



**HAL**  
open science

## Performance of diagnostic scores in thrombotic microangiopathy patients in the intensive care unit: a monocentric study

Eric Mariotte, Lara Zafrani, Jehane Fadlallah, Lionel Galicier, Etienne Ghrenassia, Lionel Kerhuel, Laure Calvet, Audrey de Jong, Virginie Lemiale, Sandrine Valade, et al.

### ► To cite this version:

Eric Mariotte, Lara Zafrani, Jehane Fadlallah, Lionel Galicier, Etienne Ghrenassia, et al.. Performance of diagnostic scores in thrombotic microangiopathy patients in the intensive care unit: a monocentric study. *Thrombosis and Haemostasis*, In press, 10.1055/a-1378-3804 . hal-03126013

**HAL Id: hal-03126013**

**<https://hal.science/hal-03126013>**

Submitted on 28 May 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Performance of Diagnostic Scores in Thrombotic Microangiopathy Patients in the Intensive Care Unit: A Monocentric Study

Eric Mariotte<sup>1</sup> Lara Zafrani<sup>1,2</sup> Jehane Fadlallah<sup>2,3</sup> Lionel Galicier<sup>3</sup> Etienne Ghrenassia<sup>1,2</sup>  
Lionel Kerhuel<sup>1,2</sup> Laure Calvet<sup>1</sup> Audrey De Jong<sup>1</sup> Virginie Lemiale<sup>1</sup> Sandrine Valade<sup>1</sup>  
Bérangère S. Joly<sup>2,4</sup> Alain Stepanian<sup>2,4</sup> Elie Azoulay<sup>1,2,5</sup> Michael Darmon<sup>1,2,5</sup>

<sup>1</sup>Service de Médecine Intensive-Réanimation, Hôpital Saint-Louis, APHP, Paris, France

<sup>2</sup>UFR Médecine, Université de Paris, Paris, France

<sup>3</sup>Département d'Immunopathologie, Hôpital Saint-Louis, APHP, Paris, France

<sup>4</sup>Service d'Hématologie Biologique, Hôpital Lariboisière, APHP, Paris, France

<sup>5</sup>UMR1153, Équipe ECSTRRA, INSERM, Université Paris Diderot, Paris, France

**Address for correspondence** Eric Mariotte, MD, Medical Intensive Care Unit, Saint Louis University Hospital, Paris, France (e-mail: eric.mariotte@aphp.fr).

## Abstract

Early thrombotic thrombocytopenic purpura (TTP) recognition is critical as this disease is almost always lethal if not treated promptly with therapeutic plasma exchanges. Currently, as ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity is not widely available in emergency, scores have been developed to help differentiating TTP from other thrombotic microangiopathies (TMAs). The aim of this work was to study the accuracy of these diagnostic scores in the intensive care unit (ICU) setting. Performance of both Coppo and PLASMIC scores was studied in a cohort of adult TMA patients requiring admission to one university hospital ICU from 2006 to 2017. Receiver operating characteristic (ROC) curves were established, and confidence intervals of the area under the curve (AUC) were determined. Multivariate logistic regression analysis was performed to identify parameters specifically associated with TTP, to compare diagnostic scores and to elaborate more accurate diagnostic models. During the study period, 154 TMA patients required ICU admission, including 99 (64.2%) TTP and 55 (35.7%) non-TTP patients. AUC under the ROC curve in predicting TTP was 0.86 (95% confidence interval [CI]: 0.81–0.92) for the Coppo score, 0.67 (95% CI: 0.58–0.76) for the PLASMIC score, and 0.86 (95% CI: 0.81–0.92) for platelet count alone. Platelet count  $\leq 20$  G/L, determined as the best cut-off rate for thrombocytopenia, performed similarly to the Coppo score and better than the PLASMIC score to differentiate TTP from non-TTP patients, both using AUC ROC curve and logistic regression. In a monocentric cohort of TMA patients requiring ICU admission, the PLASMIC score had limited performance for the diagnosis of TTP. The performance of the Coppo score was good but similar to a single highly discriminant item: platelet count  $\leq 20$  G/L at admission.

## Keywords

- ▶ diagnostic scores
- ▶ thrombotic microangiopathy
- ▶ thrombotic thrombocytopenic purpura

## Introduction

The thrombotic microangiopathy (TMA) syndrome encompasses a large and miscellaneous group of diseases characterized by widespread thrombosis of small vessels leading to hemolytic mechanical anemia, peripheral thrombocytopenia, and eventually end-organ damage.<sup>1</sup> The pathophysiology underlying the TMA syndrome is not completely understood but has been elucidated for several conditions and diseases, including thrombotic thrombocytopenic purpura (TTP), defined by a severely deficient ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity; typical hemolytic uremic syndrome (tHUS), related to infections by Shiga toxin-producing bacteria; and atypical hemolytic uremic syndrome (aHUS) that can be associated with complement system dysregulation.<sup>2</sup>

As TTP is lethal in more than 80% of cases in absence of therapeutic plasma exchanges (TPEs), it would be of critical importance to be able to promptly confirm this diagnosis in the acute care setting.<sup>3</sup> This would allow starting TPEs, along with steroids, rituximab and caplacizumab, as soon as possible in TTP patients to avoid early deaths, and to avoid starting an ineffective, expensive, and potentially harmful treatment in most other types of TMA. ADAMTS13 activity is needed to make the differential diagnosis for TTP with other TMA syndromes. However, despite a recently described automated method,<sup>4</sup> ADAMTS13 activity measurement is still limited to expert laboratories, which can result in a time delay of several days.<sup>5,6</sup> Some authors have proposed diagnostic scores to help identify TMA patients at high or low risk of severe ADAMTS13 activity deficiency.<sup>5,6</sup> These scores have been developed and sometimes validated in mixed TMA cohorts but their value in the intensive care unit (ICU) setting has not been studied.

