“Aféresis en microangiopatía trombótica”

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- Thrombotic microangiopathy or TMA
- Hallmark:
  - THROMBOCYTOPENIA
  - MICROANGIOPATHIC HEMOLYTIC ANEMIA
    - SCHISTOCYTES

TABLE II. Disease Conditions to be Considered Before Selecting Therapy

Identified mechanism

1. ADAMTS13 deficiency
2. Complement regulatory defects
3. Shiga toxin
4. Disseminated malignancy
5. Malignant hypertension
6. Vasculitis

7. Neuramidase-associated (*S. pneumoniae*)
8. Cobalamine metabolic defects

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TABLE II. Disease Conditions to be Considered Before Selecting Therapy

Other relatively specific syndromes

1. Post transplantation
2. Infection (e.g. HIV)
3. HELLP syndrome, preeclampsia
4. Catastrophic antiphospholipid antibody syndrome
5. Medications—autoimmune (ticlopidine, quinine)
6. Medications—toxic (calcineurine inhibitors, gemcitabine, mitomycin C, clopidogrel, bevacizumab)

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Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Sixth Special Issue

Joseph Schwartz,[1] Jeffrey L. Winters,[2] Anand Padmanabhan,[3] Rasheed A. Balogun,[4] Meghan Delaney,[5] Michael L. Linenberger,[6] Zbigniew M. Szczepiorkowski,[7] Mark E. Williams,[8] Yanyun Wu,[9] and Beth H. Shaz[10,11]*

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Grade Recommendations
ASFA Categories
McLeod's Criteria

Grade	Description	Methodological Quality of Supporting Evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low- quality evidence	Observational studies or case series	May change when higher quality evidence becomes available

Guyatt G et al *Chest* 2006;129:174-181

Grade	Description	Methodological Quality of Supporting Evidence	Implications
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Guyatt G et al *Chest* 2006;129:174-181

TABLE I. Indications for Therapeutic Apheresis–ASFA 2013 Categories [1]

Category	Description
I	**Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.**

Examples: Thrombotic thrombocytopenic purpura (TTP) and Atypical HUS due to Factor H autoantibodies

J Clin Apher. 2013;28:145-284

II Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.

<u>Example</u>: Atypical HUS due to Complement factor gene mutation

III Optimum role of apheresis therapy is not established. Decision making should be individualized.

<u>Examples</u>: *S pneumoniae*-assoc HUS, clopidogrel-associated TMA, and refractory TMA associated with stem cell transplant

IV Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

<u>Examples</u>: aHUS caused by membrane cofactor protein mutations, Shiga toxin-producing *E coli-assoc* HUS, gemcitabine and quinine-induced aHUS

***J Clin Apher.* 2013;28:145-284**

McCleod's Criteria

- Plausible pathogenesis
- Better blood
- Perkier patient

McLeod BC J Clin Apher 2002;17:124-132

HUS, ATYPICAL

HEMOLYTIC UREMIC SYNDROME, ATYPICAL

Incidence: 3.3/1,000,000/yr (<18 yo); 7/1,000,000/yr (children in European community)

Condition	Procedure	Recommendation	Category
Complement factor gene mutations	TPE	Grade 2C	II
Factor H autoantibodies	TPE	Grade 2C	I
MCP mutations	TPE	Grade 1C	IV

# of reported patients*: >300

	RCT	CT	CS	CR
Complement factor gene mutations	0	0	4(23)	21(26)
Factor H autoantibody	0	0	2(6)	2(2)

MCP = membrane cofactor protein

TPE for Condition	Recommendation Grade	Category
Complement factor gene mutation	2C	II
Factor H autoantibodies	2C	I
Membrane cofactor protein mutations	1C	IV

HUS, INFECTION-ASSOCIATED

HEMOLYTIC UREMIC SYNDROME, INFECTION ASSOCIATED

Incidence: D+HUS: 0.5–2/100,000 in general population

Condition	Procedure	Recommendation	Category
STEC-HUS	TPE	Grade 1C	IV
pHUS	TPE	Grade 2C	III

# of reported patients*: >300

	RCT	CT	CS	CR
D+HUS	1 (35)	1 (37)	52 (1365)	96 (110)

D+HUS = diarrhea-associated HUS; HUS = hemolytic uremic syndrome; pHUS = *Streptococus pneumonia* associated HUS; STEC-HUS = Shiga toxin-producing *Escherichia coli* associated HUS.

