Hematopoietic Stem Cell Transplant-associated Thrombotic Microangiopathy ((TA-TMA))

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Introduction

- Thrombotic microangiopathy is a **well-recognized potentially life-threatening** complication following **both allogeneic and autologous** hematopoietic stem cell transplantation .

- Both **peripherally mobilized stem cells or bone marrow** stem cells; the incidence seems to be the **same.**

- TA-TMA is one of the most difficult to identify and manage complications.

- Clue : **you should think of in order it to recognize it .**

Incidence :

- Depends on which criteria used and what population :

Jodele criteria : estimated the incidence of TA-TMA to be **39%** in pediatric and young adult patients.

City of Hope criteria : **13% definite TMA** and an additional **26% probable TMA**

Mortality

- from 40 to 84% .

Response rates : different therapy strategies vary from 25 to 93%,

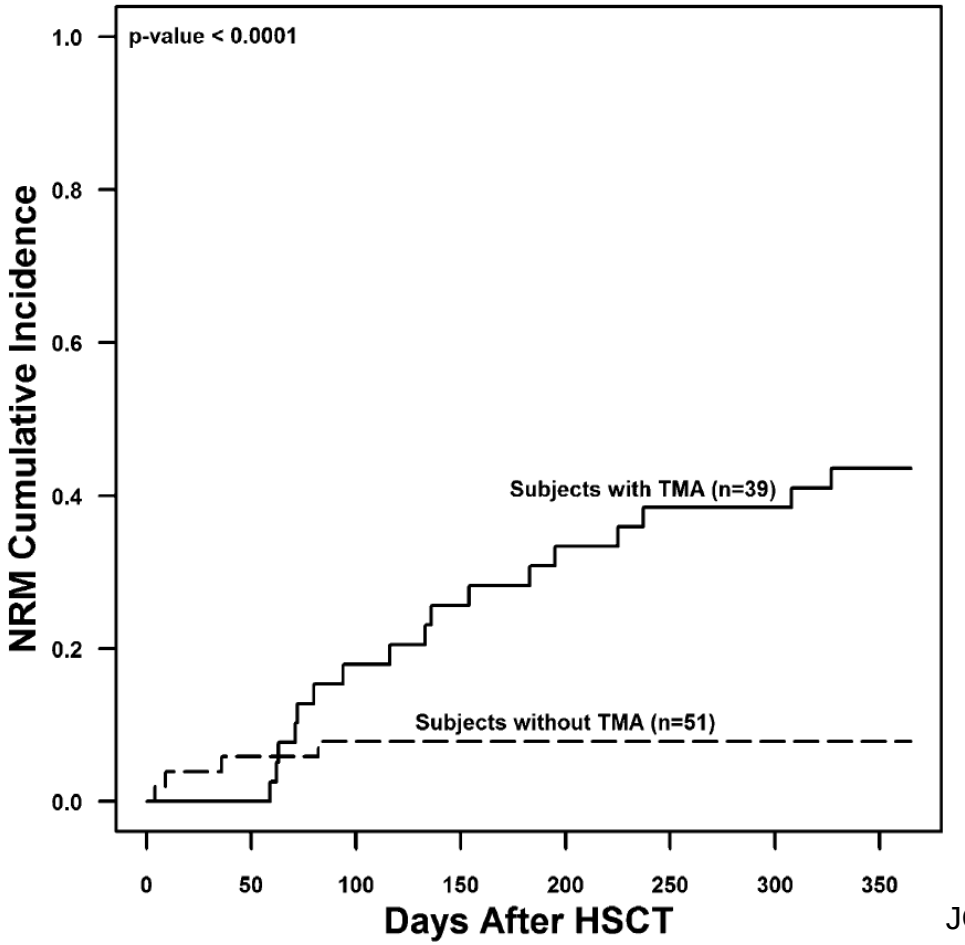
lower response rates reported with **plasma exchange.**

higher response rates with **complement directed therapy.**

Time Frame for Development of TA-TMA

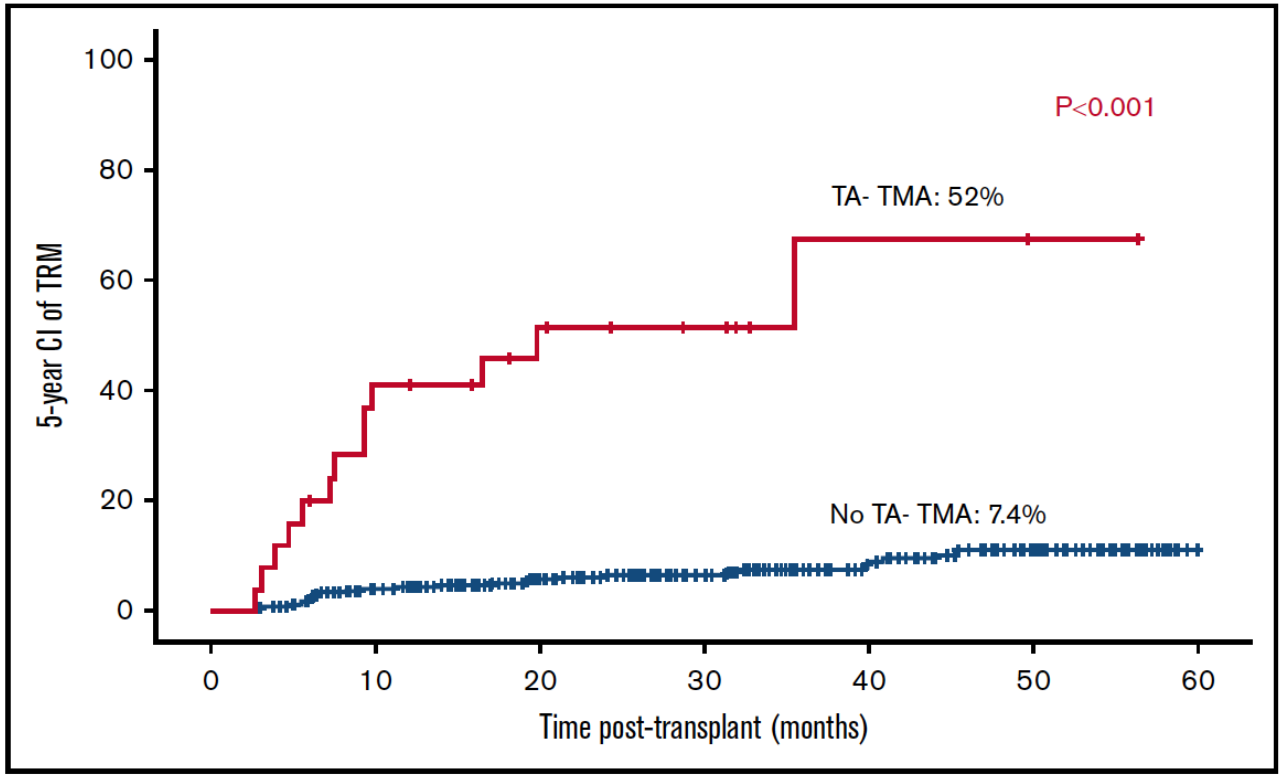
- Usually, first 20 to 100 days after the transplant.
- reports of TMA past day 100 ((in the context of GVHD)).

NRM



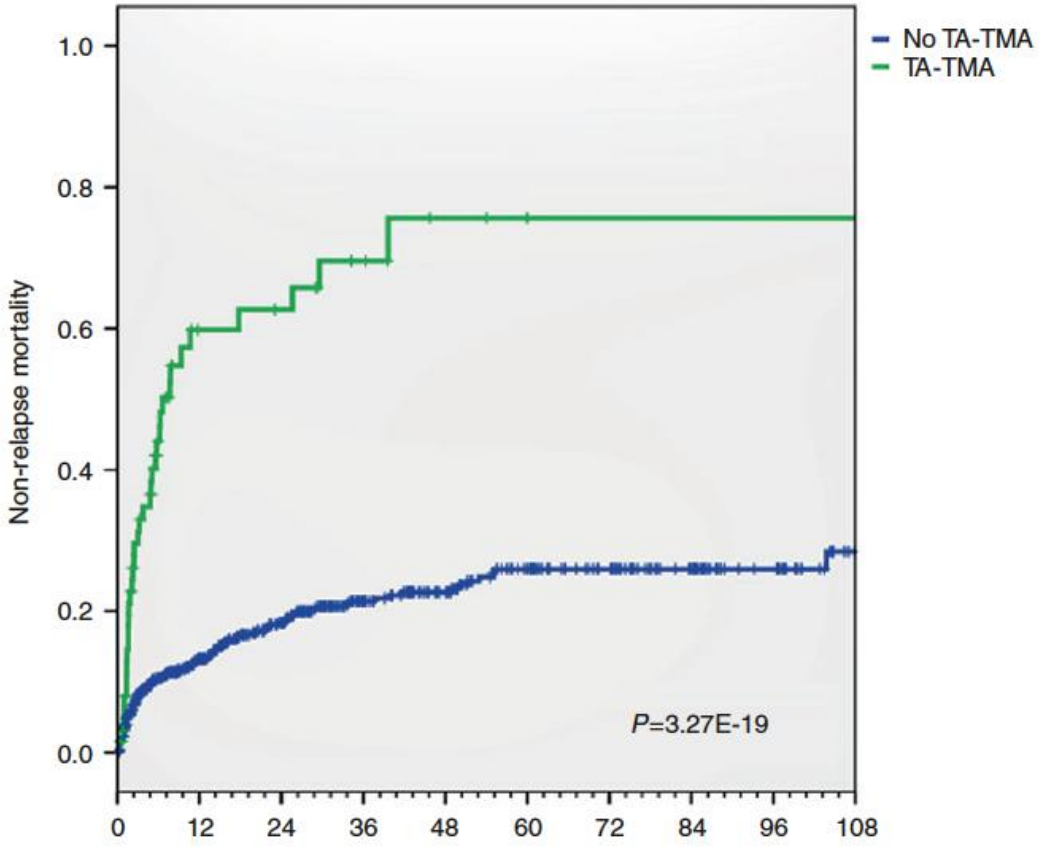
JODELE et al. Blood. 2014;124(4):645-653

Increased 5-year TRM among patients with TA-TMA vs patients who had no TA-TMA



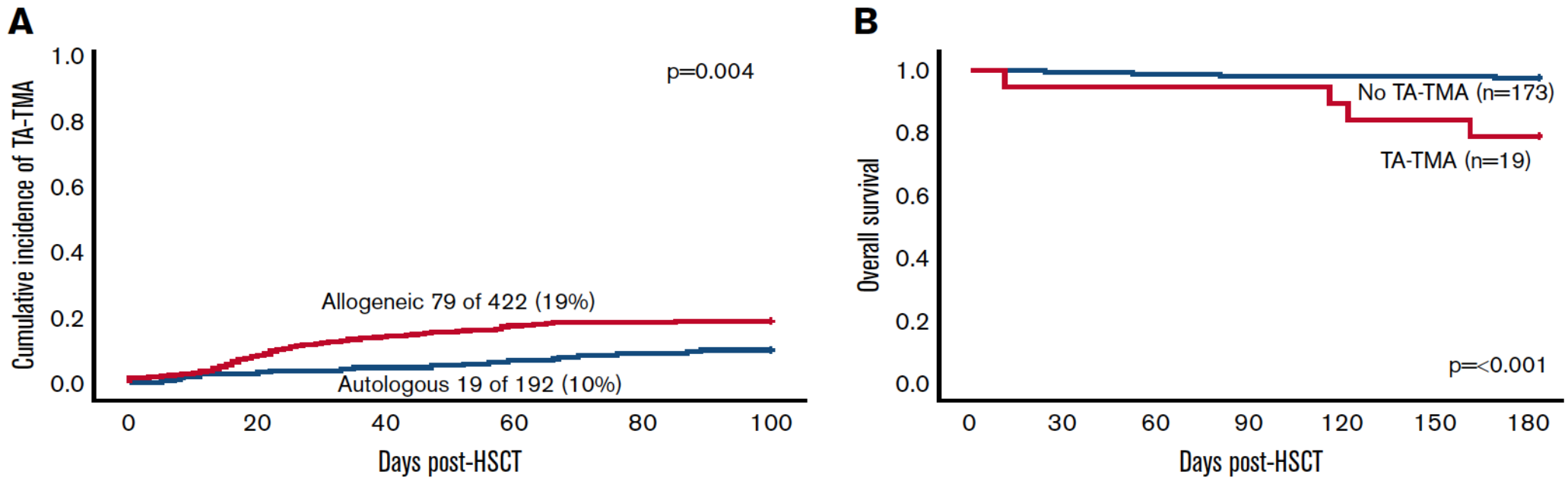
ELFEKY et al. Blood advances 9 JUNE 2020 x VOLUME 4, NUMBER 11

High mortality in hematopoietic stem cell transplant-associated thrombotic microangiopathy



