Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study

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Summary

Background **Among the syndromes characterised by thrombotic microangiopathy, thrombotic thrombocytopenic purpura is distinguished by a severe deficiency in the ADAMTS13 enzyme. Patients with this disorder need urgent treatment with plasma exchange. Because ADAMTS13 activity testing typically requires prolonged turnaround times and might be unavailable in resource-poor settings, a method to rapidly assess the likelihood of severe ADAMTS13 deficiency is needed.**

Methods **All consecutive adult patients presenting to three large academic medical centres in Boston, MA, USA, with thrombotic microangiopathy and a possible diagnosis of thrombotic thrombocytopenic purpura between Jan 8, 2004, and Dec 6, 2015, were included in an ongoing multi-institutional registry (the Harvard TMA Research Collaborative). Univariate analysis was used to identify covariates for a logistic regression model predictive of severe ADAMTS13 deficiency (≤10% activity). A clinical point score was generated, and its diagnostic performance was assessed using internal and external validation cohorts and compared to clinical assessment alone.**

Findings **214 patients with thrombotic microangiopathy were included in the derivation cohort. A seven-component clinical prediction tool, termed the PLASMIC score, was developed and found to reliably assess the pretest probability of severe ADAMTS13 deficiency (*C* statistic 0·96, 95% CI 0·92–0·98). Our diagnostic model was reproducibly accurate in both the internal (0·95, 0·91–0·98) and external (0·91, 0·85–0·95) validation cohorts. The scoring system also more consistently diagnosed thrombotic microangiopathy due to severe ADAMTS13 deficiency than did standard clinical assessment, as measured by *C* statistic (0·96, 95% CI 0·92–0·98 for PLASMIC *vs* 0·83, 0·77–0·88 for clinical assessment; p<0·0001) and mean Brier score (0·065 for PLASMIC *vs* 0·111 for clinical assessment; mean paired difference 0·05, 95% CI 0·01–0·08; p<0·0001). When utilised in addition to clinical assessment, the PLASMIC score contributed significant discriminatory power (integrated discrimination improvement 0·24, 95% CI 0·11–0·37).**

Interpretation **We have developed and validated a clinical prediction tool—the PLASMIC score—to stratify patients with thrombotic microangiopathy according to their risk of having severe ADAMTS13 deficiency. We have shown that this scoring system is superior to standard clinical assessment in addressing the diagnostic challenge presented by thrombotic microangiopathy. Its use, together with clinical judgment, may facilitate treatment decisions in patients for whom timely results of ADAMTS13 activity testing are unavailable.**

Funding **The Luick Family Fund of Massachusetts General Hospital.**

Lancet Haematol 2017

Published Online
March 1, 2017
http://dx.doi.org/10.1016/S2352-3026(17)30026-1

See Online/Comment
http://dx.doi.org/10.1016/S2352-3026(17)30024-8

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Introduction

The thrombotic microangiopathies are a disparate group of uncommon but serious disorders that present as the combination of thrombocytopenia and microangiopathic haemolytic anaemia. A range of disorders or clinical events can manifest as a thrombotic microangiopathy, including haemolytic uraemic syndrome, disseminated intravascular coagulation, malignant hypertension, and haemopoietic-stem-cell transplantation or solid-organ transplantation. Thrombotic thrombocytopenic purpura is a rare form of thrombotic microangiopathy caused by acquired or congenital deficiency of the von Willebrand factor regulatory enzyme, ADAMTS13.[1–3] In patients with acquired thrombotic thrombocytopenic purpura, inhibitory autoantibodies against ADAMTS13 result in uncontrolled formation of von Willebrand factor-rich platelet thrombi in the microvasculature, with consequent end-organ dysfunction and death.

Because acquired thrombotic thrombocytopenic purpura is associated with substantial morbidity and mortality, optimum care relies on urgent diagnosis and treatment with plasma exchange,[4,5] which removes the autoantibody and repletes the missing ADAMTS13 enzyme.[6] However, the lengthy turnaround times needed at most centres for ADAMTS13 activity testing render this assay unsuitable for real-time clinical decision making.[7] Furthermore, the ADAMTS13 activity assay is unavailable in many developing countries, where clinicians generally must manage patients with thrombotic microangiopathy and decide on the allocation of scarce blood-product resources without objective guidance. In such settings, patients with thrombotic

Research in context

Evidence before this study

We reviewed relevant English language studies by searching PubMed for the terms "ADAMTS13", "score", and "clinical prediction tool". We identified two studies that reported diagnostic scoring systems for severe ADAMTS13 deficiency. One was derived from a national registry experience whereas the other utilised a small single-centre case series. Neither score was validated externally or shown to add value to clinical practice.