TPE for Condition	Recommendation Grade	Category
Shiga toxin-producing *E coli-assoc* HUS	1C	IV
S pneumoniae-assoc HUS	2C	III

TMA, DRUG-ASSOCIATED

THROMBOTIC MICROANGIOPATHY, DRUG-ASSOCIATED

Incidence: Clopidogrel/Ticlopidine: .001% to .0625%; Cyclosporine / Tacrolimus: rare; Gemcitabine: .015% to 1.4%; Mitomycin 2–15%; Quinine: rare

Condition	Procedure	Recommendation	Category
Ticlopidine	TPE	Grade 2B	I
Clopidogrel	TPE	Grade 1B	III
Cyclosporine/ tacrolimus	TPE	Grade 2C	III
Gemcitabine	TPE	Grade 2C	IV
Quinine	TPE	Grade 2C	IV

# of reported patients*: >300

	RCT	CT	CS	CR
Ticlopidine/Clopidogrel	0	0	4(152)	5(5)
Cyclosporine/Tacrolimus[+]	0	0	6(90)	7(7)
Gemcitabine	0	0	3(39)	9(11)
Bevacizumab	0	0	1 (6)	2 (2)
Quinine	0	0	3(32)	8(8)

[+] Evaluated in aggregate since these are frequently prescribed on alternating or tandem schedules.

TPE for Condition	Recommendation Grade	Category
Ticlopidine	2B	I
Clopidogrel	1B	III
Cyclosporine/tacrolimus	2C	III
Gemcitabine	2C	IV
Quinine	2C	IV

TMA, HSCT-ASSOCIATED

THROMBOTIC MICROANGIOPATHY, HEMATOPOIETIC STEM CELL TRANSPLANT ASSOCIATED

Incidence: 1-year cumulative 13% (non-myeloablative) versus 15% (high-dose); **Prevalence**:10–25%	**Condition**	**Procedure**	**Recommendation**	**Category**
	Refractory	TPE	Grade 2C	III

# of reported patients*: >300

RCT	**CT**	**CS**	**CR**
0	0	23(345)	6(6)

TPE for Condition	Recommendation Grade	Category
Refractory	2C	III

TTP

232 Schwartz et al.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Incidence: 0.37/100,000/year (US)	Procedure	Recommendation	Category
	TPE	Grade 1A	I

