Immune-mediated thrombotic thrombocytopenic purpura prognosis is affected by blood pressure

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BRIEF REPORT

Immune-mediated thrombotic thrombocytopenic purpura prognosis is affected by blood pressure

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Abstract

Background: The prevalence, prognostic role, and diagnostic value of blood pressure in immune-mediated thrombotic thrombocytopenic purpura (iTTP) and other thrombotic microangiopathies (TMAs) remain unclear.

Methods: Using a national cohort of iTTP ($n = 368$), Shigatoxin-induced hemolytic uremic syndrome ($n = 86$), atypical hemolytic uremic syndrome ($n = 84$), and hypertension-related thrombotic microangiopathy ($n = 25$), we sought to compare the cohort's blood pressure profile to assess its impact on prognosis and diagnostic performances.

Results: Patients with iTTP had lower blood pressure than patients with other TMAs, systolic (130 [interquartile range (IQR) 118–143] vs 161 [IQR 142–180] mmHg) and diastolic (76 [IQR 69–83] vs 92 [IQR 79–105] mmHg, both $p < 0.001$). The best threshold for iTTP diagnosis corresponded to a systolic blood pressure <150 mmHg. iTTP patients presenting with hypertension had a significantly poorer survival (hazard ratio 1.80, 95% confidence interval 1.07–3.04), and this effect remained significant after multivariable adjustment (hazard ratio = 1.14, 95% confidence interval 1.00–1.30). Addition of a blood pressure criterion modestly improved the French clinical score to predict a severe A disintegrin and metalloprotease with thrombospondin type 1 deficiency in patients with an intermediate score (i.e., either platelet count $<30 \times 10^9$/L or serum creatinine <200 μM).

Conclusions: Elevated blood pressure at admission affects the prognosis of iTTP patients and may help discriminate them from other TMA patients. Particular attention should be paid to blood pressure and its management in these patients.

KEYWORDS
ADAMTS13, blood pressure, complement, hemolytic uremic syndrome, hypertension, prognosis, thrombotic microangiopathies, thrombotic thrombocytopenic purpura

Essentials

- The role of hypertension in thrombotic microangiopathies remains to be explored.
- In our national cohort, blood pressure was lower in thrombotic thrombocytopenic purpura.
- Thrombotic thrombocytopenic purpura patients with higher blood pressure had a poorer survival.
- On the other hand, the added value of blood pressure to the French clinical score was modest.

1 | INTRODUCTION

Thrombotic microangiopathies (TMAs) are a heterogeneous group of severe diseases defined by the association of mechanical hemolytic anemia, thrombocytopenia, and ischemic organ injury. Hypertension can be a direct cause of TMA[1] but is also prevalent in other TMA syndromes, particularly in the hemolytic uremic syndrome.[2-4] Besides, it is well known that hypertension plays an important role in the endothelial injury[2,5] accompanying all TMAs. From a retrospective pilot study including various TMAs,[6] we previously pointed out the potential of initial blood pressure to discriminate immune-mediated thrombotic thrombocytopenic purpura (iTTP) from other TMAs. Moreover, high blood pressure at admission was associated with an increased risk of end-stage renal disease. However, the influence of blood pressure on the prognosis of TMA patients and its diagnostic performance for discrimination of TMA syndromes remain to be evaluated in a large and multicentric cohort of TMAs. In this study, we sought to compare blood pressure profiles among patients with iTTP, Shigatoxin-induced hemolytic uremic syndrome (STEC-HUS), atypical hemolytic uremic syndrome (aHUS), and hypertension-related thrombotic microangiopathy (HT-TMA) to assess its impact on prognosis and diagnostic performance.