Added value of this study

We report a clinical prediction tool for severe ADAMTS13 deficiency that was derived in a multicentre consortium and validated externally using a dataset assembled at a separate institution. This scoring system includes historical and laboratory variables that would be obtainable rapidly in a wide range of clinical settings. We showed the superiority of our prediction score to a previously proposed diagnostic score for thrombotic microangiopathy and assessed directly the potential contribution of our scoring system to clinical practice using three independent metrics.

Implications of all the available evidence

Profound thrombocytopenia associated with normal or mildly impaired renal function in patients presenting with thrombotic microangiopathy is predictive of severe ADAMTS13 deficiency. Our results indicate that a seven-component clinical prediction score containing platelet count and measures of renal function is appropriate for use in settings in which ADAMTS13 activity testing might not be available readily and that our scoring system represents an improvement over use of clinical assessment alone.

thrombocytopenic purpura might benefit substantially from plasma transfusion and immunosuppressive therapy, even when plasma exchange is not available.[8,9]

In view of the need to promptly recognise and treat patients with thrombotic thrombocytopenic purpura before knowing the level of ADAMTS13 activity, a means to rapidly identify individuals with thrombotic microangiopathy and severe ADAMTS13 deficiency would be of considerable benefit. Using a cohort of patients in the Harvard TMA Research Collaborative registry,[10] we aimed to develop and validate externally a simple but accurate diagnostic scoring system capable of ascertaining the pretest probability of severe ADAMTS13 deficiency.

Methods

Study population and setting

The study population consisted of participants in the Harvard TMA Research Collaborative registry, an observational cohort of all patients with thrombotic microangiopathy and possible thrombotic thrombocytopenic purpura presenting to three large academic medical centres in Boston, MA, USA—Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, and Massachusetts General Hospital. Details of the registry and criteria for the assignment of diagnoses have been described previously.[10] Permission to conduct the study was granted by the institutional review board at each hospital in the registry.

We identified via the electronic medical record all consecutive patients who had an ADAMTS13 assay sent during the study period (Jan 8, 2004, to Dec 6, 2015). Of these, we included patients aged 18 years or older who presented with thrombocytopenia ($<150\times10^9$ platelets per L) and microangiopathic haemolytic anaemia (defined as the presence of schistocytes on the peripheral smear). We excluded individuals who were seen as outpatients or had known interferences with the ADAMTS13 assay (eg, receipt of plasma before the test or extreme hyperbilirubinaemia).[11]

For external validation of the clinical score, we used an independent dataset of consecutive patients who presented at the University of Alabama at Birmingham Hospital and received ADAMTS13 activity testing between Jan 1, 2003, and Aug 1, 2013. To these cases, we applied the same inclusion and exclusion criteria used for the Harvard dataset. This project was approved by the institutional review board of the University of Alabama at Birmingham.

Procedures

For patients in the Harvard TMA Research Collaborative registry, ADAMTS13 assays were done at the BloodCenter of Wisconsin (Milwaukee, WI, USA) until Aug 28, 2012, and at Mayo Clinical Laboratories (Rochester, MN, USA) thereafter. All tests sent from the University of Alabama at Birmingham Hospital were done at the BloodCenter of Wisconsin. From Jan 8, 2004, to April 19, 2006, the ADAMTS13 activity level was measured using a collagen-binding assay to detect residual von Willebrand factor.[12] After this date, a fluorescence resonance energy transfer (FRETS)-based assay utilising the VWF73 substrate[13,14] was used at both the BloodCenter of Wisconsin and Mayo Clinical Laboratories. Reflex testing for an autoantibody inhibitor to ADAMTS13 by the Bethesda assay was done if ADAMTS13 activity level was less than 31%. For our study, we defined severe deficiency in ADAMTS13 as an activity level of 10% or lower.[15,16]

We used the electronic medical record to abstract relevant clinical and laboratory data for univariate analysis. We did not capture data recorded in the patient's physical chart—eg, vital signs. Data obtained retrospectively from patients in the Harvard TMA Research Collaborative registry who presented between Jan 8, 2004, and May 1, 2012, formed the derivation cohort. We evaluated by univariate analysis 29 clinical and laboratory variables

for every patient to identify those associated with severe ADAMTS13 deficiency at a p value of 0·15 or lower. We generated receiver operating characteristic (ROC) curves for continuous variables, and we set dichotomous cutoff points to maximise the associated *J* statistic (Youden's index). We calculated odds ratios for all categorical variables and dichotomised continuous variables.

To create a parsimonious clinical prediction score, we included a subset of variables identified by univariate analysis in multivariable regression modelling based on clinical relevance, predictive power, and universal availability in different clinical settings. We developed multivariable logistic regression models by a process in which variables were included or excluded to maximise model fit and parsimony. We used the Hosmer-Lemeshow test to show that the final model fit the data. We incorporated variables predictive of severe ADAMTS13 deficiency in the multivariable logistic regression model into a clinical scoring algorithm. We used β coefficients resulting from the multivariable logistic regression to assign weights to each covariate.

