performed. Harmonization criteria were also applied using only clinical criteria and did not consider sC5b-9. MIDAS-Severe used no sC5b-9 levels, did not require engraftment and met high-risk Harmonization criteria. Center-reported refers to the clinical documentation in the patient's medical record.

Not all TA-TMAs are created equal

Cumulative incidence by
day 100 post-HCT
Median onset: 14.5 days

Severe TA-TMA has significantly worse OS and
higher NRM

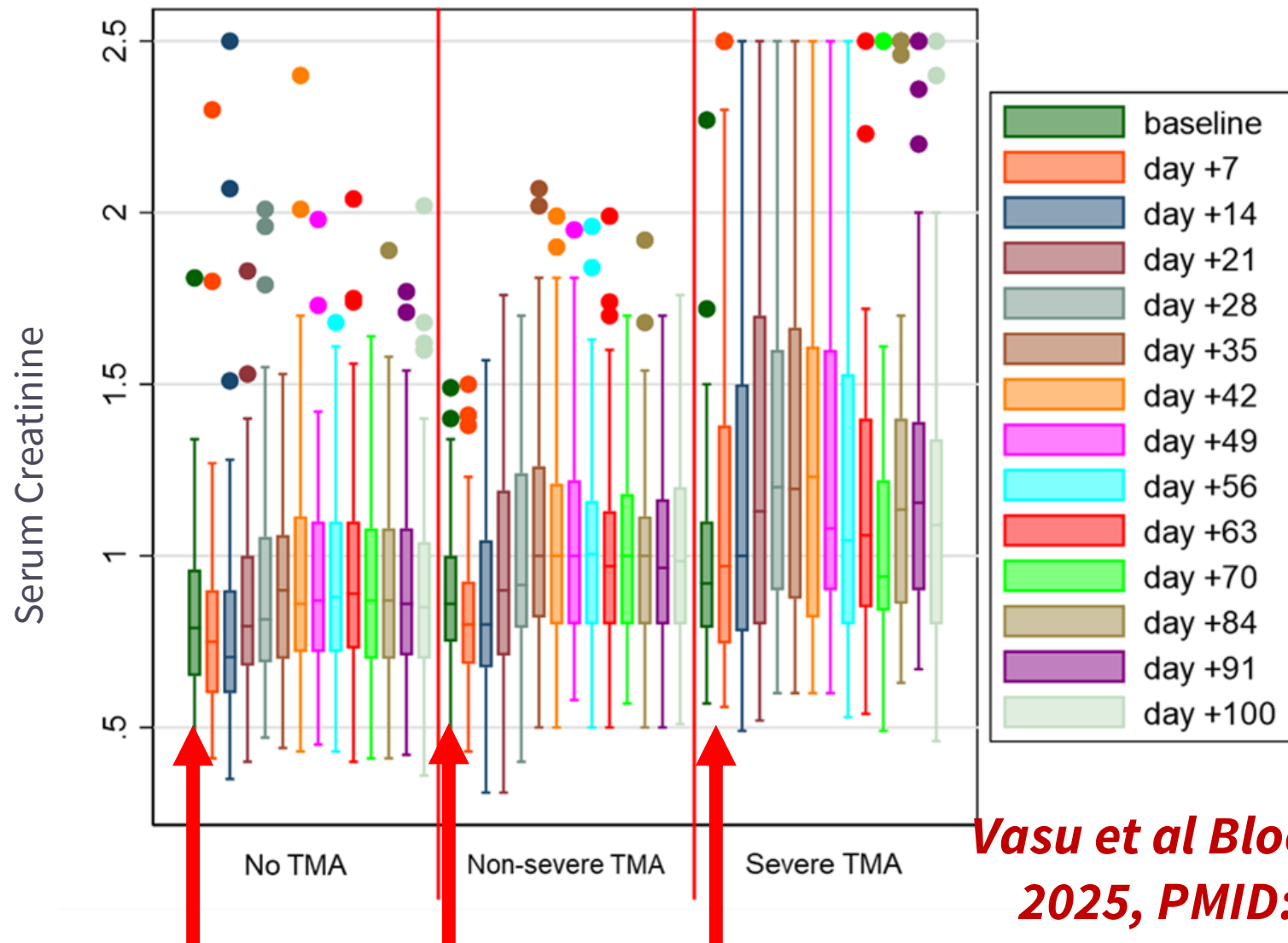


OS: Overall survival
NRM: Non-relapse mortality

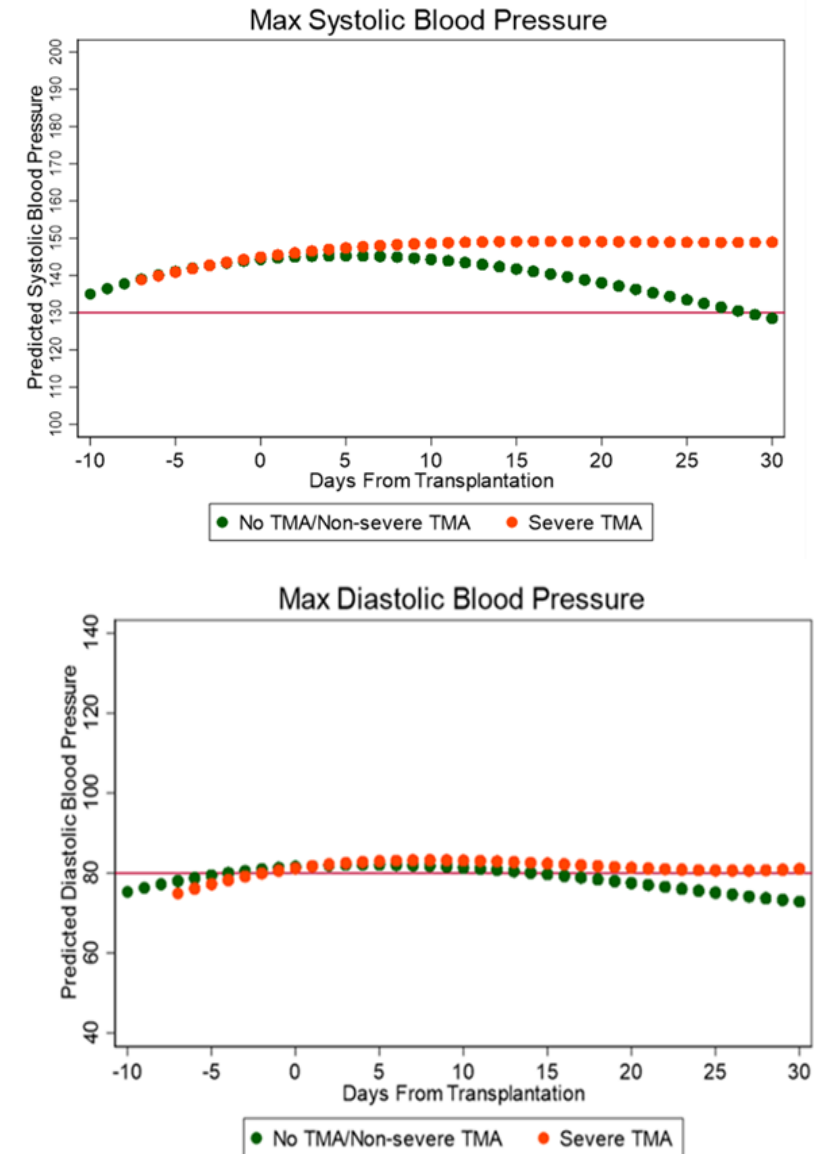
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Severe TA-TMA can cause persistent renal morbidity.