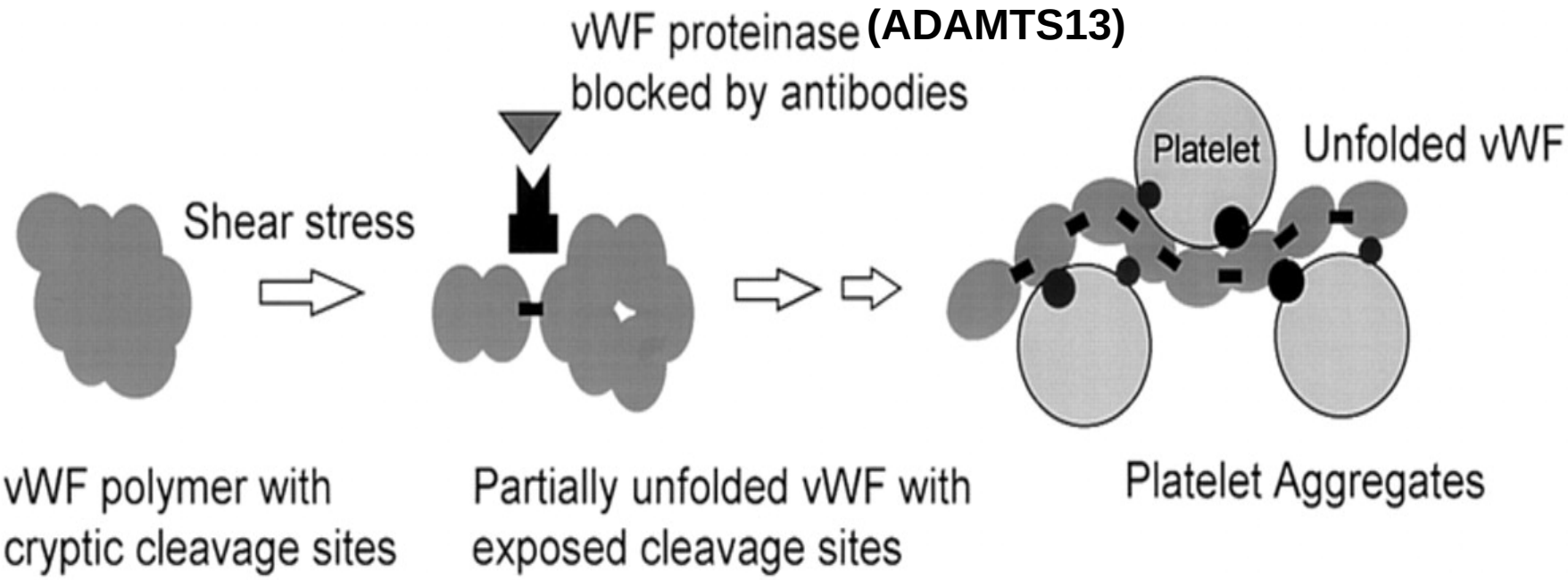
# of reported patients*: >300

RCT	CT	CS	CR
7 (301)	2 (133)	26 (980)	46 (83)

TPE for Condition	Recommendation Grade	Category
Thrombotic thrombocytopenic purpura	1A	I

Massive hemolysis due to thrombotic thrombocytopenic purpura in a patient with AIDS

TRANSFUSION 2012;52:1408-1409.



Tsai, et al. *Annals of Internal Medicine* (2000)

First symptoms in patients with thrombotic thrombocytopenic purpura: what are they and when do they occur?

- 34 patients from UAB and Oklahoma with ADAMTS13 <10%
- Single most common symptom: Abdominal pain (23.5%)
    - with or without nausea/vomiting
- Less than 10% with bleeding

- Mean n of days pre-TPE: 12
- Median n of days pre-TPE: 5.5

} 62% treated within 7 days

First symptoms in patients with thrombotic thrombocytopenic purpura: what are they and when do they occur?

- Other diagnosis considered (11):
  - Meningitis, arthritis, gastroenteritis, systemic lupus erythematosus, immune thrombocytopenia, stroke, urosepsis, diabetic nonketotic hyperosmolar acidosis, pernicious anemia, pancreatitis, antiphospholipid syndrome.

Platelet Count and Prothrombin Time Help Distinguish Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome From Disseminated Intravascular Coagulation in Adults

Yara A. Park, MD,[1] Michael R. Waldrum, MD,[2] and Marisa B. Marques, MD[3]

Table 2

Univariate Analysis of the Relationship Between Admission Laboratory Values in Patient Groups*

Parameter	TTP-HUS (n = 27)	DIC (n = 51)	*P*
Hemoglobin, g/dL (g/L)	9.0 ± 1.8 (90 ± 18)	9.3 ± 2.0 (93 ± 20)	.440
Platelet count, × 10^3/μL (× 10^9/L)	32.9 ± 32.3 (32.9 ± 32.3)	64.8 ± 36.9 (64.8 ± 36.9)	<.001
D-dimer, μg/mL (nmol/L)	4.425 ± 4.605 (24.23 ± 25.22)	6.254 ± 6.290 (34.25 ± 34.44)	.187
PT, s	15.5 ± 2.5	22.2 ± 6.2	<.001
INR	1.2 ± 0.3	2.0 ± 0.7	<.001
PTT, s	34.1 ± 15.8	48.5 ± 27.6	.015
Fibrinogen, mg/dL (g/L)†	386 ± 128 (3.9 ± 1.3)	432 ± 274 (4.3 ± 2.7)	.329
LDH, U/L (μkat/L)‡	1,447 ± 833 (24.2 ± 13.9)	1,654 ± 1,823 (27.6 ± 30.4)	.657

Am J Clin Pathol 2010;133:460-465

Table II. Presenting clinical and laboratory data.

Number of Episodes	TTP (n = 38)	TMA (n = 30)	P-value*
Median ADAMTS13 activity (range), %	Undetectable (<10%)	51 (33–122%)	
ADAMTS13 inhibitor present, n (%) [mean/range units]	28 (74) [2·29, 0·6–7·6]	NA†	NA
Neurological features present, n (%)	23 (61)	9 (30)	**0·0155**
Creatinine (mean ± SD), μmol/l	112·3 ± 76	244·9 ± 199	**0·0003**
Platelet count	23 ± 26	65 ± 41	**0·0001**
Undetectable haptoglobin	94%	61%	**0·004**

Shah N, Sarode R, et al. Br J Haematol 2014

Derivation and Validation of a Score for the Rapid Diagnosis of TTP: the 'PLASMIC' Score

Pavan K. Bendapudi, M.D.