The aim of this article was to evaluate the diagnostic yield of two diagnostic scores, the Coppo score (or French score)<sup>7</sup> and the PLASMIC score,<sup>8</sup> in a population of critically ill TMA patients.

## Methods

### Patients

This study was a retrospective monocenter cohort study. All consecutive adult patients admitted to the ICU of Saint-Louis University Hospital with a diagnosis of TMA and a suspicion of TTP between 2006 and 2017 were identified using the electronic database of the ward and were included in the study. This study was approved by the French Intensive Care Society Ethics Committee (CE 19–67). In accordance with the French legislation on noninterventional studies, no informed consent was required.

### Definitions

TMA was diagnosed on the association of hemolytic anemia (low or decreasing hemoglobin levels and any of the following signs: elevated reticulocyte count, presence of schistocytes on blood smear, raised lactate dehydrogenase, low haptoglobin), thrombocytopenia, and, in some patients, organ dysfunctions potentially ascribable to small-vessel occlusion.

Patients with a diagnosis of TMA and in whom a clinical suspicion of TTP could not be ruled out received a standardized work-up presented in ► **Supplementary Table S1** (available in the online version).

TTP was defined as a TMA with a severe functional deficiency in ADAMTS13 (activity <10% of normal) at diagnosis using the reference method FRETs-VWF73 described elsewhere.<sup>9,10</sup> Immune TTP was defined by the presence of positive anti-ADAMTS13 immunoglobulin G. All tests were performed at least in duplicate.

tHUS was defined as a TMA with detectable ADAMTS13 activity and positive Shiga toxin detection by polymerase chain reaction on stools or rectal swab.<sup>11</sup>

Secondary HUS was defined as a TMA with detectable ADAMTS13 activity, negative Shiga toxin, and the presence of a condition known to be associated to secondary HUS (namely cancer, transplantation, drugs, pregnancy, acquired immune deficiency syndrome, systemic rheumatic diseases, hypertensive crisis).

aHUS or complement-mediated HUS was defined as a TMA with detectable ADAMTS13 activity, negative Shiga toxin, and absence of condition known to be associated with secondary HUS.

Demographical, clinical, biological, and follow-up data were abstracted from the patients' charts.

Neurological involvement of the TMA was categorized as mild, defined by headaches or transient dizziness, or severe if there was any other neurological manifestation (altered consciousness, seizure, confusion, focal deficiency...). Renal involvement was categorized as mild if creatininemia was above but under three times the upper limit of the laboratory reference range without the need for renal replacement therapy, or severe if creatininemia was over three times the upper limit of the laboratory reference range and/or patients required renal replacement therapy. Cardiac involvement was categorized as mild, defined as acute angina and/or ECG anomaly and/or a troponin level above the upper limit of the laboratory reference range, or severe, defined as signs of acute cardiac insufficiency and/or cardiogenic shock and/or cardiac arrest.

Coppo and PLASMIC scores<sup>7,12</sup> (► **Table 1**) were retrospectively calculated by one investigator of the study (E.M.), based on data at ICU admission. The investigator was not blinded to the ADAMTS13 level and ultimate diagnosis of the cases.

### Statistical Analysis

Data are described as median and interquartile range (IQR) or number and percentage. Categorical variables were compared using Fisher's exact test and continuous variables using the nonparametric Wilcoxon test, Mann-Whitney test, or Kruskal-Wallis test.

Dataset contained only 3.2% of missing data, none of them occurring in major or outcome variables. No imputation of missing data was performed.

It was preplanned to assess diagnostic performance of the Coppo score,<sup>7</sup> PLASMIC score,<sup>8</sup> and thrombocytopenia at ICU admission as continuous variables. Scores and cytopenia were plotted against definite diagnosis as the receiver operating characteristic (ROC) curves of the proportion of true positives

**Table 1** Description of Coppo and PLASMIC scores

Coppo score	PLASMIC score
• Platelet count $\leq 30$ G/L	• Platelet count $\leq 30$ G/L
• Creatinine $\leq 200$ $\mu\text{mol/L}$	• Creatinine $\leq 176$ $\mu\text{mol/L}$
• Positive ANA	• INR $< 1.5$
	• MCV $< 90$ fL
	• Hemolysis variables
	• No active cancer
	• No history of organ or stem cell transplant
3 items: high risk	0–4 items = low risk, 5 items = intermediate risk, 6–7 = high risk

Abbreviations: ANA, antinuclear antibodies; INR, international normalized ratio; MCV, mean corpuscular volume.