S. Kraft et al. Bone marrow transplantation. 2019 Apr;54(4):540-8.

Cumulative incidence and 6-month survival in patients with and without TA-TMA



DANDOY et al. Blood advances 12 JANUARY 2021 x VOLUME 5, NUMBER 1

Pathophysiology of TA-TMA

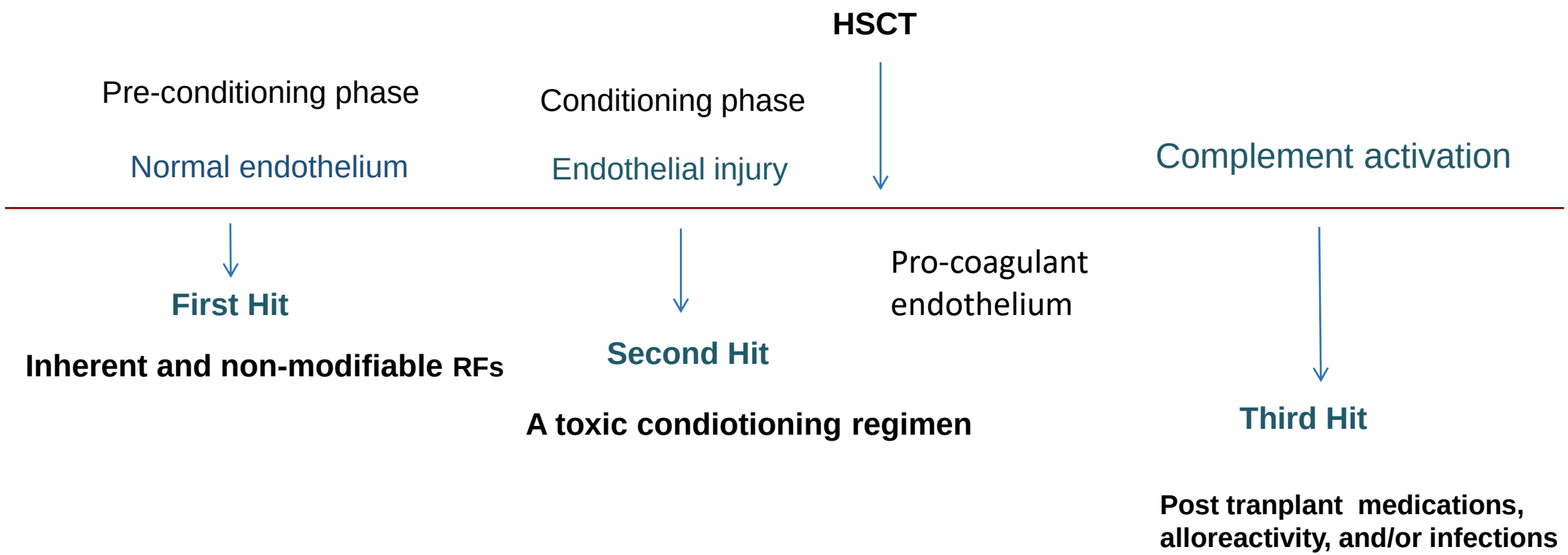
1. Activation of endothelial cells to produce a pro-coagulant state.
2. Activation of antigen-presenting cells (macrophages and neutrophils) and lymphocytes.
3. Activation of the complement cascade and microthrombi formation.

without the depletion of ADAMTS13

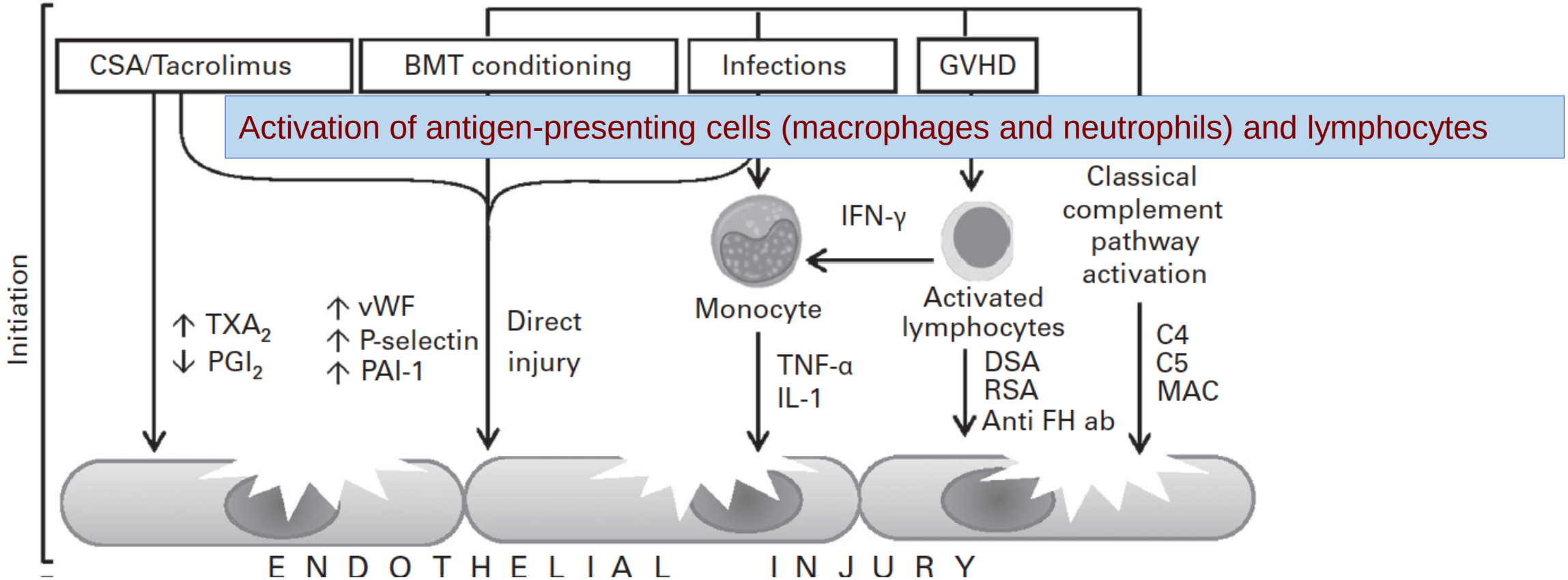
Activation of endothelial cells to produce a pro-coagulant state

Endothelial injury is fundamental to the pathogenesis of TA-TMA

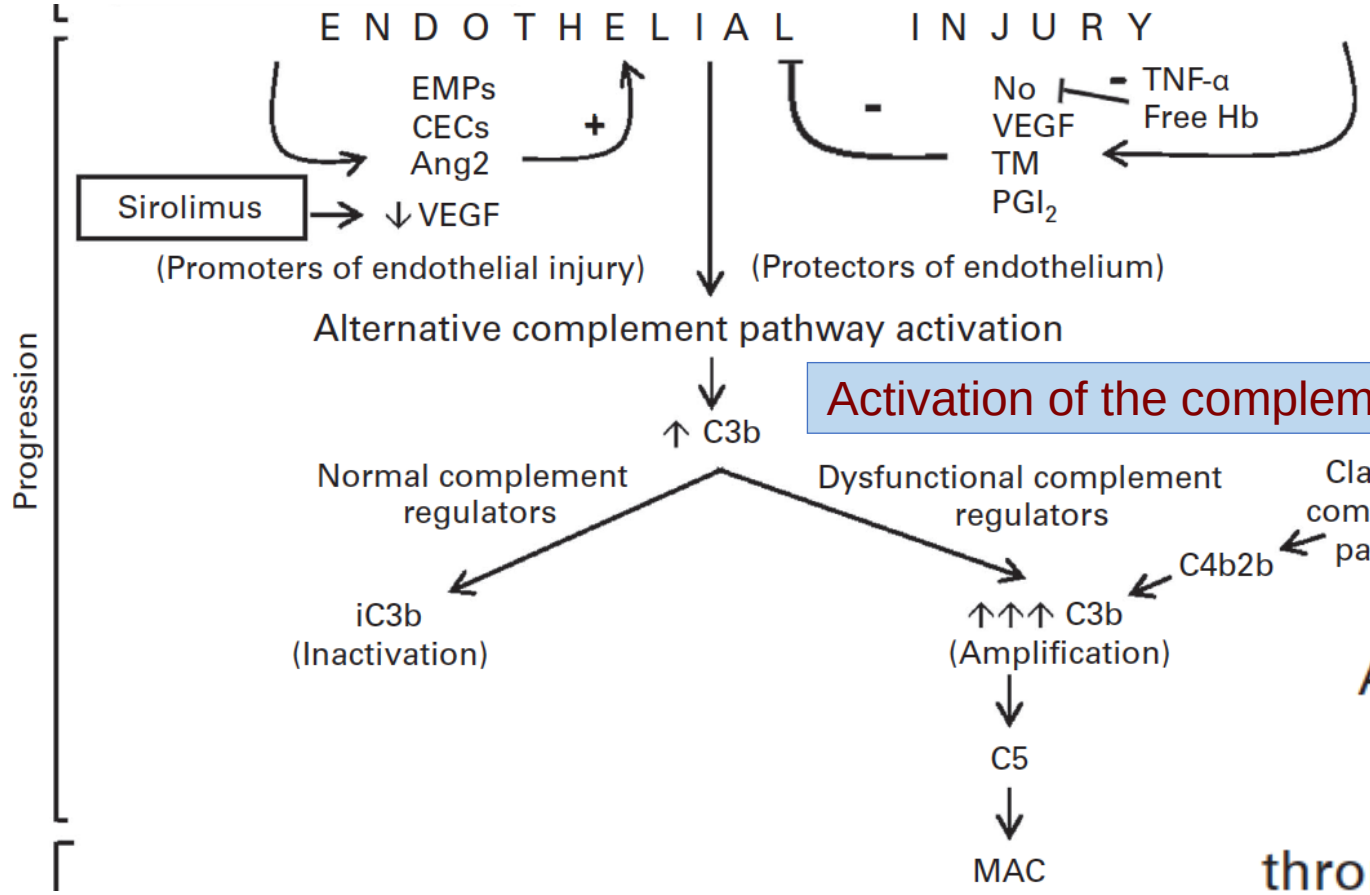
Three-hit hypothesis



Pathophysiology of TA-TMA



Pathophysiology of TA-TMA



Activation of the complement cascade and microthrombi formation

Aggravated endothelial injury
plateled aggreagation
microthrombi formation
thrombocytopenia, hemolytic anemia

Clinical manifestations of TA-TMA by organ system

Renal
Acute kidney injury, chronic kidney disease, proteinuria or hypertension

Pulmonary
Pulmonary hypertension, pleural effusion

Gastrointestinal
Diarrhea, vomiting, abdominal pain or intestinal bleeding, ascites

Neurological
Confusion, headache, hallucinations or seizures

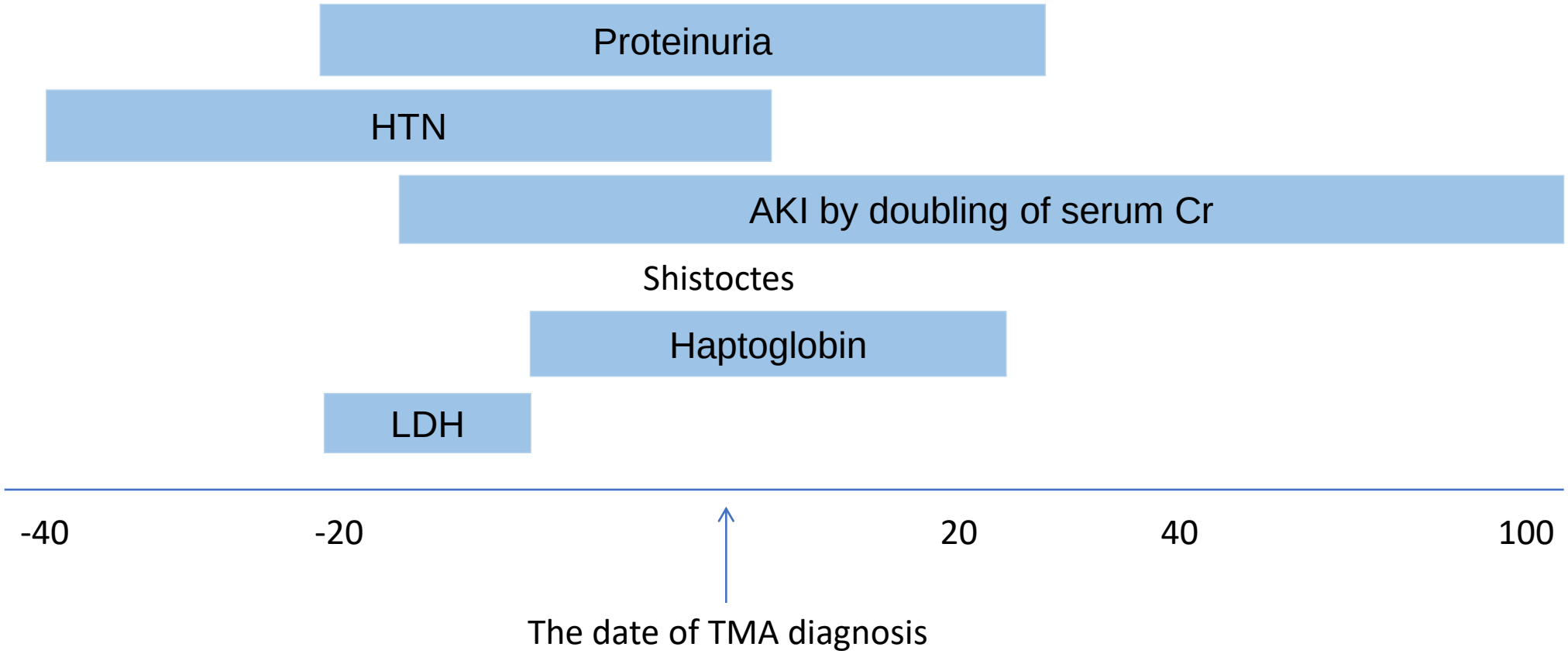
Polyserositis
Pericardial effusion, pleural effusion, ascites

Diagnostic criteria for TA-TMA with comparison of proposed definitions

Clinical or laboratory marker	CTN-TMA [19]	IWG-TMA [71]	City of Hope (COH)[f] [76]	Overall-TMA, Cho et al. [50]	Joint Study Group, Uderzo et al. [73]	TA-TMA by Jodele et al.[g] [15]
Schistocytosis	≥2/HPF	>4% (8/HPF)	Yes	≥2/HPF	>1–2/HPH	Yes
Negative direct and indirect Coombs test	Yes	–	–	Yes	Yes	–
Concurrent renal and/or neurologic dysfunction without other explanations[a]	Yes	–	SCr > 1.5 × baseline	–	Proteinuria and hypertension	Proteinuria and hypertension
Decrease in serum haptoglobin	–	Yes	–	Yes	–	–
De novo thrombocytopenia[b]	–	Yes	Yes	Yes	Yes	Yes
De novo anemia[c]	–	Yes	–	Yes	Yes	Yes
**Increase in serum LDH*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
**Hypertension*[d]	–	–	–	–	*Yes*	*Yes*
**■Proteinuria*[e]	–	–	–	–	*Yes*	*Yes*
■Terminal complement activation (Elevated sC5b-9)	–	–	–	–	*Yes*	*Yes*

J. A. Young et al. Bone Marrow Transplantation (2021) 56:1805–1817

Time course of clinical and laboratory markers in relation to date of TMA diagnosis



Risk Factors

Earliest markers of TMA in post-HSCT patients
10–14 days before the diagnosis of TMA

- Proteinuria ⩾ 30 mg/dL
- Hypertension
- Elevated LDH

Better markers of renal dysfunction compared with serum creatinine, which typically remains normal until significant injury has occurred.