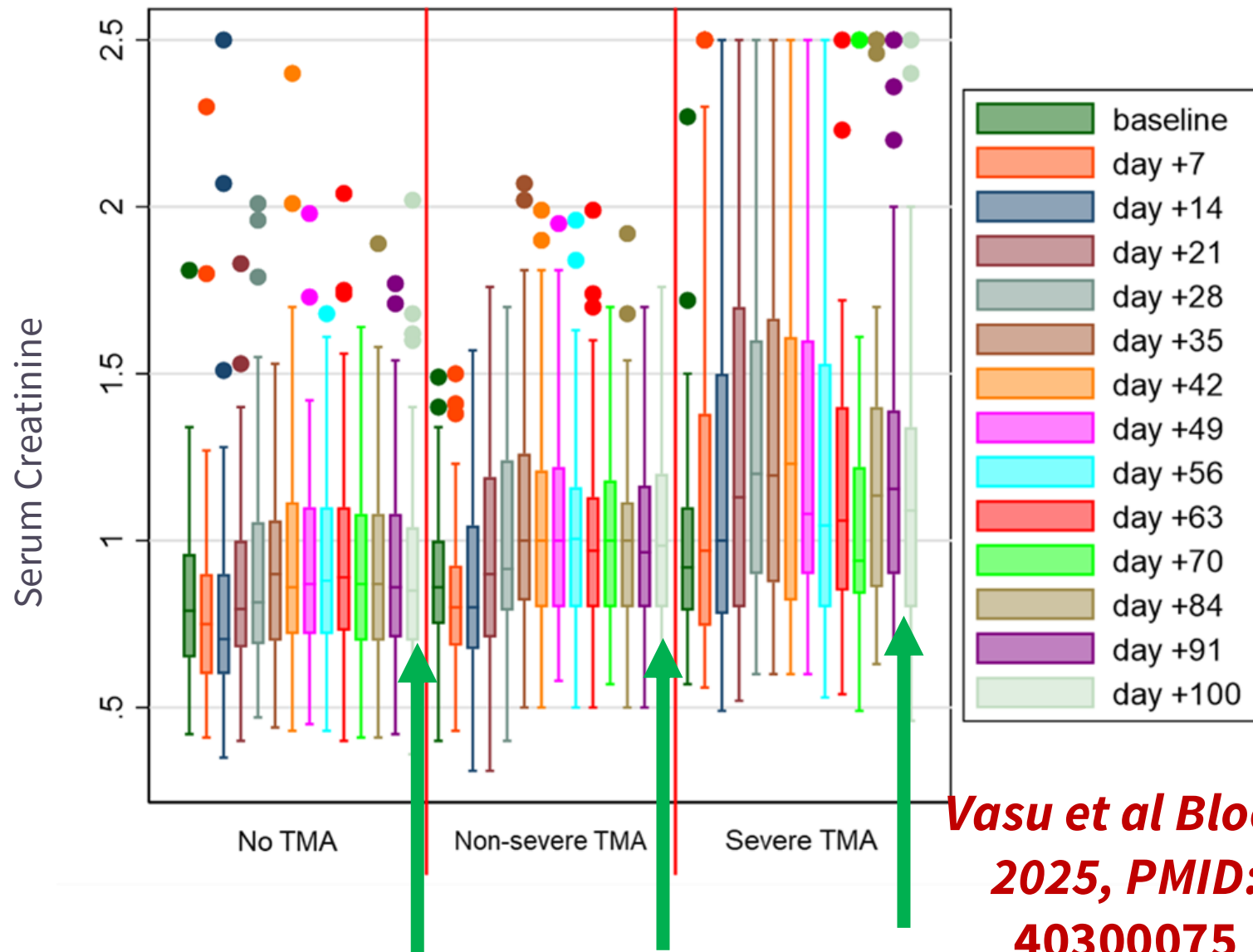
Systolic Hypertension in first 30 days may be an early indicator