against the proportion of false positive to classify patients. Confidence interval (CI) of the area under the curve (AUC) was calculated and AUROC curves compared according to the DeLong method.<sup>13,14</sup> Sensitivity and specificity CIs were approximated using bootstrapping methods.<sup>14,15</sup> Optimal cut-point was defined according to optimal Youden's J statistic.<sup>16</sup> AUCs of ROC curves were compared using DeLong methods.<sup>13,14</sup>

Adjusted associations between TTP and scores/thrombocytopenia were analyzed using conditional stepwise regression with 0.2 as the critical *p*-value for entry into the model, and 0.1 as the *p*-value for removal. The variable of interest was TTP. First a model of variables associated with TTP was built. Then scores and thrombocytopenia were forced one by one, excluding variables in the final model that could be correlated with thrombocytopenia or scores. Interactions and correlations between the explanatory variables were carefully checked. Continuous variables for which log-linearity was not confirmed were transformed into categorical variables according to median or IQR. The final models were assessed by calibration, discrimination, and relevancy. Residuals were plotted, and the distributions inspected. Models' ability to explain variance in the dataset was compared using ANOVA (analysis of variance) chi-square test. Finally, discriminations of models were plotted and compared.

All tests were two-sided, and *p*-values less than 0.05 were considered statistically significant. Analyses were done using R software version 3.4.4 (<https://www.r-project.org>), including "pROC" packages.

## Results

During the study period, 154 patients were admitted to the ICU for management of an acute episode of TMA and were considered for a possible diagnosis of TTP.

Of these, 99 (64.3%) patients presented with TTP including 72 (91.1%) immune-mediated TTP. Of note, all patients

with undetectable ADAMTS13 activity at diagnosis and no detectable anti-ADAMTS13 antibodies recovered a detectable ADAMTS13 activity during follow-up, excluding a diagnosis of late-onset congenital TTP. Fifty five patients (35.7%) had other TMA including 6 (10.9%) Shiga toxin-associated HUS, 41 (74.5%) secondary HUS, and 8 (14.5%) complement-mediated HUS. The clinical and biological features of these patients are presented in **Table 2** (and in **Supplementary Table S2**, available in the online version).

Seventy one percent of TTP patients were females versus 41.8% of the other TMA group (*p* = 0.001). Concerning clinical presentation, neurological involvement was more frequent in TTP patients (83.9 vs. 58.2%, *p* = 0.002), whereas renal involvement was more common in other TMA patients (92.8 vs. 56.6%, *p* < 0.001). The degree of renal dysfunction was also more intense in patients with other TMA, as illustrated by levels of plasma creatinine of 267  $\mu\text{mol/L}$  (141–510.5) in the other TMA group versus 96  $\mu\text{mol/L}$  (75–146) in TTP patients (*p* < 0.001), and by a more frequent need for renal replacement therapy during ICU stay in other TMA patients in comparison to TTP patients (52.7 vs. 16.2% respectively, *p* < 0.001). The incidence of cardiac involvement at admission was similar in TTP and non-TTP patients (respectively 63.7 vs. 57.4%, *p* = 0.491). TTP patients presented with more severe cytopenia at ICU admission when compared with patients with other TMA, with hemoglobin levels of 7.55 (6.12–9) versus 8.6 g/dL (7.1–10) (*p* = 0.011); and platelet count of 11 G/L versus 45 G/L (23.5–70.5) (*p* < 0.001) (**Fig. 1**). Two patients in the other TMA group had an undetectable ADAMTS13 activity and were not classified as TTP cases because they presented for one, multiple organ dysfunction secondary to acute on chronic liver failure in a context of hepatic cirrhosis and severe infection, and for the other one, multiple organ failure in a context of multiple myeloma with *Cryptococcus neoformans* fungemia. None of these two patients had anti-ADAMTS13 autoantibodies. Most of the cases of TTP were idiopathic, whereas most of the cases of other TMA were secondary to another condition (no associated condition in 51 [51.5%] cases vs. 9 [16.3%] cases respectively, *p* < 0.001). In ICU and last follow-up, mortality rates were similar between TTP and non-TTP patients (6.1 vs. 16.4%, *p* = 0.075; and 11.1 vs. 21.8%, *p* = 0.121) with a longer follow-up period for TTP patients (823 days [212–2,108] vs. 28 days [3.5–1,129], *p* < 0.001).

The Coppo score (2 [2–3] vs. 1 [0–1]; *p* < 0.001) and the PLASMIC score (4 [4–5] vs. 4 [3–4]; *p* < 0.001) were higher in the TTP group in comparison to the other TMA group, as illustrated in **Fig. 1**. Platelet count alone was also highly discriminant in differentiating TTP from other TMA (**Fig. 1**). The ROC curves of the Coppo score, the PLASMIC score, and platelet count are presented in **Fig. 2**, the AUC being respectively 0.86 [95% CI: 0.81–0.92], 0.67 [95% CI: 0.58–0.76], and 0.86 [95% CI: 0.81–0.92].