2 | MATERIALS AND METHODS

2.1 | Inclusion criteria and data extraction

From January 2000 to June 2018, all adult (>18 years old) patients who fulfilled criteria for TMA were prospectively recruited from 88 centers in France and included in the registry of the French reference center for Thrombotic Microangiopathies (CNR-MAT, www.cnr-mat.fr). The study protocol was reviewed and approved by the institutional review board and ethical committee (no. P020501). Informed consent was obtained from all patients. Patients with hemolytic anemia (hemoglobin level <12 g/dL) with schistocytes and thrombocytopenia (platelet count $<150 \times 10^9$/L), with or without organ damage, were included as TMA patients. Patients lacking one of these criteria could be included if they had a biopsy showing unequivocal pathologic signs of TMA. TMAs related to pregnancy, bone marrow or solid organ transplantation, malignancy, drug exposure, or HIV infection were excluded. iTTP was defined by an undetectable A disintegrin and metalloprotease with thrombospondin type 1 repeats (ADAMTS13) activity (<10%) associated with anti-ADAMTS13 antibodies.[7] STEC-HUS was defined based on evidence of Shigatoxin gene by polymerase chain reaction analysis, or STEC in stool cultures. aHUS was defined as a TMA with detectable ADAMTS13 activity in the absence of any coexisting condition or treatment acknowledged to trigger TMA.[8] HT-TMA was defined as TMA with severe hypertension in the absence of any coexisting condition, complement mutation or undetectable ADAMTS13 activity, or treatment acknowledged to trigger TMA, and without relapse after blood pressure control. Demographic, clinical, and biological data at admission, treatments, time to durable platelet count recovery time, and status at end of follow-up were extracted from patients' medical charts. The first blood pressure reading at admission was recorded, and hypertension was classified according to the 2018 European Society of Cardiology guidelines[9] in grade 1 (systolic blood pressure 140–159 mmHg and/or diastolic blood pressure 90–99 mmHg), grade 2 (systolic blood pressure 160–179 mmHg and/or diastolic blood pressure 100–109 mmHg), and grade 3 (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg). Renal sequelae were defined as estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 at discharge from the hospital, using the Modification of Diet in Renal Disease equation.[10] Because results of antinuclear antibodies are often unavailable in an emergency context, we removed them from the French score[11,12] in the present study.

2.2 | Statistics

2.2.1 | Descriptive statistics and comparisons between groups

Results were expressed as medians and interquartile range for continuous data and numbers and percentages for categorical data. Quantitative variables were compared using the Wilcoxon test, and qualitative variables were compared using the χ^2 test.

2.2.2 | Diagnostic performances and incremental value of blood pressure to the French score for iTTP diagnosis

Diagnostic performance of blood pressure was evaluated by area under the receiver operating characteristic (ROC) curve and the best threshold based on Youden index (sensitivity + specificity − 1) was calculated. For the assessment of incremental value of the addition of blood pressure to the previously published French score,[11] we planned to focus on patients with an intermediate French score (i.e., either platelet count $<30 \times 10^9$/L or serum creatinine <200 μM) because they represent an unmet diagnostic need.[12]

2.2.3 | Survival analyses

Kaplan-Meier curves were compared using log-rank tests on the complete cohort. Association of blood pressure and other selected variables with overall and relapse-free survival in iTTP patients was investigated using univariate and multivariable Cox models. All statistical tests were two-sided with a α level of 0.05. Statistics were managed using R software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

TABLE 1 Clinical and biological characteristics at admission in patients hospitalized for thrombotic microangiopathy syndromes according to diagnosis