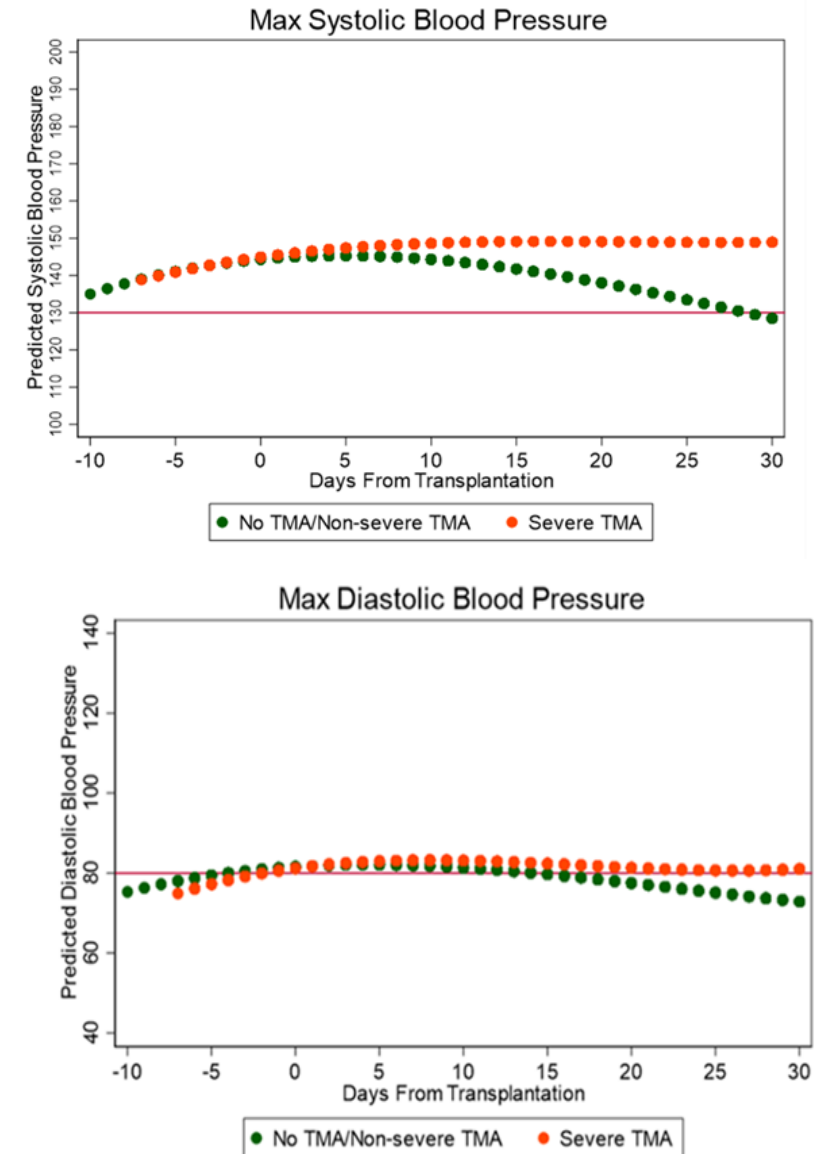
Vasu et al Blood
2025, PMID:
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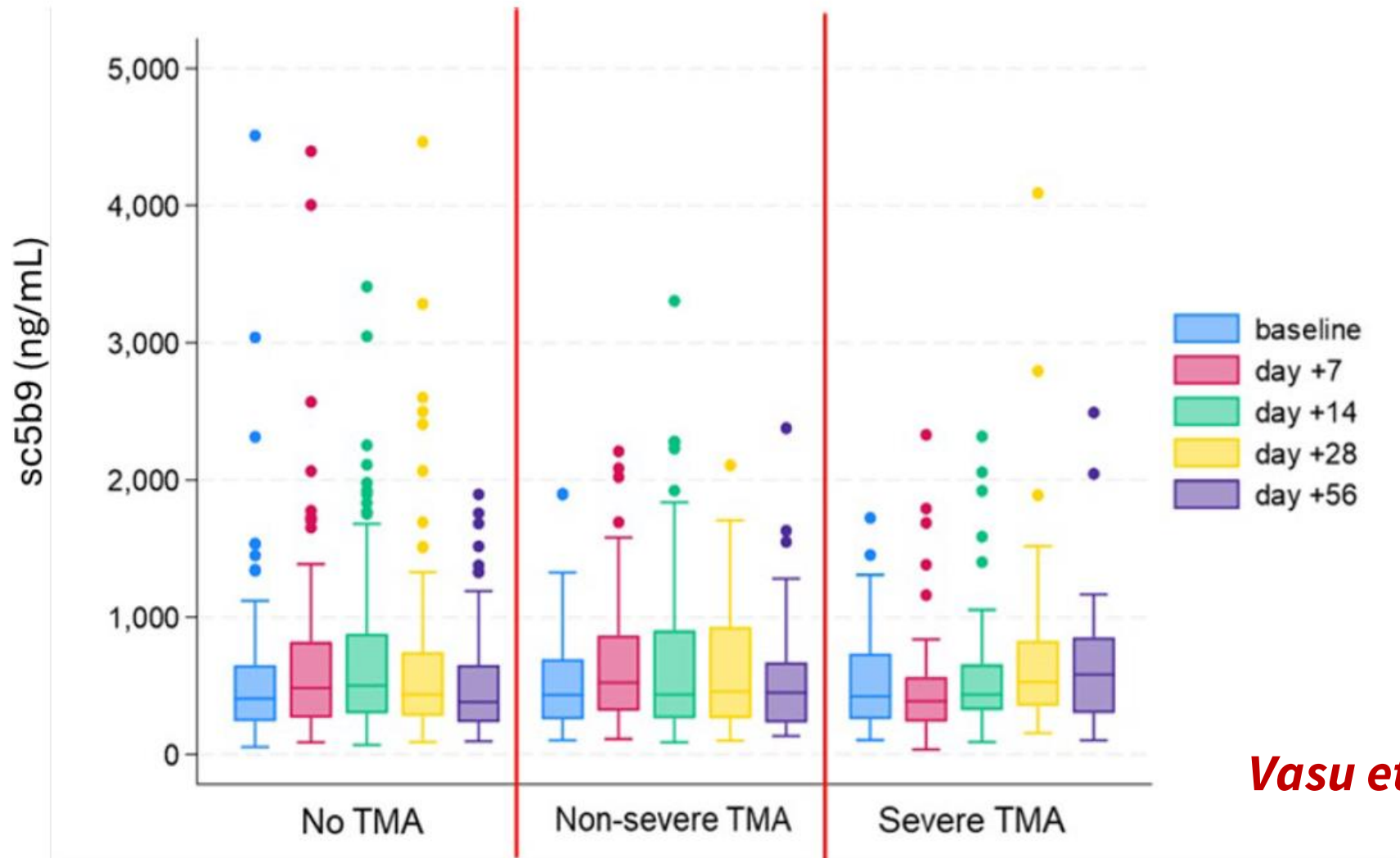
Severe TA-TMA can cause persistent renal morbidity. Systolic Hypertension in first 30 days may be an early indicator



Vasu et al Blood
2025, PMID:
40300075



sC5b-9 did not significantly predict Severe TA TMA at any time



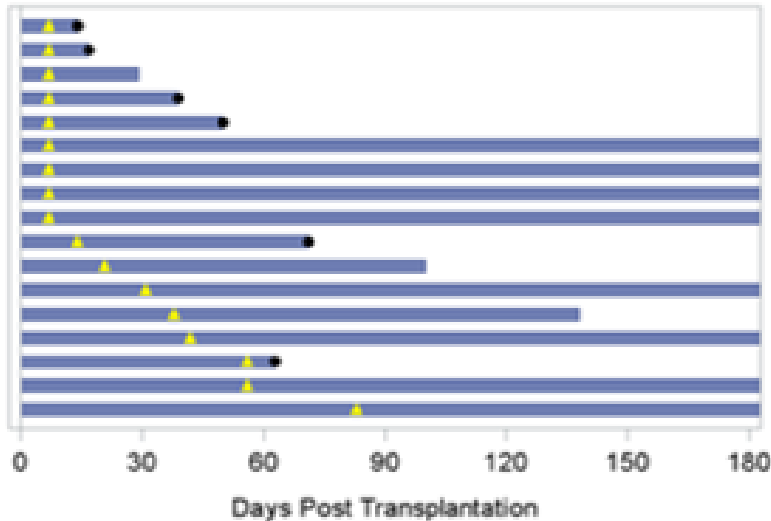
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TA-TMA can occur independent of aGVHD

No acute GVHD

Proportion of severe TMA: 10.5%

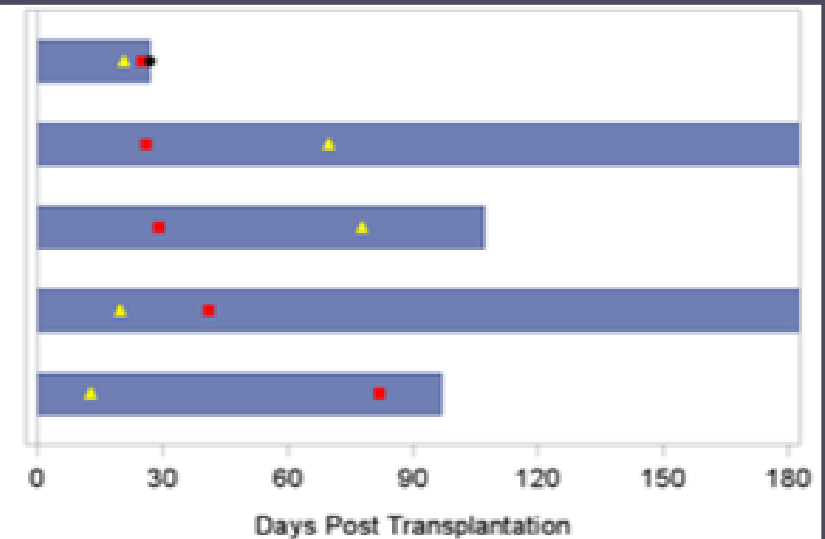
In patients with no acute GVHD, yellow triangles show the time to onset of severe TA-TMA



Max aGVHD grade I

Proportion of severe TMA: 8%

In patients with maximum overall grade I acute GVHD, yellow triangles show time to onset of severe TA-TMA and red squares show time to onset of GVHD