Risk Factors

Inherent and non-modifiable	Transplant approach associated	Post-transplant event relate
• Gene variants • African- American patients • Female sex • CMV seropositive recipients • Severe aplastic anemia (SAA)	• Prior transplant • HLA-mismatched donors • Minor ABO mismatch • Myeloablative conditioning • Total body irradiation (TBI) • Fludarabine-based conditioning regimens • PBSCs are associated with a slightly higher risk	• CNI ± Sirolimus • Infection • Acute GVHD • sirolimus-containing GVHD prophylaxis. **(esp after busulfan conditiong regimen)**

Note : CD34 stem cell dose **does not** influence the development of TA-TMA.

9 JUNE 2020 x VOLUME 4, NUMBER 11

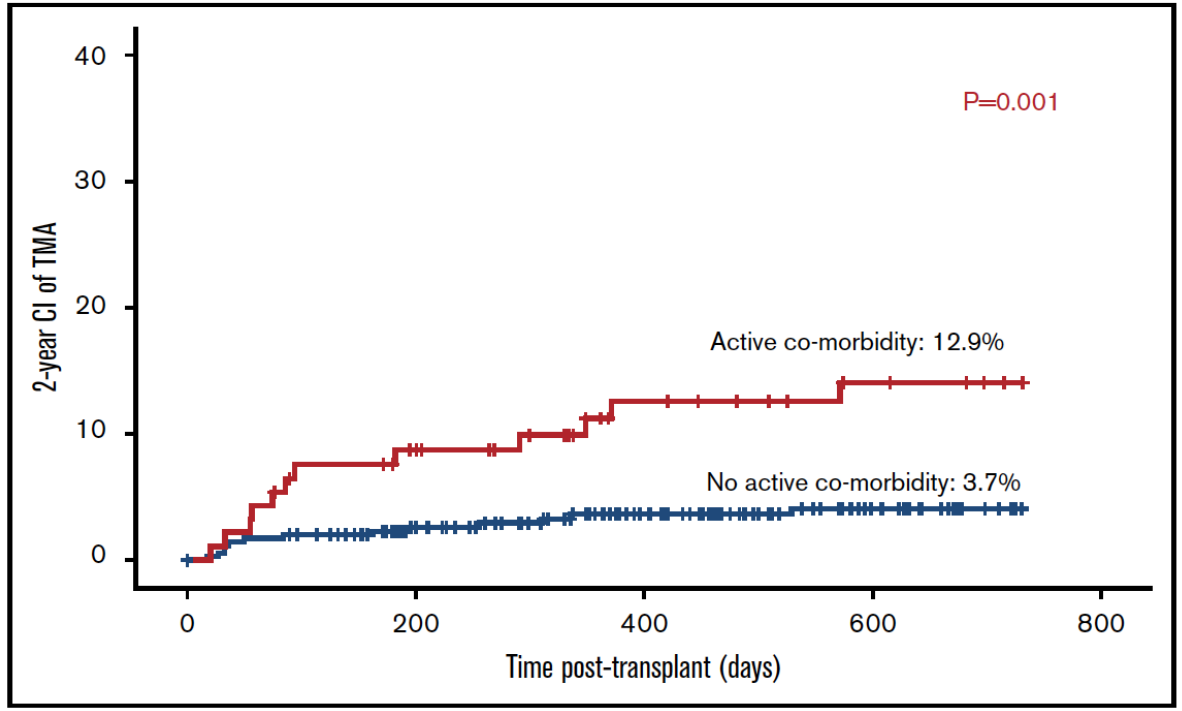
blood advances

New insights into risk factors for transplant-associated thrombotic microangiopathy in pediatric HSCT

Between 2013 and 2016, 439 children underwent HSCTs
in United Kingdom centers. occurred among 25 of 441 evaluable cases (5.6%)

Active comorbidity at D0 is a risk factor for TA-TMA.

1.Uncontrolled infection :
fungal infection
Bacterial infection
viral infection
2.**Cardiovascular instability.**
heart failure treatment
3.**cardiac thrombus.**
requiring continuation of anticoagulant
4.**Pulmonary instability with poor lung function** :requirement of oxygen



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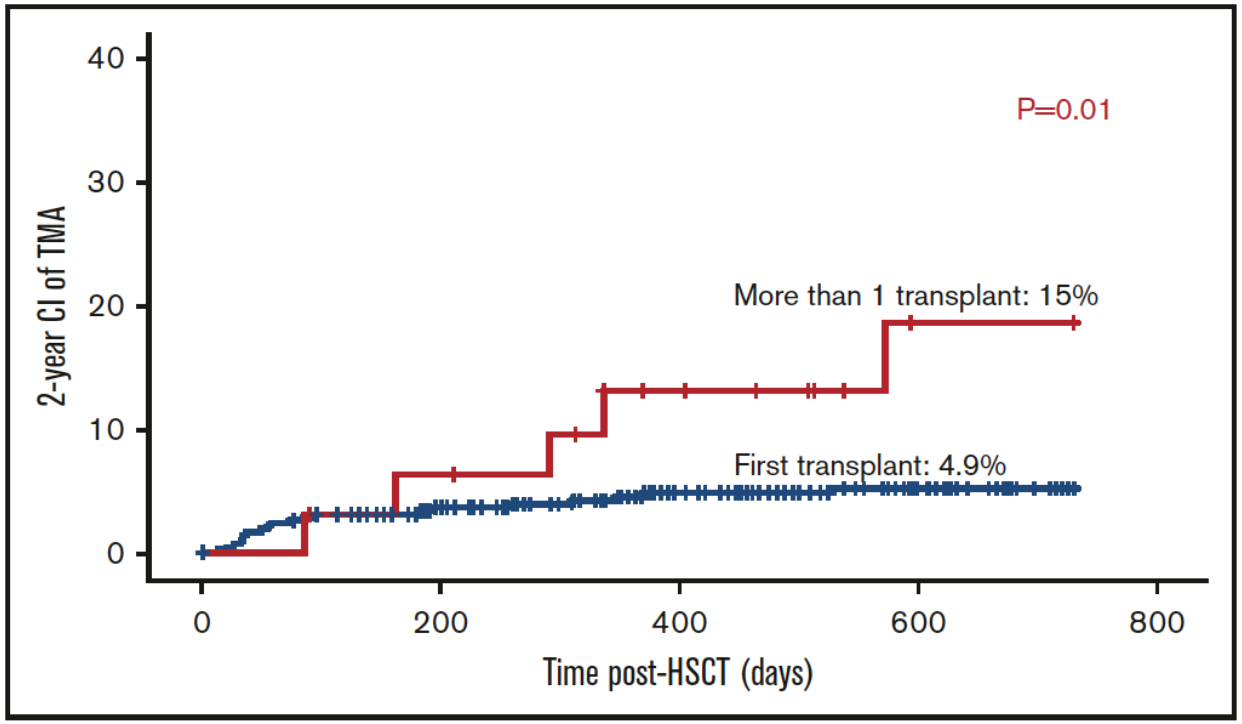
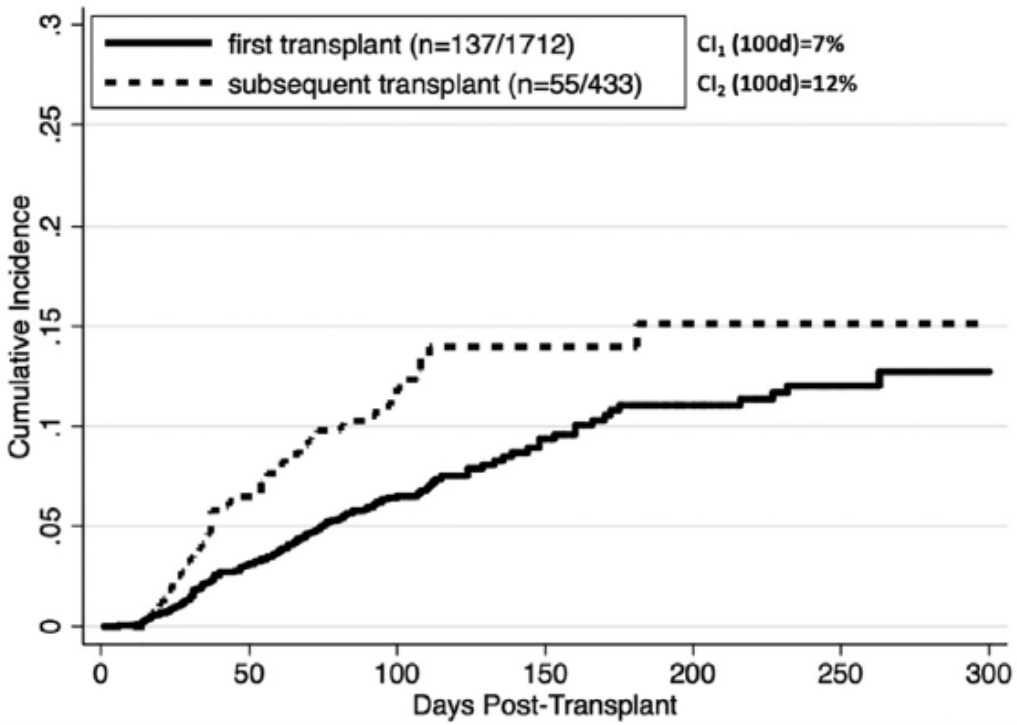
Number of transplants

- increases the risk for TA-TMA.





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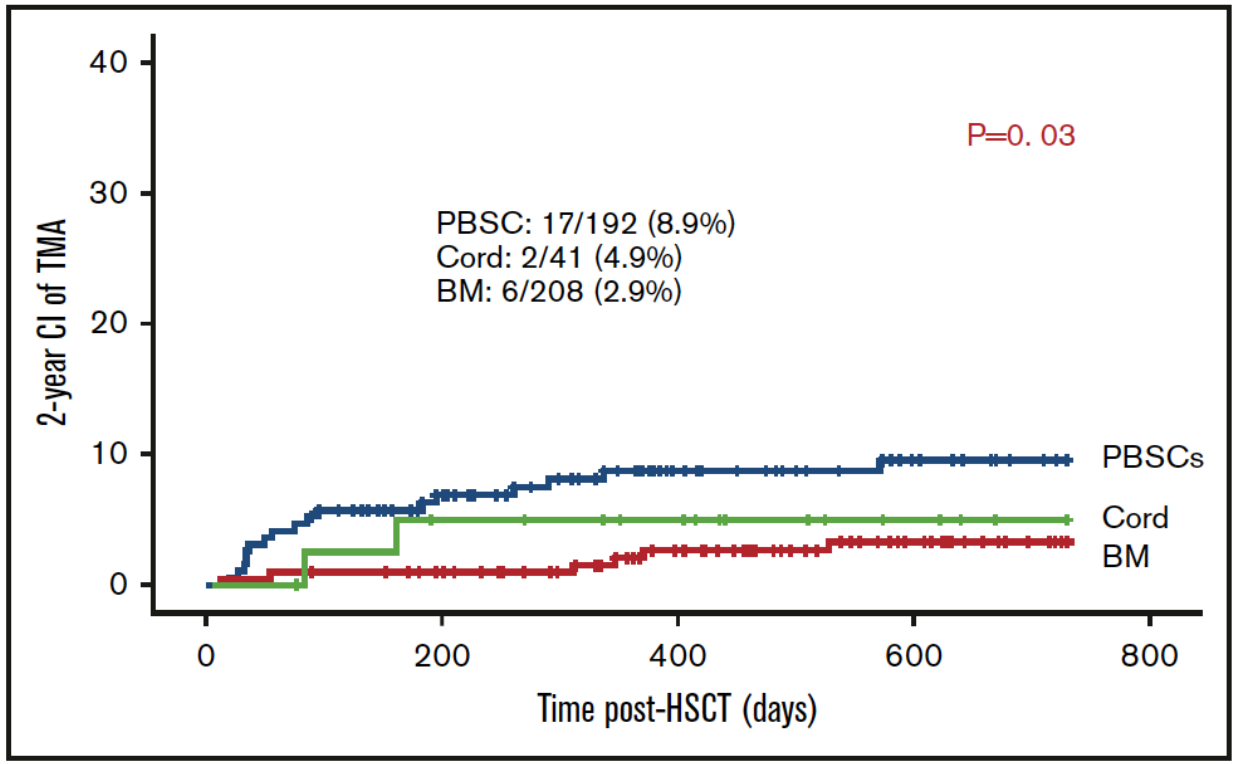
A. Li et al. Biol Blood Marrow Transplant 25 (2019) 570576