A platelet count less than 20 G/L had the optimal performance in predicting TTP (specificity: 0.80 [95% CI: 0.69–0.91] and sensitivity: 0.77 [95% CI: 0.69–0.84]). The Coppo score above 1 had the optimal performance in predicting TTP (specificity 0.84 [95% CI: 0.75–0.93] and sensitivity: 0.81 [95% CI: 0.73–0.89]). The PLASMIC score above 3 had the

**Table 2** Characteristics of 154 patients with acute TMA requiring ICU admission

	TTP (n = 99)	Other TMA (n = 55)	p-Value
Age (y)	44 (29.5–53)	49 (34.5–58.5)	0.06
Female, n (%)	70 (71)	23 (41.8)	0.001
Clinical presentation, n (%)			
Neurologic involvement or features <sup>a</sup>			0.002
Mild	25 (25.3)	11 (20.0)	
Severe	58 (58.6)	21 (38.2)	
Renal involvement or features <sup>b</sup>			<0.001
Mild	51 (51.5)	26 (47.3)	
Severe	5 (5.1)	25 (45.5)	
Cardiac involvement or features <sup>c</sup>			0.491
Mild	57 (57.6)	26 (48.1)	
Severe	6 (6.1)	5 (9.3)	
Laboratory parameters			
Hemoglobin (g/dL)	7.55 (6.12–9)	8.60 (7.1–10)	0.011
Platelet count (G/L)	11 (8–20)	45 (23.5–70.5)	<0.001
Creatinine (μmol/L)	96 (75–146)	267 (141–510.5)	<0.001
Troponin T over ≥14 ng/mL, n (%)	59 (62.1)	27 (64.3)	0.959
Total bilirubin (μmol/L)	40 (23.75–63.25)	22 (13.5–37)	<0.001
Antinuclear antibodies > 1/64, n (%)	56 (60.9)	4 (12.5)	<0.001
ADAMTS13 ≥10%, n (%)	3 (3)	28 (93.3)	<0.001
Anti-ADAMTS13 IgG ≥25 U/mL, n (%)	72 (91.1)	0 (0)	<0.001
Scores			
Coppo score	2 (2–3)	1 (0–1)	<0.001
PLASMIC score	4 (4–5)	4 (3–4)	<0.001
Associated conditions, n (%)			
None	51 (51.5)	9 (16.3)	<0.001
Autoimmune disease	20 (20.2)	6 (10.9)	0.211
HIV infection	14 (14.1)	3 (5.5)	0.168
Cancer	6 (6)	14 (25.9)	<0.001
Drugs	5 (5.1)	9 (16.4)	0.041
Transplantation	1 (1)	8 (14.5)	0.002
Severity			
Day 1 SOFA score	6 (5–8)	7 (5–8.5)	0.621
Therapy, n (%)			
Plasma exchanges	98 (99)	30 (54.5)	<0.001
Steroids	96 (97)	28 (50.9)	<0.001

**Table 2** (Continued)

	TTP (n = 99)	Other TMA (n = 55)	p-Value
Rituximab	42 (42.4)	4 (7.3)	<0.001
Vasoactive drugs	19 (19.2)	6 (10.9)	0.268
Mechanical ventilation	29 (29.3)	16 (29.1)	1
Renal replacement therapy	16 (16.2)	29 (52.7)	<0.001
Outcomes			
Death in ICU, n (%)	6 (6.1)	9 (16.4)	0.075
Death at last follow-up, n (%)	11 (11.1)	12 (21.8)	0.121
Follow-up (d)	823 (212–2108)	28 (3.5–1129)	<0.001

Abbreviations: ICU, intensive care unit; IgG, immunoglobulin G; HIV, human immunodeficiency virus; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

<sup>a</sup>Mild neurologic involvement was defined as headaches or transient dizziness; severe neurologic involvement as any other neurological manifestation (altered consciousness, seizure, confusion, focal deficiency...).

<sup>b</sup>Mild renal involvement was defined as creatinemia above but under three times the upper limit of the laboratory reference range without the need for renal replacement therapy; severe renal involvement was defined as creatinemia over three times the upper limit of the laboratory reference range and/or need for renal replacement therapy.

<sup>c</sup>Mild cardiac involvement was defined as acute angina and/or ECG anomaly and/or a troponin level above the upper limit of the laboratory reference range; severe cardiac involvement was defined as signs of acute cardiac insufficiency and/or cardiogenic shock and/or cardiac arrest.

