

The Oklahoma TTP Registry
A Program for Research, Education,
and Patient Care

Dutch Transfusion Society
Dutch Hemovigilance Organization

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Outline

- **1972, 1974 : My experience with TTP**
- **1990: My experience with the
Oklahoma Blood Institute (OBI)**
- **1995: Routine collection of serum samples**
- **1997: A project becomes a Registry**
- **2018: What I've learned**
- **2019: What's next?**

Patient Story: 1972

- 19 yo, 36th week, 1st pregnancy, transient numbness of face/arm
- Hct 15%, Plt 14,000, Cr 1.9
- Renal failure, dialysis, seizures, stroke
- Died, 3 months

JAMA 1976; 235: 2126

Her Sister: 1974

- 19 yo, 36th week, 1st pregnancy, numbness of face/arm.
- Hct 15%, Plt 14,000, Cr 1.9
- Renal failure, dialysis, seizures, stroke
- Died, 3 months
- 17 yo, 38th week, 1st pregnancy, petechiae, no neurologic signs
- Hct 23%, Plt 22,000, Cr 1.6
- Renal failure, dialysis, seizures, stroke
- Died, 6 weeks

JAMA 1976; 235: 2126

TTP: Diagnostic Criteria, v1 ("The Pentad")

- **Thrombocytopenia**
- **Microangiopathic hemolytic anemia**
- **Neurologic abnormalities**
- **Renal failure**
- **Fever**

Evolution of TTP

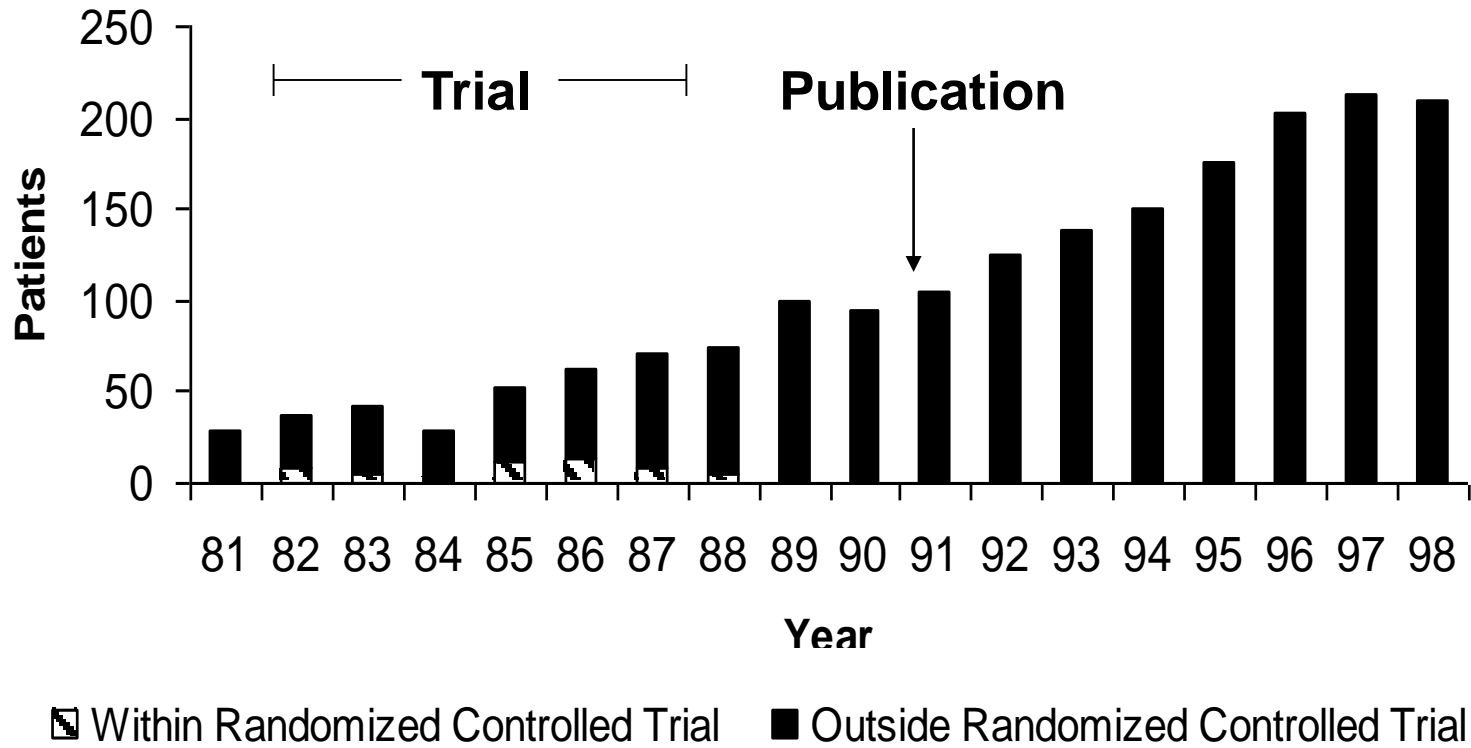
	1925-1964	1964-1980	1982-1989
Thrombocytopenia	96%	96%	100%
Hemolytic anemia	96%	98%	100%
Neurologic symptoms	92%	84%	63%
Renal disease	88%	76%	59%
Fever	98%	59%	26%
Survival	10%	46%	78%