For internal validation of the clinical prediction score, we used data obtained from patients in the Harvard TMA Research Collaborative registry who presented between May 2, 2012, and Dec 6, 2015. For external validation of the prediction score, investigators based in Birmingham (AF and MBM) provided Boston-based investigators (PKB and RSM) with de-identified data needed to apply the score to all patients in the University of Alabama at Birmingham registry. The Boston-based investigators were unaware of ADAMTS13 activity results for these patients. After all cases had been scored, the team from Birmingham revealed the ADAMTS13 activity levels for patients in the external validation cohort, and results were subsequently cross-checked by both groups of investigators. We characterised model discrimination in the derivation and both validation cohorts using ROC curves, from which we calculated *C* statistics.

We compared the clinical diagnostic score with the consensus clinical assessment of three clinicians (AMB, JMG, and SV). Participating clinicians were trainees in haematology and board-certified in internal medicine. They were unaware of the results of ADAMTS13 testing. We defined clinical consensus for each case as agreement between at least two of the three clinicians with respect to the presence of severe ADAMTS13 deficiency. We compared Brier scores[17] for diagnoses made by consensus clinical assessment and the clinical prediction score.[18,19] A lower Brier score reflects more accurate prediction of actual events.[17] Additionally, we calculated the integrated discrimination improvement (IDI)[20] of adding the prediction tool to clinical consensus. To compute the IDI, we compared the average clinical consensus score among those without severe ADAMTS13 deficiency to the score among those with severe deficiency to generate a discrimination slope. In a similar manner, we compared the average clinical diagnostic score among those without severe ADAMTS13 deficiency to the score among those with severe deficiency to generate a separate discrimination slope. The difference in these two slopes provides an estimate of the discrimination improvement when adding the new model to consensus clinical assessment. We subsequently performed bootstrapping with replacement across 1000 repetitions to generate bias-corrected confidence intervals around the point estimate, similar to previous studies using this method.[21]

Valid comparison of our score with a prediction method described previously by the French TMA Reference Center[22] required a large cohort containing a diverse group of patients from which neither score was derived. Therefore, we constructed a combined dataset consisting of both the internal and external validation cohorts. We quantified the performance of our score relative to the French score by comparing the area under the ROC curve (*C* statistic) for each method.

Statistical analysis

For continuous variables, we used the Shapiro-Wilk test to determine whether data were normally distributed. Since the null hypothesis of normality was rejected for 17 of 19 continuous variables, we used the Mann-Whitney *U* test for statistical comparisons of all continuous variables. We used Fisher's exact test for statistical comparisons of categorical variables. We used the log-rank test to compare survival curves generated by Kaplan-Meier analysis. We compared ROC curves obtained using different scoring methods applied to the same test population using the method of Delong,[23] and we calculated p values using the *Z* test. We used the Kruskal-Wallis test with Dunn's post-hoc test to compare the results of our prediction tool across different diagnoses of thrombotic microangiopathy. We used the Wilcoxon signed rank test to compare the Brier scores obtained from consensus clinical assessment and the prediction tool. We did statistical calculations in MedCalc version 16.8.4 (Ostend, Belgium), SAS version 9.4 (SAS Institute, Cary, NC, USA), LogXact version 10 (Cytel, Cambridge, MA, USA), and Stata version 12.1 (Stata, College Station, TX, USA).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 8, 2004, and Dec 6, 2015, 647 patients were part of the Harvard TMA Research Collaborative registry, of whom 368 with thrombotic microangiopathy