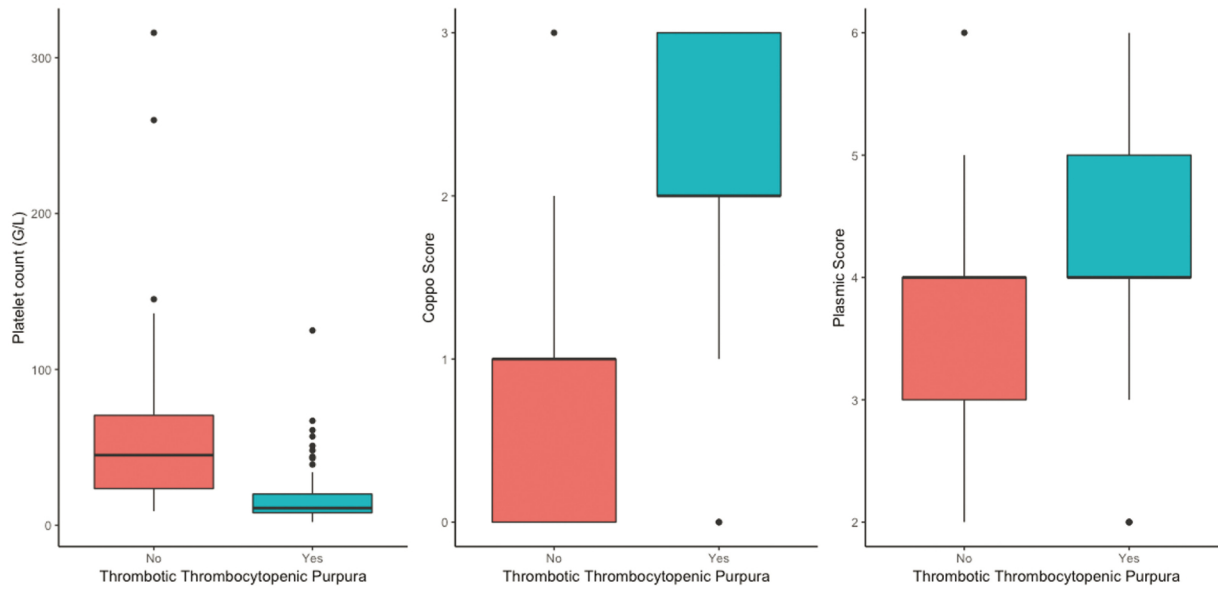
optimal performance in predicting TTP (specificity: 0.47 [95% CI: 0.35–0.60] and sensitivity: 0.81 [95% CI: 0.74–0.89]).

When using logistic regression, renal, and neurological involvement, autoimmune disease and thrombocytopenia were associated with TTP (►Table 3). When forced in the final model, thrombocytopenia ≤20 G/L, the Coppo and PLASMIC scores remained associated with TTP (►Table 3). The final model with thrombocytopenia explained more observed variance than the final models with the Coppo and PLASMIC scores. Discrimination of any of these models was excellent (C-stat > 0.90; ►Table 4) and systematically higher than the performance of isolated scores and thrombocytopenia.

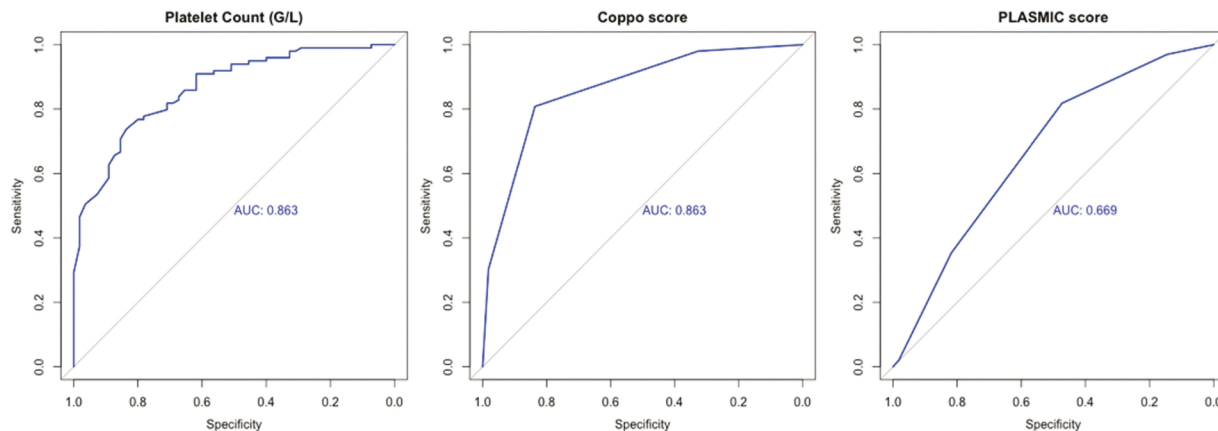
## Discussion

This report is, to the best of our knowledge, the first to report the performance of two widely used diagnostic scores for the identification of patients with severe acute TTP in the ICU setting. These data are of importance as these patients may benefit the most from an early diagnosis of TTP. In this French monocentric cohort of 154 severe TMA patients requiring ICU admission, the Coppo score performed better than the PLASMIC score for the differentiation of acquired TTP from other TMA. Interestingly, thrombocytopenia alone seems to have a similar discrimination in identifying acquired TTP patients.

The Coppo score was developed in 2010 using the French TMA reference center cohort including 160 (44%) TTP patients and 201 (66%) other TMA patients recruited between 2000 and



**Fig. 1** Boxplot depicting distribution of the values of platelet count (G/L), Coppo score, and PLASMIC score in patients with and without TTP. TTP, thrombotic thrombocytopenic purpura.



**Fig. 2** Performance of platelet count (per G/L), Coppo score (per point), and PLASMIC score (per point) in identifying TTP. Results are reported as AUC. 95% CI are reported in text and tables. AUC, area under the curve; CI, confidence interval; TTP, thrombotic thrombocytopenic purpura.

2007.<sup>7</sup> Our ICU department is one constitutive center of the French TMA reference center and some patients of this report ( $n=25$ ; 16.2%) may also have been included in the study of Coppo et al. It seems unlikely that this may have had a significant effect on the results of the present study.