	iTTP (*n* = 368)	STEC-HUS (*n* = 86)	aHUS (*n* = 84)	HT-TMA (*n* = 25)
Demographics and medical history				
Female sex (*n* (%))	264 (72)	60 (70)	50 (60)	7 (28)
Age (years) (median [IQR])	40.8 [29.6–52.1]	62 [50.4–73.7]	37.8 [25.3–50.3]	39.8 [36–43.6]
Ethnicity (*n* (%))				
White	249 (70)	69 (95)	75 (93)	14 (58)
Afro-Caribbean	51 (14)	1 (1)	4 (5)	7 (29)
North Africa	42 (12)	2 (3)	2 (2)	0 (0)
Other	14 (4)	1 (1)	0 (0)	3 (13)
Body mass index (kg/m^2) (median [IQR])	25.6 [21.6–29.7]	23.7 [20–27.5]	22.4 [20.7–24.1]	25.9 [23–28.9]
History of chronic kidney disease (*n* (%))	2 (1)	3 (4)	3 (4)	2 (8)
History of hypertension (*n* (%))	62 (17)	30 (41)	18 (23)	11 (46)
Clinical characteristics at admission				
Systolic blood pressure (median [IQR])	130 [118–143]	140 [123–157]	154 [131–177]	220 [203–237]
Diastolic blood pressure (median [IQR])	73 [65–81]	80 [70–90]	90 [80–100]	130 [113–148]
Hypertension (*n* (%))	144 (39)	49 (57)	63 (75)	25 (100)
Hypertension grade (*n* (%))				
Normal blood pressure <140/90 mmHg)	224 (61)	37 (43)	21 (25)	0 (0)
Grade 1 hypertension (140–159/90–99 mmHg)	97 (26)	25 (29)	20 (24)	1 (4)
Grade 2 hypertension (160–179/100–109 mmHg)	27 (7)	15 (17)	14 (17)	0 (0)
Grade 3 hypertension (≥180/110 mmHg)	20 (5)	9 (11)	29 (35)	24 (96)
Neurological signs at admission (*n* (%))	244 (67)	52 (62)	32 (39)	13 (52)
Headache	129 (36)	12 (14)	21 (25)	9 (36)
Confusion	80 (22)	33 (39)	10 (12)	4 (16)
Seizures	24 (7)	10 (12)	4 (5)	4 (16)
Coma	35 (10)	8 (10)	1 (1)	3 (12)
Focal deficit	125 (35)	17 (20)	4 (5)	4 (17)
Classification of hypertensive retinopathy (*n* (%))				
0	35 (69)	13 (72)	14 (47)	2 (11)
1	2 (4)	0 (0)	3 (10)	0 (0)
2	9 (18)	2 (11)	3 (10)	4 (21)
3	5 (10)	3 (17)	10 (33)	13 (68)
Biological characteristics at admission				
Creatinine (µmol/L) (median [IQR])	92 [66–119]	363 [191–535]	523 [260–787]	301 [100–503]
Estimated glomerular filtration rate (MDRD) (ml/min/1.73 m^2) (median [IQR])	69 [50–89]	7 [–2–16]	7 [–1–15]	19 [3–36]
Leucocytes (×10^9/L) (median [IQR])	9.8 [6.9–12.8]	10.9 [8.6–13.3]	8.8 [6.3–11.3]	10 [8.3–11.7]
Hemoglobin (g/dL) (median [IQR])	7.7 [6.4–9]	9 [7.8–10.3]	8.3 [7–9.6]	8.9 [7.5–10.3]
Platelets (×10^9/L) (median [IQR])	14 [7–22]	43 [26–60]	71 [28–115]	101 [68–134]
Lactate dehydrogenase (UI/L) (median [IQR])	1755 [902–2609]	1847 [1117–2577]	2024 [973–3075]	1049 [522–1577]
ADAMTS13 activity (%) (median [IQR])[a]	0 (0)	65 (34)	63 (40)	49 (25)

Abbreviations: ADAMTS13, A disintegrin and metalloprotease with thrombospondin type 1 repeats; aHUS, atypical hemolytic uremic syndrome; HT-TMA, hypertension-related thrombotic microangiopathy; IQR, interquartile range; iTTP, immune-mediated thrombotic thrombocytopenic purpura; MDRD, Modification of Diet in Renal Disease; STEC-HUS, Shigatoxin-producing *Escherichia coli*–associated hemolytic uremic syndrome.

[a]No patient with iTTP had ADAMTS13 activity ≥10% and no patient with STEC-HUS, aHUS, or HT-TMA had ADAMTS13 activity <10%.

3 | RESULTS AND DISCUSSION

During the study period, 2307 patients with TMAs were included in the CNR-MAT registry. After exclusion of other TMAs ($n = 1536$) and patients without blood pressure readings ($n = 208$), 368 patients with iTTP, 84 with aHUS, 86 with STEC-HUS, and 25 with HT-TMA were included in the study (Table 1).

3.1 | Blood pressure profiles in TMA patients

Overall, 149 (56%) patients presented with hypertension (76 [29%] grade 1, 19 [7%] grade 2, and 54 [20%] grade 3). Hypertension was more prevalent in aHUS patients (63/84, including 29 grade 3 hypertension) compared with STEC-HUS (49/86, including nine grade 3 hypertension, $p = 0.01$) and iTTP patients (144/368, including 20 grade 3 hypertension, $p < 0.001$). Median systolic/diastolic blood pressure readings were 130 (118–143)/73 (65–81) mmHg (iTTP), 154 (131–177)/90 (80–100) mmHg (aHUS), 140 (123–157)/80 (70–90) mmHg (STEC-HUS) and 220 (203–237)/130 (113–148) mmHg (HT-TMA) (Figure 1A). Grade 3 hypertension was more prevalent in aHUS patients compared with STEC-HUS ($p < 0.001$) and iTTP patients ($p < 0.001$) (Figure 1B).