PBSC

- associated with a slightly higher risk for TA-TMA



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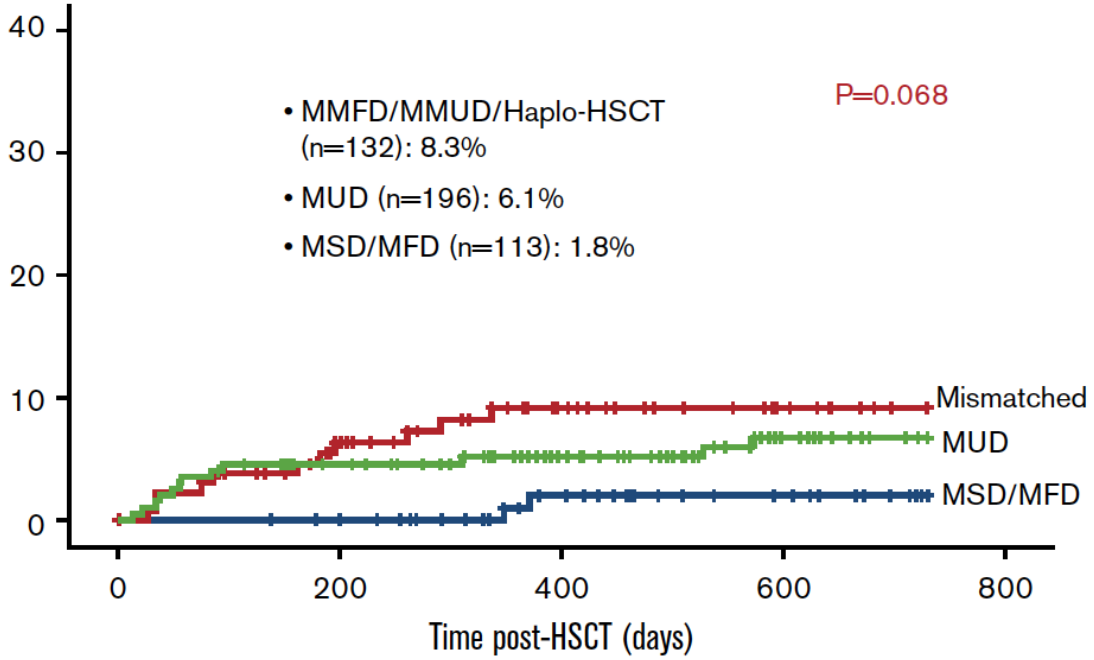
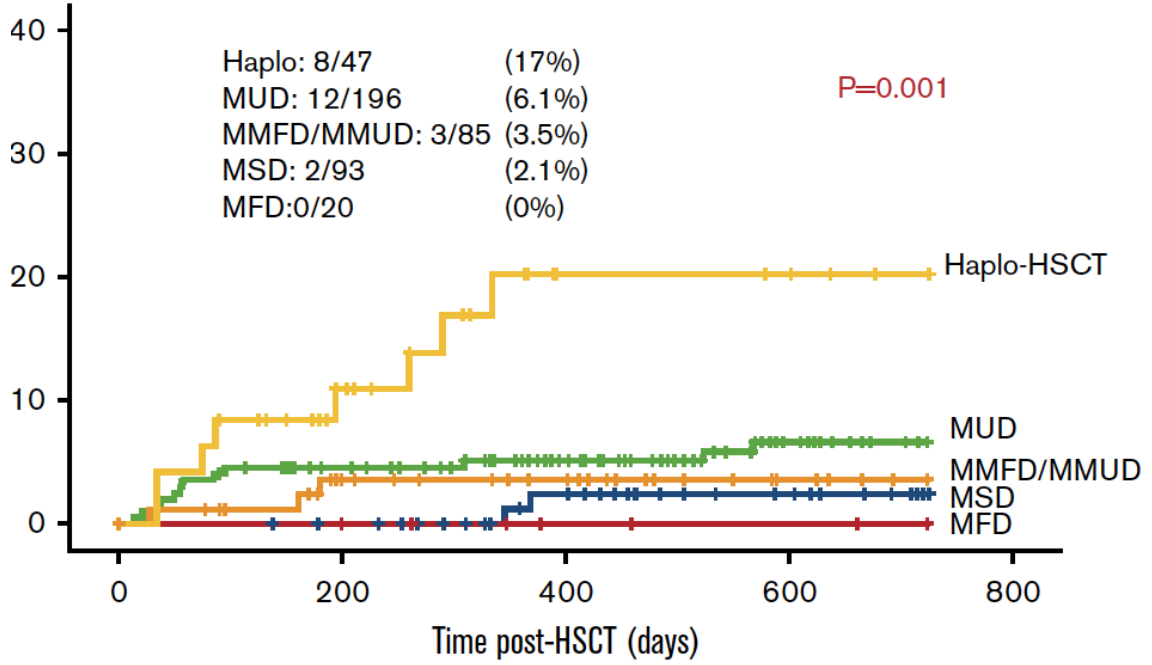
Mismatched grafts



Mismatched grafts are slightly associated with increased risk for TA-TMA.



Haplo- HSCT was associated with increased risk for TA-TMA.

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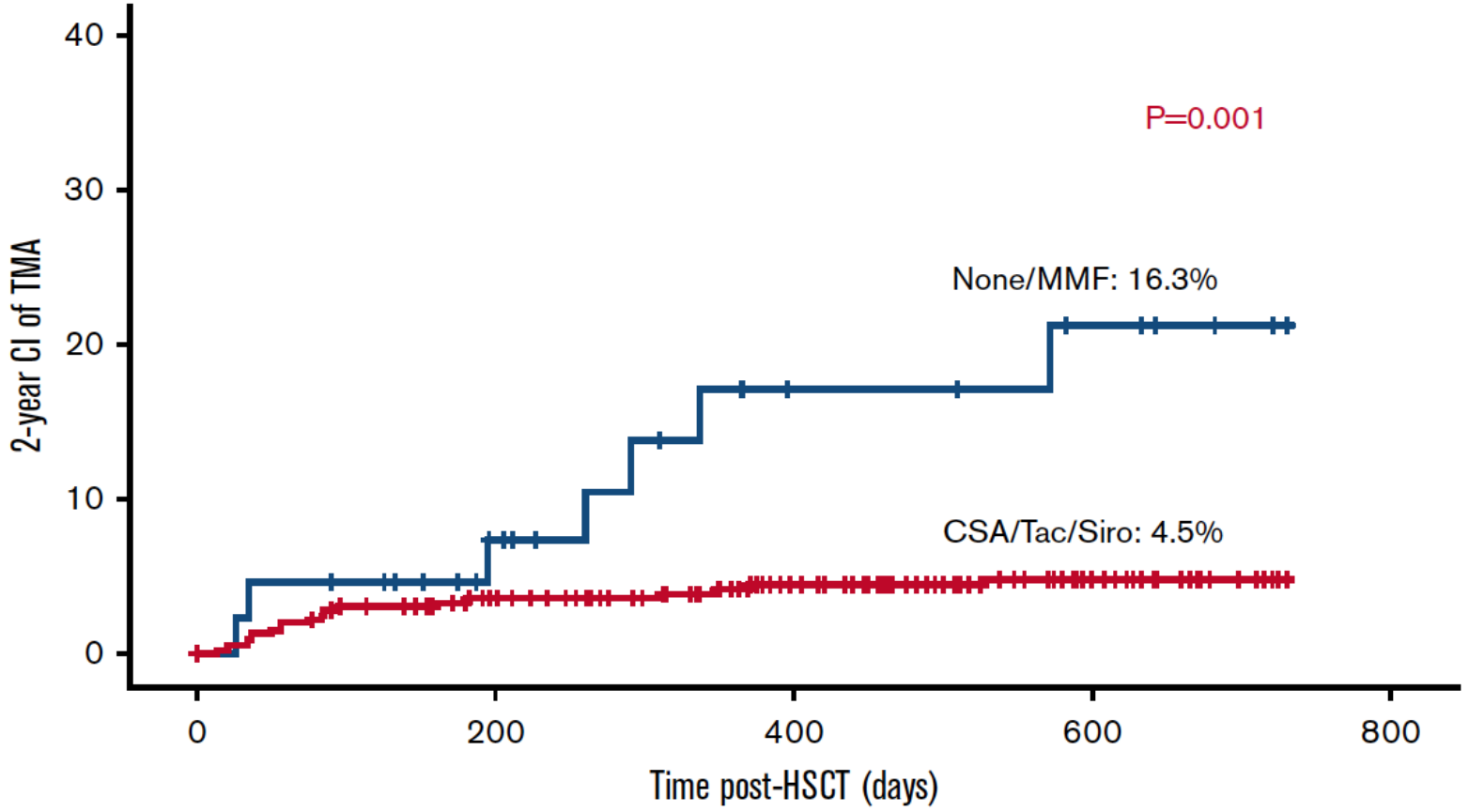
The use of calcineurin inhibitors is not associated with TA-TMA



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Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Transplant-Associated Thrombotic Microangiopathy Is a Multifactorial Disease Unresponsive to Immunosuppressant Withdrawal

Ang Li[1,*], Qian Wu[2], Chris Davis[2], Kedar S. Kirtane[1], Phuqui D. Pham[1], Mohamed L. Sorror[2,3], Stephanie J. Lee[2,3], Ajay K. Gopal[2,3], Jing-Fei Dong[1,4], David A. Garcia[1], Noel S. Weiss[5], Sangeeta R. Hingorani[2,6,7]

favor drug continuation

tacrolimus

cyclosporine

favor drug withdrawal

sirolimus plus CNI dual

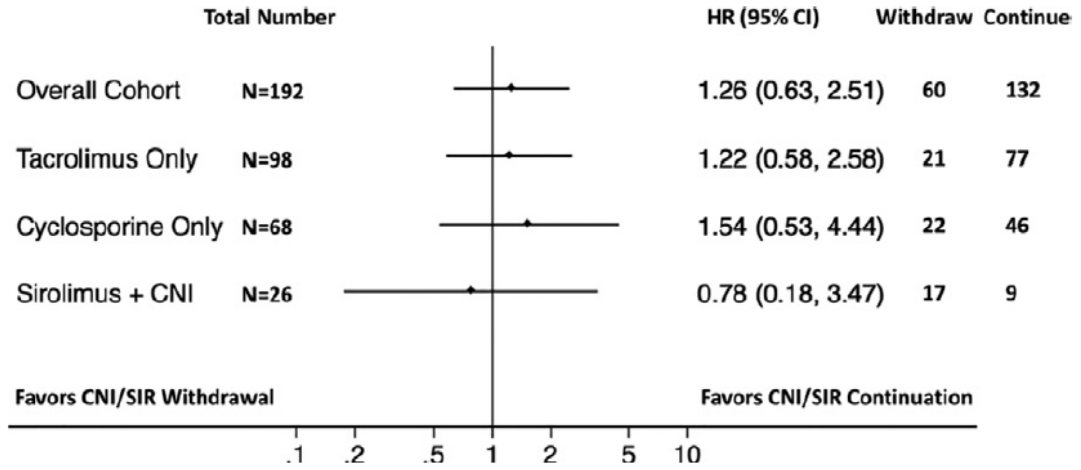


Figure 4. Outcome (overall survival) in relation to CNI or sirolimus continuation versus withdrawal in the calibration weighted cohort. The forest plot shows the relative survival associated with continuation versus withdrawal of immunosuppressants as well as individual subgroup analysis.

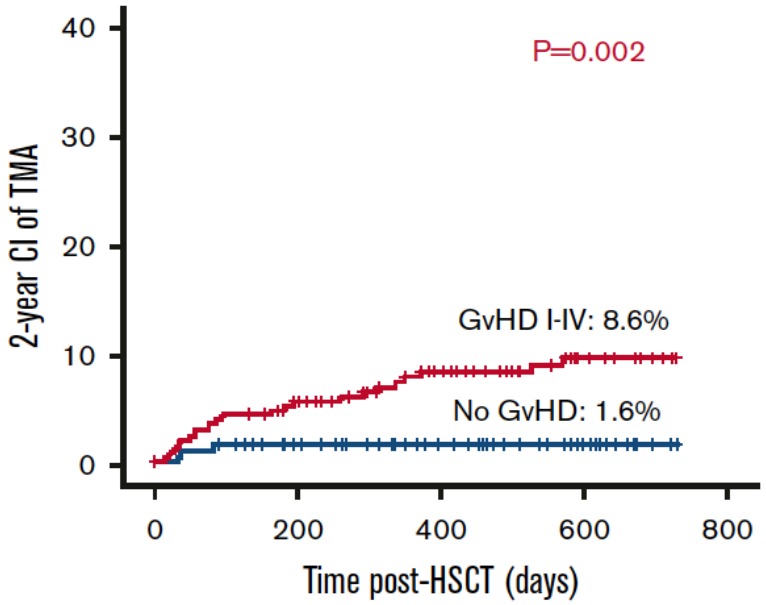
- retrospective analysis
- A small number of the patients in this study

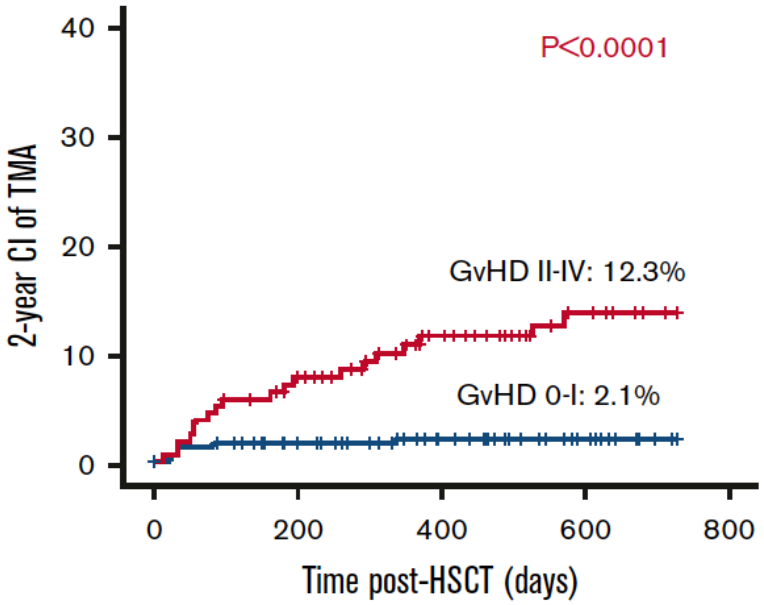
- stringent criteria

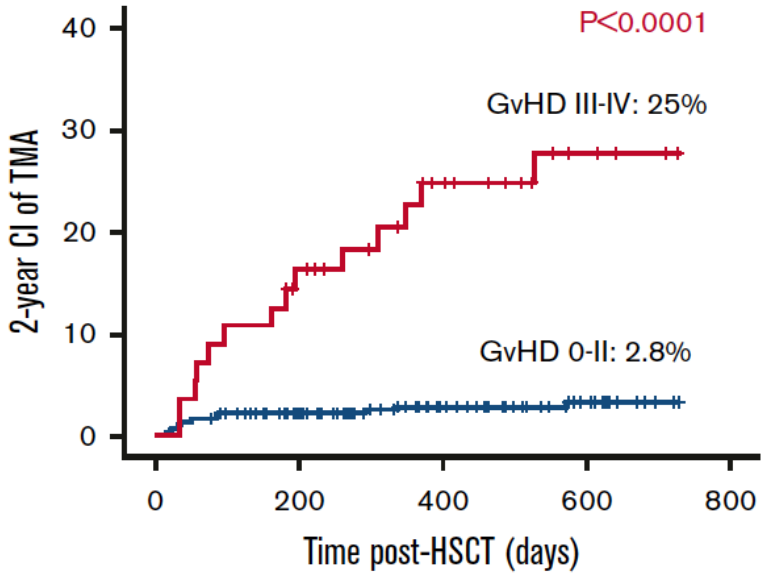
who fulfill all the criteria
At the end
patient is pretty [ill]

