Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA Reference Center experience

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Online Supplementary Design and Methods

Inclusion criteria

TTP diagnosis criteria included the presence of Coombs-negative microangiopathic hemolytic anemia (schistocytes on peripheral blood smear) and acute thrombocytopenia (< 150×10^9/L). Patients with organ failure and cytopenias related to an associated condition and not only to the microangiopathic process were not included, regardless of ADAMTS13 activity. To work on a homogeneous population of patients, we did not include patients with an idiopathic TMA and a detectable ADAMTS13 activity (≥ 20%), since these forms may correspond to a specific subset of patients with a distinct presentation and outcome. Neither did we include patients with a past history of TTP, who usually have a better prognosis than patients with a first diagnosis. In the rare patients with a borderline ADAMTS13 activity (between 10% and 20%), anti-ADAMTS13 antibodies and/or a plasma ADAMTS13 inhibitor were systematically investigated, and positive patients were considered as having an acquired deficiency and included in the present study.

Treatment

Treatment was administered according to written recommendations detailed in previous studies, with a comparable protocol between patients in the study group and those in the validation group. Briefly, patients received daily plasma exchange with solvent-detergent viro-inactivated plasma immediately after the diagnosis of TTP. The volume exchanged was 1.5 times the predicted plasma volume for the first procedure and 1.0 time the predicted plasma volume (standard intensive treatment), until a remission was achieved. The plasma exchange sessions were then tapered over three weeks (maintenance treatment) and finally stopped. The occurrence of an exacerbation or of a relapse led to resumption of the daily plasma exchange sessions. Patients without active infection received glucocorticoid therapy, 1 mg/kg/d for three weeks. All patients received folic acid orally or intravenously. Rituximab was usually administered in patients with a suboptimal response to treatment. This latter was defined as a refractory disease after four days of standard treatment, or a flare-up of the disease in patients who initially started to improve their condition. A complete response was defined as full resolution of any neurological manifestations and recovery of a normal platelet count (>150×10^9/L) for at least two days. A durable remission was a complete response with no further thrombocytopenia or clinical worsening for more than 30 consecutive days from the first day of platelet count recovery (this period included the time on maintenance plasma exchange). The time to durable remission was the number of days from the first TPE to the 30th consecutive day with no further platelet count decline. Refractory TTP was defined as absence of platelet

count doubling after four days of standard intensive treatment with persistently elevated LDH levels. A relapse was the reappearance of neurological manifestations and/or thrombocytopenia ($<100\times10^9$/L for at least two days) with no other identifiable cause after achieving a durable remission. An exacerbation was defined as worsening neurological manifestations and/or recurrent thrombocytopenia ($<100\times10^9$/L for at least two days) and/or worsening thrombocytopenia (i.e. platelet count decrease of more than one-third the highest count, for at least two days) with no other identifiable cause, before achieving a durable remission.

ADAMTS13 analysis

Anti-ADAMTS13 antibodies were systematically investigated from 2005, whereas the search for an ADAMTS13 inhibitor was not performed after 2007. Anti-ADAMTS13 IgG titer was considered positive for values over 25 U/mL. ADAMTS13 activity and anti-ADAMTS13 antibodies were determined on diagnosis before any treatment, and during follow up in some cases.

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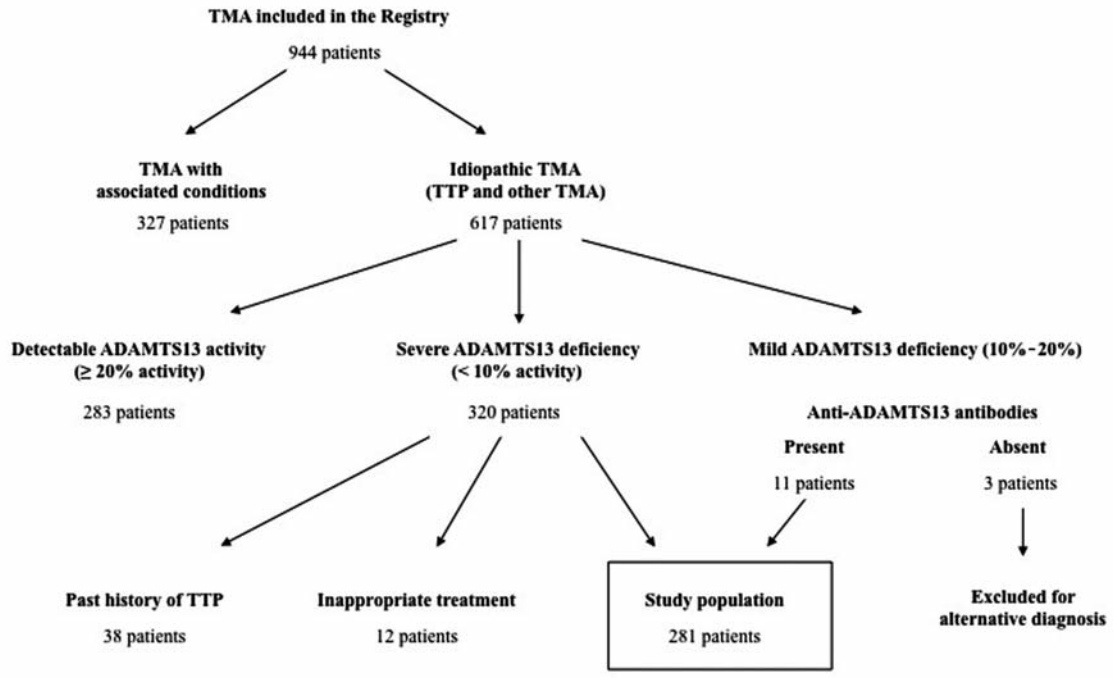

Online Supplemental Figure S1. Flow diagram of the study. From the 944 patients of our registry, 610 were not included in the present study because of an associated condition (327 cases) or a detectable ADAMTS13 activity (283 cases). From the remaining patients with an undetectable ADAMTS13 activity and considered as having a TTP, 38 had a past history of TTP and 12 were not treated according to our standard guidelines (in most cases, TPE were not performed daily), leaving 281 patients for analysis.