Treatment and outcomes are detailed in Table 2. During hospitalization, 93/238 (39.1%) iTTP patients required antihypertensive treatments compared with 63/66 (91.3%, $p < 0.001$) aHUS, 48/62 (77.4%, $p < 0.001$) STEC-HUS, and 24/24 (100%, $p < 0.001$) HT-TMA patients. Most antihypertensive medications during hospitalization in iTTP patients were calcium-channel blockers (12.8% of patients) and angiotensin-converting enzyme inhibitors (12.0%).

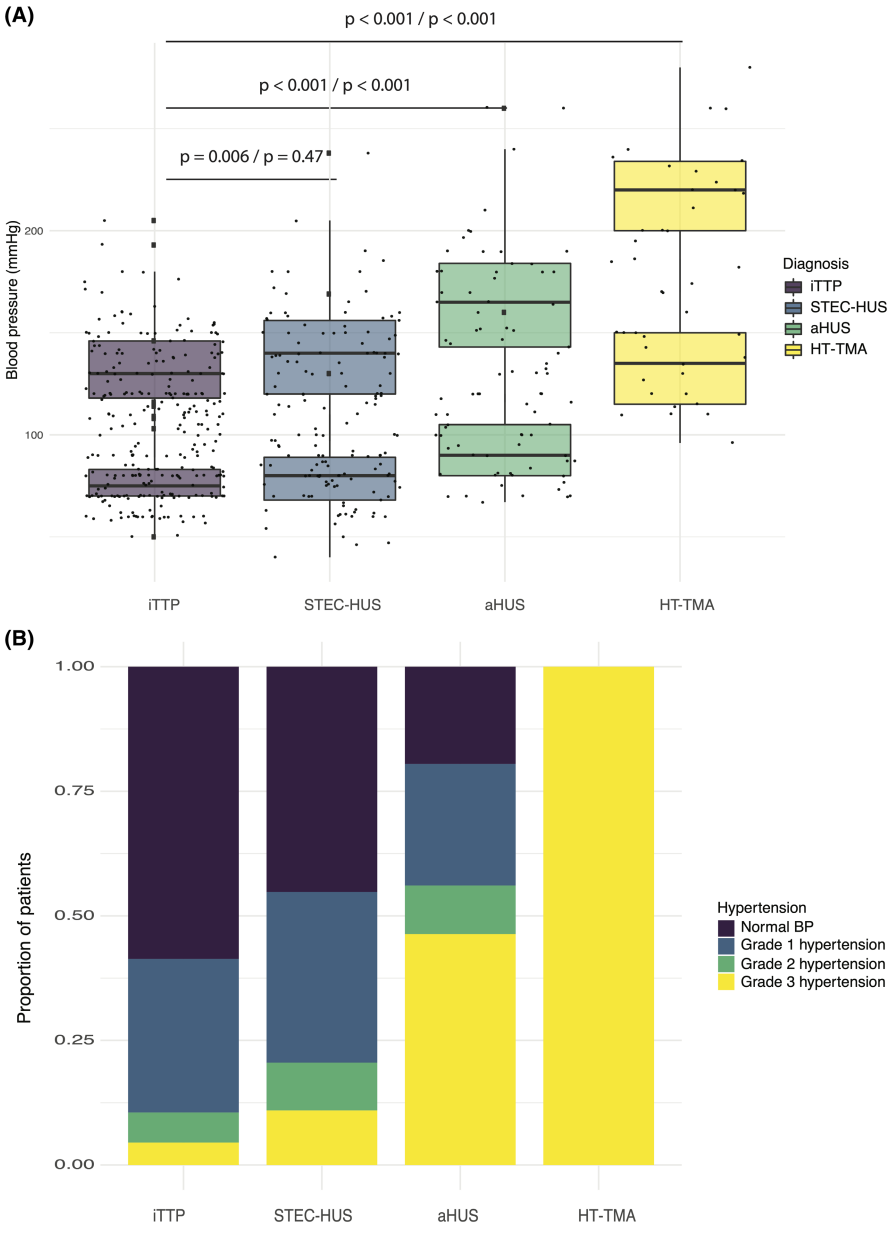

FIGURE 1 (A) Systolic and diastolic blood pressure in patients with thrombotic microangiopathy syndromes. (B) Repartition of hypertension grades in patients with thrombotic microangiopathy syndromes. Blood pressure levels were compared using the Wilcoxon test. All patients from the study were included. Comparison iTTP/STEC-HUS: <0.001/0.01. Abbreviations: aHUS, atypical hemolytic uremic syndrome; HT-TMA, hypertension-related thrombotic microangiopathy; iTTP, immune-mediated thrombotic thrombocytopenic purpura; STEC-HUS, Shigatoxin-producing *Escherichia coli*–associated hemolytic uremic syndrome.

3.2 | Prognostic impact of hypertension in TMA patients

3.2.1 | Association of blood pressure with overall survival

Median follow-up in the whole cohort was 36.7 months (95% confidence interval [CI] 29.5–41.1), with a median follow-up of 46.5 months (40.4–53.3) for iTTP patients, 33.1 months (20.9–50.5) for aHUS patients, 6.41 months (3.71–12.45) for STEC-HUS patients, and 19.8 months (13.5–55.8) for HT-TMA patients. iTTP patients presenting with hypertension had a significantly higher mortality risk compared with those presenting with normal blood pressure (hazard ratio [HR] 1.80, CI 1.07–3.04, $p = 0.03$) (Figure 2). This effect was seen with both systolic (HR 1.96, CI 1.15–3.35, $p = 0.04$) and diastolic (HR 2.31, CI 1.26–4.23, $p = 0.01$) hypertension and was mainly driven by grades 2 and 3 hypertension. Hypertensive iTTP patients with hypertensive retinopathy had a nonsignificant decrease in overall survival (HR 3.84 [0.34–43.2], $p = 