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Prognostic and Long-term Survival of Immune Thrombotic Thrombocytopenic Purpura in older patients

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Abstract:

Background: Immune Thrombotic Thrombocytopenic Purpura (iTTP) is a potentially lethal auto-immune disease. Older age is associated with increased iTTP mortality. Yet, data are scarce regarding iTTP occurring among older patients and their short- and long-term mortalities.

Objective: To assess clinical features and long-term impact of iTTP on mortality in older patients (>60 yo).

Patients and methods: Characteristic and prognosis of adult iTTP patients with acquired severe ADAMTS-13 deficiency (<10%) enrolled in the registry of the French Reference Center for Thrombotic Microangiopathies between 2000 and 2016 were described according to age **(<60 yo or ≥60 yo**). Long-term mortality of iTTP older survivors was compared with this of non-iTTP geriatric French Three-City cohort subjects**.**

Results: Comparing respectively older iTTP patients (N=71) with younger patients (N=340), time from hospital admission to diagnosis was longer (p<0.0001); at diagnosis, delirium (p=0.034), behavior impairment (p=0.045), renal involvement (p<0,0001) and elevated troponin level (p=0.025) were more important whereas cytopenias were less profound **(platelet count 22 G/L [9-57] *vs* 13 G/L [9-21], respectively, p=0.002, and hemoglobin level 9 g/dL [8-11] *vs* 8 d/dL [7-10], respectively, p=0.0007)**. Short- and mid-term mortalities were higher (p<0.0001) and increased for every 10-years of age range. Age ≥60, cardiac involvement, increased plasma creatinine level and total plasma exchange volume, were independently associated with 1-month mortality. Compared with a non-iTTP geriatric population, older survivors showed an increased long-term mortality (HR=3.44, p<0.001).

Conclusion: Older iTTP patients have a frequent atypical neurological presentation, which may delay the diagnosis. Age impacts negatively 1-month and 1-year mortality. A

Conflict of interest: COI declared - see note

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Prognostic and Long-term Survival of Immune Thrombotic Thrombocytopenic Purpura in older patients

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KEYPOINTS

- iTTP in older patients has atypical clinical features delaying diagnosis; 1-month and 1-year mortality rates are higher.
- A history of iTTP in older patients negatively impacts the life expectancy in survivors.

Abstract

Background: Immune Thrombotic Thrombocytopenic Purpura (iTTP) is a potentially lethal auto-immune disease. Older age is associated with increased iTTP mortality. Yet, data are scarce regarding iTTP occurring among older patients and their short- and long-term mortalities.

Objective: To assess clinical features and long-term impact of iTTP on mortality in older patients (>60 yo).

Patients and methods: Characteristic and prognosis of adult iTTP patients with acquired severe ADAMTS-13 deficiency (<10%) enrolled in the registry of the French Reference Center for Thrombotic Microangiopathies between 2000 and 2016 were described according to age (<60 yo or ≥60 yo). Long-term mortality of iTTP older survivors was compared with this of non-iTTP geriatric French Three-City cohort subjects.

Results: Comparing respectively older iTTP patients (N=71) with younger patients (N=340), time from hospital admission to diagnosis was longer (p<0.0001); at diagnosis, delirium (p=0.034), behavior impairment (p=0.045), renal involvement (p<0,0001) and elevated troponin level (p=0.025) were more important whereas cytopenias were less profound (platelet count 22 G/L [9-57] *vs* 13 G/L [9-21], respectively, p=0.002, and hemoglobin level 9 g/dL [8-11] *vs* 8 d/dL [7-10], respectively, p=0.0007). Short- and mid-term mortalities were higher (p<0.0001) and increased for every 10-years of age range. Age ≥60, cardiac involvement, increased plasma creatinine level and total plasma exchange volume, were independently associated with 1-month mortality. Compared with a non-iTTP geriatric population, older survivors showed an increased long-term mortality (HR=3.44, p<0.001).

Conclusion: Older iTTP patients have a frequent atypical neurological presentation, which may delay the diagnosis. Age impacts negatively 1-month and 1-year mortality. A history of iTTP impacts negatively long-term mortality of older survivors.

Introduction

Immune Thrombotic Thrombocytopenic Purpura (iTTP) is a Thrombotic MicroAngiopathy (TMA) characterized by the association of microangiopathic hemolytic anemia, profound thrombocytopenia and organ impairment [1]. The diagnosis is confirmed by the identification of a severe deficiency in ADAMTS-13, the von Willebrand factor-cleaving protease, and presence of anti-ADAMTS-13 antibodies [2]. ADAMTS-13 deficiency triggers the adhesion and aggregation of platelets to ultralarge von Willebrand multimers in capillaries and arterioles, resulting in microvascular thrombosis responsible for organ failure [3]. iTTP is lethal in the absence of treatment. Older age, neurological and cardiac involvements and lactate deshydrogenase (LDH) levels have been identified as risk factors for mortality [4,5]. Nevertheless, prognosis has been dramatically improved combining daily plasma exchange, corticosteroids and B-cell depletion with the monoclonal antibody rituximab [6], with current survival rates of more than 85%. Moreover, the recently available anti-von Willebrand factor nanobody caplacizumab could still improve survival [7,8]. However, early mortality in iTTP was found systematically higher among older patients [4,9,10]. Surprisingly, while the proportion of older patients in iTTP registries is significant (17% of patients have > 60 yo and 13% have > 70 yo) and may increase in the next future as a result of a more systematic long-term follow-up of these older patients [11], the characteristics of iTTP among older patients have been poorly investigated so far [4]. A history of iTTP was reported to impair long-term survival in younger patients and this long-term effect could be even more pronounced among older patients [12]. It is therefore crucial to better understand the characteristics of iTTP among older patients, including short-term and long-term outcomes, to improve its prognosis in this population.