- Days to Acute GVHD Onset
- ▲ Days to TMA
- Days to Death

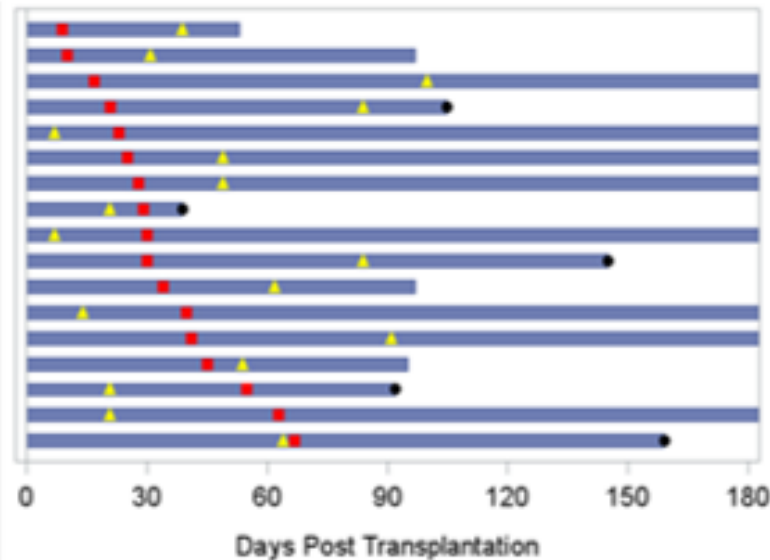
TA-TMA incidence rises with higher grades of aGVHD

Max aGVHD grade II

Proportion of severe TMA: 18.5%

- Days to Acute GVHD Onset
- ▲ Days to TMA
- Days to Death

In patients with maximum overall grade II acute GVHD, yellow triangles show the time to onset of severe TA-TMA and red squares show time to onset of GVHD

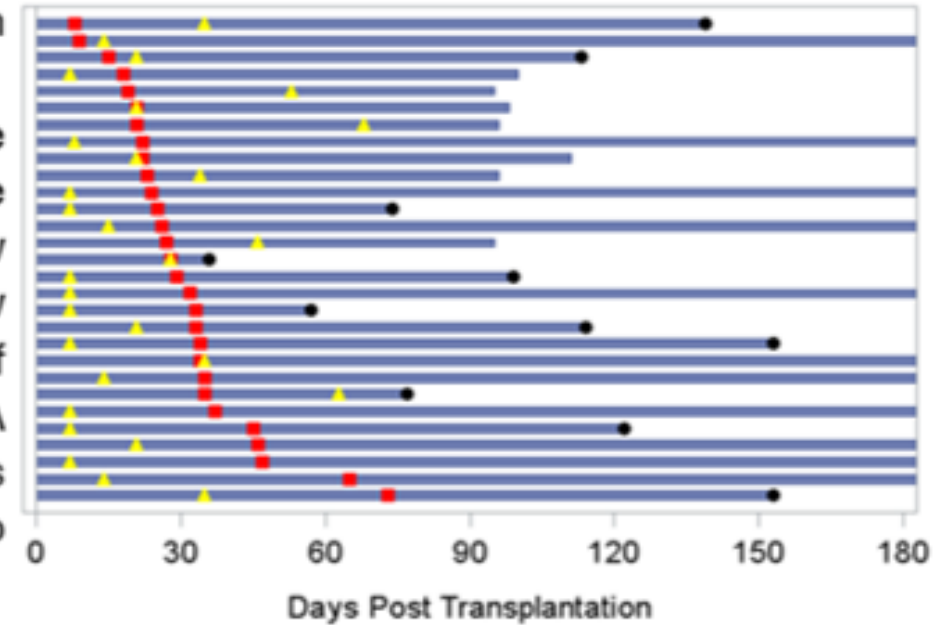


Max aGVHD grade III/IV

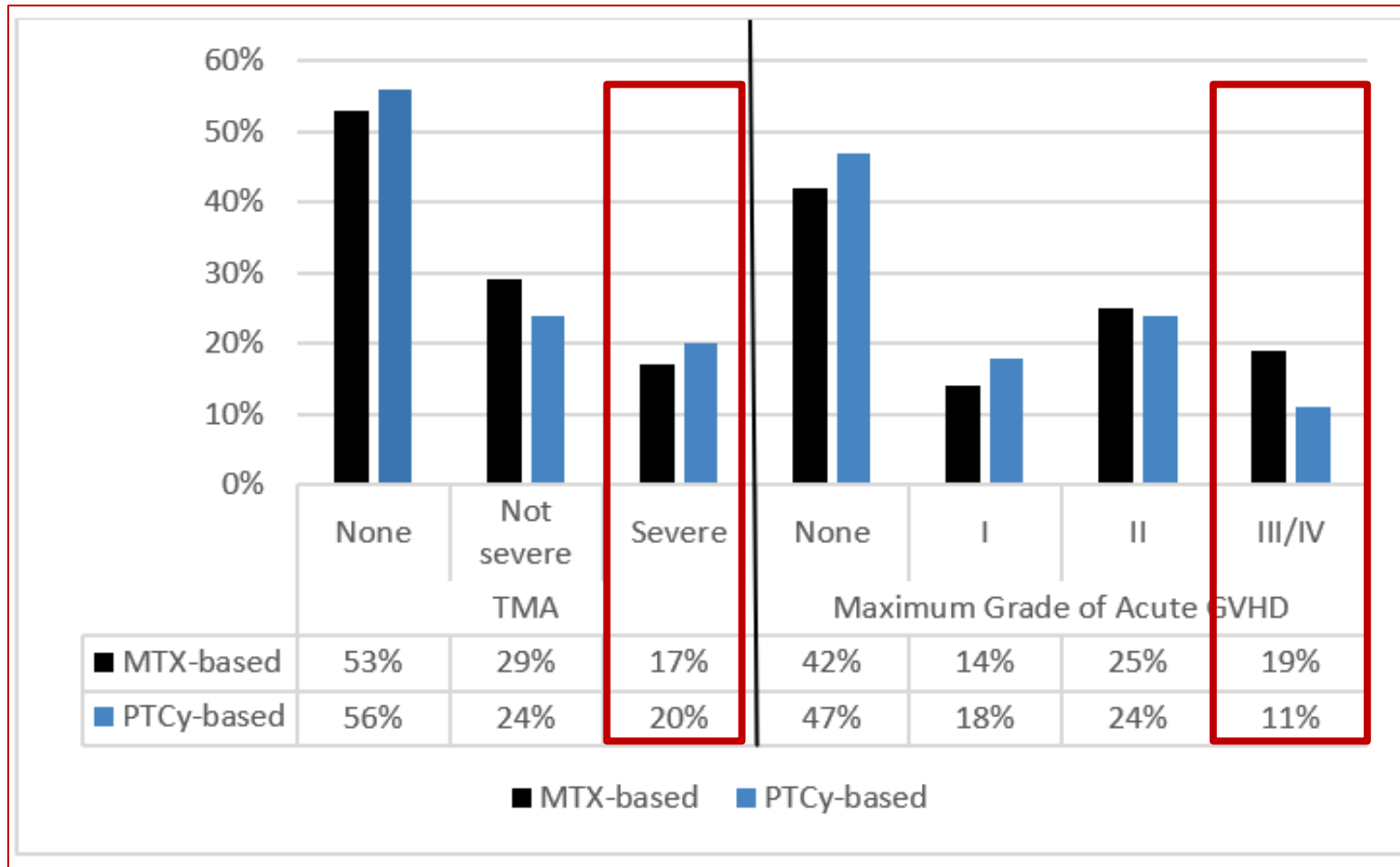
Proportion of severe TMA: 53.7%

Steroid refractory aGVHD occurred in 32% of pts with severe TMA vs 2.5% in those without TMA