Online Supplementary Table S1. Clinical characteristics of patients on diagnosis according to age.

	Age ≤ 60 (N=241)	Age > 60 (N=40)	*P*
Ethnicity (%)			0.386
Caucasians	86	90	
Afro-Caribbean	11	5	
Others	3	5	
Females (%)	68	65	0.718
Cardiovascular risk factors and pre-existing comorbidities (%)			
Arterial hypertension	6	52.5	9.10^{-12}
Diabetes	4	33	4.10^{-5}
Ischemic stroke	1	7.5	6.10^{-5}
Ischemic heart disease	4	17.5	4.10^{-5}
Cerebral involvement			
Headache	27	5	0.001
Stupor	13	32.5	0.004
Seizure	6	20	0.008
Focal deficiency	27	60	0.185
Fever	23	37.5	0.075
Hemoglobin level (g/dL)	7.8±2	8.4±2.5	0.073
Reticulocyte count (N=179)	204±127	154±89	0.067
LDH level (xN)	6.0±4.2	5.5±3.6	0.597
LDH > 10N (%)	13	5	0.274
Platelet count ($x10^9$/L)	18±17	25±30	0.355
Serum creatinine (µmol/L)	116±90	164±104	0.002
Estimated glomerular filtration rate (mL/min)	73±32	47±25	2.10-6
ANA (N=253)	52	37.5	0.135
APLA (N=187)	9	21	0.147
ADAMTS13 inhibitor (N=177)	113 (74)	18 (72)	0.809
IgG anti-ADAMTS13 Abs (N=126) (U/mL)	109±169	97±70	0.751
Death (%)	8.3	32.5	0.0001

xN: number of times the upper normal value; ANA: antinuclear antibodies; APLA: antiphospholipid antibodies; Abs: antibodies. In case of missing values, the number of patients tested is specified in parentheses in the left column.

Online Supplementary Table S2. Full model of logistical regression.

	Odds Ratio	95% CI	*P*
Cerebral involvement	2.7	[1.0, 7.7]	0.042
Age			0.024
≤40	1	-	
41-60	2.2	[0.7, 6.7]	
> 60	3.5	[1.3, 18.4]	
Serum creatinine (µmol/L)	0.998	[0.95, 1.05]	0.93
Estimated glomerular filtration rate (mL/min)	0.84	[0.68, 1.04]	0.10
LDH level ≥ 10N	3.1	[1.0, 9.6]	0.047

95% CI: 95% confidence interval; xN: number of times the upper normal value.

Online Supplementary Table S3. Clinical characteristics of patients at diagnosis according to outcome in the validation cohort.

	Survivors (N=54)	Non-survivors (N=12)	*P*
Ethnicity (N=47)			
Caucasians	30 (65)	12 (100)	0.07
Afro-Caribbeans	10 (21)	0 (0)	
Others	7 (19)	0	
Age (year-old)	38.7±13.1	49.6±14.7	0.027
Females	46(85)	8 (67)	0.21
Cardiovascular risk factors and pre-existing comorbidities (N=63)			
Arterial hypertension	8 (15)	1 (10)	1
Diabetes	2 (4)	0 (0)	1
Ischemic stroke	2 (4)	1 (10)	0.43
Ischemic heart disease	1 (2)	0 (0)	1
Cerebral involvement	37 (68)	10 (83)	0.48
Headache (N=64)	31 (60)	2 (20)	0.01
Stupor	7 (13.5)	5 (42)	0.039
Seizure	4 (8)	1 (8)	1
Focal deficiency	17 (33)	7 (58)	0.013
Fever (N=54)	5 (11)	3 (30)	0.15
Hemoglobin level (g/dL) (N=58)	8±2.0	8.3±1.5	0.54
Reticulocyte count (N=33)	213±158	228±110	0.33
LDH level (xN)	4.8±2.8	8.1±4.6	0.008
LDH > 10N (%)	4 (7.4)	3 (25)	0.11
Platelet count (x10^9/L) (N=61)	21±18	14±10	0.12
Serum creatinine (µmol/L) (N=51)	117±102	130±68	0.43
Estimated glomerular filtration rate (mL/min) (N=51)	71.3±29	56.7±27	0.27
ANA (N=43)	19 (53)	5 (71)	0.44
APLA (N=18)	1 (7)	0 (0)	1
ADAMTS13 inhibitor (N=59)	43 (88)	8 (80)	0.61
IgG anti-ADAMTS13 Abs (U/mL) (N=46)	77±54	111±73	0.16

xN: number of times the upper normal value; ANA: antinuclear antibodies; APLA: antiphospholipid antibodies; Abs: antibodies. In case of missing values, the number of patients tested is specified in parentheses in the left column.