Data from published registries have shown that the presentation of TTP patients may differ depending on their country of origin, possibly owing to different genetic backgrounds and differences in local systems of care.<sup>17–21</sup> The better accuracy of the Coppo score in our cohort may be partly explained by the same ethnic distribution of the patients, resulting in a clinical presentation close to the one of the cohort on which the Coppo score was developed.

The PLASMIC score was developed and validated on a cohort of 214 patients from the United States and subsequently validated on an internal validation cohort of 154 patients, including respectively 62 (29%) and 71 (47%) TTP patients.<sup>8</sup> In this population, the negative predictive value of a score of 5 and less was excellent for the diagnosis of severe ADAMTS13 activity.

This was confirmed in several subsequent studies, included in a recent meta-analysis<sup>22</sup> that defined a score of 5 points or more as the optimal cut-off, associated with the highest sensitivity and negative predictive values. In contrast, in the present study, a score of 4 or more was found to provide the best sensitivity, but the PLASMIC score still performed poorly. The worst performance of this score in our severe TMA cohort may be due to differences in the profile of patients included in the studies. For example, the definition of TMA syndrome by Bendapudi et al was the association of thrombocytopenia and microangiopathic hemolytic anemia, resulting in a relatively low proportion of patients with organ dysfunctions (e.g., neurological symptoms, 36–41%). In our cohort of severe TMA syndromes, organ dysfunctions secondary to small-vessel occlusion were present in most patients (e.g., neurological symptoms in 75% of the cases). The PLASMIC study also included a relatively high proportion of patients with cancer-associated TMAs (29%) and organ transplant recipients (17%) that were less frequent in our study (13 and 6%, respectively). As patients in our cohort

**Table 3** Logistic regression model with TTP as variable of interest

Variable	OR	95% CI	p-Value
<b>Model 1</b>			
No renal dysfunction <sup>a</sup>	Ref.	–	–
Mild renal dysfunction	0.24	0.04–1.08	0.08
Severe renal dysfunction	0.02	0.002–0.14	<0.001
No neurological dysfunction <sup>b</sup>	Ref.	–	–
Mild neurological dysfunction	3.59	0.63–23.70	0.16
Severe neurological dysfunction	7.90	1.70–46.90	0.01
Autoimmune disease	30.50	8.53–142.00	<0.001
Platelet count (per G/L)	0.97	0.94–0.99	0.005
<b>Model 2</b>			
Platelet count ≤ 20 G/L <sup>c,d,e</sup>	4.83	1.47–17.00	0.01
<b>Model 3</b>			
Coppo score (per point) <sup>d,f,g</sup>	4.54	2.26–10.50	<0.001
<b>Model 4</b>			
PLASMIC score (per point) <sup>e,f,g</sup>	2.05	1.24–3.58	0.007

Abbreviations: CI, confidence interval; OR, odds ratio; TTP, thrombotic thrombocytopenic purpura.

<sup>a</sup>Mild renal involvement was defined as creatininemia above but under three times the upper limit of the laboratory reference range without the need for renal replacement therapy; severe renal involvement was defined as creatininemia over three times the upper limit of the laboratory reference range and/or need for renal replacement therapy.

<sup>b</sup>Mild neurologic involvement was defined as headaches or transient dizziness; severe neurologic involvement was defined as any other neurological manifestation (altered consciousness, seizure, confusion, focal deficiency...).

<sup>c</sup>Platelet count <20 G/L included in the model instead of platelet count as continuous variable.

<sup>d</sup>Platelet model explaining significantly more variance than the Coppo score model (ANOVA chi-square test, deviance difference = –11.1,  $p = 0.003$ ).

<sup>e</sup>Platelet model explaining significantly more variance than the PLASMIC score model (ANOVA chi-square test, deviance difference = –24.5,  $p < 0.001$ ).

<sup>f</sup>Coppo score and PLASMIC score included instead of renal involvement and platelet count.

<sup>g</sup>Coppo score model explaining significantly more variance than the PLASMIC score model (ANOVA chi-square test, deviance difference = –13.5,  $p = 0.004$ ).

were referred to an ICU, mostly to discuss the potential indication of TPE, advanced cancer patients and bone marrow transplant recipients may have been underrepresented in our study, lowering the accuracy of these parameters in the PLASMIC score.

One surprising fact of our study was that a platelet count less than 20 G/L alone performed as well as the whole Coppo score for determining which TMA patients had severe acquired TTP. Of note, profound thrombocytopenia is found in both existing diagnostic scores and has already been identified as one of their most important items. In critically ill

**Table 4** Accuracy of developed models in identifying TTP patients. Results are reported as AUC (95% CI) of the models

Model	AUC	95% CI
Model 1 (optimal model)	0.96	0.93–0.99
Mode 2 (platelets as binary variable)	0.95	0.93–0.99
Model 3 (model + Coppo score)	0.94	0.89–0.99
Model 4 (model + PLASMIC score) <sup>a</sup>	0.91	0.86–0.97
Platelet count alone <sup>b,c</sup>	0.86	0.81–0.92
Coppo Score (per point) alone <sup>b,d</sup>	0.86	0.81–0.92
PLASMIC score (per point) alone <sup>b,e,f</sup>	0.67	0.58–0.76

Abbreviations: AUC, area under the curve; CI, confidence interval; TTP, thrombotic thrombocytopenic purpura.

<sup>a</sup>p-Value when compared with full model and model + platelets of respectively 0.006 and 0.03.