In patients with maximum overall grade III-IV acute GVHD, yellow triangles show time to onset of severe TA-TMA and red squares show time to onset of GVHD



PT CY lowers incidence of aGVHD but not Severe TA-TMA



Hahn, T....Vasu, S Blood Advances 2026

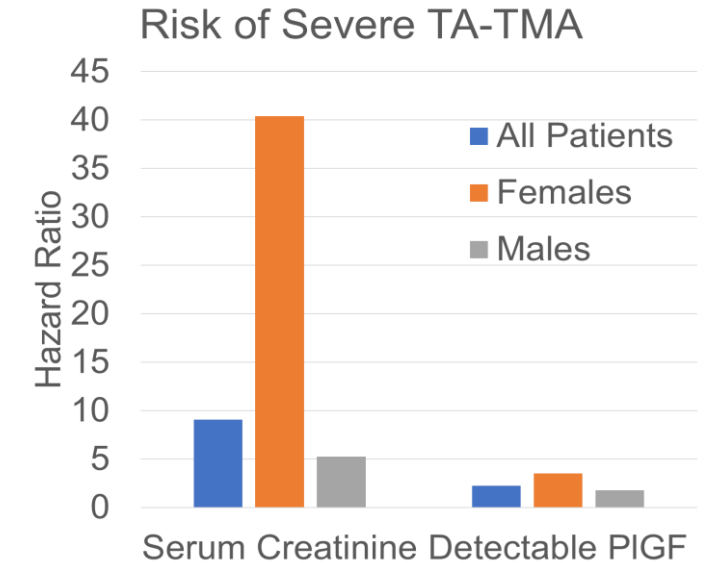
Multivariable analyses of biomarkers

Significant Factors	Severe TA-TMA	
	HR (95% CI)	P
Baseline Prediction Analysis (pre-HCT)		
Female (vs Male)	2.16 (1.24-3.76)	0.0065
Serum Creatinine (each 1 mg/dL increase)	9.07 (4.28-19.25)	<0.0001
Detectable PIGF (vs not detectable)	2.25 (1.34-3.79)	0.0023
Landmark Analyses (Day+28 post-HCT)		
Serum Creatinine (each 1 mg/dL increase)	5.34 (3.11-9.15)	<0.0001
ST2	2.76 (2.12-3.6)	<0.0001
Association Analysis (Day +28 post-HCT)		
Serum Creatinine (each 1 mg/dL increase)	2.56 (1.99-3.29)	<0.0001
ST2	1.93 (1.56-2.40)	<0.0001

Multivariable Prediction Analysis of severe TA-TMA			
All patients	HR	95% CI	P
Female vs Male	2.16	1.24-3.76	0.0065
Serum creatinine *	9.07	4.28-19.25	<0.0001
Detectable PIGF	2.25	1.34-3.79	0.0023
Female patients	HR	95% CI	P
Serum creatinine *	40.38	14.4-113	<0.0001
Detectable PIGF	3.5	1.65-7.43	0.001
Male patients	HR	95% CI	P
Serum creatinine *	5.27	2.0-13.9	0.001
Detectable PIGF	1.78	0.89-3.59	0.11
* HR for each 1 mg/dL increase, PIGF: placental growth factor (member of the VEGF family)			

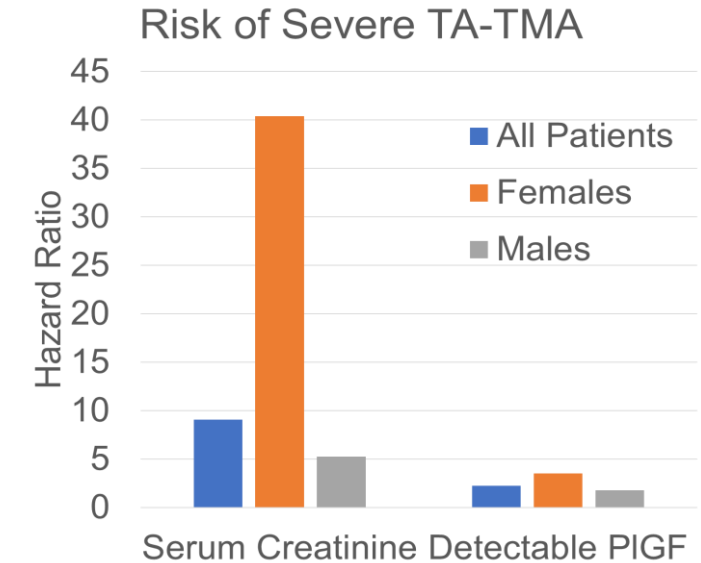
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Multivariable analyses of biomarkers

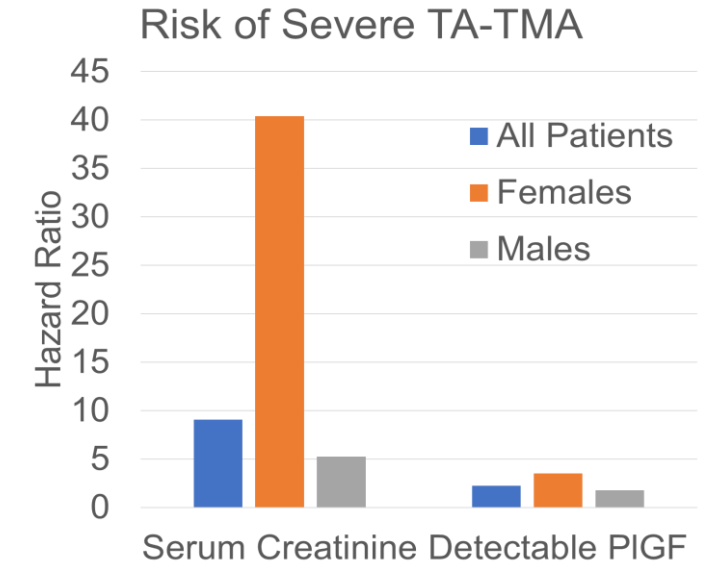
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Landmark Analyses (Day+28 post-HCT)		
Serum Creatinine (each 1 mg/dL increase)	5.34 (3.11-9.15)	<0.0001
ST2	2.76 (2.12-3.6)	<0.0001
Association Analysis (Day +28 post-HCT)		
Serum Creatinine (each 1 mg/dL increase)	2.56 (1.99-3.29)	<0.0001
ST2	1.93 (1.56-2.40)	<0.0001



	Non-Relapse Mortality	
	HR (95% CI)	P
Baseline Prediction Analysis (pre-HCT)		
Serum Creatinine (each 1 mg/dL increase)	3.97 (1.91-8.27)	0.0002
Landmark Analyses (Day+28 post-HCT)		
ST2	2.26 (1.53-3.33)	<0.0001
sFLT-1	3.49 (1.87-6.53)	0.0001
EGF	0.56 (0.4-0.8)	0.0012
Association Analysis (Day +28 post-HCT)		
ST2	2.26 (1.53-3.33)	<0.0001
sFLT-1	3.49 (1.87-6.53)	0.0001
EGF	0.56 (0.4-0.8)	0.0012