TTP: Diagnostic Criteria, v2

- **Thrombocytopenia**
- **Microangiopathic hemolytic anemia**
- **No alternative disorder**

Plasma Exchange for TTP

Data from the Canadian Apheresis Group



Clark, et al. *JAMA* 2003; 290:1351

Oklahoma



The Oklahoma TTP Registry

Serum collected immediately before beginning the first plasma exchange, November 13, 1995 – December 31, 2017

- 401 **consecutive** patients with PEX **requested** for a **1st episode** of **suspected TTP**
- ADAMTS13 measured in 383 (96%)
- Measurements (immunoblot, FRETs) by Drs. Bernhard Lämmle and Johanna Kremer (Bern, Switzerland)

TTP: Diagnostic Criteria, v3

- **Thrombocytopenia**
- **Microangiopathic hemolytic anemia**
- **ADAMTS13 activity <10%**
- **No alternative disorder**

Patient 1, 1998

- **41 yo previously healthy BM**
 - **3 days of abdominal pain, nausea, vomiting, diarrhea, weakness. Hct 28, Plt 7, Cr 1.2**
 - **Hospital day 3: transient aphasia, numbness left face and arm. Hct 19, Plt 12, LDH 1946, red cell fragments**
- **Recovered with 6 PEX, no corticosteroids**
- **3 relapses: 2000, 2001**

Patient 1

- **2001: our first ADAMTS13 measurements**
- **1st episode:**
ADAMTS13: IB 60%, FRETs 53%

Patient 1

Episode	ADAMTS13 Activity		ADAMTS13 Inhibitor	
	IB	FRETS	IB	FRETS
1 (1998)	60%	53%	-	-
2 (2000)	-	-	-	-
3 (2000)	50%	15%	-	1.4
4 (2001)	6%	<5%	Tr	0.8
5 (2003)	<5%	<5%	1	1.1
6 (2008)	<5%	<5%	1-2	1.4

Diagnosis of TTP in 89 Patients: 1995-2017

- Clinical features 89
- ADAMTS13 activity
 - <10%, either FRETTS or IB 83
 - 10-20%, either FRETTS or IB 4*
 - FRETTS, 53%, IB, 60% 1
- Died before PEX, ADAMTS13 not measured. Diagnosis by autopsy 1

**American J Hematol 2017; 92: E644*

TTP: Diagnostic Criteria, v4

- Thrombocytopenia
- Microangiopathic hemolytic anemia
- ADAMTS13 activity **usually** <10%
- No alternative disorder

Patient 2, 2008

- **55 yo previously healthy WF**
 - **3 days of chest pain, dyspnea, then persistent right-side weakness, aphasia**
 - **Hct 33, Plt 33, Cr 1.6, LDH 1084, red cell fragments, neg DAT, nl coagulation tests**
 - **EKG, chemistries: MI; MRI: left MCA infarct, multiple cerebellar infarcts; TEE: aortic valve vegetation and regurgitation**
 - **Blood cultures: *Enterococcus faecium***

Patient 2

- **Diagnoses: Bacterial endocarditis (+ TTP)**
- **Treatment: Antibiotics, PEX, steroids**
- **Recovery to normal Plt, Cr, and LDH**
- **3 months later: aortic valve replacement**

Patient 2

Time of measurement	ADAMTS13 Activity		ADAMTS13 Inhibitor	
	IB	FRETS	IB	FRETS
Before PEX	<5%	<5%	0	0
2009	100%	92%	-	-
2010	50%	<5%	-	0

Patient 2

- **February, 2016: Hospitalized in Colorado**
 - **TTP relapse**
 - **ADAMTS13 <5%, Inhibitor 1.2 BU**

TTP: Diagnostic Criteria, v5

- **Thrombocytopenia**
- **Microangiopathic hemolytic anemia**
- **ADAMTS13 activity usually <10%**
- **Usually** no additional disorder
(clinical judgment required)