<sup>b</sup>p-Value when compared with full model <0.001.

<sup>c</sup>p-Value when compared with logistic regression model with platelets <0.001.

<sup>d</sup>p-Value when compared with logistic regression model with Coppo score <0.001.

<sup>e</sup>p-Value when compared with logistic regression model with PLASMIC score <0.001.

<sup>f</sup>p-Value when compared with AUC of platelet count alone and Coppo score alone <0.001.

patients with an established diagnosis of TMA, the platelet count at admission may represent an easy surrogate marker of a severely deficient ADAMTS13 activity. In critically ill patients, severe thrombocytopenia may be more specific of TMA syndrome than acute renal dysfunction; the latter can be ascribed to many other confounding factors.<sup>23</sup> Interestingly, in their principle paper, Coppo et al noted that a few patients ≥55 years old were misclassified as non-TTP patients based on a creatinine level >200 μmol/L.<sup>7</sup> A higher proportion of patients over 55 years old in our study may account for the increased accuracy of the thrombocytopenia parameter alone. Our study has however several limitations. First, the TTP definition was based on the association of a TMA syndrome with an ADAMTS13 activity <10%. As ADAMTS13 activity dosage may vary with different techniques used,<sup>21</sup> we cannot exclude that some patients of the study were misdiagnosed as TTP or other TMAs. However, all dosages were performed at least in duplicate using a reference technique at a national reference center for ADAMTS13 studies. In addition, the case mix restriction of our study to severe TMA and the well-known specific expertise of our center for TTP management have led to a very high proportion of TTP in our study (64%), although TTP is usually reported to represent roughly 20% of all TMAs in unselected populations.<sup>24</sup> Even if this point can be expected in severe adult TMA patients, overrepresentation of TTP in the current study is likely to influence extrinsic performance of both scores and platelet count. Thus, attention may be required in interpreting our results in settings where TTP is unlikely. Our retrospective and monocentric study design could also limit external validity and larger multicenter studies are warranted to confirm our findings. We cannot exclude that scorers of the study were somehow biased as they could

not be blinded to the ultimate diagnosis of patients and future studies should also be implemented with investigators blinding to the results of diagnostic work-up. Last, although we assessed intrinsic and extrinsic performances of these scores and platelet count, we were unable to assess usefulness and ease of use of these three diagnostic tools in clinical practice. Further study assessing how these scores perform prospectively as decision aids may be required.

In conclusion, in a French population of TMA patients requiring ICU admission, the Coppo score performed better than the PLASMIC score for the identification of acquired TTP cases. Interestingly, considering the specific enrollment of our TTP-focused hyperspecialized center, our study emphasizes that platelet count is the most powerful parameter of the Coppo score to predict acquired TTP diagnosis. Further investigations are however needed to validate these results on an external cohort and may be helpful for the early diagnosis of severe acute TTP.

### What is known about this topic?

- Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy secondary to a severely decreased ADAMTS13 activity.
- The diagnosis of TTP may be difficult, owing to its rarity (prevalence: 3–6/million/year), to its highly variable inaugural clinical manifestations, and to ADAMTS13 study's poor availability in routine practice.
- As TTP is lethal in more than 80% of the cases in absence of treatment with plasma therapy, diagnostic scores have been developed to help identify TMA patients at high or low risk of severe ADAMTS13 activity deficiency.
- These scores have been developed and sometimes validated in mixed TMA cohorts but their value in the most severe forms of TMA has not been studied.

### What does this paper add?

- In this study, the diagnostic yield of two diagnostic scores, the French score (or Coppo score) and the PLASMIC score, was evaluated in a population of TMA patients referred to one intensive care unit specialized in the management of thrombotic thrombocytopenic purpura, to discuss emergent plasma exchange therapy onset.
- In this particular population characterized by a high proportion of thrombotic thrombocytopenic purpura cases (64.2%), the Coppo score performed better than the PLASMIC score (AUC ROC curve in predicting TTP was 0.86 [95% CI: 0.81–0.92] for the Coppo score, 0.67 [95% CI: 0.58–0.76] for the PLASMIC score, and 0.86 [95% CI: 0.81–0.92] for the platelet rate alone).
- A platelet count  $\leq 20$  G/L, determined as the best cut-off rate for thrombocytopenia, performed similarly to the Coppo score and better than the PLASMIC score to differentiate TTP from non-TTP patients, both using AUC ROC curve and logistic regression.

### Author Contributions

E.M. contributed to the literature search, study design, data collection, data analysis, and writing of the manuscript. M.D. contributed to the literature search, study design, data collection, data analysis, statistical analysis, and writing of the manuscript. L.Z., J.F., L.G., E.G., L.K., L.C., A.D.J., V.L., S.V., B.S.J., A.S., and E.A. contributed equally to the literature search, data analysis, and writing of the manuscript.

### Funding

None.