at that point **changing the CNI [calcineurin inhibitor] doesn’t help.**

Noticeable rise of the risk for TA-TMA with higher grades of aGVHD







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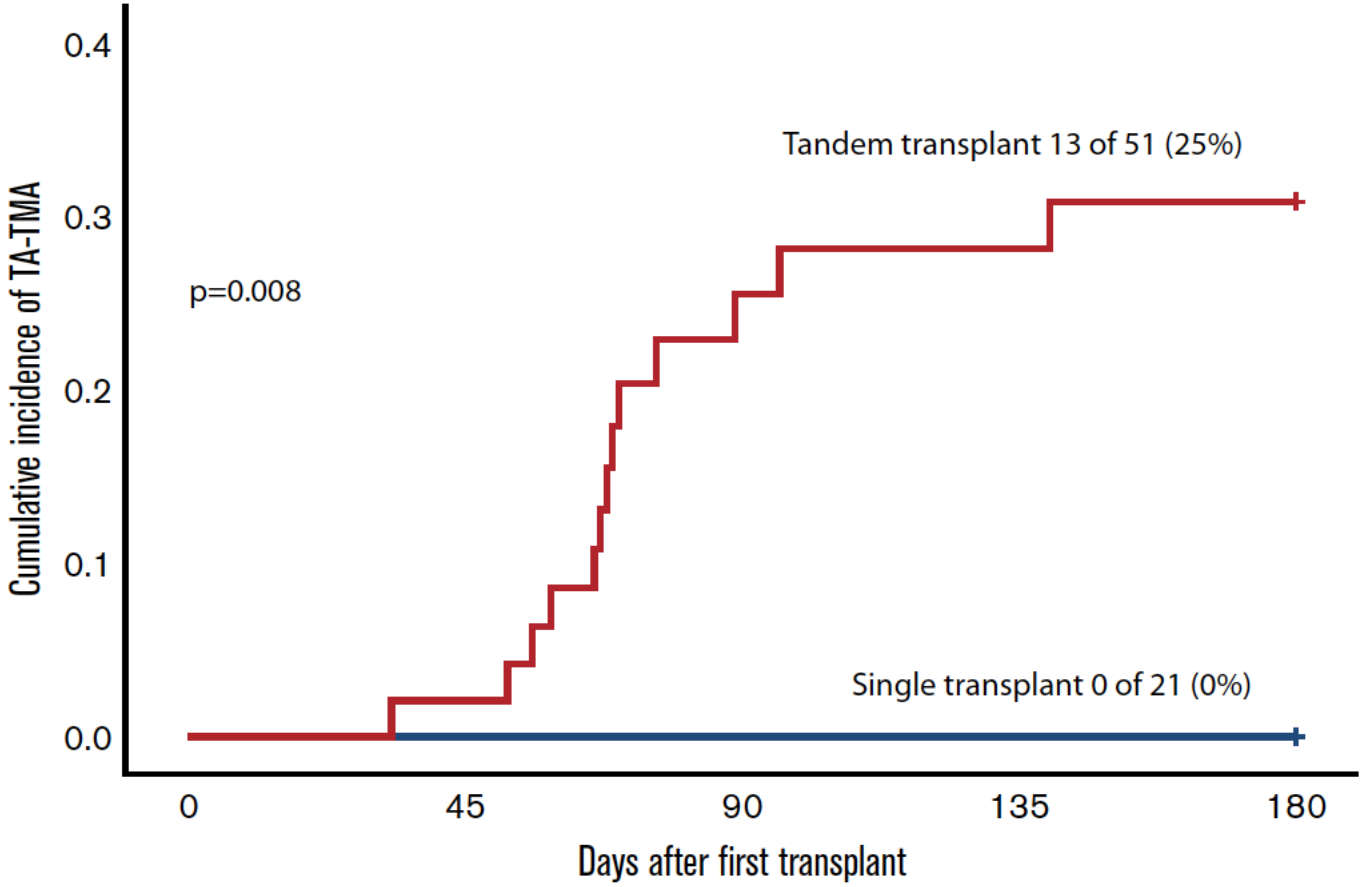
Cumulative incidence of TA-TMA in neuroblastoma patients



DANDOY et al. Blood advances 12 JANUARY 2021 x VOLUME 5, NUMBER 1

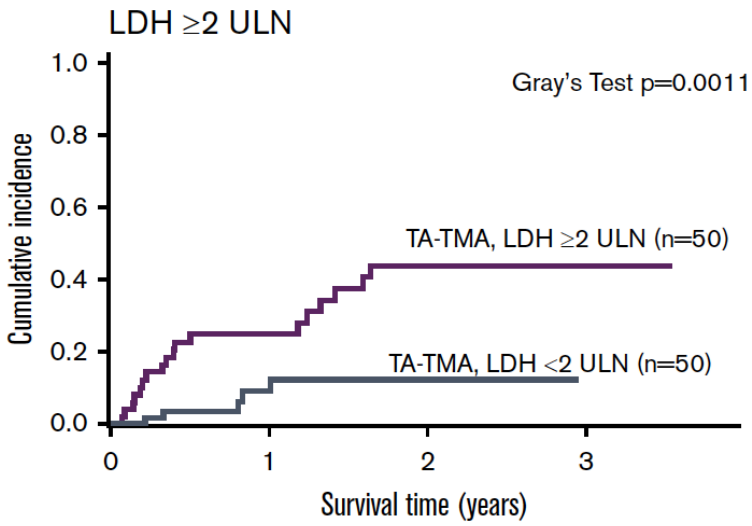
Poor prognostic factors in patients with TA-TMA

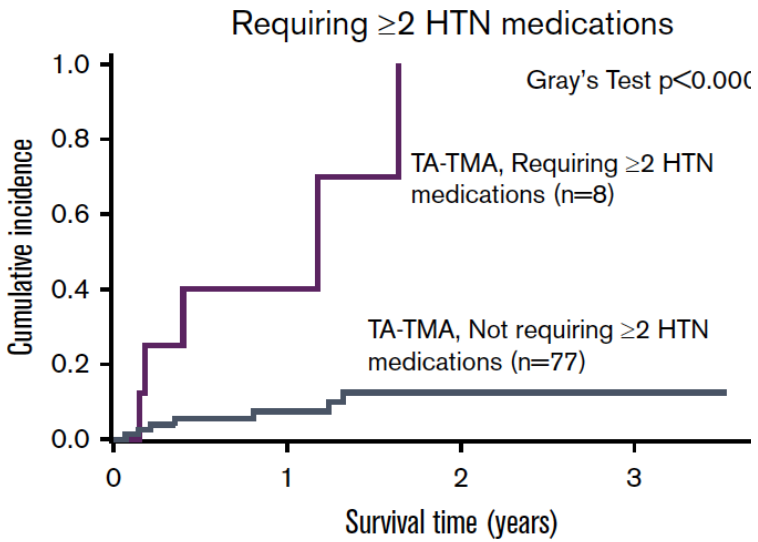
Proteinuria ⩾30 mg/dL

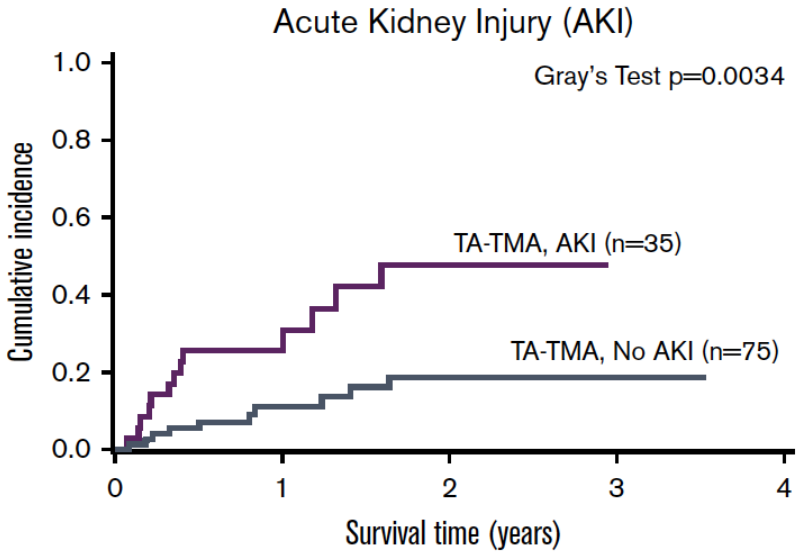
Elevated serum C5b-C9 levels (>244 ng/mL)

- Age ⩾18 years
- Unrelated or haploidentical donors
- TMA index (LDH/platelets ratio) ⩾20
- Schistocyte count > 5–10/hpf
- Elevated serum creatinine

Risk stratification: characteristics associated with increased TRM in patients MC-TA-TMA

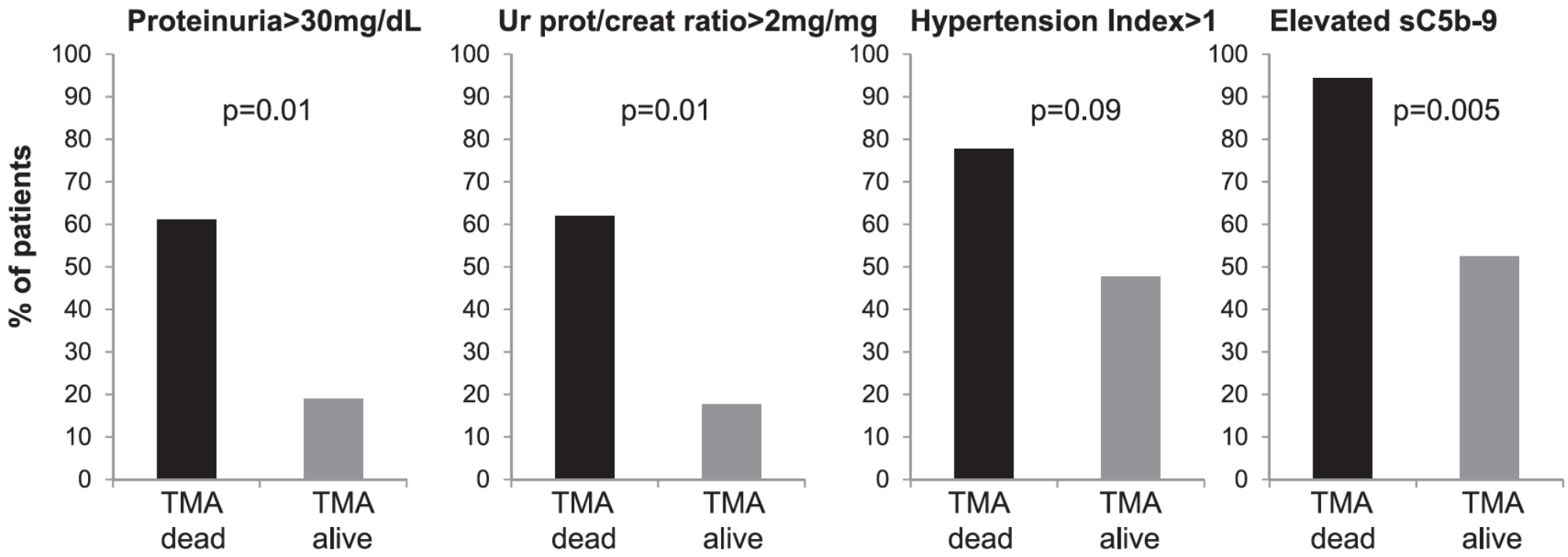






SCHOETTLER et al. Blood advances 9 JUNE 2020 x VOLUME 4, NUMBER 11

Association between markers at the time of TMA diagnosis and death by 1 year after HSCT