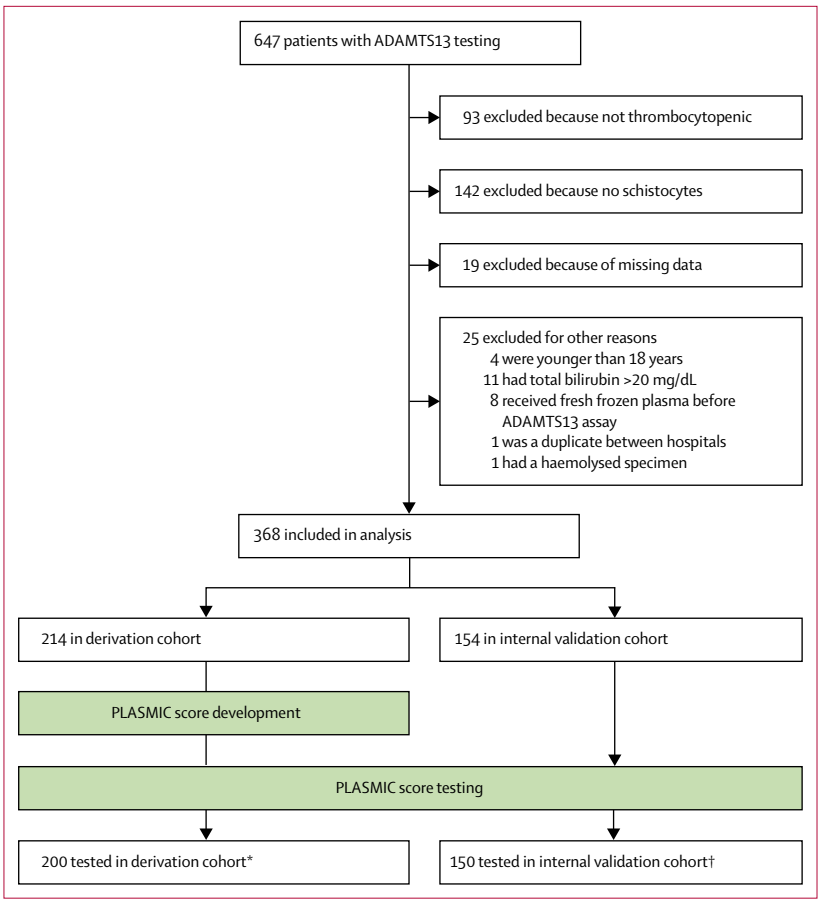

Figure 1: **Patients' enrolment and model development**
*Data for 214 cases were included in model development, but only 200 of these cases contained data for all seven components needed to calculate the score. †Of 154 cases accrued in the internal validation cohort, 150 contained complete data for all seven components.

met inclusion criteria and were part of this analysis (figure 1). 214 consecutive cases presented between Jan 8, 2004, and May 1, 2012, and these patients formed the derivation cohort (table 1). 62 (29%) of 214 patients had an ADAMTS13 activity result of 10% or lower. Median follow-up for this cohort was 4·3 years (IQR 2·1–6·7). 154 cases were enrolled in the Harvard registry between May 2, 2012, and Dec 6, 2015, and these patients comprised the internal validation cohort (figure 1; appendix p 1). 21 (14%) of 154 patients had an ADAMTS13 activity level of 10% or lower. 152 patients with suspected thrombotic thrombocytopenic purpura were cared for at the University of Alabama at Birmingham between Jan 1, 2003, and Aug 1, 2013, and these patients formed the external validation cohort. 71 (47%) of 152 patients in this dataset had an ADAMTS13 activity level of 10% or lower. Patients comprising the external validation cohort were geographically, ethnically, and clinically distinct from individuals in the derivation cohort (table 1).

See Online for appendix

Univariate analysis of 29 clinical and laboratory variables from each patient in the derivation cohort identified 21 variables associated with severe ADAMTS13 deficiency at a p value of 0·15 or lower (appendix pp 2–4). Of these, a subset of 11 covariates (appendix p 4) was chosen for further evaluation by multivariate analysis based on clinical relevance, predictive power, and availability across different clinical settings. One variable, the timing of ADAMTS13 activity testing relative to admission, was recorded as part of a quality improvement initiative and included in the univariate analysis, but because it is not a true laboratory or clinical variable, it was excluded from further consideration. Continuous variables were dichotomised and cutoff points selected to maximise sensitivity and specificity.

Five independent predictors of severe ADAMTS13 deficiency were identified through multivariable regression analysis (table 2), comprising a model that was calibrated appropriately to the derivation dataset (Hosmer-Lemeshow p=0·93). The factors associated most strongly by odds ratio with an ADAMTS13 activity level of 10% or less were platelet count lower than 29×10^9 per L, creatinine less than 1·8 mg/dL, and international normalised ratio (INR) less than 1·3. Other variables included mean corpuscular volume (MCV) less than 86·5 fL ($8·65\times10^{-14}$ L) and a combined haemolysis variable judged positive if the patient had any of the following: reticulocyte count more than 2·5%; or undetectable haptoglobin; or indirect bilirubin greater than 2·0 mg/dL. To incorporate these five variables into a clinical prediction score, each variable was weighted according to its β coefficient obtained from the multivariable regression; because all β values fell within a small range, each covariate was assigned a weight of one point.