Methods

Patients and data collection

All data from iTTP patients referred to the French TMA National Reference Center from 2000 to 2016 were analyzed. We only considered for the present study patients with complete

data for clinical presentation, treatment and long-term follow-up. iTTP patients were separated according to their age (under 60 yo, or 60 yo and above). As in previous studies, TTP diagnosis criteria were as follows [13,14]: (i) the presence of Coombs-negative microangiopathic hemolytic anemia or microangiopathic hemolysis ; (ii) acute peripheral thrombocytopenia (< 150 x 10^3/mm^3) with the absence of any other identifiable cause of thrombocytopenia and microangiopathic hemolytic anemia (severe disseminated intravascular coagulopathy, malignant hypertension); and (iii) severe acquired ADAMTS-13 deficiency (< 10% of activity) with anti-ADAMTS13 antibodies ≥ 15 U/mL. Cerebral involvement was considered in case of presence of headaches, delirium, seizures, focal deficiency, vigilance and behavioral impairment. Cardiac involvement included novel sign of heart failure, chest pain, and when available electrocardiogram abnormality and increased troponin level. ADAMTS-13 activity and anti-ADAMTS-13 antibodies and other biological parameters were assessed as previously reported [1]. Collected data included any past history of cardiovascular risk factors (dyslipidemia, hypertension, diabetes mellitus and previous or current tobacco use), a pre-existing history of ischemic heart disease, ischemic stroke, chronic kidney disease (according to KDIGO classification), cognitive impairment, institutionalization and use of anti-hypertensive treatment, antiplatelet or vitamin K antagonist. iTTP-associated comorbidities such as cancer or auto-immune disease, drugs or infection were collected.

Treatment and outcomes

Delays from admission to diagnosis and from diagnosis to treatment and iTTP management were analysed. Adverse events related to iTTP treatment were reported. Assessment of response to treatment was performed as previously described and in accordance with international recommendations [15]: a complete response was defined as full resolution of any clinical manifestations and platelet count recovery (> 150 x 10^3/mm^3) for at least 2 days. Refractoriness was defined as the absence of platelet count doubling after four full days of standard intensive treatment with persistently elevated Lactate DeHydrogenase (LDH) levels.

Exacerbation was defined by initial treatment response but reappearance of clinical manifestations and/or thrombocytopenia (< 100 x 10^3/mm3 for at least 2 days) before durable remission (complete response with no further thrombocytopenia or clinical worsening for > 30 consecutive days from the first day of platelet count recovery including the time on maintenance plasma exchange). Relapse was the reappearance of clinical features of iTTP (thrombocytopenia [< 100 x 10^3/mm^3 for at least 2 days], associated or not with neurologic manifestations) with no other identifiable cause after durable remission had been achieved [5]. Survival status at 1 year (mid-term) and at the time of completion of the study (long-term), were completed by registry office and phone call to general practitioners.

Ethics

The study has been approved by the French Data Protection Authority ('Commission Nationale Informatique et Libertés', CNIL) authorization no. DR-2012-158.

The Three-City Study

In order to evaluate the impact of iTTP on long-term mortality in older patients, we compared the survival rate of older patients from our study (iTTP patients) still alive at 1 month with the one of older non-iTTP subjects, all participants of a population-based cohort on aging and dementia, the Three City (3C) Study. The protocol has been detailed previously [16]. The present sample included 1,755 community dwelling adults, initially aged 65 years, over living in Bordeaux (N=2,104) and followed-up every two to three years over 17 years since 1999. The 1,755 analyzed patients where those who completed all the clinical data at the first visit after inclusion. Vital status of all participants was ascertained from the family, the general practitioners, or the native City council until 17 years after the baseline visit. This study was conducted according to the guidelines laid down in the Declaration of Helsinki.

Statistics

Quantitative variables were summarized as median [interquartile range] and compared by use of Mann-Whitney Wilcoxon's rank-sum test. Categorical data were summarized as count (%) and compared by use of the chi-squared or Fischer tests. To explore the effect of age, all analyses distinguished two age groups: patients 60 and above *vs* patients under 60. Risk factors for short- and mid-term mortalities were investigated by logistic regression. First, a univariate analysis was carried out. Only variables with a p-value < 0.20 and with less than 20% of missing data were included in the multivariable analysis.

We then evaluated the impact of iTTP on long-term survival in older patients compared with a control aging population. Data were available for 38/45 older iTTP survivors (mean length of follow-up after iTTP diagnosis: 1,678 days (±1,257), median: 1,682 (IQR: 1,728)). A first comparison on clinical characteristics was done between the two populations. Then, survival analyses have been conducted using first Kaplan-Meier methods with point-wise limits, then a Cox proportional hazards model. We applied a backward stepwise selection controlled for sex, age, tobacco consumption, diabetes mellitus, stroke, cancer, hypertension, ischemic coronary disease, dementia, chronic kidney disease and (chronic obstructive pulmonary disease) COPD. Statistical analyses were assessed by the R 3.5.1 statistical software (R foundation for Statistical Computing Vienna, Austria).