0.28$) compared with hypertensive iTTP patients with a normal retinal examination. The association between systolic blood pressure and prognosis remained significant (HR 1.14 [1.00–1.30], $p = 0.05$) in a multivariable Cox model including age, history of hypertension, estimated GFR (Modification of Diet in Renal Disease), seizures, leukocyte count, and plasma exchange. In contrast, elevated blood pressure did not have any significant effect on survival in the other TMA groups, including aHUS patients treated ($p = 0.7$) or not treated ($p = 0.5$) with eculizumab.

3.2.2 | Association of blood pressure with other outcomes in iTTP patients

Hypertension was not associated with relapse-free survival in iTTP patients (HR 1.17 [0.83–1.66], $p = 0.37$) and did not influence time to platelet count recovery. However, it correlated with the degree and renal damage (HR 0.34, $p < 0.001$ between serum creatinine and systolic blood pressure) and was associated with the risk of dialysis during hospitalization (HR 4.06 [1.72–1.04], $p < 0.001$) and renal sequelae at discharge (HR 3.37 [1.62–7.18], $p < 0.001$), that occurred in 8% and 16% of iTTP patients, respectively (Table 2).

3.3 | Diagnostic performances of blood pressure for iTTP discrimination

Systolic (130 vs 154 mmHg, $p < 0.001$) and diastolic (73 vs 90 mmHg, $p < 0.001$) blood pressure were significantly lower in iTTP patients compared with other TMAs, respectively, and yielded areas under the ROC curves for diagnosis of iTTP of 0.752 (0.707–0.796) for systolic blood pressure, 0.705 (0.657–0.753) for diastolic blood pressure, 0.736 (0.691–0.781) for mean blood pressure, and 0.698 (0.650–0.746) for pulse blood pressure. The best threshold for iTTP diagnosis corresponded to a systolic blood pressure inferior to 150 mmHg, with a specificity of 53% and a sensitivity of 86%. Patients with systolic blood pressure >180 mmHg (odds ratio [OR] 0.56, 95% CI 0.49–0.63) or diastolic blood pressure >130 mmHg (OR 0.54, 95% CI, 0.43–0.68) were unlikely to be diagnosed with iTTP. Systolic