Ang Li, Ayad Hamdan, Ashley Fry, Lynne Uhl, Marisa B. Marques, Richard Kaufman, Chris Stowell, Walter Dzik, and Robert S. Makar for the Harvard TMA Research Collaborative

ASH, December 8, 2014

Harvard TMA Research Collaborative

- Partnership between 3 main Harvard teaching hospitals (BIDMC, BWH, and MGH).
- All suspected cases of TTP with thrombocytopenia and schistocytes for which ADAMTS13 was sent between 2004-2014 (n = 254).
- Excluded: age < 18, hemolyzed specimen, outpatients, total bili >20, ADAMTS13 tested after receipt of FFP.
- Data collected retrospectively from 2004-2012 and prospectively from 2012-2014.

Patient Demographics

	ADAMTS13 ≤10% (N=68)	ADAMTS13 >10% (N=186)	p-value
Age, yrs	42.4 ± 16.4	55.1 ± 16.1	<0.0001
Sex, female	50 (73.5%)	96 (51.6%)	0.003
Caucasian	42 (63.6%)	145 (81.5%)	0.006
Non-Caucasian	24 (36.4%)	33 (18.5%)	
Neuro Symptoms (%)	27 (39.7)	68 (37.4)	0.77
Fever Symptoms (%)	24 (35.3)	63 (34.1)	0.88
History of Cancer (%)	0 (0)	73 (39.2)	<0.0001
Solid Organ or Marrow Transplant (%)	0 (0)	40 (21.5)	<0.0001