Results

Population characteristics and iTTP presentation

A total of 770 adult patients with features of TMA and a severe ADAMTS13 deficiency were included in our registry between October, 2000 and December, 2016. Among these patients, 27 had an alternative diagnosis (mostly severe sepsis/septic shock) and 22 had a congenital form of the disease. Three hundred and ten others had insufficient data regarding clinical presentation and management and/or an incomplete follow-up or were lost to follow-up, leaving 411 patients, of whom 71 (17%) were ≥ 60 yo (**Figure 1**). To ascertain that our cohort of studied patients was fully representative of the whole iTTP population, we verified that the main

initial characteristics remained unchanged with and without the non-included patients. Among the 310 non-included patients, data about initial characteristics were available for 173 (136 under 60 yo and 37 60 yo or above). We found that comparisons were similar when those patients were included in the analysis **(Supplemental Table 1).** As expected, older patients presented more comorbidities as suggested by the Charlson score, mostly cardiovascular diseases and cancer; hence they were receiving more often anti-hypertensive treatment, antiplatelet therapy and vitamin K antagonists. Patients with an initial episode and those with relapses were in comparable proportions between older and younger patients **(Table 1)**. Most patients lived at home.

Older iTTP patients presented more frequently delirium with behavioral disturbance compared to younger ones, while headaches and abdominal pain were associated with younger age. Acute renal and cardiac injuries were more prevalent in older patients with increased plasma creatinine and troponin levels, respectively. Moreover, thrombocytopenia and anemia were more pronounced in younger patients. Interestingly, when we applied the French score on both groups of patients [14], we found that among patients most likely to have a severe ADAMTS13 deficiency on diagnosis (platelets ≤ 30 G/L and serum creatinine ≤ 2.25 mg/dL), 80% of patients of the younger group had a confirmed severe ADAMTS13 deficiency, *vs* only 61% in the older group (p< 0.0001) **(Supplemental Table 2)**, highlighting that diagnosing iTTP among older patients on the basis of clinical scores can be more challenging.

While a history of cancer was more frequently observed in older iTTP patients compared with younger ones, auto-immune diseases were less often present. Other iTTP-associated diseases were comparable between groups.

iTTP treatment and morbi-mortality

Time from hospital admission to diagnosis was longer for older than for younger iTTP patients (3 days *vs* 1 day respectively, p: 0.0001), consistent with a delayed diagnosis in the elderly, whereas time from diagnosis to treatment initiation was similar. To tentatively address

the reasons leading to a delayed diagnostic, we focused more on the diagnostic context in older patients from individual clinical records when available (N=67). In 17 patients, no obvious diagnostic delay could be evidenced. In the remaining patients with a possible diagnostic delay however, iTTP diagnosis was preceded by neurological manifestations (26 cases) including malaise with or without loss of consciousness (3 cases), transient ischemic stroke leading typically to focal deficiency and/or aphasia (14 cases), behavior abnormalities/delirium/vigilance impairment (6 cases), seizure (2 cases), and dizziness (1 case). One additional patient had a myocardial infarction. In 16 other patients, we found that iTTP diagnostic was preceded by an infectious-like process, especially a diarrhea (7 cases).

Treatment was comparable between age groups, including the proportion of patients treated with rituximab. Moreover, the increasing use of rituximab through the inclusion period was comparable between both groups as the slopes of the curves representing the percentage of patients treated by rituximab year per year were comparable between earlier and later years **(Supplemental Figure 1)**. Nevertheless, when treated older patients received on average one less rituximab infusion than younger patients (**Table 2**).

Lethal and non-lethal catheter-related adverse events were similar between age groups. However, older patients experienced more frequently catheter self-removals or physical restraints prescription in order to avoid these removals (**Table 2**).

Short-term and mid-term mortality rates were increased in older patients (**Table 3**) and 1-month mortality increased for every 10-years range of age (**Figure 2**). Short-term mortality was mostly due to cardiac and neurological events. In fact, cause of death was tentatively identified for 18/26 patients; eight of them died from a cardiac event (4 cardiogenic shocks, 3 cardiac arrests and 1 ventricular arrhythmia), 8 died from a neurological event (6 ischemic strokes and 2 intracranial hemorrhages), 1 from mesenteric ischemia and 1 from septic shock. Regarding mid-term mortality, cause of death was identified for 5/8 patients: stroke and septic shocks secondary to pneumonia (2 cases each), and cancer (1 case). Older iTTP survivors were also less likely to stay at home after discharge than younger survivors. No difference was found

comparing older iTTP 1-month survivors to younger ones regarding relapse rate (3/30 (10%) *vs* 68/308 (22%) respectively, p: 0.23) and time to relapse (610 days [410;695] *vs* 845 days [373;1338] respectively, p: 0.37) (**Table 3**).

Assessed by multivariate analysis, age above 60 (OR: 33.3; IC95 [7.14–1,000]), cardiac involvement (OR: 5.88; IC95 [1.11–33.3]) and increased plasma creatinine level (per +10µmol/L: OR: 1.04; IC95 [1.01 – 1.1]) were independently associated with 1-month mortality in the whole iTTP population. Plasma exchange volume was independently associated with a lower 1-month mortality (per + 100mL/kg: OR: 0.81; IC95 [0.60 – 0.98]) (**Table 4**). Regarding mid-term mortality among older iTTP patients, we found cardiac involvement to be an independent risk factor (OR: 6.67, 97.5%CI [1.89-25], p: 0.004).