TABLE 2 Treatments and outcomes in patients hospitalized for thrombotic microangiopathy syndromes according to diagnosis

	iTTP	STEC-HUS	aHUS	HT-TMA
n	368	86	84	25
Treatments during hospitalization				
Renal replacement therapy (*n* (%))	30 (8)	51 (61)	58 (74)	12 (48)
Number of days (median [IQR])	14 [8–21]	16 [6–26]	7 [2–12]	132 [36–229]
Plasma exchange (*n* (%))	338 (93)	71 (83)	62 (75)	8 (32)
Number of plasma exchanges (median [IQR])	16 [11–22]	9 [4–14]	13 [7–19]	5 [3–7]
Corticosteroids (*n* (%))	299 (83)	19 (23)	37 (46)	5 (20)
Eculizumab (*n* (%))	0 (0)	25 (31)	20 (24)	1 (4)
Other immunosuppressive therapy (*n* (%))	177 (49)	23 (28)	25 (43)	2 (8)
Outcomes				
Time in the hospital (days) (median [IQR])	30 [16–45]	33 [14–53]	37 [24–51]	20 [14–26]
Death during hospitalization (*n* (%))	42 (12)	8 (9)	3 (4)	1 (4)
Complete remission at discharge (*n* (%))	305 (85)	66 (84)	56 (76)	11 (44)
Time to platelet recovery (days) (median [IQR])	23 [14–33]	18 [10–26]	23 [11–35]	12 [8–16]
Renal sequelae (*n* (%))	42 (16)	44 (69)	64 (83)	23 (100)
Dialysis at 3 months (*n* (% of patients requiring renal replacement therapy))	4 (11)	2 (7)	28 (40)	7 (58)
Relapse (*n* (%))	106 (31)	1 (1)	16 (20)	0 (0)

Abbreviations: aHUS, atypical hemolytic uremic syndrome; HT-TMA, hypertension-related thrombotic microangiopathy; IQR, interquartile range; STEC-HUS, Shigatoxin-producing *Escherichia coli*–associated hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