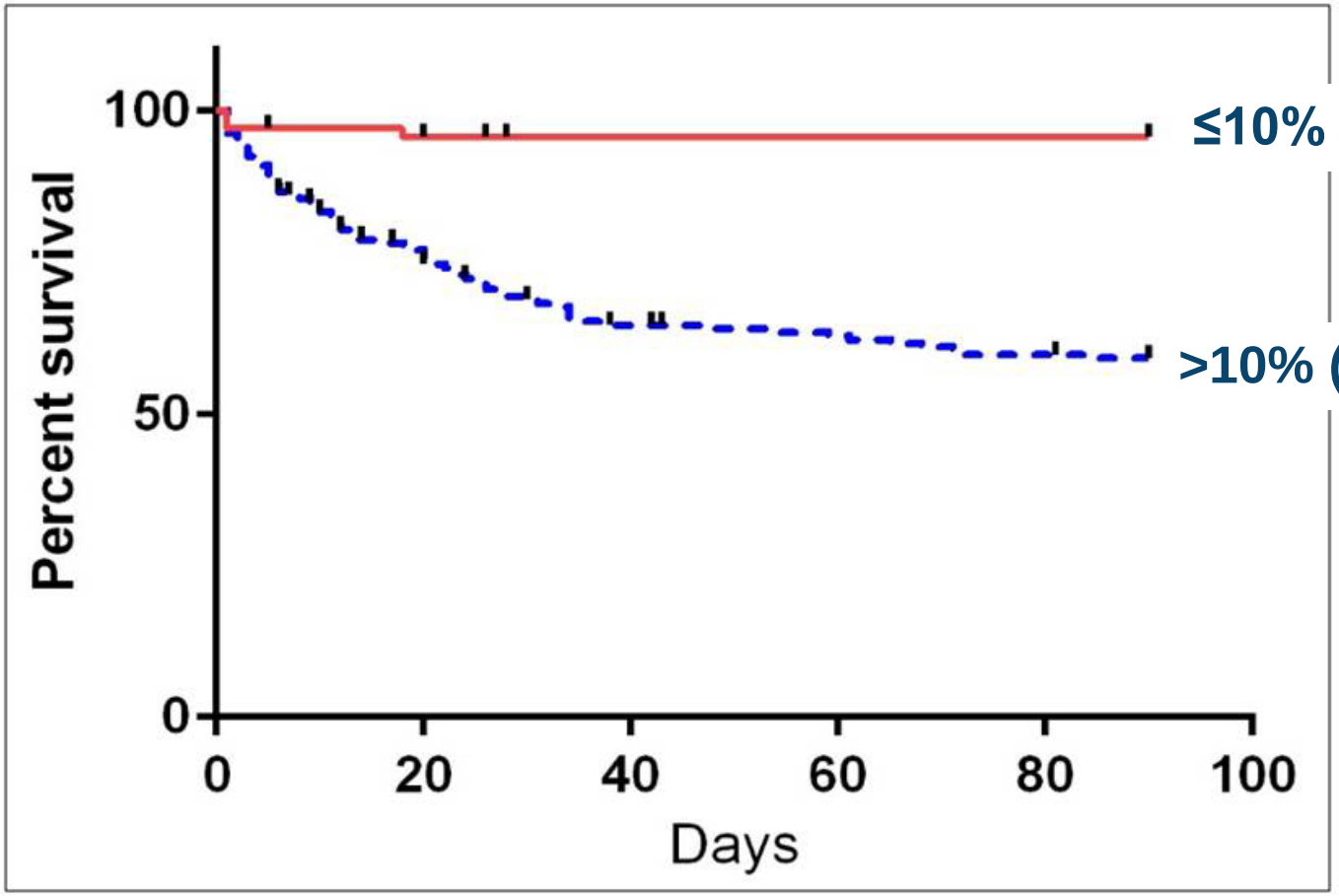
Harvard TMA Registry

Presenting Laboratory Findings

	ADAMTS13 ≤10% (N=68)	ADAMTS13 >10% (N=186)	p-value
Hematocrit, %	26.7 ± 6.1	26.3 ± 4.7	0.57
Platelet Count, $10^3/\mu L$	20.1 ± 14.3	54.6 ± 34.8	<0.0001
Creatinine, mg/dL	1.2 ± 0.6	3.6 ± 3.5	<0.0001
LDH, U/L	1129 ± 508	1323 ± 1618	0.33
Inhibitor Positive (%)	56 (82.4)	1 (0.5)	<0.0001
Blood Group O (%)	35 (52.2)	94 (51.1)	0.89

Harvard TMA Registry

90-day Survival by ADAMTS13 Activity



How to rapidly identify the population with ADAMTS13 ≤10%?

Harvard TMA Registry

Diagnostic Score: Initial Approach

- 29 clinical and laboratory parameters
  - CBC, BMP, LDH, hemolysis markers, blood group, etc.
  - Demographics
  - Presenting symptoms, clinical history
- Parameters associated with ADAMTS13 ≤10% in univariate analysis with p <0.1 further analyzed
- Laboratory cutoff values selected by generating ROC curves to identify cutoffs that maximized discrimination

Parameters Associated with ADAMTS13 ≤ 10% (Univariate Analysis)

Parameter	Dichotomized Value	O.R.	95% CI		*P*
			LL	UL	
Cancer	Not present	56.0	10.0	∞	<0.0001
Transplant	Not present	27.8	4.9	∞	<0.0001
Platelet Count	<29	26.4	10.6	65.8	<0.0001
INR	<1.3	13.6	4.1	45.4	<0.0001
Serum Creatinine	<1.8	13.0	5.6	30.5	<0.0001
Composite for Hemolysis	Hapto Undetectable or Retic >2.5 or Indirect Bili >2.0	4.2	1.7	10.4	0.0021
MCV	<87	4.0	2.1	7.6	<0.0001

Harvard TMA Registry

Diagnostic Score: Multivariate Logistic Regression

Parameter	Beta Coefficient	OR	P
Platelet Count <29	3.2	25.1	<0.0001
Creatinine <1.8	2.8	17.0	0.0001
INR <1.3	2.8	16.2	0.006
MCV <87	2.3	10.1	0.0006
No Cancer	2.0	7.7	0.06
No Transplant	2.0	7.1	0.10
Hemolysis Combo[1]	1.9	6.5	0.05

- *Rounded cutoffs (plt count <30, Cr <2.0, INR <1.5, MCV <90) did not impact predictive performance of the model*
- *Each parameter assigned a value of 1 point*

The "PLASMIC" Score

- 7 features
  - Platelets <30,000/µL
  - Lysis (Indirect Bili >2.0; Retic >2.5; or Absent haptoglobin)
  - Active cancer - absent
  - Stem cell or solid organ transplant - absent
  - MCV <90 fL
  - INR <1.5
  - Creatinine <2.0 mg/dL