Acute Kidney Injury

At presentation and during course

None	37 (47.5%)
Minor	37 (47.5%)
Severe	4 (5%)
Required RRT	3 (4%)

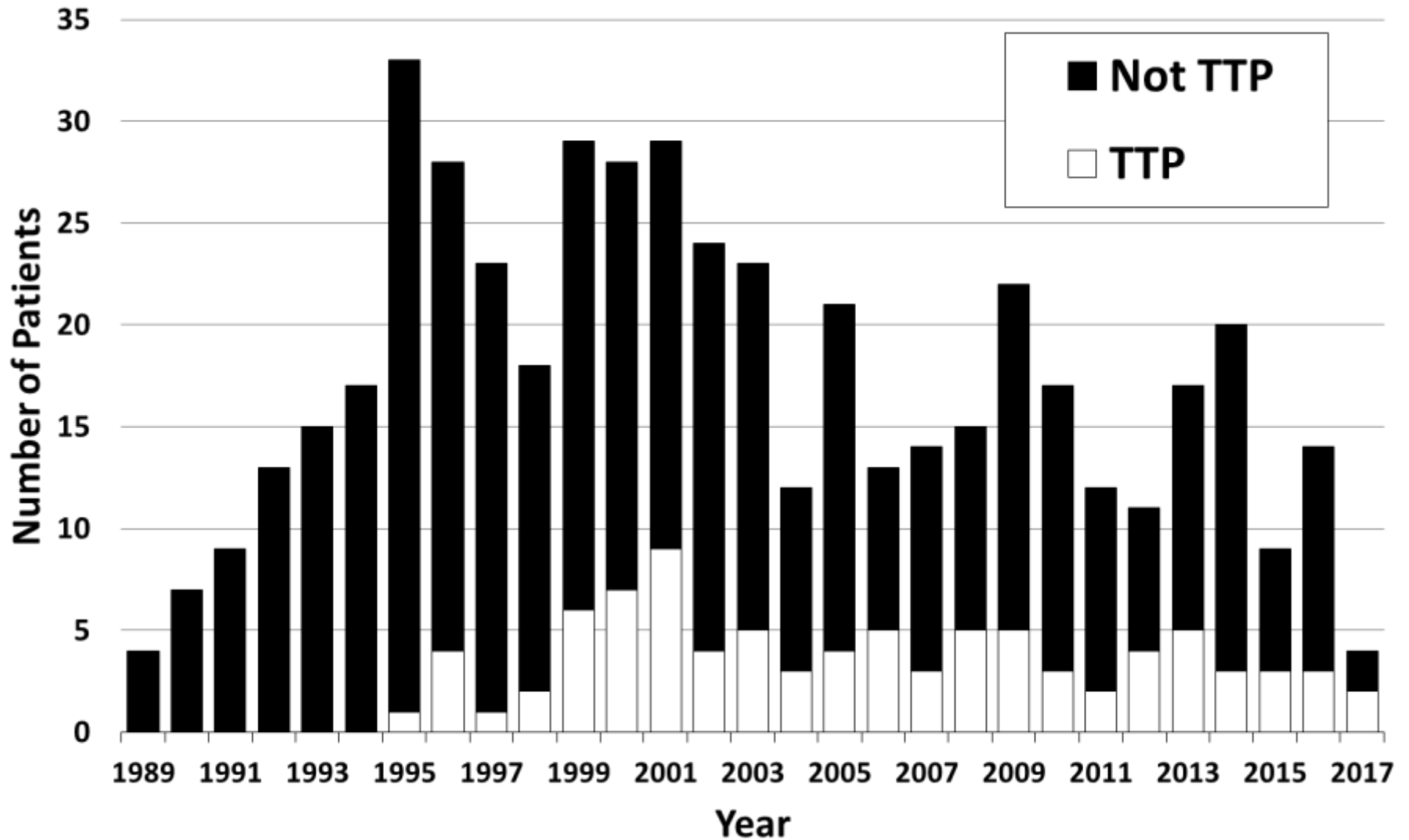
Blood Advances 2017; 1: 590 (78 patients)

TTP: Diagnostic Criteria, v6

- **Thrombocytopenia**
- **Microangiopathic hemolytic anemia**
- **ADAMTS13 activity usually <10%**
- **Usually** no severe acute kidney injury
- **Usually** no additional disorder