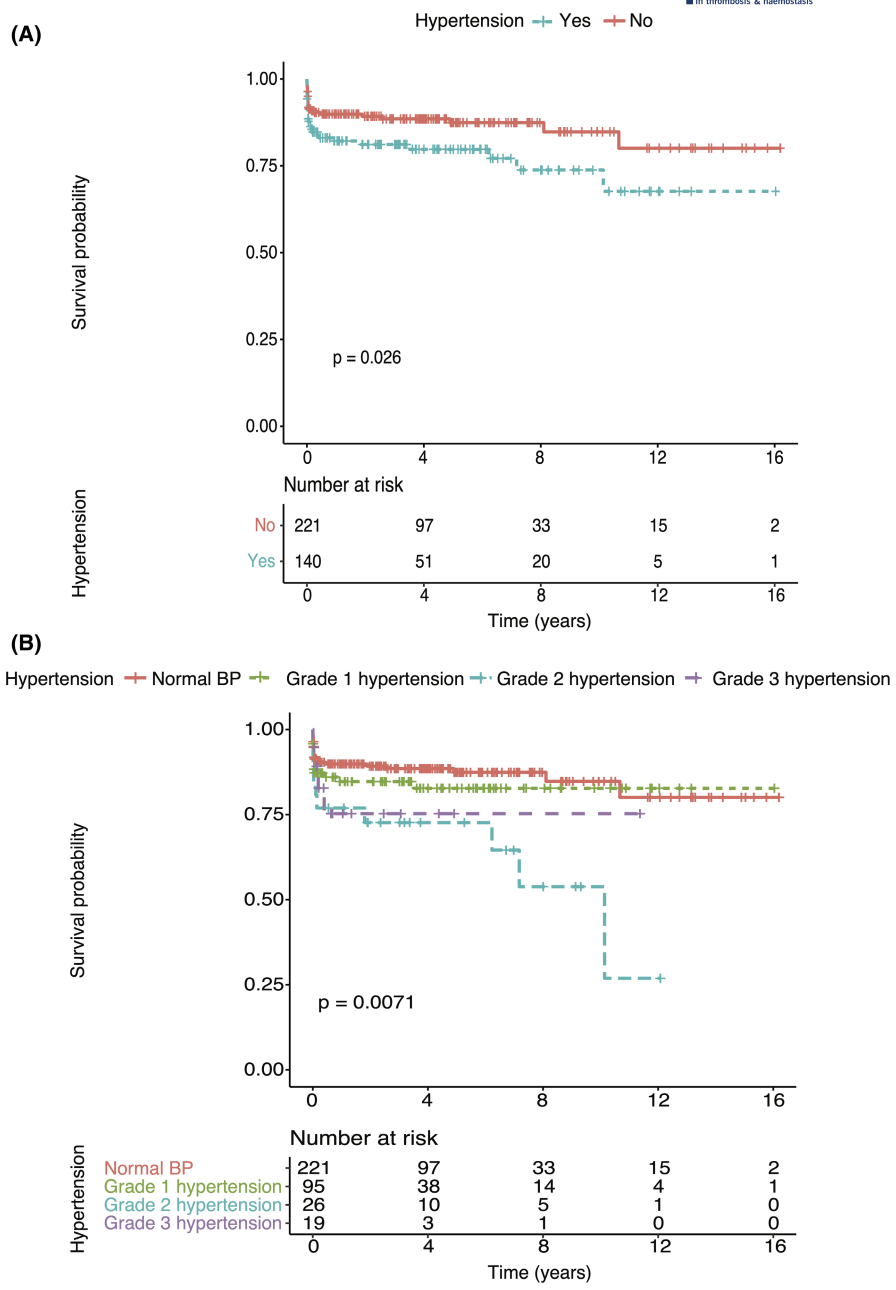

FIGURE 2 Kaplan–Meier curves for survival of patients with immune-mediated thrombotic thrombocytopenic purpura with and without hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) (A), and according to hypertension grade (grade 1 = blood pressure [140–160]/[90–100], grade 2 = blood pressure [160–180]/[100–110]. grade 3 = blood pressure ≥180/≥110 mmHg) (B). *p* Values were determined by the log-rank test. Tables show the number of patients at risk in each group at baseline and at several time points

blood pressure remained significantly associated with iTTP diagnosis in a multivariable model after adjustment for GFR, platelet count, total bilirubin, focal deficit, and digestive signs (OR 0.98 [0.97–0.99] per 10 mmHg increase). We next addressed whether blood pressure could improve the performance of the French score for patients with an intermediate score (score = 1; platelet count $<30 \times 10^9$/L or serum creatinine <200 μM).[11,12] In a two-step algorithm, addition of a systolic blood pressure criterion (>180 mmHg [150–180 mmHg] or ≤150 mmHg) for the diagnosis of iTTP allowed a correct classification of 50.7% of patients with an undetermined (i.e., score = 1) French score (30 iTTP and 6 other TMAs/71), whereas the others remained misclassified or undetermined (Figure S1). In contrast, patients with a French score of 0 or 2 did not benefit from the addition of a systolic blood pressure criterion for diagnosis of iTTP. Overall, the added value of the addition of blood pressure to the French score was modest.

Performances of the French score have been reported to be poorer in older patients.[13,14] Accordingly, area under the ROC curve was 0.868 (0.764–0.971) for patients ≥60 years and 0.931 (0.884–0.978) for patients <60 years. In patients with a French score of 1, the addition of a systolic blood pressure criterion allowed a correct classification of 61.5% of patients <60 years (25.6% misclassified) and 31% of patients ≥60 years (31% misclassified) in this specific group.

We report an evaluation of the prognostic and diagnostic impact of elevated blood pressure in a large cohort of iTTP and other TMAs with more than 3 years of median follow-up. Our main finding is that elevated blood pressure at admission is an independent

factor strongly impacting iTTP prognosis because it was associated with the risks of dialysis, renal sequelae at discharge, and a poorer long-term prognosis. Besides, we showed that iTTP present with lower blood pressure compared with other TMAs, and addition of systolic blood pressure to the previously published French clinical score modestly improves its diagnostic performances in patients for whom the French score remains undetermined (i.e., with either platelet count >30 × 10^9/L or serum creatinine >200 μM).

Blood pressure is rarely recorded in cohorts of iTTP[15-17] or TMA patients.[18,19] Previous studies from the Oklahoma registry[20,21] had shown an increased prevalence of hypertension in patients recovering from iTTP, along with an increased risk for death unrelated to iTTP. This finding highlights the importance of blood pressure measurements in iTTP patients.