Multivariable analyses of biomarkers

Significant Factors	Severe TA-TMA	
	HR (95% CI)	P
Baseline Prediction Analysis (pre-HCT)		
Female (vs Male)	2.16 (1.24-3.76)	0.0065
Serum Creatinine (each 1 mg/dL increase)	9.07 (4.28-19.25)	<0.0001
Detectable PIGF (vs not detectable)	2.25 (1.34-3.79)	0.0023
Landmark Analyses (Day+28 post-HCT)		
Serum Creatinine (each 1 mg/dL increase)	5.34 (3.11-9.15)	<0.0001
ST2	2.76 (2.12-3.6)	<0.0001
Association Analysis (Day +28 post-HCT)		
Serum Creatinine (each 1 mg/dL increase)	2.56 (1.99-3.29)	<0.0001
ST2	1.93 (1.56-2.40)	<0.0001



	Overall Survival	
	HR (95% CI)	P
Baseline Prediction Analysis (pre-HCT)		
Serum Creatinine (each 1 mg/dL <u>increase</u>)	3.26 (1.32-8.06)	0.01
Landmark Analyses (Day+28 post-HCT)		
ST2	2.31 (1.74-3.06)	<0.0001
sFLT-1	3.18 (1.74-5.8)	0.0002
EGF	0.59 (0.4-0.84)	0.0037
Association Analysis (Day +28 post-HCT)		
ST2	2.31 (1.74-3.06)	<0.0001
sFLT-1	3.18 (1.74-5.8)	0.0002
EGF	0.58 (0.4-0.84)	0.0037

Day +28 EASIX is significant for Severe TA-TMA, NRM and OS

	Severe TA-TMA		Grade III-IV Acute GVHD		Non-Relapse Mortality		Overall Survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Univariable Landmark Analysis								
EASIX								
Pre-HCT	1.13 (0.98-1.32)	0.1	1.02 (0.87-1.2)	0.8	1.33 (1.13-1.57)	0.0007	1.38 (1.18-1.62)	0.0001
Day +7	1.4 (1.27-1.54)	<0.0001	1.16 (1.01-1.33)	0.03	1.61 (1.42-1.82)	<0.0001	1.62 (1.43-1.83)	<0.0001
Day +14	1.6 (1.3-1.97)	<0.0001	1.39 (1.08-1.79)	0.01	2.13 (1.6-2.85)	<0.0001	2.22 (1.83-2.7)	<0.0001
Day +28	1.65 (1.3-2.1)	<0.0001	1.19 (0.98-1.44)	0.07	1.46 (1.16-1.83)	0.0011	1.62 (1.41-1.87)	<0.0001
Univariable Association Analysis								
EASIX								
Pre-HCT	1.13 (0.98-1.32)	0.1	1.02 (0.87-1.2)	0.8	1.33 (1.13-1.57)	0.0007	1.38 (1.18-1.62)	0.0001
Day +7	1.4 (1.27-1.54)	<0.0001	1.16 (1.01-1.33)	0.03	1.61 (1.42-1.82)	<0.0001	1.62 (1.43-1.83)	<0.0001
Day +14	1.67 (1.41-1.99)	<0.0001	1.38 (1.14-1.66)	0.001	2.28 (1.87-2.77)	<0.0001	2.21 (1.82-2.67)	<0.0001
Day +28	1.67 (1.5-1.88)	<0.0001	1.25 (1.11-1.42)	0.0004	1.62 (1.36-1.93)	0.0011	1.64 (1.42-1.88)	<0.0001
Multivariable Landmark Analysis								
EASIX Day +28	1.68 (1.5-1.88)	<0.0001	NA	NA	1.51 (1.27-1.79)	<0.0001	1.55 (1.3-1.85)	<0.0001
ST2 Day +28	---	---			1.85 (1.26-2.74)	0.0019	1.88 (1.39-2.55)	<0.0001
sFLT-1 Day+28	---	---			2.77 (1.61-4.76)	0.0002	2.49 (1.4-4.46)	<0.0001
Multivariable Association Analysis								
EASIX Day +28	1.54 (1.36-1.75)	<0.0001	1.34 (1.19-1.51)	<0.0001	1.5 (1.27-1.79)	<0.0001	1.55 (1.3-1.85)	<0.0001
ANG-2 Day+28	1.0 (1.0-1.0)	0.0008	---	---	---	---	---	---
PTCy vs MTX	---	---	0.38 (0.22-0.66)	0.0007	---	---	---	---
ST2 Day +28	---	---	---	---	1.85 (1.25-2.73)	0.0019	1.88 (1.39-2.55)	<0.0001
sFLT-1 Day+28	---	---	---	---	2.76 (1.61-4.74)	0.0002	2.49 (1.4-4.46)	0.002
Legend: EASIX, sFLT-1 and ST2 were analyzed as <u>log transformed</u> values. Landmark analyses predicted the outcome after the landmark time point and excluded patients with events prior to each timepoint. Association analyses assessed each outcome including all events before or after the measured time point.								

Severe TA-TMA is frequent in adults

- Prospective screening identifies higher proportion of severe TA-TMA
- Simple, inexpensive tests used in screening strategy
- Both TA TMA and severe TA-TMA were under-reported by the centers.
- Incidence of TA-TMA varies according to the diagnostic criteria used.
- Median onset of TA-TMA is 14.5 days