Long-term mortality among older patients after durable iTTP remission compared with control non-iTTP elders (3C study)

Long-term mortality data were available for 38/45 older iTTP survivors (mean length of follow-up after iTTP diagnosis: 1,678 days (±1,257), median: 1,682 (IQR: 1,728)) and were compared with those of 1,755 non-iTTP geriatric cohort participants (Three-City Study cohort). Older iTTP 1-month survivors had more cardiovascular comorbidities and COPD (**Supplemental Table 3**). They exhibited a lower long-term survival rate (**Figure 3**). A history of iTTP remained an independent risk factor for death (HR: 3.44; 95%CI [2.02; 5.87]) even after controlling for age, sex, cardiovascular risk factors and events, COPD, chronic kidney disease and dementia (**Table 5**).

Discussion

Our data highlight the frequent atypical presentation of iTTP among older patients with more organ involvement, delirium and behavioral abnormalities, and less pronounced cytopenias than younger patients, which may have contributed to a later diagnosis. Alternatively, organ damage in older patients following microthrombi formation may occur

earlier than in younger patients, accounting for earlier clinical manifestations with older age; in younger patients, conversely, organs may be more tolerant to microthrombi and ischemia, leaving cytopenias get worse. As a consequence of these features, we provide evidence that the diagnosis of iTTP based on clinical scores aimed at predicting a severe ADAMTS13 deficiency [14,17], may be less reliable among older patients. Delirium and acute behavioral abnormalities but also ischemic stroke, are very common reasons to admit an old patient to hospital. They are not specific to a disease and they are less alarming than in the young patients. This presentation could explain the delayed iTTP diagnosis in this age group. In this context, the presence of a thrombocytopenia with anemia should alert physicians to this possible rare diagnosis. Treatment between the 2 age groups was comparable; however, maintaining a catheter was more difficult in the older group because of poor venous access and behavioral disturbance frequently leading to catheter self-removals.

Short-term (1-month) and mid-term (1-year) mortality rates were higher among older patients than among younger patients. Age, increased plasma creatinine level and total plasma exchange volume were independently associated with short-term mortality, whereas cardiac involvement was independently associated both with short- and mid-term mortalities.

Moreover, when compared with a control geriatric cohort of non-iTTP elders, iTTP 1-month survivors had a threefold higher risk of long-term mortality, independently to several survival risk factors. This shortened life expectancy in patients with a history of iTTP is consistent with a previous report from the Oklahoma group [18] and could result from more prevalent long-term disorders including hypertension, depression and cognitive impairment [12,18] as well as iTTP-related sequelae, especially in older survivors. Nevertheless, the mechanisms underlying this excess of mortality in patients with a history of iTTP are still unclear but could be explained by a iTTP-induced decline of chronic conditions like chronic renal and cardiac failure or cognitive impairment. Data on functional status are lacking but all older patients enrolled in this study lived at home, which is an indirect marker of independence. Especially, future works should address the possible deleterious synergistic effect of iTTP-related

microthrombi combined with vascular wall remodeling events involved in chronic diseases such as diabetes and hypertension, as well as with senescent processes. iTTP and cardiovascular ageing could therefore share common mechanisms of endothelial dysfunction including alteration of the NO pathway and inflammation[19–26]. More generally, the occurrence of iTTP in a patient with a previously senescent endothelium could result in a more severe presentation with short-term but also more long-term consequences.

The management of iTTP in the older patients needs to be adapted at the light of the new available strategies in the field. Importantly, in the very next future, the anti-vWF nanobody caplacizumab should become part of the standard treatment of iTTP on the basis of a recent positive randomized controlled trial [7]. However, given the increased bleeding risk in patients receiving caplacizumab, there is an urgent need to assess more accurately the benefit-risk and the side effects associated with the use of caplacizumab in older patients as they receive more antiplatelet agents and/or anticoagulants. Moreover, caplacizumab could decrease the organ impairment at the acute phase [27]. As older patients are less prone to recover from an acute injury, it could also have long-term consequences in older iTTP survivors. Additionally, as preemptive rituximab strategy is becoming increasingly popular to prevent relapses, there is a need to assess the risk of repeated infusions of rituximab among those older patients who could suffer from an increased risk of infectious complications [28]. Apart from the evaluation of such new treatment strategies in older patients, a comprehensive geriatric assessment including cognitive, functional and nutritional statuses could describe the prognosis of iTTP in older patients more precisely.

A potential limitation of our study is that in our national registry, only certain iTTP cases with a documented severe ADAMTS13 deficiency were reported. We may assume that frail people, like those living in nursing homes or long-term care facilities are less diagnosed. Besides, data were not available for 310 patients, which could have introduced a bias if these patients were systematically different from those included. Nevertheless, data about the initial characteristics were available for 174 of them and comparisons between younger and older

iTTP patients drawn the same conclusions when these patients were included, which reinforces these comparisons. Moreover, while cardiac involvement was negatively associated with survival, we could not associate cardiac troponin levels with prognosis [5]. However, this unexpected finding could result from a 30% rate of missing data for cardiac troponin in this study with a long period of inclusion. Our study included patients with an initial episode as well as relapses; it could therefore be argued that initial episodes and relapses should be considered separately. Although works reported a trend toward less severe presentation in terms of symptoms, laboratory data and the number of plasma exchange required in their relapse episodes compared to their initial diagnosis, this did not translate into differences in clinical outcomes [29]. On the basis of these statements, we and others consider that both in clinical practice and research, patients in their initial episode and relapse episodes should be viewed as comparable events in terms of the urgency to start plasma exchange, as well as for enrollment in clinical trials.