The Oklahoma TTP-HUS Registry

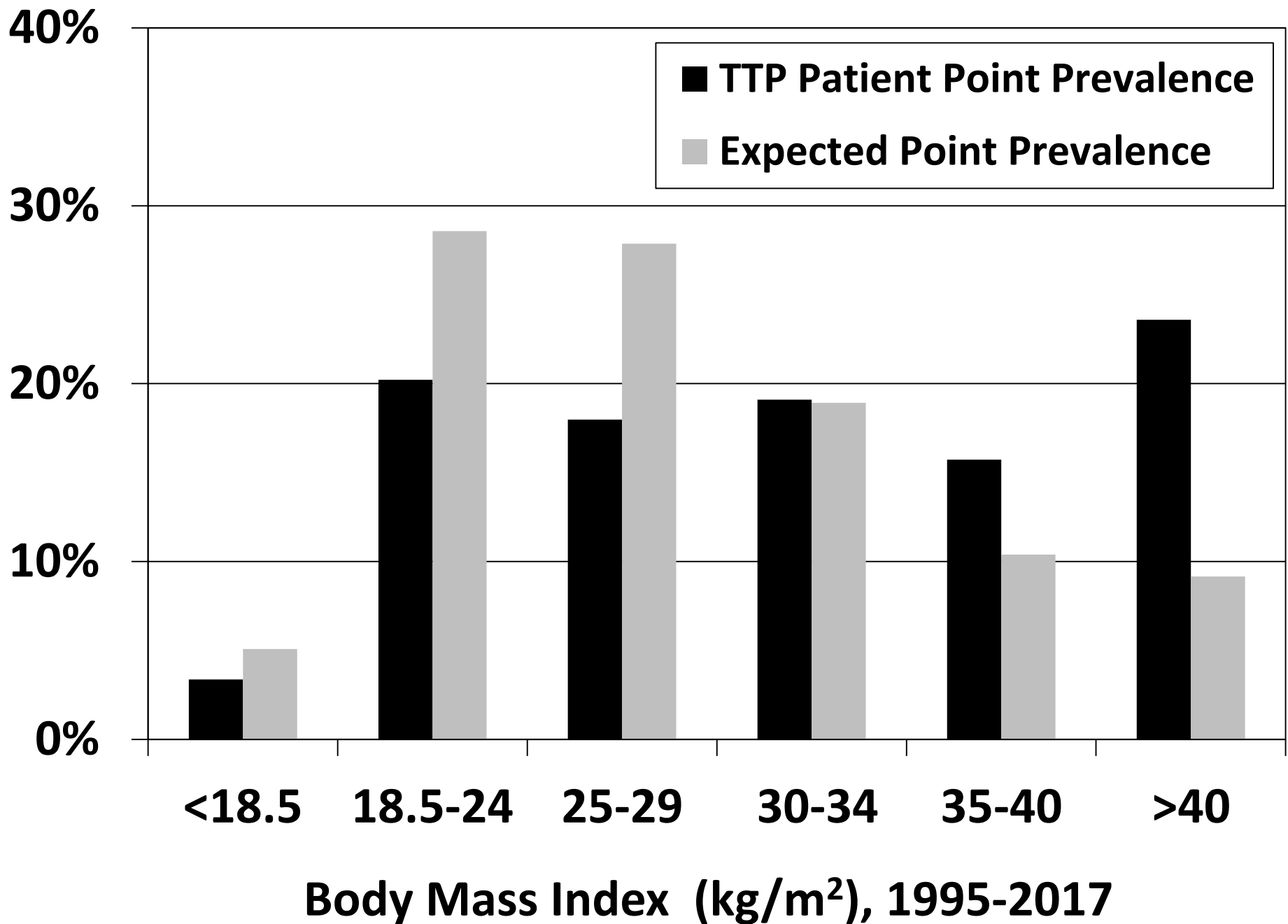
Patients per Year, 1989-2017



Demographics of TTP

89 Patients, 1995-2017

Age	41 years (9-78)
Sex	67 (75%) female
Race	36 (38%) black

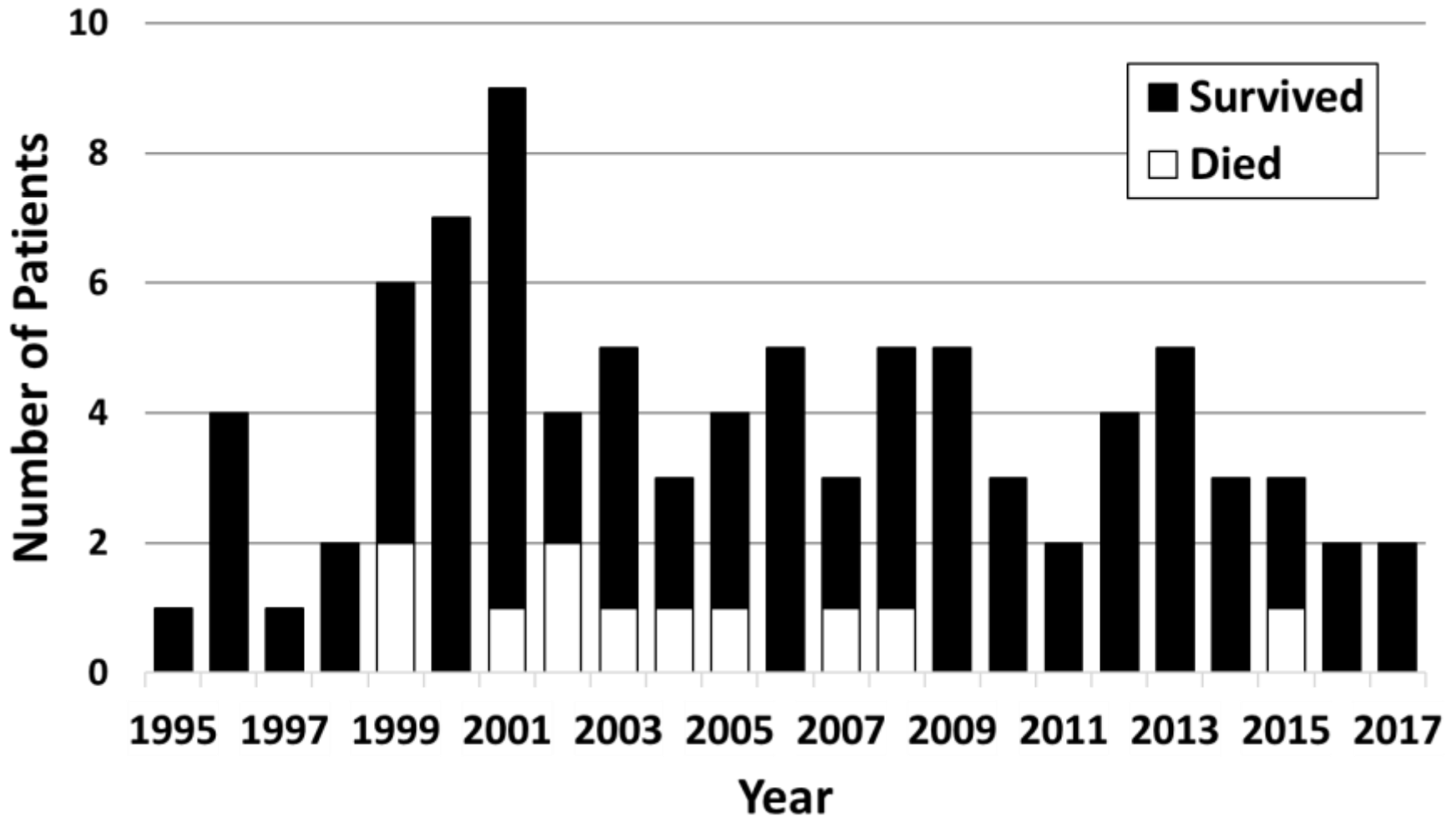


Deaths With Initial Episodes of TTP

11 (12%) of 89 patients died

- **3, before completion of 1 PEX**
- **2, before achieving a response**
- **6, after achieving a response**
 - **1, persistent coma**
 - **1, pulmonary embolism**
 - **1, eclampsia, AKI, cardiomyopathy**
 - **2, PEX complications (hemorrhage, sepsis)**
 - **1, refractory TTP (had 6 rituximab doses)**