Our study has limitations. First, even though this is one of the largest cohorts published to date, and although patients were prospectively included, the proportion of iTTP patients may have been overestimated, and statistical power may have been affected by missing values. Moreover, inclusion of patients extends over several decades, during which TMA management has greatly evolved.[22,23] Our sensitivity analyses in aHUS patients treated and not treated with eculizumab deserve to be interpreted with caution, because of the insufficient number of patients treated with eculizumab (n = 20); therefore, the impact of hypertension in aHUS patients deserves to be put into perspective with other studies reporting a poor prognosis in aHUS patients presenting with elevated blood pressure.[4,24] Likewise, the impact of hypertension in iTTP patients treated with caplacizumab remains to be evaluated. Importantly, only blood pressure at admission was recorded, and evolution blood pressure during hospitalization, time to blood pressure normalization, and its relation to the resolution of TMA signs could be of great interest. Only a minority of HT-TMA patients (9/25, 36%) had explorations of the alternative pathway of complement and we cannot exclude some overlap between aHUS and HT-TMA patients.[3,25] However, this limit could not result in any bias in our analysis on the discrimination of iTTP patients.

As a conclusion, we showed that iTTP patients present with lower blood pressure levels compared with other TMA, and elevated blood pressure significantly impacts their prognosis. Based on our results, physicians in charge of TMA patients should pay attention to blood pressure and its management because this could help early identification and tailored treatment of iTTP, as well as a focus on the management of the most severe patients.

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Data on which this article is based can be made available upon reasonable request.

RELATIONSHIP DISCLOSURE

Adrien Joseph, Martin Eloit, Gilles Kaplanski, Steven Grangé, Alexandre Lautrette, Christelle Barbet, Christiane Mousson, Jean-Philippe Coindre, Pierre Perez, Matthieu Jamme, Jean-François Augusto, Frédéric Jacobs, Khalil El Karoui, Cécile Vigneau, Marc Ulrich, Tarik Kanouni, Moglie Le Quintrec, Mohamed Hamidou, Simon Ville, Anne Charvet-Rumpler, Mario Ojeda Uribe, Pascal Godmer, Véronique Fremeaux-Bacchi, and Jean-Michel Halimi do not have any conflict of interest to declare. Elie Azoulay is part of the board of Gilead France and has received fees for lectures from Alexion and Astellas. Paul Coppo is member of the Clinical Advisory Board for Alexion, Sanofi, Shire, and Octapharma. François Provot is a member of the Clinical Advisory Board for Sanofi. Eric Rondeau is a member of the advisory board for Alexion. Frédéric Pène has received an institutional grant from Alexion and personal fees from Gilead. Pascale Poullin, Alain Wynckel, Yahsou Delmas, Claire Presne, and Agnès Veyradier have participated to Advisory boards for Sanofi.

AUTHOR CONTRIBUTIONS

Paul Coppo and Jean-Michel Halimi designed the study, interpreted the results, and wrote the manuscript. Adrien Joseph performed the statistical analysis of the French Registry for Thrombotic Microangiopathies and wrote the manuscript. Adrien Joseph, Martin Eloit, Elie Azoulay, Gilles Kaplanski, François Provot, Claire Presne, Alain Wynckel, Steven Grangé, Éric Rondeau, Frédéric Pène, Yahsou Delmas, Alexandre Lautrette, Christelle Barbet, Christiane Mousson, Jean-Philippe Coindre, Pierre Perez, Matthieu Jamme, Jean-François Augusto, Pascale Poullin, Frédéric Jacobs, Khalil El Karoui, Cécile Vigneau, Marc Ulrich, Tarik Kanouni, Moglie Le Quintrec, Mohamed Hamidou, Simon Ville, Anne Charvet-Rumpler, Mario Ojeda Uribe, Pascal Godmer, Véronique Fremeaux-Bacchi, Agnès Veyradier, Jean-Michel Halimi, and Paul Coppo enrolled patients, collected clinical and laboratory information, critically reviewed and substantially improved the manuscript.

The members of the Reference Center for Thrombotic Microangiopathies are cited in Appendix S1.

ETHICAL APPROVAL

This study was part of the TMA program study approved by our institutional review board (CPP04807) inaccordance with the Declaration of Helsinki, and the French Data Protection Authority.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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