### Conflict of Interest

E.M. reports personal fees from Sanofi, outside the submitted work; S.V. reports nonfinancial support from Pfizer, personal fees from Sanofi, personal fees from PR EDITIONS, outside the submitted work; L.Z. reports grants from Jazz Pharmaceuticals, outside the submitted work; E. A. reports personal fees from Gilead, personal fees from Pfizer, personal fees from Baxter, personal fees from Alexion, outside the submitted work; and his research group has been supported by Ablynx, Fisher & Payckle, Jazz Pharma, and MSD; M.D. reports grants from MSD, personal fees from Astelas, personal fees and nonfinancial support from Gilead-Kite, personal fees from Sanofi, outside the submitted work; L.C., A.D.J., J.F., L.G., E.G., B. S.J., L.K., V.L., and A.S. have nothing to disclose.

### Acknowledgment

The authors acknowledge Agnès Veyradier for critical review of the manuscript and Sophie Capdenat, Sylvaine Savigny, and Sandrine Thouzeau-Benghezal for expert technical assistance.

### References

- 1 Kremer Hovinga JA, Heeb SR, Skowronska M, Schaller M. Pathophysiology of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *J Thromb Haemost* 2018;16(04):618–629
- 2 George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014;371(07):654–666
- 3 Matsumoto M, Fujimura Y, Wada H, et al; For TTP group of Blood Coagulation Abnormalities Research Team, Research on Rare and Intractable Disease supported by Health, Labour, and Welfare Sciences Research Grants. Diagnostic and treatment guidelines for thrombotic thrombocytopenic purpura (TTP) 2017 in Japan. *Int J Hematol* 2017;106(01):3–15
- 4 Valsecchi C, Mirabet M, Mancini I, et al. Evaluation of a new, rapid, fully automated assay for the measurement of ADAMTS13 activity. *Thromb Haemost* 2019;119(11):1767–1772
- 5 Kalish Y, Rottenstreich A, Rund D, Hochberg-Klein S. Atypical presentations of thrombotic thrombocytopenic purpura: a diagnostic role for ADAMTS13. *J Thromb Thrombolysis* 2016;42(02):155–160
- 6 Connell NT, Cheves T, Sweeney JD. Effect of ADAMTS13 activity turnaround time on plasma utilization for suspected thrombotic thrombocytopenic purpura. *Transfusion* 2016;56(02):354–359
- 7 Coppo P, Schwarzinger M, Buffet M, et al. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference center experience. *PLoS ONE* 2010;5(04):e10208



- 8 Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol* 2017;4(04):e157–e164
- 9 Veyradier A, Obert B, Houllier A, Meyer D, Girma JP. Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. *Blood* 2001;98(06):1765–1772
- 10 Kokame K, Nobe Y, Kokubo Y, Okayama A, Miyata T. FRET-S-VWF73, a first fluorogenic substrate for ADAMTS13 assay. *Br J Haematol* 2005;129(01):93–100
- 11 Bruyand M, Mariani-Kurkdjian P, Le Hello S, et al; Réseau Français Hospitalier de Surveillance du Shu Pédiatrique. Paediatric haemolytic uraemic syndrome related to Shiga toxin-producing *Escherichia coli*, an overview of 10 years of surveillance in France, 2007 to 2016. *Euro Surveill* 2019;24(08):24
- 12 Bendapudi PK, Upadhyay V, Sun L, Marques MB, Makar RS. Clinical scoring systems in thrombotic microangiopathies. *Semin Thromb Hemost* 2017;43(05):540–548
- 13 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44(03):837–845
- 14 Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011;12:77
- 15 Fawcett T. An introduction to ROC analysis. *Pattern Recognit Lett* 2006;27:861–874
- 16 Perkins NJ, Schisterman EF. The inconsistency of “optimal” cut-points obtained using two criteria based on the receiver operating characteristic curve. *Am J Epidemiol* 2006;163(07):670–675
- 17 Mariotte E, Azoulay E, Galicier L, et al; French Reference Center for Thrombotic Microangiopathies. Epidemiology and pathophysiology of adulthood-onset thrombotic microangiopathy with severe ADAMTS13 deficiency (thrombotic thrombocytopenic purpura): a cross-sectional analysis of the French national registry for thrombotic microangiopathy. *Lancet Haematol* 2016;3(05):e237–e245
- 18 Mancini I, Pontiggia S, Palla R, et al; Italian Group of TTP Investigators. Clinical and laboratory features of patients with acquired thrombotic thrombocytopenic purpura: fourteen years of the Milan TTP registry. *Thromb Haemost* 2019;119(05):695–704
- 19 Hassan S, Westwood J-P, Ellis D, et al. The utility of ADAMTS13 in differentiating TTP from other acute thrombotic microangiopathies: results from the UK TTP Registry. *Br J Haematol* 2015;171(05):830–835
- 20 Matsumoto M, Bennett CL, Isonishi A, et al. Acquired idiopathic ADAMTS13 activity deficient thrombotic thrombocytopenic purpura in a population from Japan. *PLoS One* 2012;7(03):e33029
- 21 Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Adv* 2017;1(10):590–600
- 22 Paydary K, Banwell E, Tong J, Chen Y, Cuker A. Diagnostic accuracy of the PLASMIC score in patients with suspected thrombotic thrombocytopenic purpura: a systematic review and meta-analysis. *Transfusion* 2020;60(09):2047–2057
- 23 Dennen P, Douglas IS, Anderson R. Acute kidney injury in the intensive care unit: an update and primer for the intensivist. *Crit Care Med* 2010;38(01):261–275
- 24 Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood* 2017;129(21):2836–2846