Deaths During Initial Episode of TTP

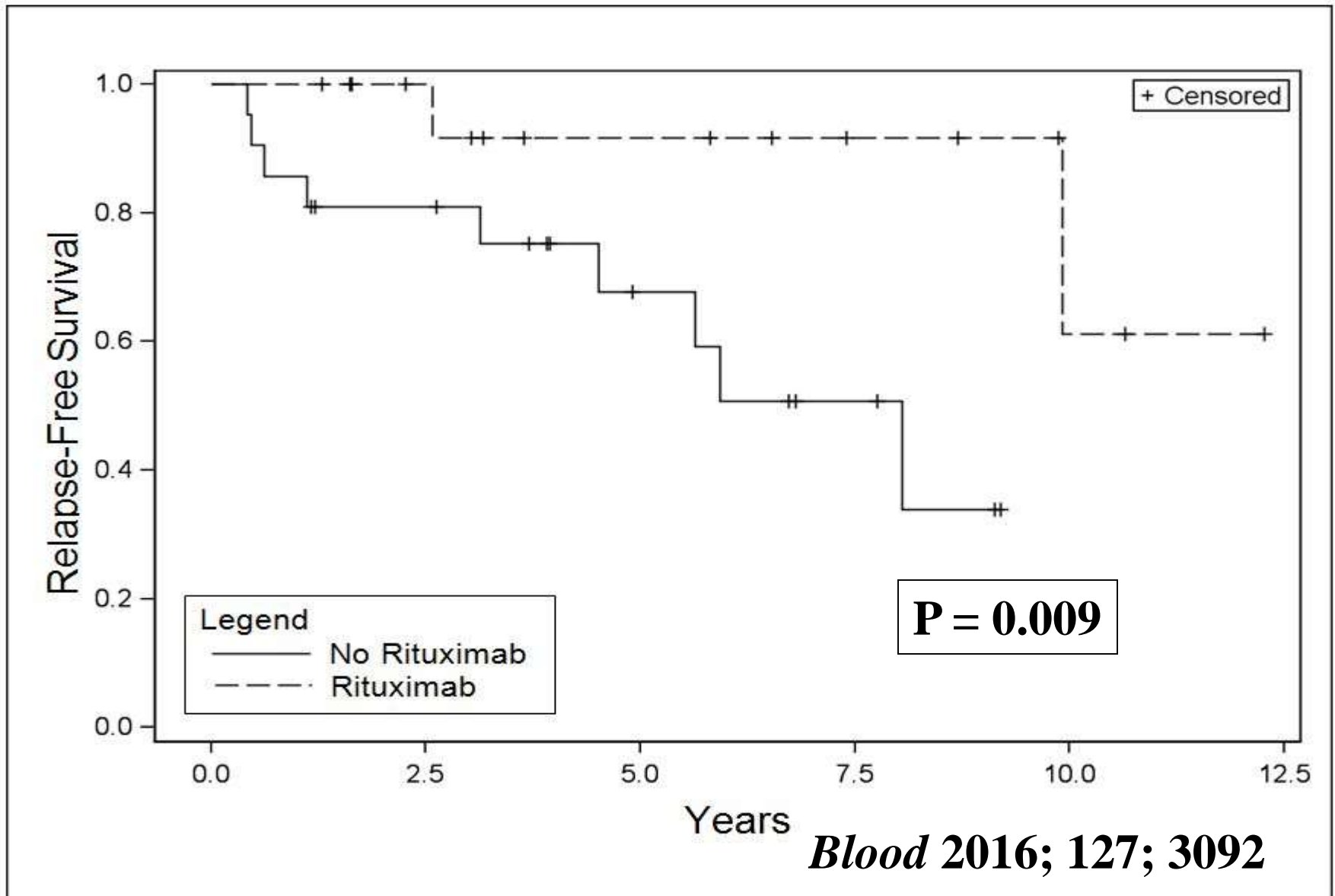


78 TTP Survivors

Long-Term Outcomes

- **Relapse**
- **Cognitive impairment**
- **Depression**
- **Risk of pregnancy**
- **Additional autoimmune disorders**
- **Kidney function**
- **Hypertension**
- **Death**

Relapse related to initial rituximab treatment (Rituximab, 16 patients; No rituximab, 21 patients)



Cognitive Impairment Following Recovery from TTP

Cognitive Ability	Patients (%)
High Average/Superior	3 (8%)
Low Average/Average	26 (72%)
Extremely Low/Borderline	7 (20%)

Depression

Following Recovery from TTP

Depression	Patients (%)
Minimal/None	21 (41%)
Mild	8 (15%)
Moderate	8 (15%)
Severe	15 (29%)

Subsequent Pregnancy Risk for TTP Relapse

- **12 women with 21 subsequent pregnancies**
 - **Recurrent TTP: 2 (17%) of 12 women,
2 (10%) of 21 pregnancies (babies healthy)**
 - **12 week fetal loss: 1 woman (twice)**
 - **20 week fetal loss: 1 woman**
 - **26 week delivery: infant death**
- **Healthy children: 17 (81%) of 21 pregnancies**