JODELE et al. Blood. 2014;124(4):645-653

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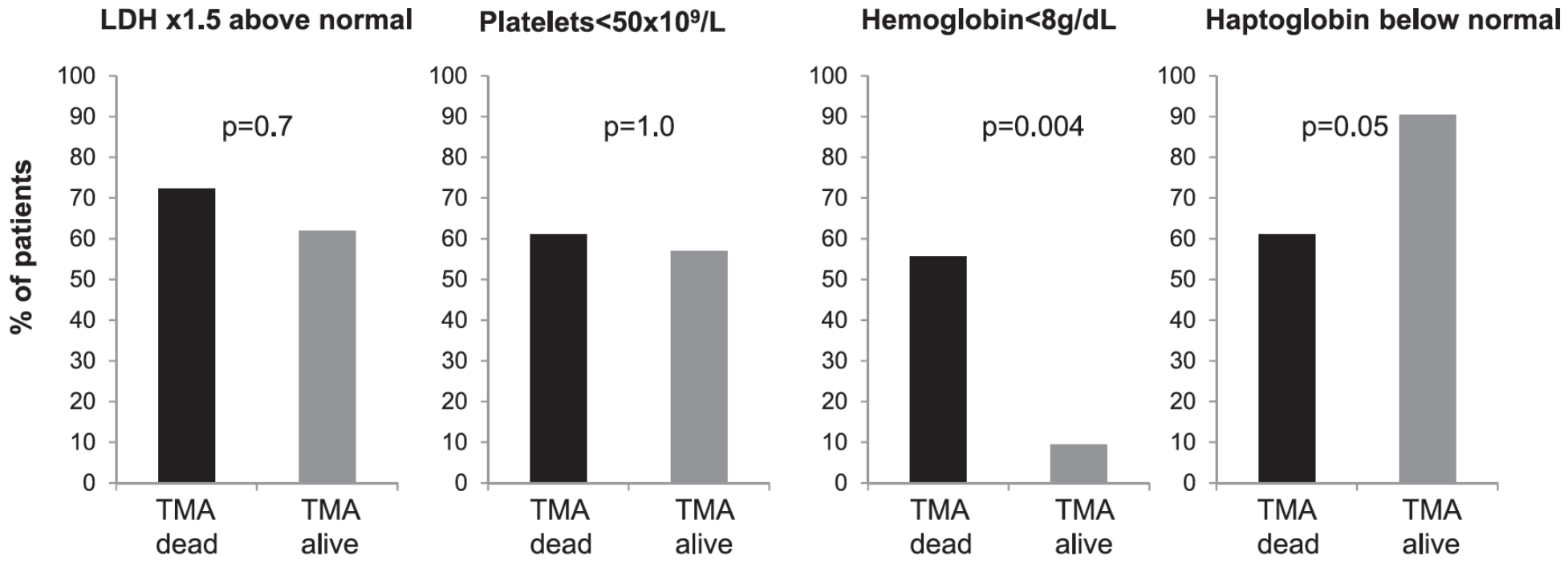
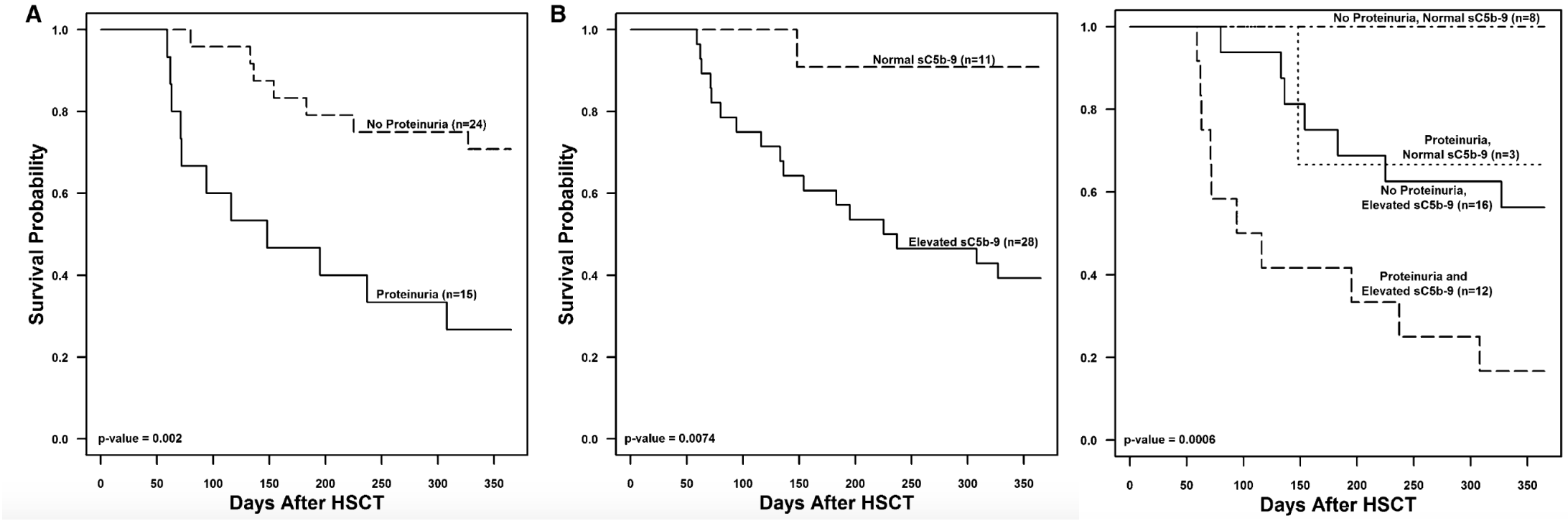


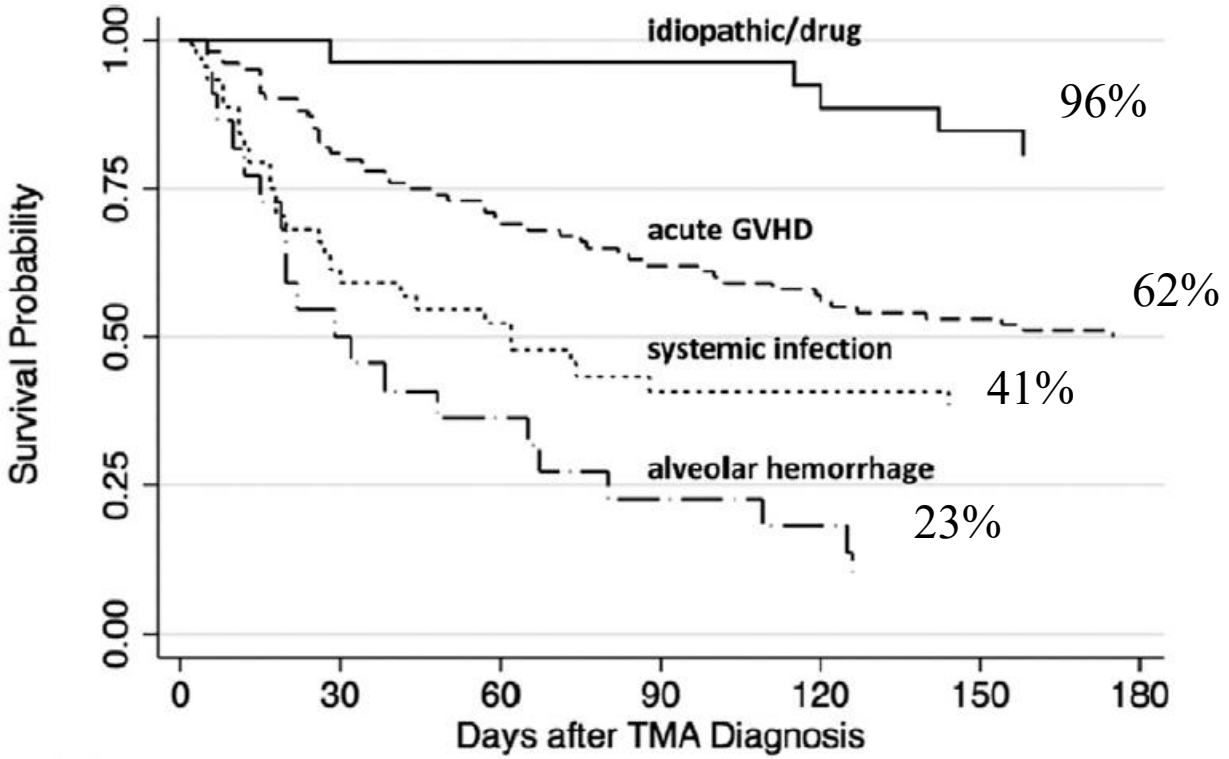
JODELE et al. Blood. 2014;124(4):645-653

Kaplan-Meier survival curves for subjects with TMA



JODELE et al. Blood. 2014;124(4):645-653

Prognosis (overall survival) for patients diagnosed with TA-TMA according to antecedent conditions.



Treatment

- Aggressive supportive care :

minimizing transfusions

aggressive hypertension management

treatment of any underlying infection

Withdrawal of CNI/mTORi

- commonly withdrawn upon recognition.
- Withdrawal should be performed **cautiously**, as exacerbation of GVHD could potentiate TA-TMA.
- Cyclosporine levels have not been correlated with TA-TMA.
- **supratherapeutic** tacrolimus levels at the time of TA-TMA diagnosis have **not been correlated with poorer outcomes.**

IL-2 inhibitor daclizumab (as an alternate to CNI & mTORi)

- explored the use of the in patients with GVHD and TA-TMA.

13- patient cohort

- 9 patients achieved complete remission of TA-TMA.
- two had stable disease, and one did not respond.

daclizumab is no longer available in US

basiliximab is available

Therapeutic plasma exchange (TPE)

- Used a lot in the past

Now :

- other complement directed therapies are not available
- clinical scenario suggests the presence of Antibodies to CFH

American Society of Apheresis guidelines, the role of TPE for TA-TMA is a weak, **grade 2C recommendation.**

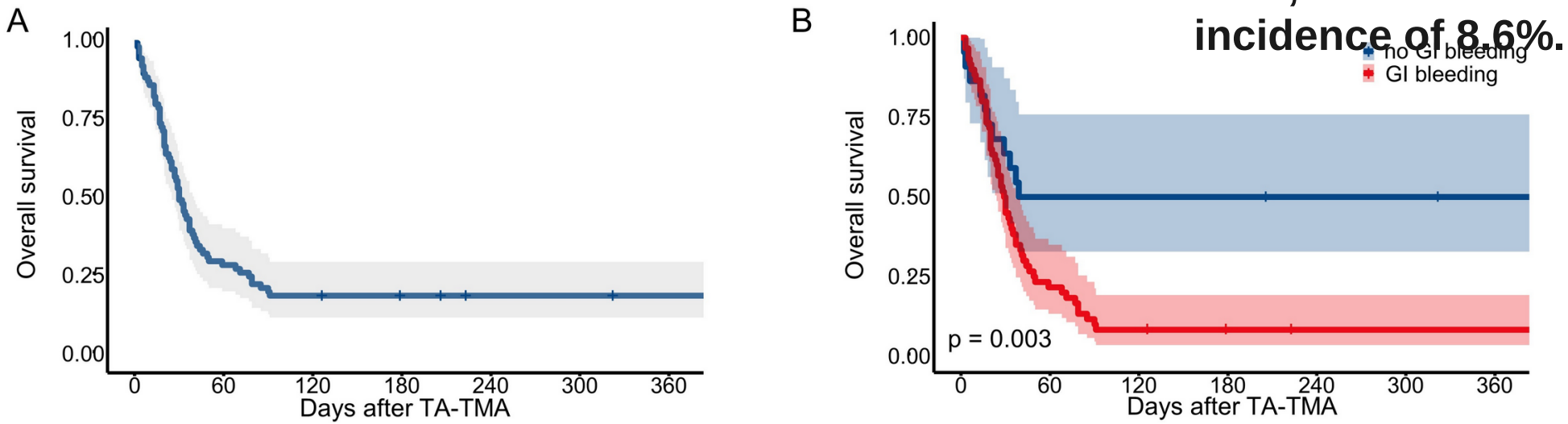
If there is any indication : **initiated early**

Treatment Outcome and Efficacy of Therapeutic Plasma Exchange for Transplant-Associated Thrombotic Microangiopathy in a Real-World Large Cohort Study

Li-Ping Yang, Peng Zhao, Ye-Jun Wu, Hai-Xia Fu, Yun He, Xiao-Dong Mo, Meng Lv, Feng-Rong Wang, Chen-Hua Yan, Yu-Hong Chen, Ying-Jun Chang, Lan-Ping Xu, Kai-Yan Liu, Xiao-Jun Huang, Xiao-Hui Zhang

Blood (2021) 138 (Supplement 1): 1013.

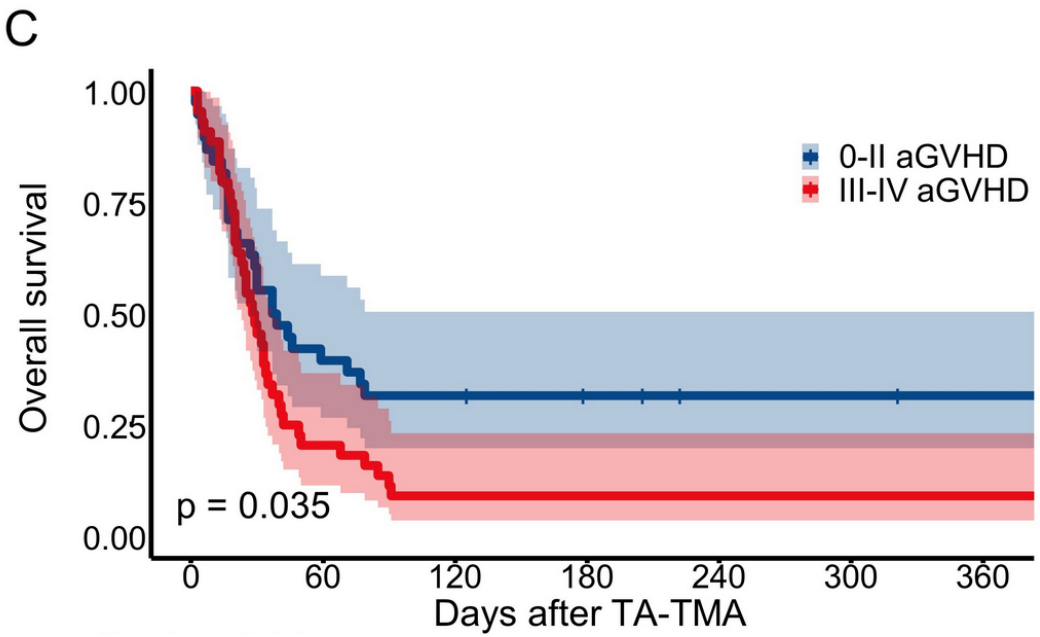
6241 underwent allo-HSCT Peking University
2010 to December 2019,
538 patients were diagnosed with TA-TMA,
incidence of 8.6%.

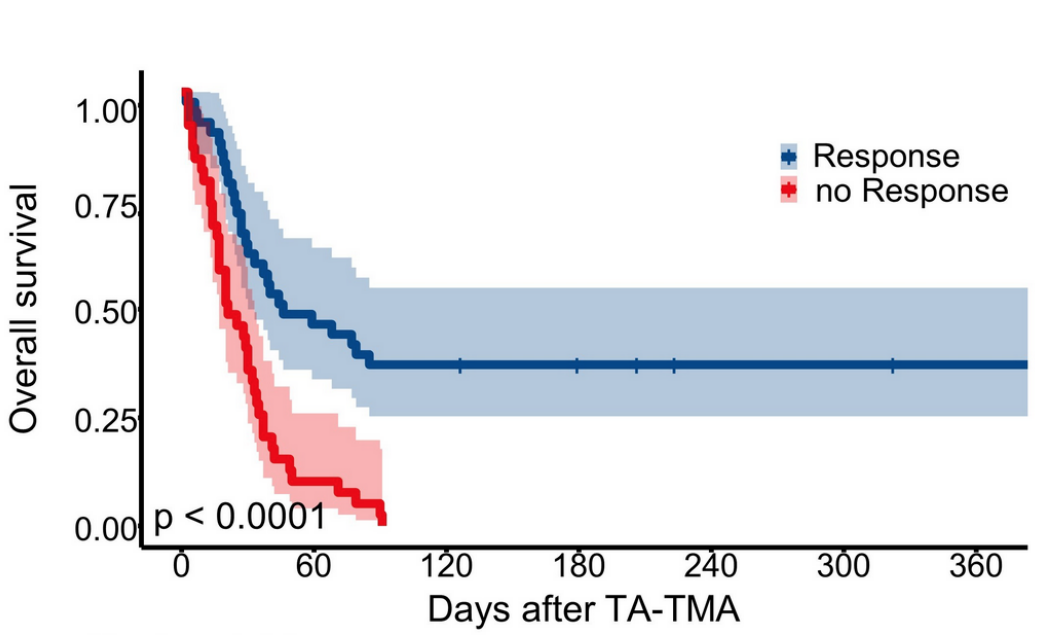


GI bleeding is independently associated with poor response to TPE and mortality.