- High = 7
- Intermediate = 5-6
- **Low ≤4**

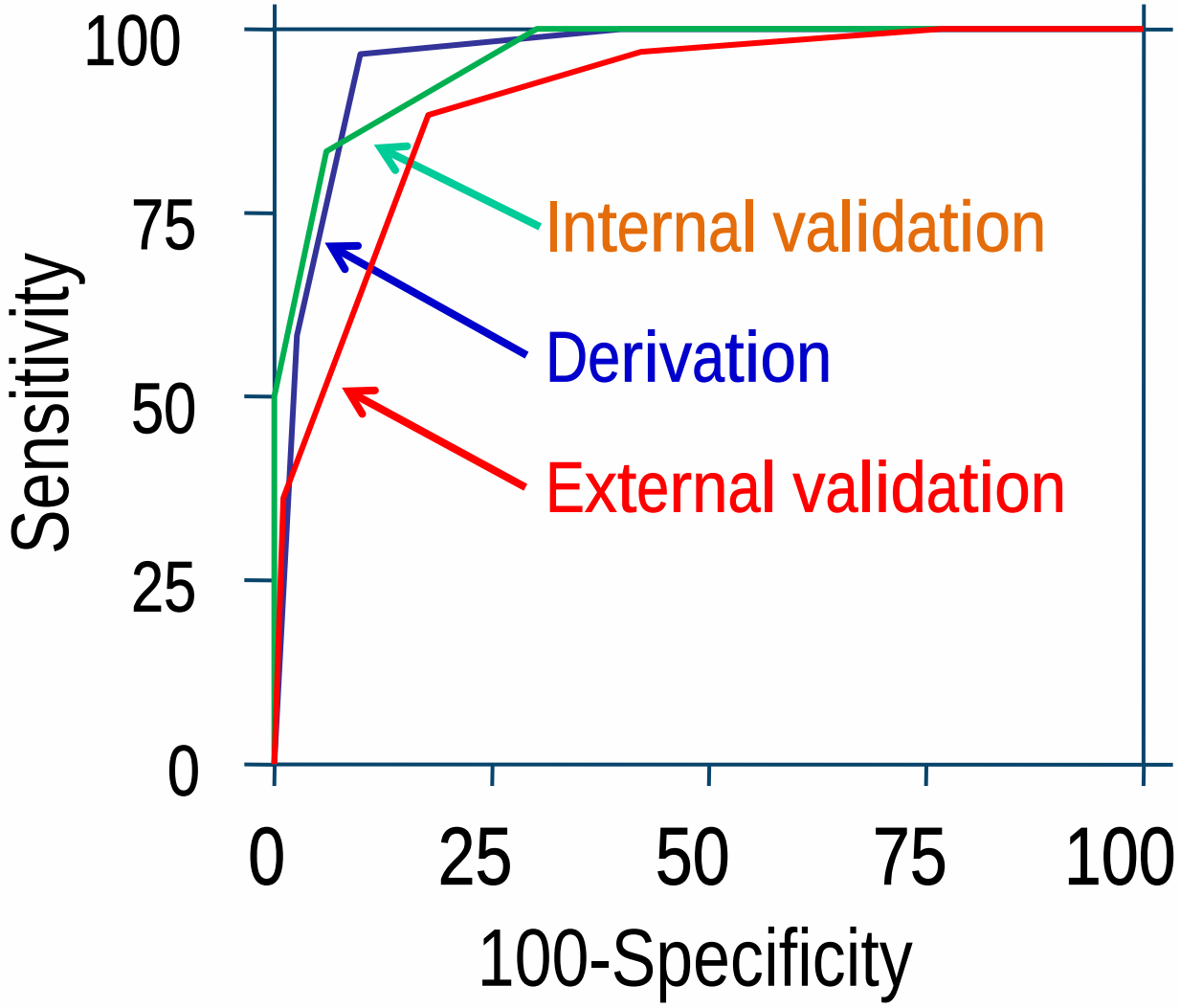
} **Risk of ADAMTS13 ≤10%**

Diagnostic Score Validations

Risk Score	ADAMTS13 ≤ 10%, n/N (%)		
		Validations	
	Derivation N = 200	Internal N = 40	External N = 145
Low (0-4 points)	0/84 (0)	0/22 (0)	2/47 (4.3)
Moderate (5-6 points)	25/77 (32.4)	3/15 (20)	42/72 (56.8)
High (7 points)	37/39 (94.9)	3/3 (100)	25/26 (96.2)