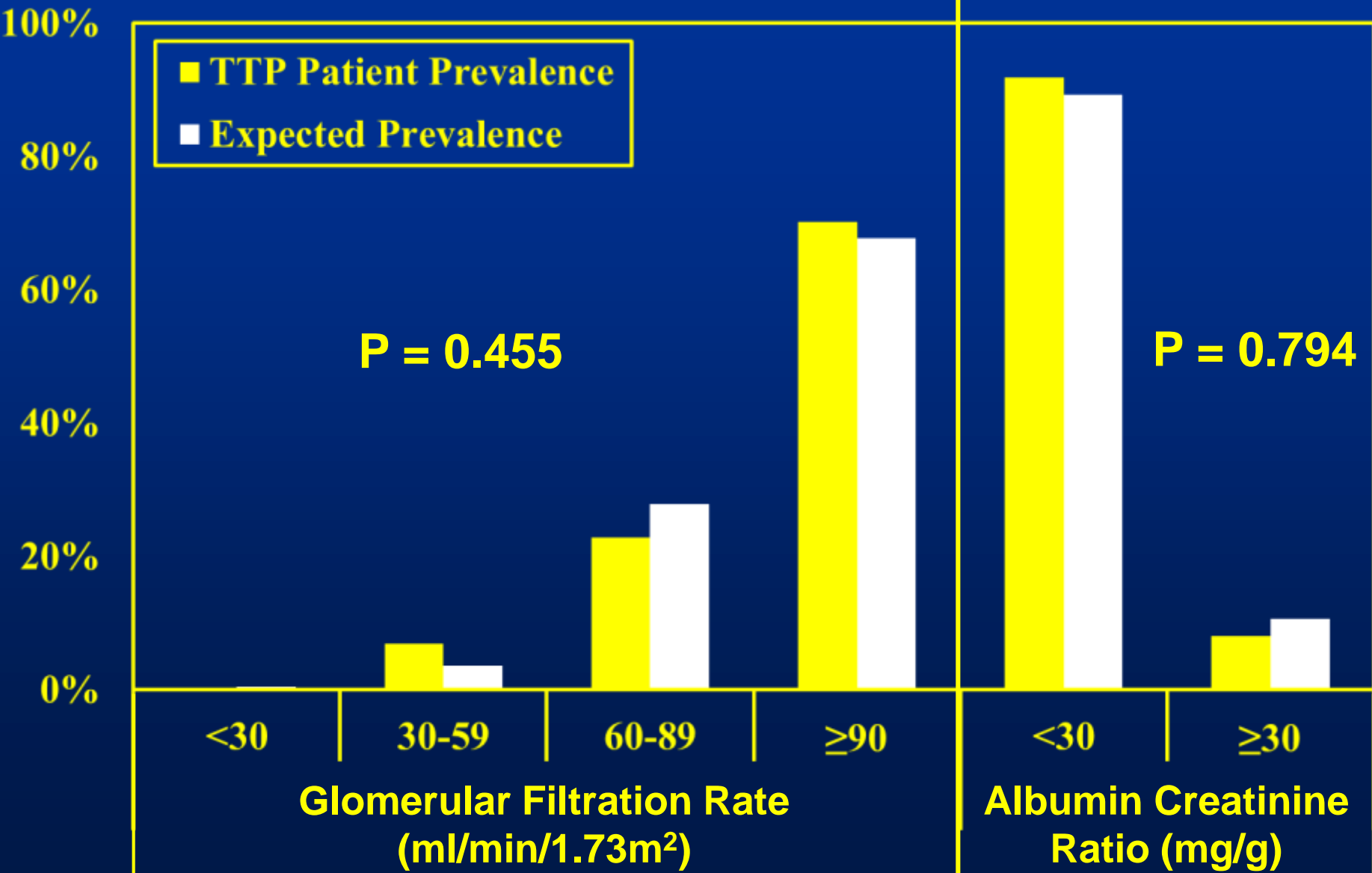
Blood 2014; 123:1674 (and subsequent experience)

Additional Autoimmune Disorders

- **10 patients: SLE**
- **4 patients: Graves' disease**
- **2 Addison's disease, Factor VIII inhibitor**
- **1 Sjögren's syndrome, Scleroderma,
Psoriasis, Polymyositis, Myasthenia Gravis,
Juvenile Rheumatoid Arthritis**