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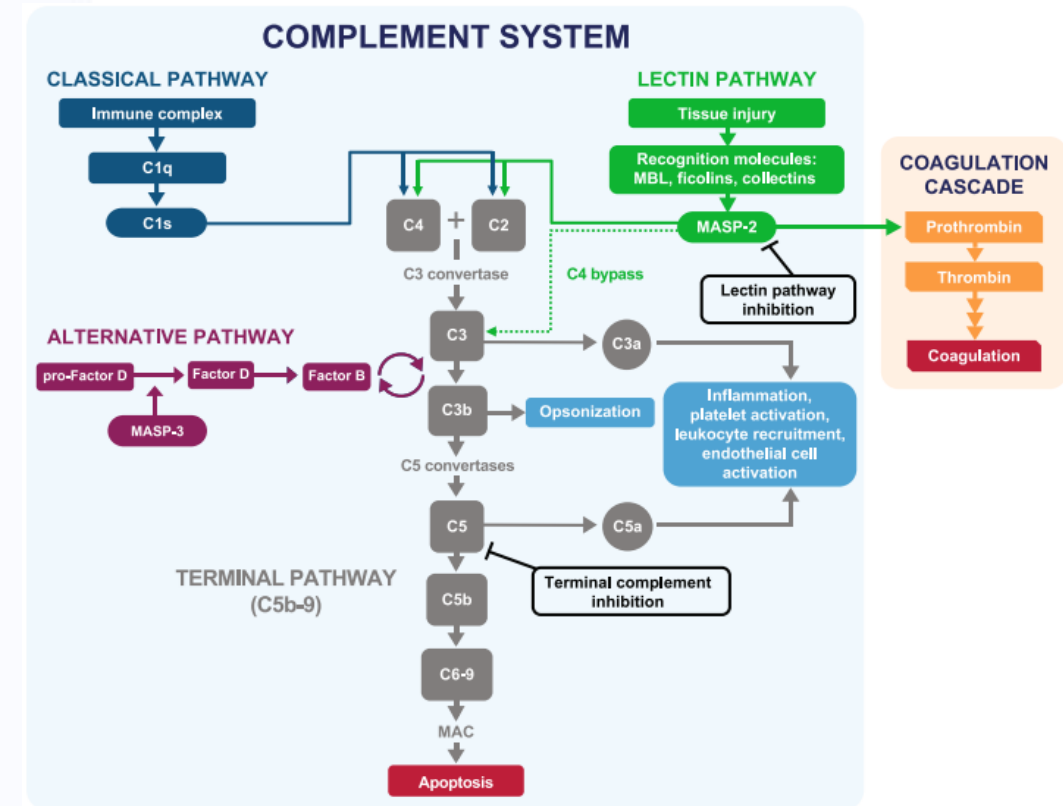
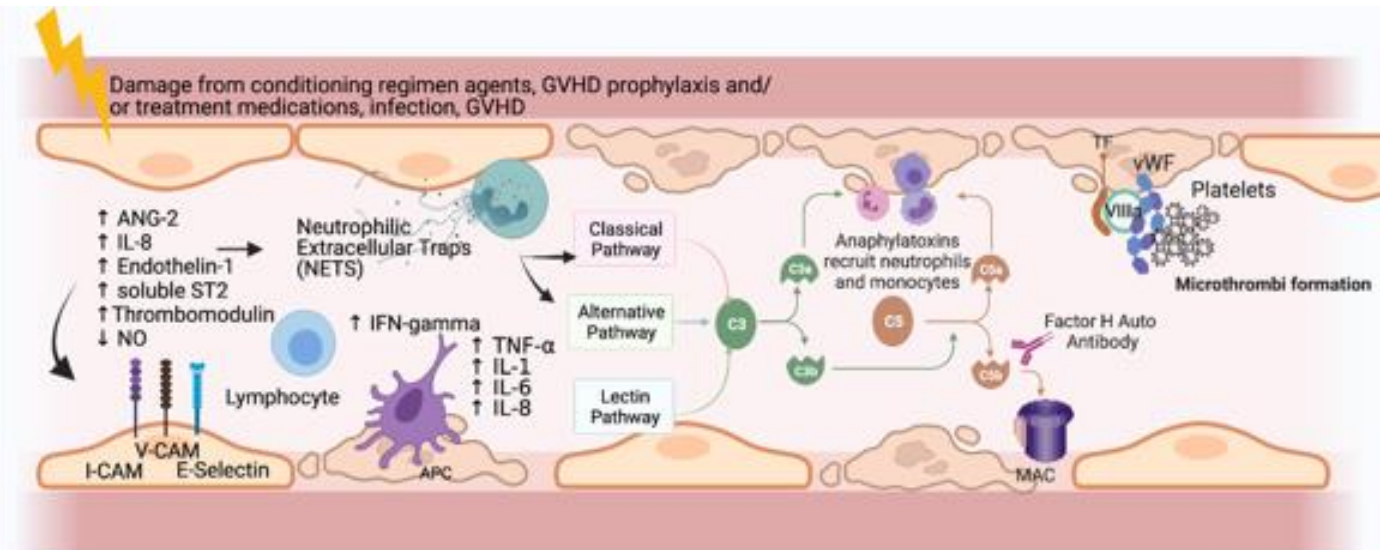
Conclusions - I

- MIDAS is the first prospective study of TA TMA to utilize Harmonization of definitions criteria in adults.
- TA-TMA is frequent (56%), but not all TA-TMA is impactful or actionable.
- Impactful, actionable cases of severe TA-TMA can be identified by harmonization of definitions high-risk criteria.
- **Severe TMA incidence is high at 18% and significantly impacts OS and NRM; 38% NRM at 12 months.**

Conclusions - II

- Harmonization of definitions criteria is sensitive for diagnosis of TA-TMA, and picks up many cases that do not have negative impact on OS and NRM
- Non-severe TA-TMA cases have identical survival to patients with no TA-TMA
- Higher grades of GVHD is a risk factor
- ST2 at day 28 is a biomarker associated with TA TMA
- Pre HCT creatinine is a strong predictive biomarker for severe TA TMA
- PTCY does not lower incidence of severe TA TMA

Therapeutic approaches to TA-TMA



Schoettler-Long et al, 2022

The James

Extensive pediatric experience of complement inhibition with eculizumab



TRANSPLANTATION

Complement blockade for TA-TMA: lessons learned from a large pediatric cohort treated with eculizumab

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Recent adult experience with eculizumab.

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Full Length Article
Analysis

Outcomes of Terminal Complement Blockade in Adults with High-Risk Transplant-Associated Thrombotic Microangiopathy: A Comparative Analysis



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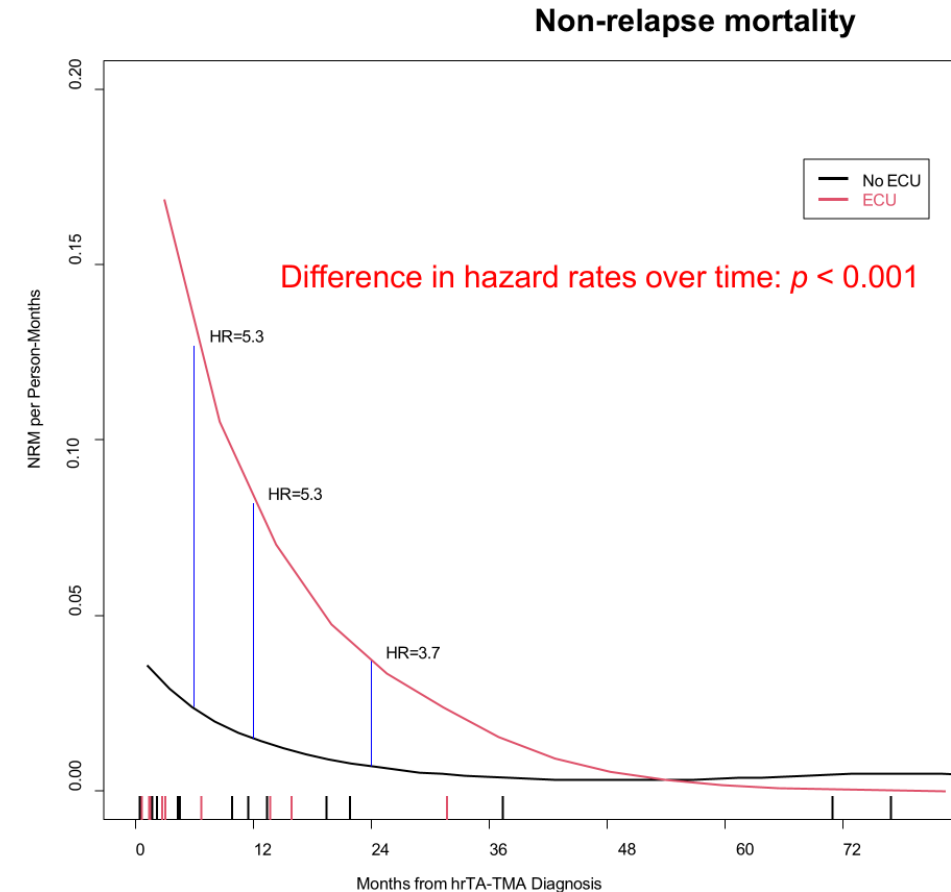
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Retrospective study from 2012 to 2023

- The benefit of terminal complement blockade in adult patients with high-risk TA-TMA is uncertain
- Compared outcomes of eculizumab (n=16) in adults with hrTA-TMA to conventional therapy (n=31)
- Eculizumab use was not associated with increase in clinical efficacy
- Eculizumab use was associated with increase in NRM and infection rates.
- Prospective studies are needed to define eculizumab role in adults with hrTA-TMA.