Blood (2021) 138 (Supplement 1): 1013.

Treatment Outcome and Efficacy of Therapeutic Plasma Exchange for Transplant-Associated Thrombotic Microangiopathy





grade III-IV aGVHD is again confirmed as predicting a dismal response to TPE

Rituximab

- Evidence for use in TA-TMA is limited to single patient **case reports .**

- It can be considered in conjunction with TPE on a. **case-by-case basis.**

Defibrotide

Retrospective study in Spain:

- 17 adult patients with TA-TMA
- defibrotide was given as monotherapy in 5
- combination with other therapies in the remainder
- complete resolution was observed in 65% with an OS of 59%

- Yeates et al. presented a series of 17 defibrotide treated patients with resolution of TA-TMA achieved in 76% .

- Bohl et al. observed that patients treated with defibrotide with or without TPE and/or rituximab had a response rate of 61% .

- These findings support efficacy of defibrotide and **evaluation in prospective trials is warranted.**

Complement directed therapy

- **ECULIZUMAB :**

humanized monoclonal anti-C5 antibody that blocks the terminal complement pathway and prevents **membrane attack complex formation.**

small retrospective cohorts

- Many of these studies involved patients **previously treated with TPE and rituximab** as well as **withdrawal of CNI/mTORi.**
- Time to initiation varied widely
- most dosing strategies : 900mg weekly for 4 weeks followed by 1200mg biweekly. ((typical dosing for CM-HUS))
- some studies dosed based on eculizumab trough values and complement levels

- Response rates : 50 to 93%
- OS : 33 to 60%
- most complete responses : initiated early.

prospective study

TRANSPLANTATION

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

- eculizumab in 64 high-risk TA-TMA pediatric patients under age 18

hrTA-TMA :

- nephrotic range of proteinuria (rUPCR >2 mg/mg)
- elevated sC5b-9 (>244 ng/mL)
- or 1 of these 2 high- risk laboratory features with clinical evidence of multiorgan dysfunction syndrome

At 1 year,

- response rate :64%
- OS : 66%.
- who died, 2 had resolution of TA-TMA before death .
- remaining 27 had signs of active TMA at death.

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higher pretherapy sC5b-9

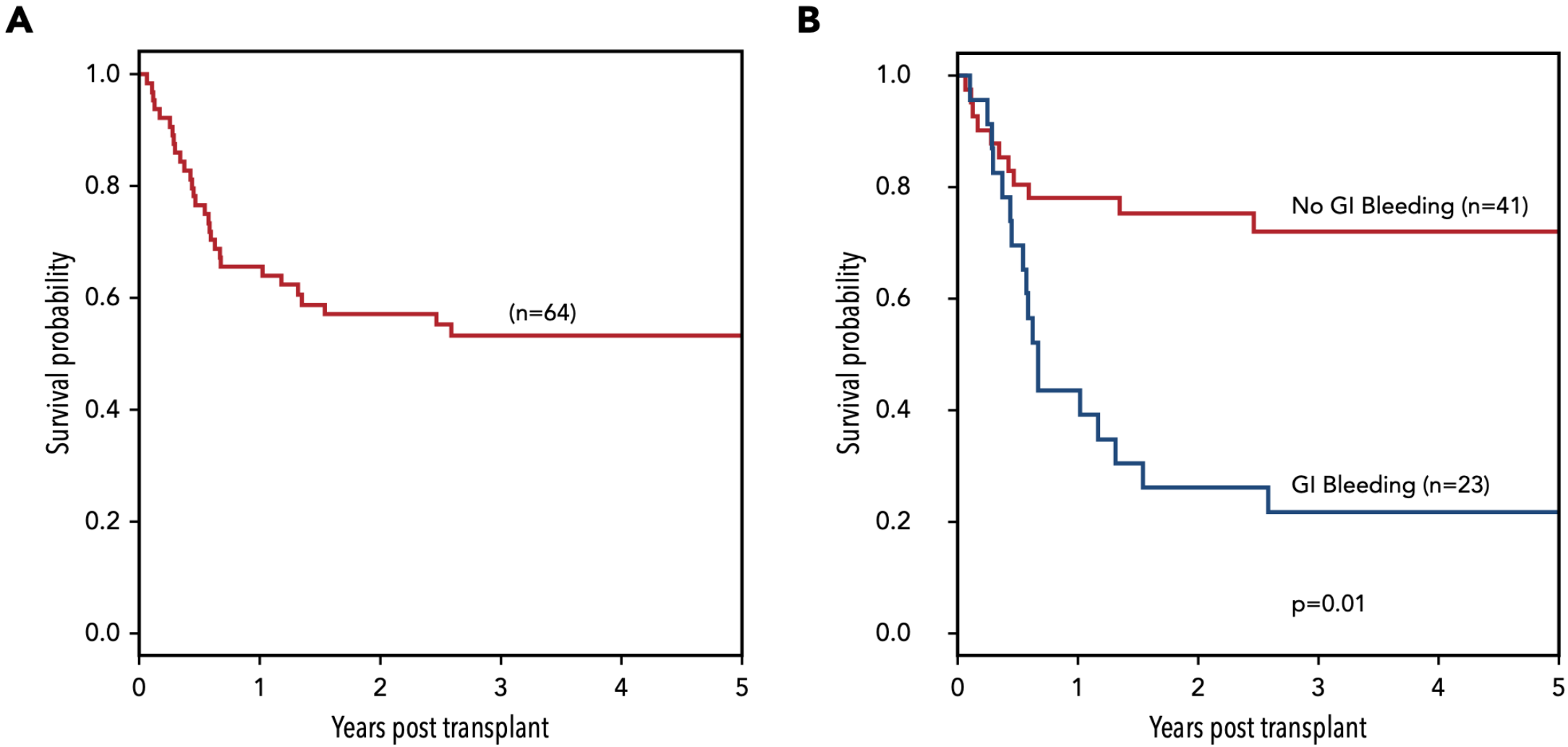
(higher systemic complement activation) :

- less likely to respond to treatment
- took longer to control complement activation
- required more doses of eculizumab
- worse outcomes

- Two main types of eculizumab NRs:

1.started on eculizumab therapy in the **terminal stages** (very advanced organ injury)

2.who had severe **intestinal bleeding**.


A
1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
(n=64)
0
1
2
3
4
5
Years post transplant
B
1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
No GI Bleeding (n=41)
GI Bleeding (n=23)
p=0.01
0
1
2
3
4
5
Years post transplant

- Unlike CM-HUS, TA-TMA may **not require life-long eculizumab**

Successful cessation

- full resolution of hematologic TMA markers and full complement blockade as determined by a low CH50 level.

meningococcal vaccination
primary prophylaxis against Neisseria meningitidis

- Still FDA has not approved eculizumab for TA-TMA.

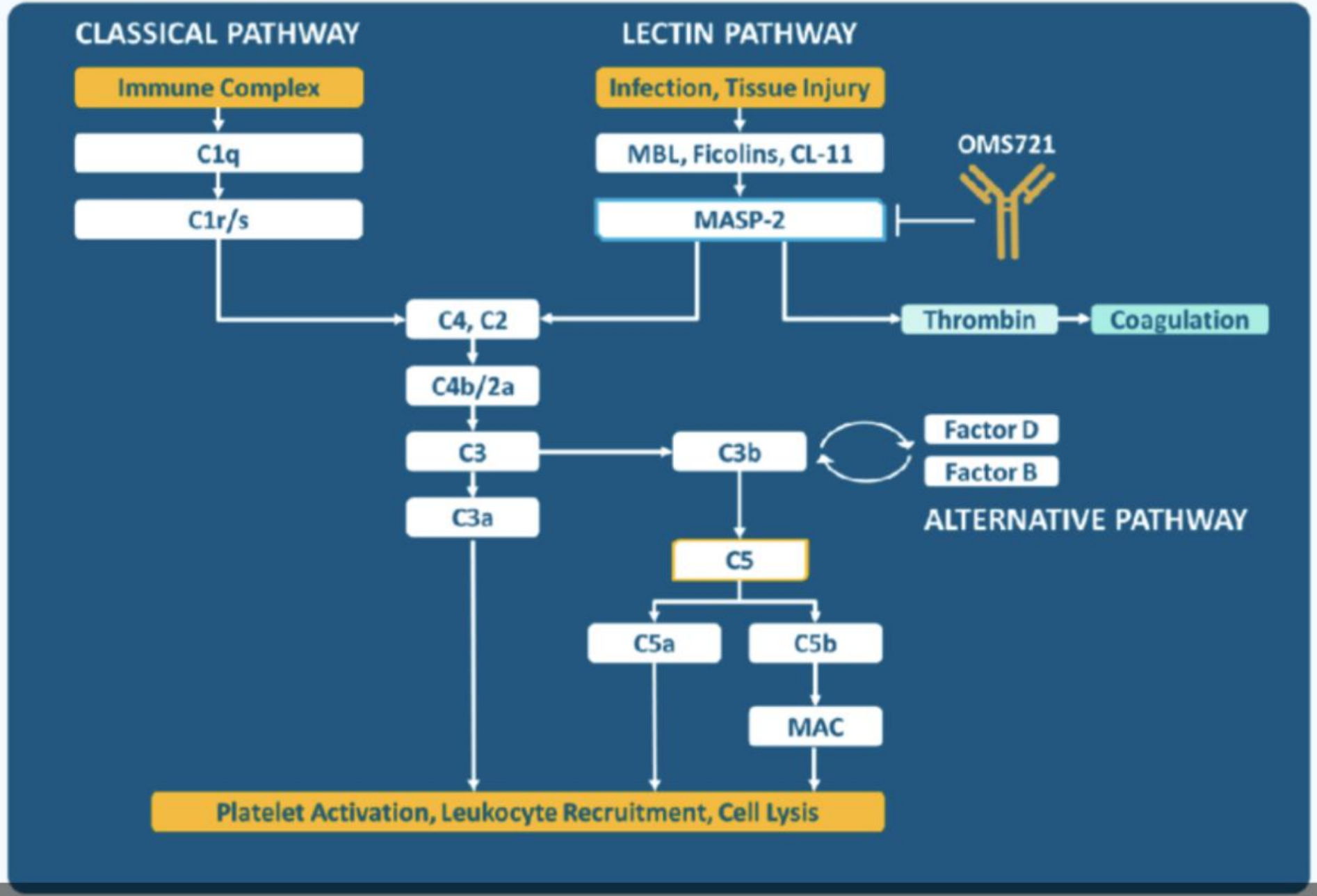
- prospective trials using eculizumab in adults with TATMA are needed

MASP-2 inhibition

narsoplimab :

- MASP-2 (mannan-binding lectin-associated serine protease-2) inhibitor
- Block effector enzyme of the lectin pathway in the complement system.
- selective complement inhibitor
- With out Immunologic dysfunction observed with broad complement inhibition.

Figure 1: Pathways of the Complement System



original reports

Narsoplimab, a Mannan-Binding Lectin-Associated Serine Protease-2 Inhibitor, for the Treatment of Adult Hematopoietic Stem-Cell Transplantation–Associated Thrombotic Microangiopathy

Samer K. Khaled, MD[1]; Kathleen Claes, MD, PhD[2,3]; Yeow Tee Goh, MBBS, MMed[4]; Yok Lam Kwong, MD[5]; Nelson Leung, MD[6]; Włodzimierz Mendrek, MD[7]; Ryotaro Nakamura, MD[1]; Jameela Sathar, MD[8]; Edmund Ng, PhD[9]; Narinder Nangia, PhD[10]; Steve Whitaker, MD[10]; and Alessandro Rambaldi, MD[11,12]; for the OMS721-TMA-001 Study Group Members

In this single-arm open-label pivotal trial

patients received intravenous narsoplimab (IV) 4 mg/kg once weeklyfor 4-8 weeks.

The primary end point **(response rate)** required clinical improvement in two categories:

(1)laboratory TMA markers (both platelet count and lactate dehydrogenase)
(2) organ function

Patients receiving at least one dose (full analysis set [FAS]; N=28) were analyzed

- response rate : 61%.

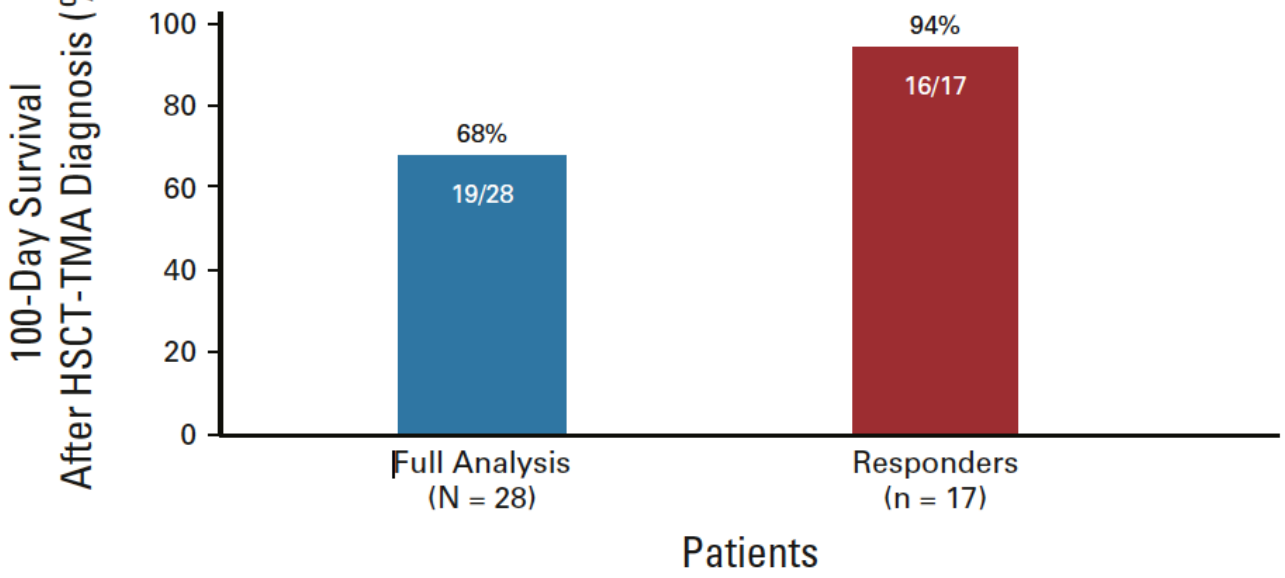
- Similar responses were **observed across all patient subgroups** defined by baseline features, HSCT characteristics, and HSCT complications.