Older patients with iTTP have a frequent atypical neurological presentation, which may delay the diagnosis. Practitioners should be aware of this in order to shorten the time to treatment, which could improve the prognosis in older iTTP patients. Promising new agents deserve evaluation in this specific population of patients characterized by a substantially increased mortality.

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Authorship contributions

R. Prevel, C. Roubaud-Baudron and P. Coppo designed the study, interpreted the results, and wrote the manuscript. S. Gourlain and K. Peres performed the statistical analysis of the comparison with the Three-City study population. M. Jamme performed the statistical analysis of the French Registry for Thrombotic Microangiopathies. Y. Benhamou, L. Galicier, E. Azoulay, P. Poullin, F. Provôt, E. Maury, C. Presne, M. Hamidou, S. Saheb, A. Wynckel, A. Servais, S. Girault, Y. Delmas, V. Chatelet, J.F. Augusto, C. Mousson, P. Perez, J.M. Halimi, T. Kanouni, A. Lautrette, A. Charvet-Rumpler, C. Deligny, D. Chauveau, A. Veyradier, P. Coppo enrolled patients and collected

clinical and laboratory information. All of the authors critically reviewed and substantially improved the manuscript.

Disclosure of Conflict of Interests

R. Prevel, C. Roubaud, S. Gourlain, K. Peres, M. Jamme, Y. Benhamou, L. Galicier, E. Azoulay, P. Poullin, F. Provôt, E. Maury, C. Presne, M. Hamidou, S. Saheb, A. Wynckel, A. Servais, S. Girault, V. Chatelet, J.F. Augusto, C. Mousson, P. Perez, J.M. Halimi, T. Kanouni, A. Lautrette, A. Charvet-Rumpler, C. Deligny, D. Chauveau, A. Veyradier do not have any conflict of interest to declare. P. Coppo is member of the Clinical Advisory Board for Alexion, Ablynx now part of Sanofi, Shire and Octapharma. Y. Delmas and C. Presne have participated to Advisory boards for Ablynx now part of Sanofi.

Appendix

The members of the Reference Center for Thrombotic Microangiopathies (CNR-MAT) are:

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Table 1. Clinical characteristics of patients at admission according to age.

	Age < 60 n = 340		Age ≥ 60 n = 71		*p*-value
Clinical characteristics at admission					
Age	38	[28-47]	74	[69-80]	
Sex-ratio (male/female)	0.51		0.38		
Relapsing TTP episode	30	9 %	3	4 %	0.24
Cerebral involvement	231	68 %	56	79 %	0.087
Headaches	120	35 %	12	17 %	0.002
Delirium	61	18 %	21	30 %	0.034
Seizures	25	7 %	11	15 %	0.038
Vigilance impairment / coma	53	16 %	15	21 %	0.29
Focal deficiency	125	37 %	34	48 %	0.11
Behaviour abnormalities	46	14 %	17	24 %	0.045
Cardiac involvement	96	29 %*	23	37 %#	0.23
Plasma creatinine (µmol/L)	89	[73;120]	124	[89;198]	<0.0001
Abdominal pain	90	26 %	8	11 %	0.006
Platelets count (G/L)	13	[9;21]	22	[9;57]	0.002
Haemoglobin level (g/dL)	8	[7;10]	9	[8;11]	0.0007
Reticulocytes count (x10^3/mm3)	184	[105;279]**	143	[77;339]##	0.92
LDH (fold laboratory higher norm)	4.6	[3;7]***	4.2	[3;7]##	0.52
Schistocytes (%)	4	[2;7]****	2.7	[1;6]##	0.095
Anti-ADAMTS-13 antibodies titers (UI/L)	82	[42;100]*	90	[36;100]##	0.81
Troponin level (ng/mL)	0.26	[0.02;1]**	0.85	[0.1;4]###	0.025
General comorbidities					
Charlson comorbity score	0	[0;1]	2	[0;3]	<0.0001
Diabetes mellitus	13	4 %	15	21 %	<0.0001
Coronary heart disease	8	2 %	9	13 %	0.0006
Tobacco use	135	40 %	15	22 %	0.004
Dyslipidemia	31	9 %	31	44 %	<0.0001
Hypertension	40	12 %	46	65 %	<0.0001
Chronic kidney disease	8	2 %	7	10%	0.006
Transient stroke / stroke	15	4 %	7	10%	0.077
Cognitive impairment	5	1 %	2	3 %	0.34
Institutionalization	1	0.3 %	0	0%	1.00
Antihypertensive treatment	31	9 %	43	61 %	<0.0001
Antiplatelets therapy	18	5 %	24	34 %	<0.0001
Vitamin K antagonist	5	1 %	7	10%	0.001
iTTP associated comorbidities					
Cancer	1	0.3 %	8	11 %	<0.0001
Auto-immune disease	102	30 %	12	17 %	0.028
Presence of antinuclear antibodies	150	44 %	24	38 %	0.34
If so, antinuclear antibodies titers	200	[100;640]	320	[80;640]	0.76
Antiphospholipid Antibodies	9	3 %	2	3 %	0.68
Drugs	11	3 %	5	7 %	0.17
Infection	62	18 %	17	24 %	0.32

iTTP: immune thrombotic thrombocytopenic purpura, LDH: lactate dehydrogenase. *: data were available for 282 patients. **: data were available for 237 patients. ***: data were available for 267 patients. ****: data were available for 252 patients. #: data were available for 62 patients. ##: data were available for 54 patients. ###: data were available for 46 patients. Data were provided as median [interquartile range] and compared by use of Mann-Whitney Wilcoxon's rank-sum test. Categorical data were summarized as count (%) and compared by use of the chi-squared or Fischer tests.