Results

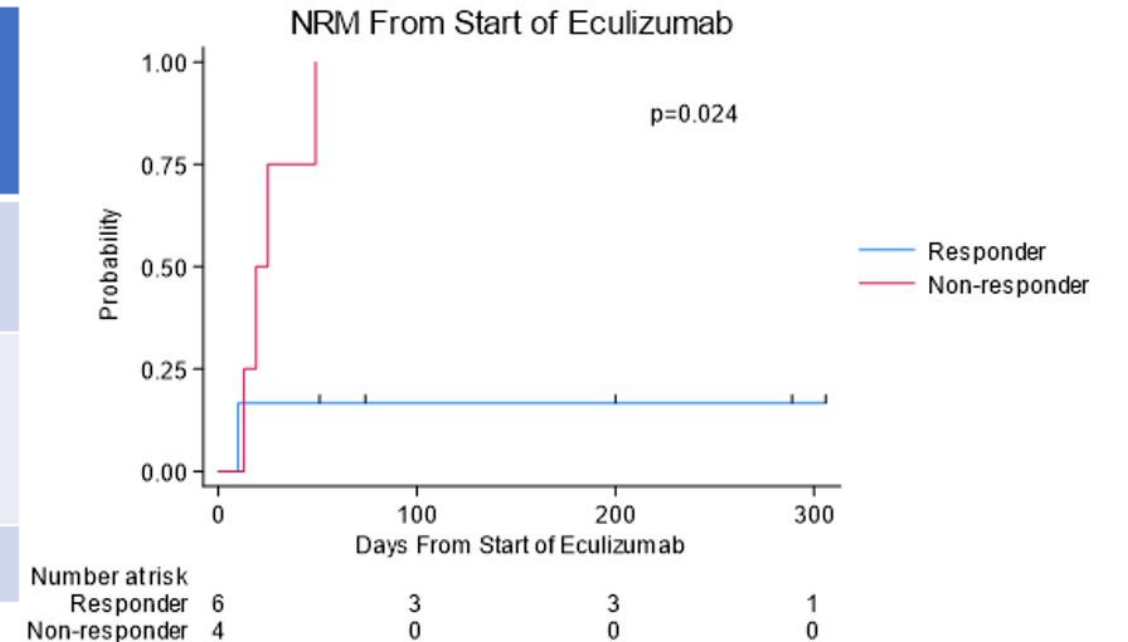
- Median follow-up: 7.3 yrs.
- **1-yr** overall survival (OS) for entire cohort was **61%** and **45%** at **2 yrs**.
- Non-relapse mortality (NRM) was **32% at 1 yr** and 44% at 2 yr.
- Clinical response occurred in **56%** with eculizumab and **71%** with conventional therapy.
- The eculizumab cohort had worse OS. This was driven by increased NRM ($P < .001$) at 6 mo, 1 yr and 2 yr.
- Survival outcomes remained consistent after adjusting for hrTA-TMA biomarkers. Deaths were mainly due to infections.



Treatment outcomes for Severe TMA in MIDAS consortium

- Number of patients who received eculizumab n=14
- Response rate to eculizumab: 54%

	Number of patients	Response after tacro discontinuation
Discontinuation of tacrolimus	6	1
Discontinuation of sirolimus	3	1
Eculizumab	14	5 responded



Unpublished data

NRM – Non-relapse mortality

Narsoplimab
n=28 pts

lectin pathway
inhibitor

TABLE 2. Primary Efficacy End Point: Response to Narsoplimab^a

Response	FAS (N = 28)
Responders	17/28 (61)
[Exact 95% CI]	[41 to 79]
Improvement in TMA markers	17/28 (61)
Platelet count ^b	14/23 (61)
Baseline $\leq 20 \times 10^9/L$	3/6 (50)
> $3 \times$ baseline and no platelet transfusion ^c	3/6 (50)
> $30 \times 10^9/L$ and no platelet transfusion ^c	4/6 (67)
Baseline > $20 \times 10^9/L$	11/17 (65)
$\geq 1.5 \times$ baseline and no platelet transfusion ^c	12/17 (71)
> $75 \times 10^9/L$ and no platelet transfusion ^c	11/17 (65)
LDH < $1.5 \times$ ULN	21/28 (75)
Improvement in organ function	20/27 (74)
Improvement in kidney function ^d	18/27 (67)
Reduction of creatinine > 40%	10/27 (37)
Creatinine < ULN and reduction of creatinine > 20%	15/27 (56)
Discontinuation of renal replacement therapy	0/1 (0)
Improvement in pulmonary function ^e	NA
Improvement in neurologic function	3/6 (50)
Improvement in reversible neurologic conditions	3/6 (50)
Stabilization of irreversible neurologic conditions	0/6 (0)
Improvement in GI function	1/1 (100)
Improvement of > 1 grade in MAGIC GI criteria	1/1 (100)
Freedom from transfusion ^f	12/25 (48)
Freedom from platelet transfusion ^g	8/18 (44)
Freedom from RBC transfusion ^g	11/22 (50)

*Khaled SK, Journal of
Clinical Oncology 2022*

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Randomized study of ultomiris (Ravulizumab) in adults

Date: 29 July 2026

Protocol: ALXN1210-TMA-313

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Ravulizumab in Adult and Adolescent Participants who have Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT)

RE: ALXN1210-TMA-313 Press Release

Dear Investigator,

Thank you for your participation in the ALXN1210-TMA-313 Phase III trial investigating *Ultomiris* (ravulizumab) in adults and adolescents with HSCT-TMA.

The purpose of this letter is to inform you that Alexion has announced high-level results from the ALXN1210-TMA-313 study. Please refer to the press release, dated Jul-27-2026. The high-level results indicated that the study did not achieve statistical significance for the primary endpoint of event-free survival through 26 weeks compared to placebo in adults and adolescents (aged 12 years or older) with HSCT-TMA. *Ultomiris* showed a trend toward treatment benefit in adults and adolescents with HSCT-TMA at 26 weeks compared to placebo. Discussions with health authorities are ongoing regarding the interpretation of these data, including in the context of real-world evidence.

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Treatment of Severe TA TMA



In patients with severe TA-TMA, tacrolimus taper decisions should take into consideration both GVHD risk and timing post transplant.



In patients with severe TA TMA, consider narsoplimab.

Hahn Blood Advances 2026

Khaled SK, Journal of Clinical Oncology 2022

Take home messages

- Severe TA-TMA has high non-relapse mortality post transplant
- Incidence is 18.5%, higher than previously thought (Prospective screening recommended until day 100 , and then at onset of GVHD)
- GVHD well-known risk factor, PTCY is not protective against TA TMA
- Pre-transplant creatinine is an important predictive marker and day 28 ST2 also significant in TA-TMA
- sC5b-9 not significant in TMA; differences between kids and adults
- Day +28 ST2 is predictive of TA TMA
- Narsoplimab, a lectin pathway inhibitor is the only FDA approved therapy in TMA

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