GFR

ACR



Albuminuria Following Recovery

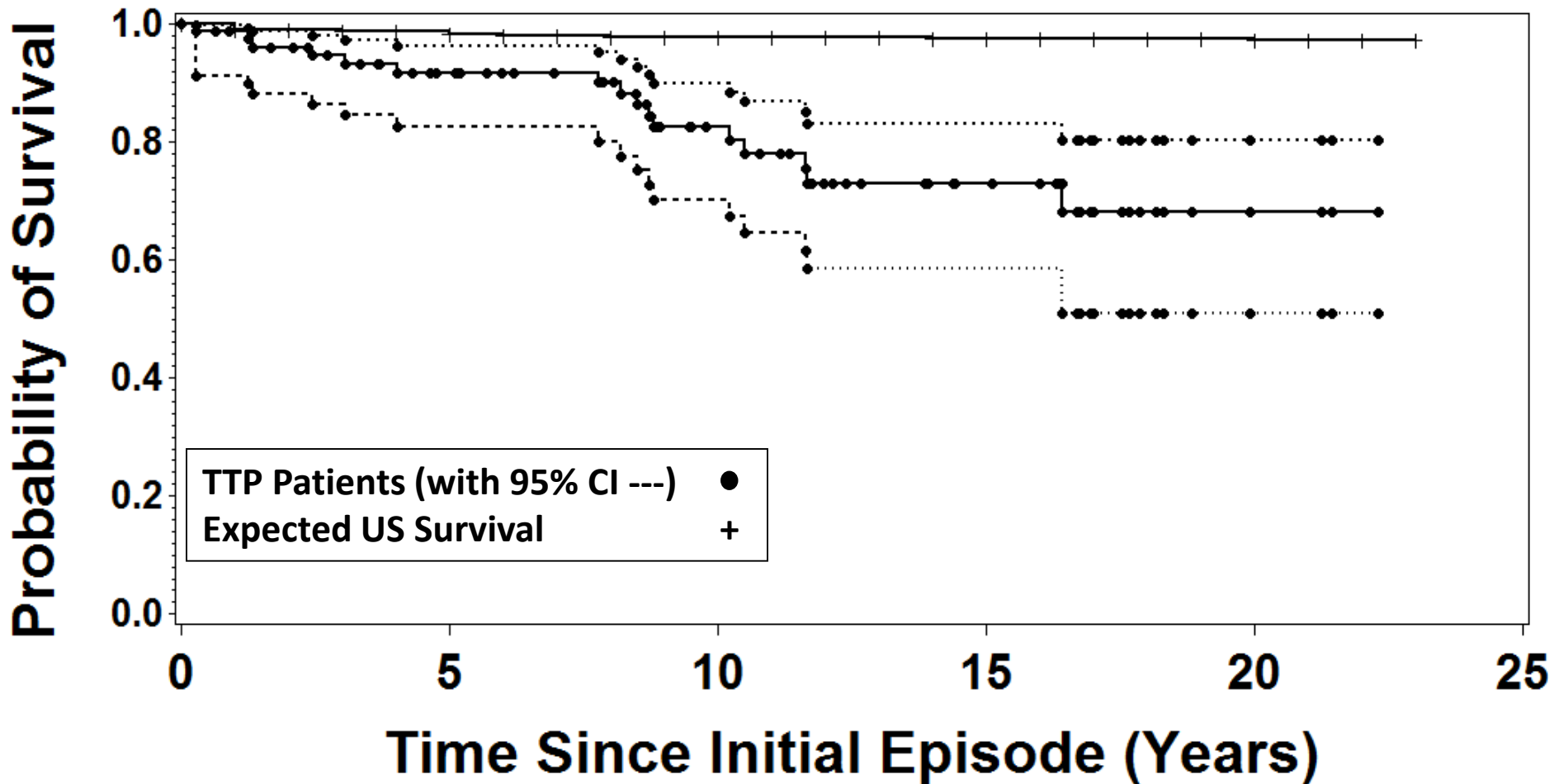
ACR	Patients	Expected	P
<10 $\mu\text{g}/\text{mg}$	18 (49%)	67%	0.014
$\geq 10 \mu\text{g}/\text{mg}$	19 (51%)	33%	

Kidney Function Following Recovery

GFR	ACR			
	<10	10-29	30-299	≥300
≥ 105	7	5	2	0
90-104	5	8	1	0
75-89	3	0	0	0
60-74	2	3	0	0
45-59	1	0	0	0
0-44	0	0	0	0

Shaded cells: increased risk for cardiovascular death

Survival of 78 Patients Following Recovery From Their Initial Episode of TTP, 1995-2018



Management Issues

- **Routine initial rituximab**
- **Role of caplacizumab**
- **Management of ADAMTS13 deficiency during remission**

Deaths With Initial Episodes of TTP

Are 6 Deaths Preventable?

11 (12%) of 89 patients died

- 3, before completion of 1 PEX (1)
- 2, before achieving a response (1)
- 6, after achieving a response
 - 1, persistent coma (after cardiac arrest)
 - 1, pulmonary embolism (1)
 - 1, postpartum eclampsia, AKI, cardiomyopathy
 - 2, PEX complications (hemorrhage, sepsis)
 - 1, refractory TTP (had 6 rituximab doses)

Rituximab for Patients with ADAMTS13 Deficiency During Remission

- **Accumulating anecdotes that ADAMTS13 activity <10-20% during remission is a risk for relapse**
- **Rituximab treatment for low ADAMTS13 activity during remission may decrease risk for relapse**

Conclusions

- **Diagnosis of TTP**
 - **Clinical judgment required**
- **Management of TTP**
 - **Potential value of initial treatment with rituximab and caplacizumab**
- **Long-term outcomes**
 - **Requirement for continuing medical care**
 - **Rituximab for activity <20%**