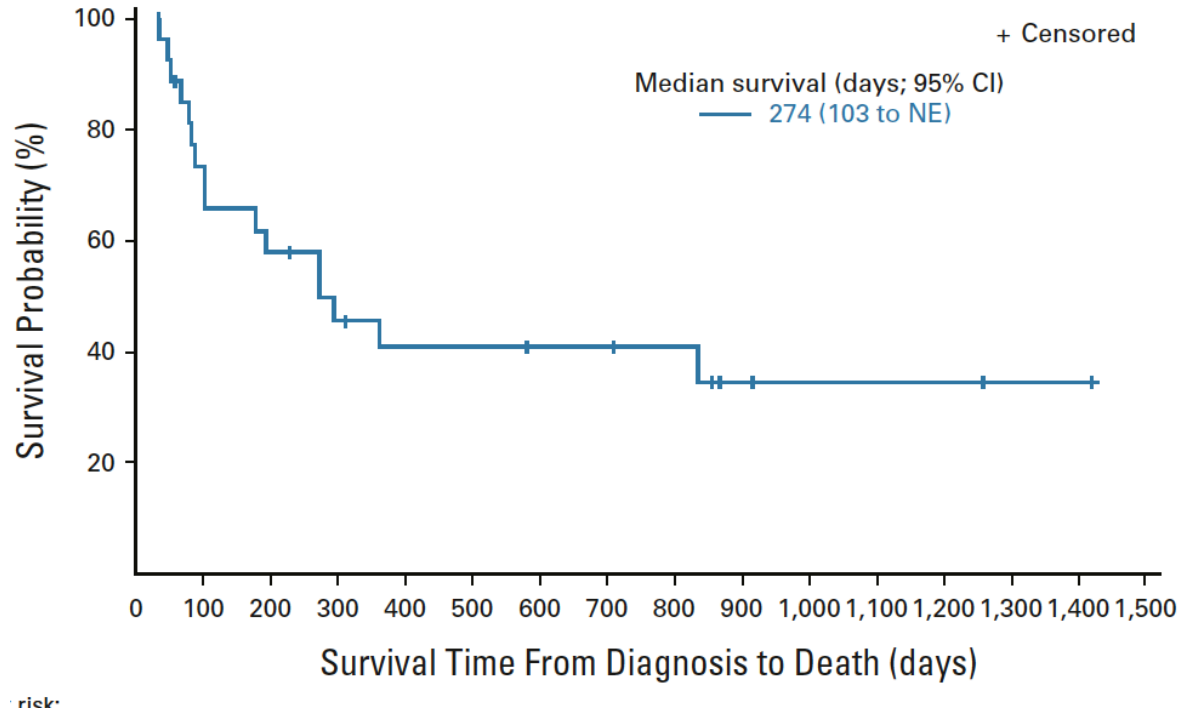
- Improvement in organ function : 74%

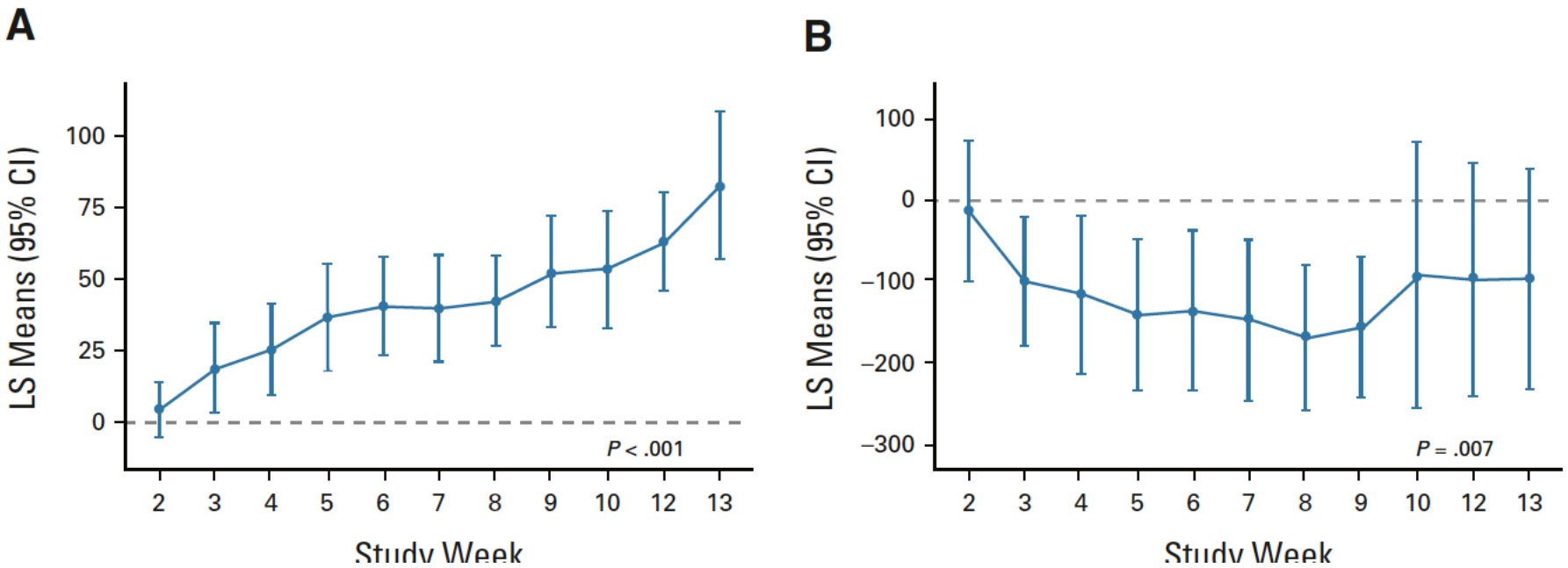
- median overall survival : 274 days in the FAS population.

- Narsoplimab was well tolerated, and adverse events were typical of this population, with no apparent safety signal of concern.

A

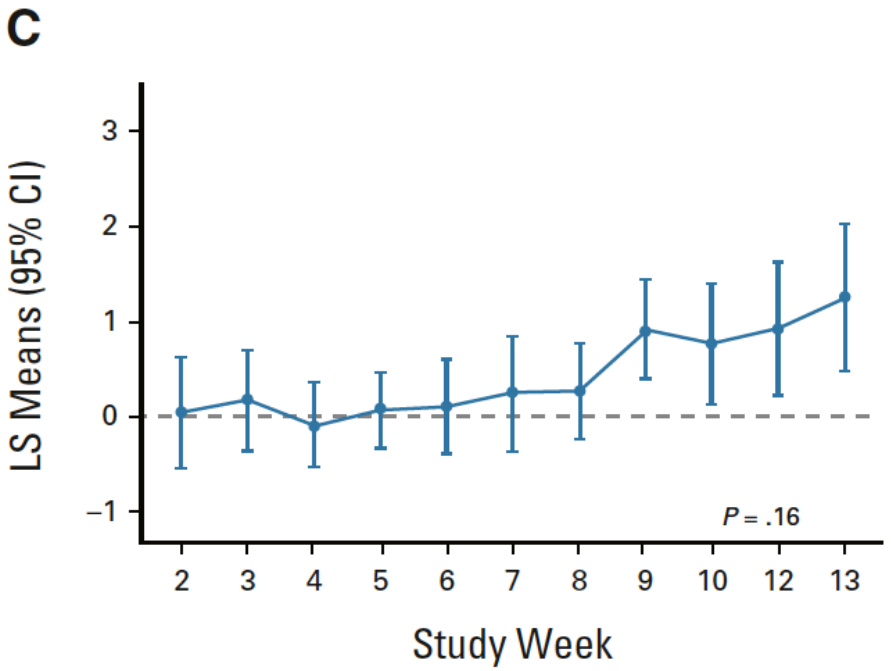

100-Day Survival
After HSCT-TMA Diagnosis (%)
100
80
60
40
20
0
68%
19/28
94%
16/17
Full Analysis
(N = 28)
Responders
(n = 17)
Patients


+ Censored
Median survival (days; 95% CI)
274 (103 to NE)
Survival Probability (%)
100
80
60
40
20
0
100
200
300
400
500
600
700
800
900
1,000
1,100
1,200
1,300
1,400
1,500
Survival Time From Diagnosis to Death (days)

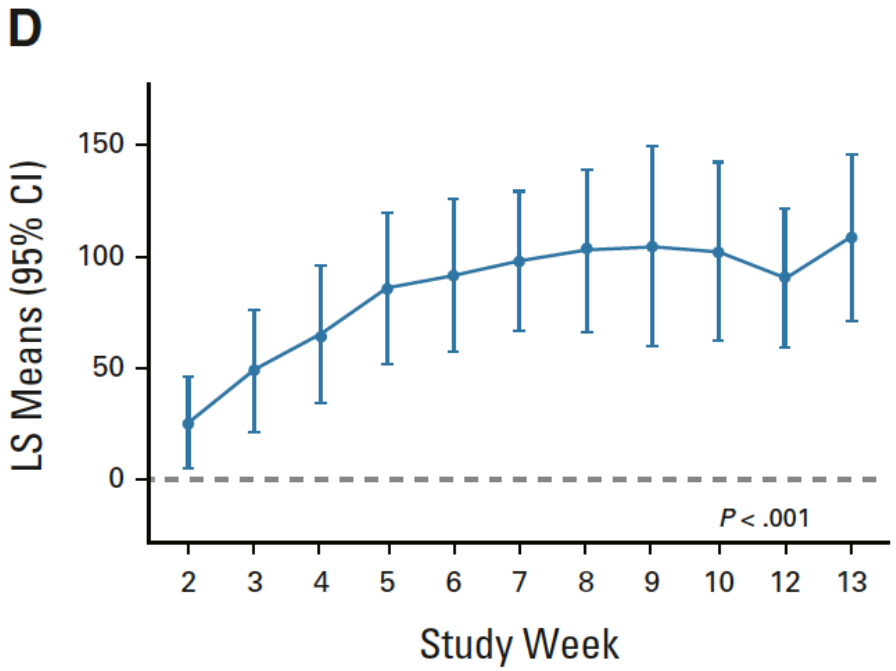


platelet count

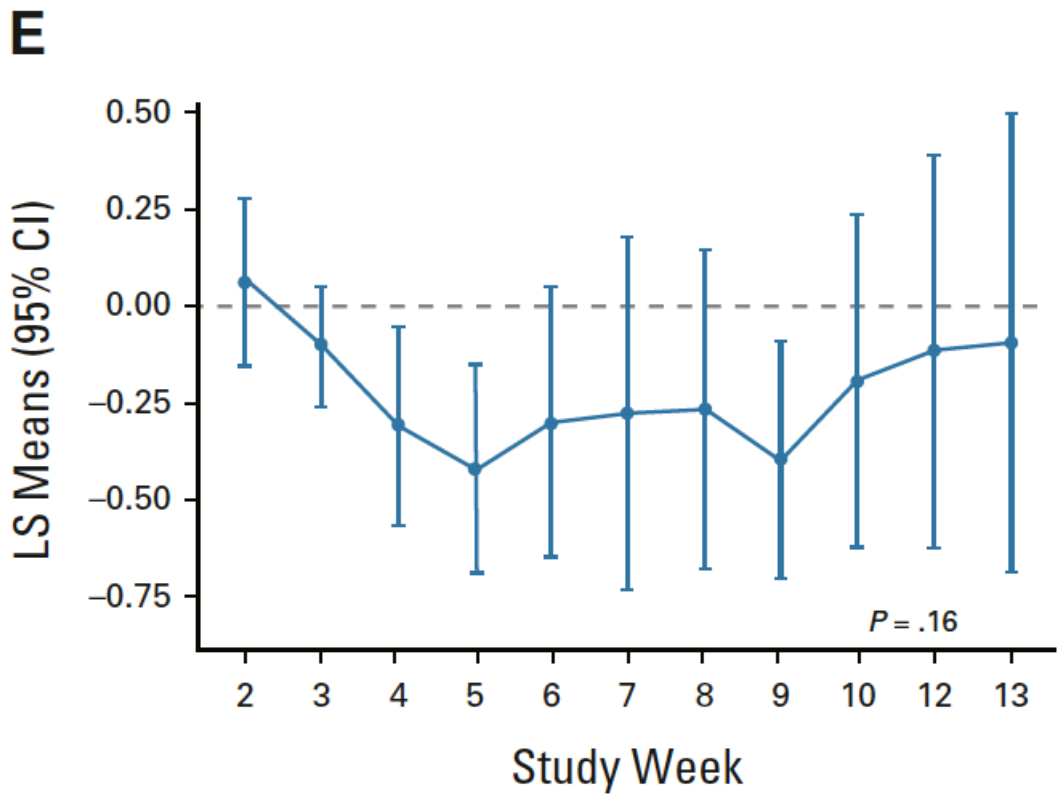
LDH



hemoglobin



haptoglobin


E
0.50
0.25
0.00
–0.25
–0.50
–0.75
LS Means (95% CI)
P = .16
2
3
4
5
6
7
8
9
10
12
13
Study Week

creatinine

FOR A BETTER WORLD WE DO CARE