A parsimonious integer-based score was developed based on the multivariable model. Selected cutoff points were adjusted to the nearest whole or half integer to maximise ease of use. Comparison of the ROC curves generated using the five-variable logistic regression model showed a small but significant decrement in predictive performance when the adjusted cutoff points were used (appendix p 5). Two additional variables (history of active cancer within the preceding year and absence of previous haemopoietic-stem-cell transplant or solid-organ transplant) were absent in all patients with severe ADAMTS13 deficiency in the derivation cohort and were included in the final clinical prediction score based on their performance in univariate analysis and their high negative predictive value. Their addition to the five-variable model with adjusted cutoff points resulted in a *C* statistic of 0·96 (95% CI 0·92–0·98), representing a significant increase in predictive performance (appendix p 5). The resulting algorithm was termed the PLASMIC score (table 3), in reference to its seven components: platelet count; combined haemolysis variable; absence of active cancer; absence of stem-cell transplant or solid-organ transplant; MCV; INR; and creatinine. Of 214 patients in the derivation cohort,

200 (93%) had all data components necessary for calculation of the PLASMIC score. Within this group, none of 84 patients with a PLASMIC score of 0–4 had severe ADAMTS13 deficiency, in contrast to two (5%) of 44 patients with a score of 5, and 58 (81%) of 72 patients with a score of 6 or 7 (table 4).

The ability of the PLASMIC score to distinguish between thrombotic thrombocytopenic purpura and other forms of thrombotic microangiopathy was tested by comparing the median score of patients with thrombotic thrombocytopenic purpura in the derivation cohort with those of patients with other diagnoses (appendix p 6). Patients with a diagnosis of thrombotic thrombocytopenic purpura had a median PLASMIC score of 7 (IQR 6–7), in contrast to patients with thrombotic microangiopathy associated with rheumatological disorders, drug-associated thrombotic microangiopathy, and disseminated intravascular coagulation, who had scores of 5 (4–6), 4 (3–5), and 4 (3–4), respectively. The PLASMIC score also seemed to discriminate between thrombotic thrombocytopenic purpura and typical and atypical haemolytic uraemic syndrome (median score 5, IQR 4–5), entities that typically have strikingly similar clinical presentations. Consistent with these observations suggesting that the PLASMIC score distinguishes between thrombotic thrombocytopenic purpura and other types of thrombotic microangiopathy that tend to carry a poorer prognosis, Kaplan-Meier analysis showed that patients with higher PLASMIC scores had significantly improved 90-day survival than did those with lower scores (figure 2). Median survival for patients with a PLASMIC score of 6 or 7 was not reached, whereas it was 1670 days (95% CI 292–1899) for those with a score of 5, and 287 days (36–1044) for those with a score of 0–4.

The PLASMIC score underwent two independent validations. In the internal validation cohort assembled within the Harvard TMA Research Collaborative registry (appendix p 1), 150 (97%) of 154 patients had all components of the PLASMIC score needed for evaluation. The *C* statistic for the resulting ROC curve was 0·95 (95% CI 0·91–0·98; figure 3). None of 89 patients assigned a score of 0–4 had severe ADAMTS13 deficiency, whereas 18 (62%) of 29 patients with a score of 6 or 7 had severe deficiency (table 4).

After internal validation, the PLASMIC score was applied to the external validation cohort. 146 (96%) of 152 patients had complete data and could be scored. 61 (82%) of 74 patients with a PLASMIC score of 6 or 7 had severe ADAMTS13 deficiency compared with two (4%) of 47 patients with a score of 0–4 (table 4). The *C* statistic for the resulting ROC curve was 0·91 (95% CI 0·85–0·95; figure 3). Based on results obtained from the derivation and both validation cohorts, we defined three categories of risk for severe ADAMTS13 deficiency: a PLASMIC score of 0–4 denotes low risk (recorded in 0–4% of patients with severe ADAMTS13 deficiency), a score of 5 denotes intermediate risk (5–24%), and a score of 6 or 7 denotes high risk (62–82%).

The PLASMIC score was superior to the two-component prediction tool reported by the French TMA Reference Center (appendix pp 7, 8). When each method was tested in an independent composite dataset (n=296; internal and external validation cohorts), the PLASMIC score was associated with a *C* statistic of 0·93 (95% CI 0·90–0·96) whereas the French score

	Derivation cohort (n=214)	External validation (n=152)	p value*
Demographic features			
Age (years)	51 (38–63) [n=214]	44 (31–57) [n=152]	0·0002
Female sex	129/214 (60%)	87/152 (57%)	0·59
White European ethnic origin	157/204 (77%)	49/150 (33%)	<0·0001
Clinical data			
Cancer treatment within 1 year	61/214 (29%)	18/152 (12%)	0·0001
Previous transplant	37/214 (17%)	18/152 (12%)	0·18
Fever	66/213 (31%)	33/142 (23%)	0·12
Neurological symptoms	75/210 (36%)	58/142 (41%)	0·37
Received plasma exchange	124/214 (58%)	109/152 (72%)	0·0081
Laboratory data			
ADAMTS13 activity (%)	44% (<5 to 63) [n=214]	23% (<5 to 58) [n=152]	0·002
Severe ADAMTS13 deficiency†	62/214 (29%)	71/152 (47%)	0·0006
Inhibitor present‡	52/214 (24%)	64/152 (42%)	0·0004
Platelet count ($\times 10^9$ per L)	34 (18–59) [n=214]	22 (13–42) [n=152]	0·0001
Haematocrit (%)	26% (23–29) [n=214]	25% (22–28) [n=152]	0·0053
Creatinine (mg/dL)	1·7 (1·1–3·4) [n=214]	1·7 (1·0–4·1) [n=152]	0·67
Lactate dehydrogenase (U/L)	963 (637–1594) [n=212]	959 (582–1582) [n=149]	0·70
INR	1·1 (1·1–1·3) [n=210]	1·2 (1·1–1·3) [n=149]	0·0046
Bilirubin (mg/dL)	1·8 (1·0–3·1) [n=214]	2·3 (1·2–3·2) [n=143]	0·025
Blood group O	111/211 (53%)	78/150 (52%)	0·92