543 **Table 2.** Immune thrombotic thrombocytopenic purpura treatment characteristics according to
544 age

	Age < 60 n = 340	Age ≥ 60 n = 71	p-value
Initial management			
Time from hospital admission to diagnosis (days)	1 [1;3]*	3 [1;7]#	0.0001
Time from diagnosis to treatment (days)	0 [0;1]*	0 [0;1]#	0.062
Corticosteroids therapy	285 84 %	55 77 %	0.22
Total plasma exchange volume (mL/kg)	541 [289;1001]	412 [256;1010]	0.20
2nd line management			
Exacerbation or refractory TTP	200 62 %**	35 63 %##	1.00
Cyclophosphamide	17 5 %	4 6 %	0.77
Rituximab	179 53 %	31 44 %	0.37
Number of infusions	4 [3;4]	3 [1;4]	0.033
Vincristine	20 6 %	5 7 %	0.78
Splenectomy	9 3 %	1 1 %	1.00
Platelet transfusion	126 37 %	19 27 %	0.10
Adverse events			
Lethal catheter-related adverse events	0 0%	1 1 %	0.16
Infection	0 0%	1 1 %	0.16
Bleeding	0 0%	1 1 %	0.16
Non-lethal catheter-related adverse events	75 23 %***	22 34 %#	0.055
Infection	45 14 %***	12 18 %#	0.33
Thrombosis	38 12 %***	6 9 %#	0.83
Bleeding	5 2 %***	2 3 %#	0.32
Accidental catheter self-removal / Contention	0 0%***	9 14 %#	<0.0001
Plasma exchange-related adverse events	60 18 %***	3 5 %#	0.005
Anaphylaxis	38 12 %***	3 5 %#	0.12
Serum sickness	1 0.3 %***	0 0%#	1.00
Others	22 7 %***	0 0%#	0.033

545 iTTP: immune thrombotic thrombocytopenic purpura. *: data were available for 328 patients. **:
546 data were available for 322 patients. ***: data were available for 326 patients. #: data were
547 available for 65 patients. ##: data were available for 56 patients. Data were provided as median
548 [interquartile range] and compared by use of Mann-Whitney Wilcoxon's rank-sum test.
549 Categorical data were summarized as count (%) and compared by use of the chi-squared or
550 Fischer tests.

551

552 **Table 3.** Patients' outcomes according to age.

	Age < 60 n = 340	Age ≥ 60 n = 71	p-value
Relapse	68 22 %*	3 10%#	0.23
Time to relapse (days)	845 [373;1338]	610 [410;695]	0.37
1-month mortality	32 9 %	26 37 %	<0.0001
1-year mortality	34 11 %**	34 49 %##	<0.0001
1-year institutionalization	14 5 %***	9 26 %###	0.001

553 *: data were available for 308 patients, ** data were available for 320 patients, ***: data were
554 available for 286 patients. #: data were available for 30 patients, ##: data were available for 69
555 patients, ###: data were available for 35 patients. Data were provided as median [interquartile
556 range] and compared by use of Mann-Whitney Wilcoxon's rank-sum test. Categorical data were
557 summarized as count (%) and compared by use of the chi-squared or Fischer tests.

558 **Table 4.** 1-month mortality associated factors by multivariate analysis

	OR	Extreme range IC	P
Plasma creatinine (per +10µmol/L)	1.04	[1.01 ; 1.10]	0.01
Cardiac involvement	5.88	[1.11 ; 33.3]	0.04
Age ≥ 60 years old	33.3	[7.14 ; 1,000]	< 0.001
Total plasma exchange volume (per +100mL)	0.81	[0.60 ; 0.98]	0.02

559

560 **Table 5.** Risk factors associated with long-term mortality among older iTTP 1-month survivors
561 compared with people included in the Three-City study (multivariate Cox model)

Variables	HR	95%CI	p-value
iTTP	3.44	[2.02 ; 5.87]	<0.001
Sex (Male)	1.73	[1.48 ; 2.01]	<0.001
Age	0.95	[0.93 ; 0.98]	<0.001
History of tobacco use	1.49	[1.10 ; 2.02]	0.010
Diabetes mellitus	1.59	[1.27 ; 2.00]	<0.001
Stroke	1.62	[1.05 ; 2.49]	0.028
Cancer	2.18	[1.59 ; 2.99]	<0.001
Hypertension	1.25	[1.03 ; 1.51]	0.024
Coronary heart disease	1.32	[0.96 ; 1.80]	0.086
Chronic kidney disease	1.16	[0.96 ; 1.40]	0.129
Dementia	2.58	[1.78 ; 3.72]	<0.001
COPD	1.56	[1.16 ; 2.09]	0.003

562 COPD: chronic obstructive pulmonary disease. HR: hazard ratio. iTTP: immune thrombotic
563 thrombocytopenic purpura.

564 **Figure 1.** Study Flow Chart. iTTP: immune Thrombotic Thrombocytopenic Purpura.