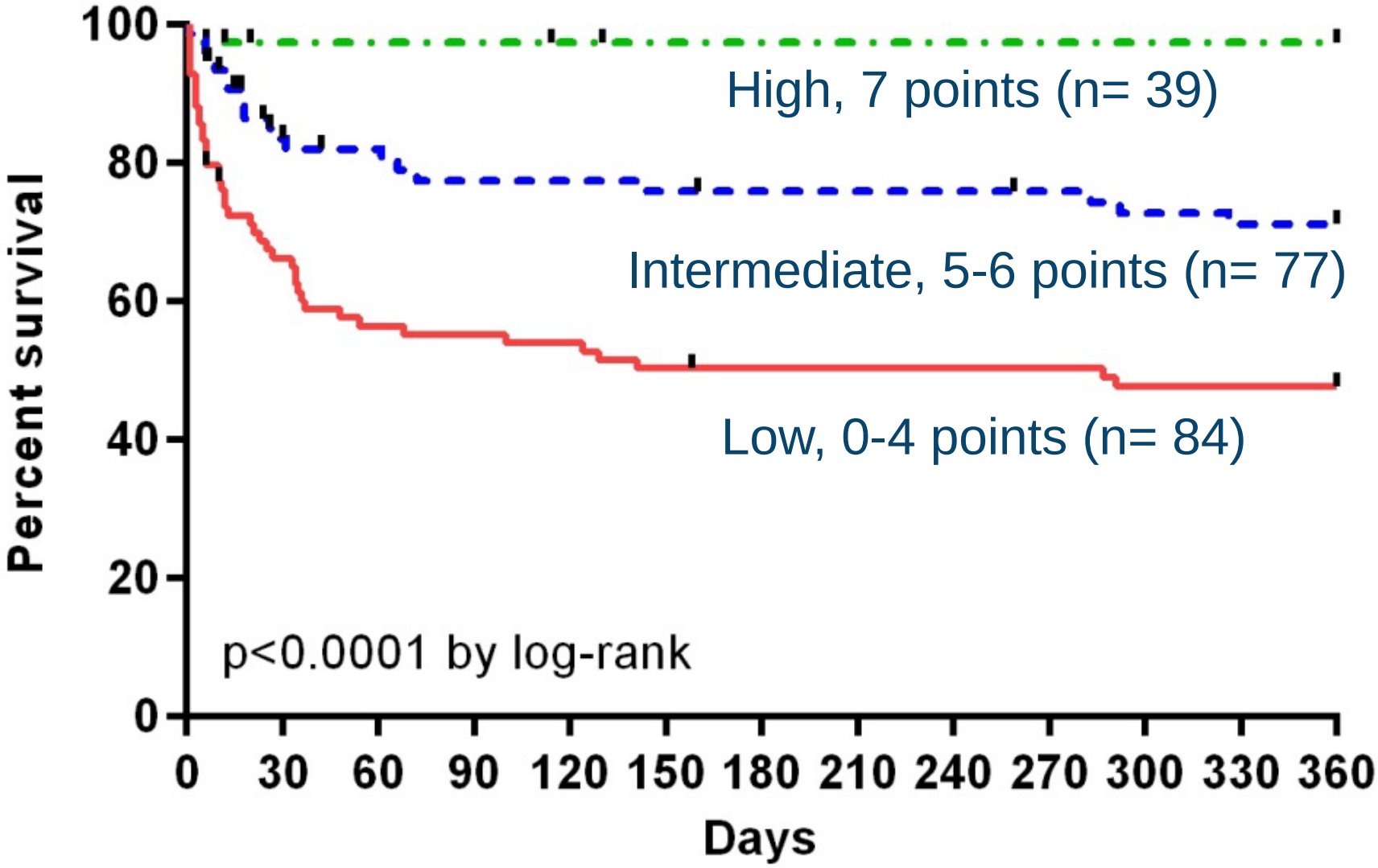
Harvard TMA Registry

Scoring System Performance (ROC)



Harvard TMA Registry

Survival by PLASMIC Score



Definitions for TTP and TPE

- Treatment response
  - Platelet count above 150,000/µL for 2 days without hemolysis and stable or improving neurologic deficits
- Durable treatment response
  - As above, for at least 30 days from last TPE

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Definitions for TTP and TPE

- Exacerbation
  - Recurrent disease within 30 days of achieving response
- Relapse
  - Recurrent disease 30 days or longer since response
- Refractory disease
  - No treatment response by day 30 and/or no durable treatment response by day 60

MUITO OBRIGADA