Data are number/total number of individuals (%) or median (IQR) (total number with data available). Relevant clinical features and laboratory findings proximate to the time of ADAMTS13 testing are reported. INR=international normalised ratio. *For continuous variables, statistical comparison is made using the Mann-Whitney test, and for categorical variables, statistical comparison is made using Fisher's exact test. †Defined as activity of ADAMTS13 ≤10%. ‡A positive inhibitor is defined as a titre >0·4 Bethesda units.

Table 1: **Demographic, clinical, and laboratory features of the derivation and external validation populations**

	β	SE	Odds ratio (95% CI)	p value
Platelet count <29 × 10^9 per L	2·83	0·58	16·9 (5·4–53·0)	<0·0001
Creatinine <1·8 mg/dL	2·74	0·61	15·5 (4·7–51·2)	<0·0001
INR <1·3	2·69	0·84	14·7 (2·8–76·5)	0·0014
MCV <86·5 fL†	2·29	0·57	9·9 (3·2–30·4)	0·0001
Haemolysis variable‡	1·80	0·74	6·0 (1·4–25·7)	0·015

INR=international normalised ratio. MCV=mean corpuscular volume.
*Of 214 patients in the derivation cohort, 200 had complete data available for the multivariate logistic regression model. †<$8{\cdot}65 \times 10^{-14}$ L. ‡Reticulocyte count >2·5%, or haptoglobin undetectable, or indirect bilirubin >2·0 mg/dL.

Table 2: **Multivariable logistic regression model of predictors of severe ADAMTS13 deficiency (n=200)***

	Points*
Platelet count <30 × 10^9 per L	1
Haemolysis variable†	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL‡	1
INR <1·5	1
Creatinine <2·0 mg/dL	1

INR=international normalised ratio. MCV=mean corpuscular volume. *Score of 0–4 denotes low risk for severe ADAMTS13 deficiency; score of 5 denotes intermediate risk; score of 6 or 7 denotes high risk. †Reticulocyte count >2·5%, or haptoglobin undetectable, or indirect bilirubin >2·0 mg/dL. ‡<9·0 × 10^{-14} L.

Table 3: **The PLASMIC score for prediction of thrombotic microangiopathy associated with severe ADAMTS13 deficiency**

	Derivation cohort (n=200)	Internal validation cohort (n=150)	External validation cohort (n=146)
0–4	0/84 (0%)	0/89 (0%)	2/47 (4%)
5	2/44 (5%)	3/32 (9%)	6/25 (24%)
6 or 7	58/72 (81%)	18/29 (62%)	61/74 (82%)

Data are number of individuals with ADAMTS13 activity of 10% or less/total number of individuals with that score (%).

Table 4: **Validation of the PLASMIC score**

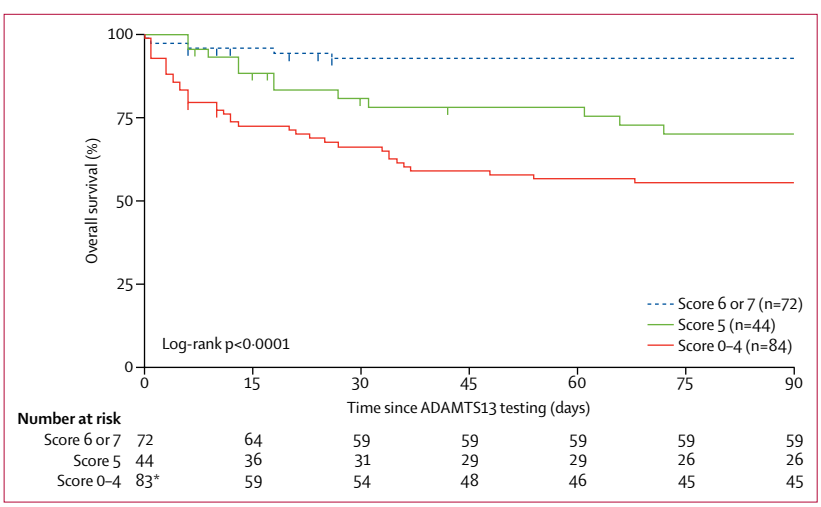

Figure 2: **90-day survival by PLASMIC score in the derivation cohort**
*One patient died on day 0.