565

566 **Figure 2.** Short- and mid-term mortality rates according to age.

567

568 **Figure 3.** Comparison of long-term survival rates according to time between older iTTP
569 survivors and the Three-City Study population (Kaplan-Meier curves).

570 Non-iTTP: population of the geriatric Three-City Study who do not have immune Thrombotic
571 Thrombocytopenic Purpura. iTTP: 1-month immune Thrombotic Thrombocytopenic Purpura
572 survivors ≥ 60yo. Log-rank: Full line: survival rate, dashed line: 95% confidence interval.

573

Figure 1.

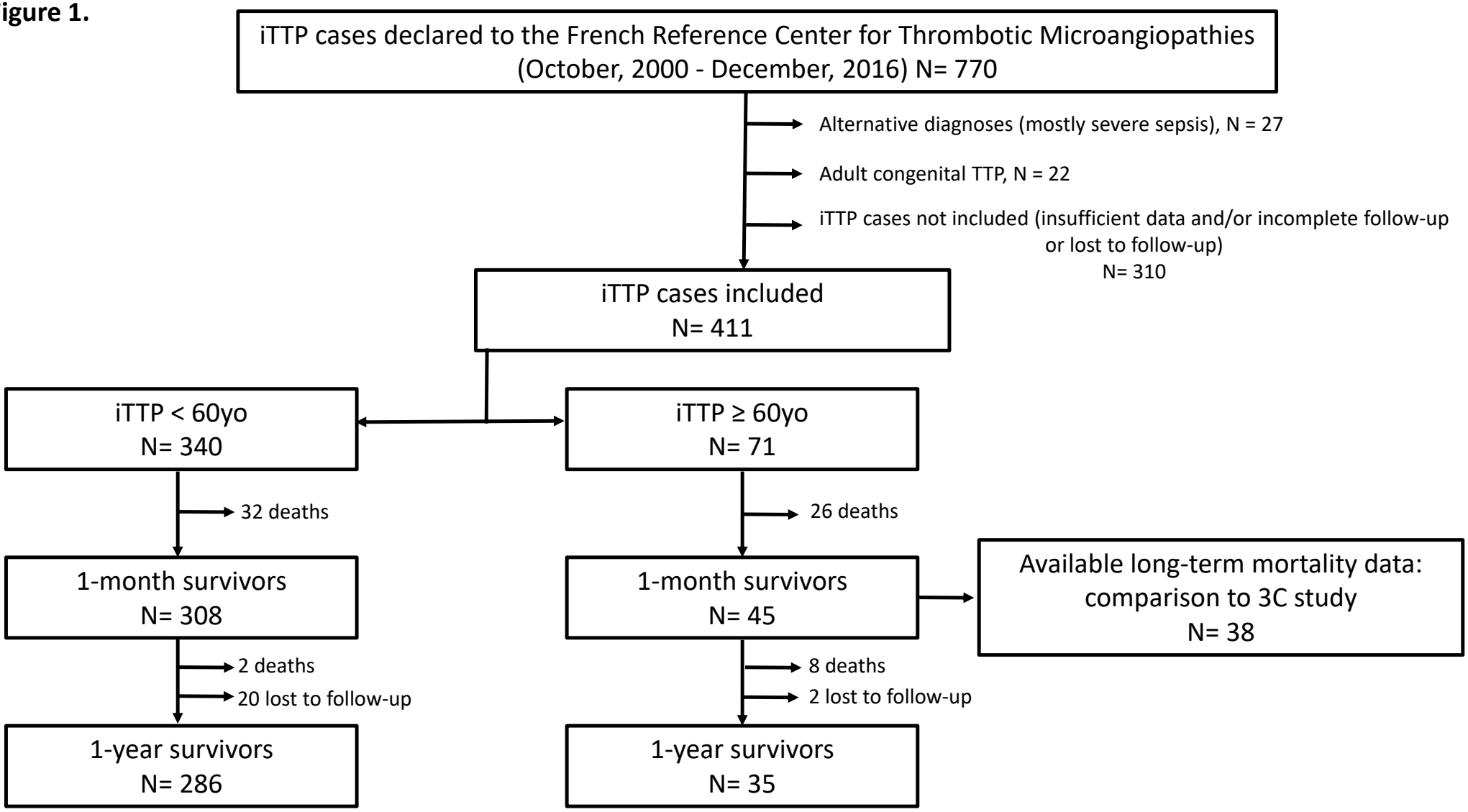

iTTP cases declared to the French Reference Center for Thrombotic Microangiopathies (October, 2000 - December, 2016) N= 770
Alternative diagnoses (mostly severe sepsis), N = 27
Adult congenital TTP, N = 22
iTTP cases not included (insufficient data and/or incomplete follow-up or lost to follow-up) N= 310
iTTP cases included N= 411
iTTP < 60yo N= 340
iTTP ≥ 60yo N= 71
32 deaths
26 deaths
1-month survivors N= 308
1-month survivors N= 45
Available long-term mortality data: comparison to 3C study N= 38
2 deaths
20 lost to follow-up
8 deaths
2 lost to follow-up
1-year survivors N= 286
1-year survivors N= 35

Figure 2.