yielded a *C* statistic of 0·88 (0·83–0·91; p=0·0032). Compared with the French score, the PLASMIC algorithm designated more cases that were not thrombotic thrombocytopenic purpura as low risk (134 [65%] of 206 *vs* 76 [37%] of 206; p<0·0001) and assigned a smaller proportion of cases to the intermediate risk category (57 [19%] of 296 *vs* 117 [40%] of 296; p<0·0001; appendix p 8).

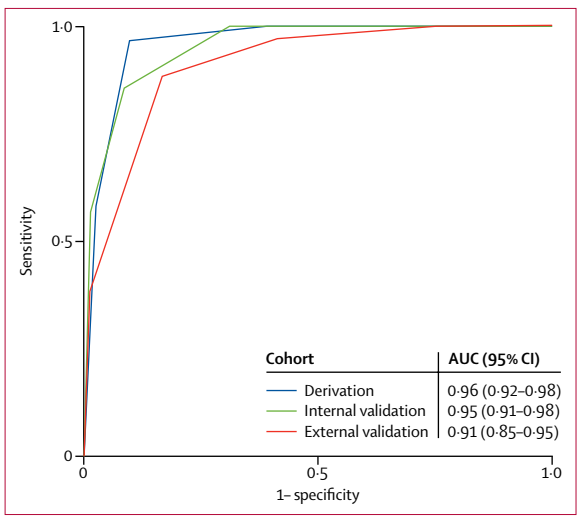

Figure 3: **Performance of the PLASMIC score in the derivation cohort and internal and external validation cohorts**
AUC=area under the curve.

After validation, the potential contribution of the PLASMIC diagnostic algorithm was gauged against clinical practice using three independent approaches. When assessing patients in the derivation cohort with sufficient data for evaluation (n=195), clinical consensus yielded a *C* statistic of 0·83 (95% CI 0·77–0·88), which was significantly lower than the *C* statistic obtained with use of the PLASMIC score in the same cohort (0·96, 0·92–0·98; p<0·0001). Second, the mean Brier score (lower Brier score reflecting more accurate prediction of actual events) for consensus clinical assessment was 0·111, compared with 0·065 for the PLASMIC score (mean paired difference 0·05, 95% CI 0·01–0·08; p<0·0001), indicating that the PLASMIC algorithm is 41·6% more accurate in correctly predicting the presence of severe ADAMTS13 deficiency than is consensus clinical assessment. To further demonstrate the real-world utility of our prediction tool, the contribution of the PLASMIC score to consensus clinical assessment was determined by calculating the IDI. The IDI was 0·24 (95% CI 0·11–0·37), and the relative IDI was 0·51 (0·08–0·94), indicating a 51% relative improvement in the discrimination slope with addition of the PLASMIC prediction score.

Discussion

In evaluating the range of patients who present with thrombotic microangiopathy, the ability to identify quickly those with thrombotic thrombocytopenic purpura is a key unmet clinical need. We have assembled a large multi-institutional dataset of patients with thrombotic microangiopathy and used it to derive and characterise a seven-component clinical prediction algorithm, the PLASMIC score, which is capable of distinguishing between cases of thrombotic microangiopathy with and without severe ADAMTS13 deficiency. Further, we

validated the PLASMIC score independently and tested its ability to improve clinical practice.

Two clinical prediction methods proposed previously for thrombotic microangiopathy—the Bentley[24] and French TMA Reference Center[22] scores—have shortcomings that we sought to address with the PLASMIC score. The Bentley score, derived in a cohort containing only 11 patients with severe ADAMTS13 deficiency, is a complex tool composed of non-integer, positive or negative point scores associated with various laboratory values and has not been widely adopted. Although much simpler to use, the two-component French score showed inferior performance to the PLASMIC score in our analysis and, importantly, failed to resolve many cases that the PLASMIC score designated correctly as low risk. Neither the Bentley nor the French method has been validated externally or compared with consensus clinical assessment alone. By contrast, the PLASMIC score was validated in an independent dataset of patients who differed from the derivation cohort in age, racial composition, and types of underlying conditions. To our knowledge, ours is the first clinical prediction score to have undergone such validation. The strong diagnostic performance of the PLASMIC score in the cohort from the University of Alabama at Birmingham (the external validation cohort) is especially notable because this dataset contained a much higher proportion of patients (71 [47%] of 152) with severe ADAMTS13 deficiency than would be encountered in routine practice. Within the derivation cohort, the PLASMIC score also seemed to have prognostic utility, with significantly better 90-day survival noted in patients with higher scores. Unfortunately, survival data were not captured for the cohort from Birmingham, and validation of our scoring system as a prognostic method remains an important focus of future research.