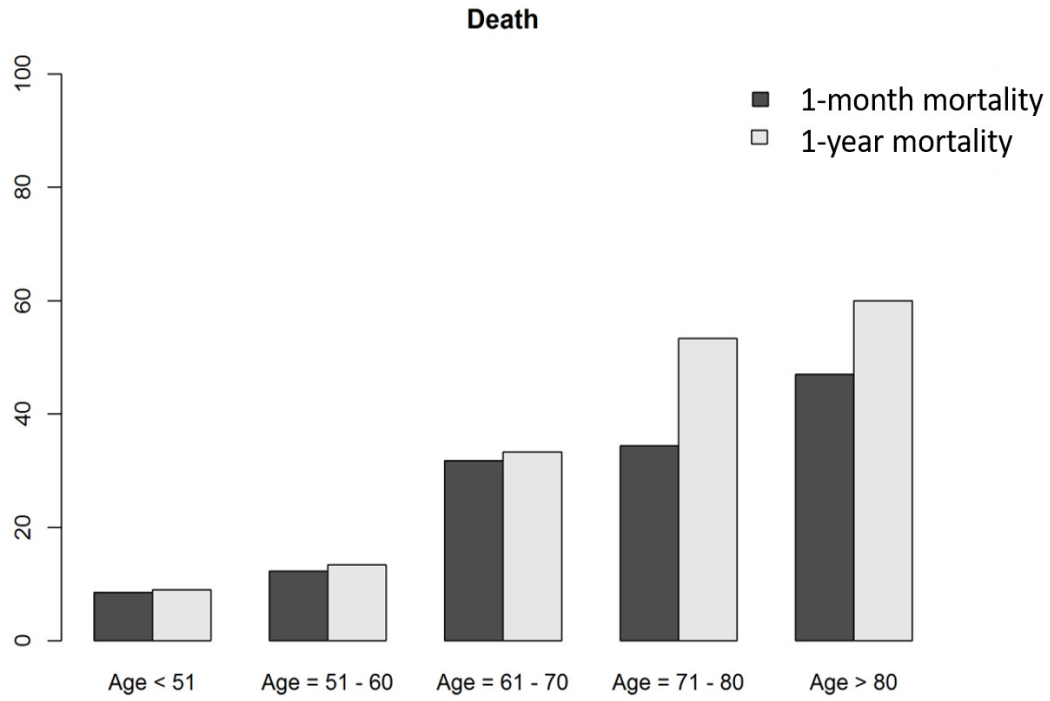
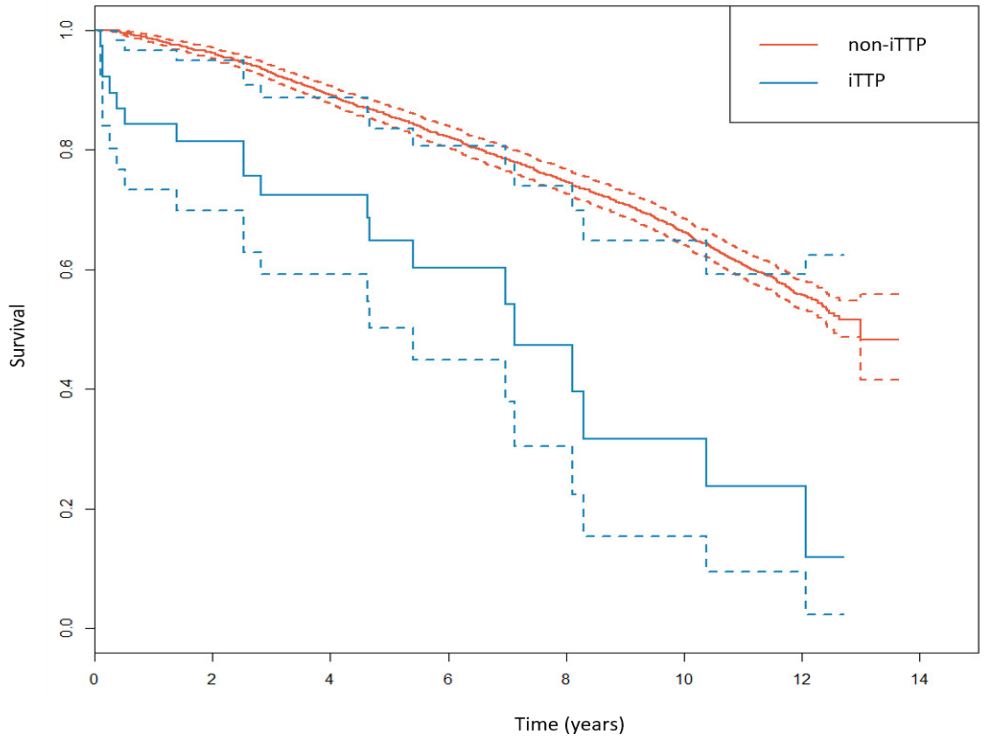

Death
1-month mortality
1-year mortality
0
20
40
60
80
100
Age < 51
Age = 51 - 60
Age = 61 - 70
Age = 71 - 80
Age > 80

Figure 3:


non-iTTP
iTTP
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
Time (years)

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Prognostic and Long-term Survival of Immune Thrombotic Thrombocytopenic Purpura in older patients

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