Our prediction score requires seven clinical and laboratory variables that are obtainable rapidly at most centres, including those in many resource-poor settings. Variables predictive of severe ADAMTS13 deficiency were first identified in univariate analysis using standard methods, after which a subset was selected for inclusion in multivariate modelling. Covariate selection was constrained by missing data, highly correlated covariates, and the desire to produce a diagnostic algorithm that would be easy to use and applicable in various clinical settings. These choices might have affected the predictive power of the resulting algorithm. To mitigate the effect of missing data and improve ease of use, the PLASMIC score was designed with a composite haemolysis variable requiring only one of three laboratory values (haptoglobin, indirect bilirubin, or reticulocyte count).

In agreement with the Bentley[24] and French[22] scores, thrombocytopenia and microangiopathic haemolytic anaemia associated with normal or mildly impaired renal function were predictive of severe ADAMTS13 deficiency in the cohorts we studied. The overall proportion of patients in our cohort presenting with neurological symptoms was consistent with published work[15,22,25,26] but did not differ between those with and without severe ADAMTS13 deficiency. This finding could be attributable to the fairly early presentations of thrombotic thrombocytopenic purpura that were seen within our consortium, as reflected by the lower mortality in our dataset compared with previous reports.[27] The degree of elevation in lactate dehydrogenase—sometimes cited as a marker of thrombotic thrombocytopenic purpura—did not add value when considered in patients with known thrombotic microangiopathy.

In seeking to define the potential effect of the PLASMIC score on clinical practice, we used three independent metrics to show that use of our algorithm is superior to clinical assessment alone in identifying patients with thrombotic microangiopathy and severe ADAMTS13 deficiency. Detailed patient-level data were available for retrospective clinical assessment only for the derivation cohort. Therefore, comparison of the PLASMIC score with clinical consensus was restricted to this population. We acknowledge that this approach might overstate the apparent effectiveness of our score relative to clinical assessment alone. However, data generated in two rounds of validation testing indicate that the PLASMIC score retains a high level of effectiveness in independent datasets. Considered together with these findings, the superior performance of the PLASMIC score compared with clinical assessment alone suggests that our prediction tool is sufficiently robust for widespread use.

Different forms of thrombotic microangiopathy can vary in their degree of similarity to thrombotic thrombocytopenic purpura. For example, the clinical presentation of haemolytic uraemic syndrome is generally felt to closely resemble thrombotic thrombocytopenic purpura, whereas typical cases of transplant-associated thrombotic microangiopathy only rarely pose a diagnostic challenge. The PLASMIC score is designed specifically to aid practitioners who might have little experience managing thrombotic microangiopathy, and it can distinguish thrombotic thrombocytopenic purpura from a broad range of thrombotic microangiopathy subtypes, including those that seem most similar to thrombotic thrombocytopenic purpura. This feature is especially evident in the external validation dataset, which was enriched for cases of thrombotic microangiopathy without a clear secondary cause because requests for ADAMTS13 testing at the University of Alabama at Birmingham are subject to approval by the transfusion medicine service. In this respect, our approach to model-building benefited from the use of all consecutive cases of thrombotic microangiopathy in which the diagnosis of thrombotic thrombocytopenic purpura was being considered actively by clinicians operating under real-world conditions.

An important limitation of our work is its retrospective nature, which was necessary because of the rarity of thrombotic microangiopathy, particularly thrombotic microangiopathy associated with severe ADAMTS13 deficiency. We recognise that this approach meant we

were relying on the recorded assessments of clinicians caring for patients included in our dataset, and small numbers of patients with severe ADAMTS13 deficiency might have reduced our ability to detect some effects. These circumstances highlight the value of revalidating the PLASMIC score in larger and more diverse cohorts of patients. Additionally, although our registry includes only cases seen at large academic medical centres and, therefore, might not reflect the mix of patients encountered in the broader community, the institutions included in our consortium serve as referral centres for a large catchment area that contains many smaller hospitals.

In summary, our data indicate that the PLASMIC score can assess reliably the pretest probability of severe ADAMTS13 deficiency in adult patients with thrombotic microangiopathy and can improve accuracy over the use of clinical assessment alone. We anticipate that this method will be beneficial when the results of ADAMTS13 activity testing are not available readily but patients are being considered for immediate plasma exchange or plasma transfusion, and in other clinical and research settings where thrombotic microangiopathy is an important consideration.

Contributors

PKB and RSM had the idea for the study and wrote the report. PKB, SH, MBM, SWW, RMK, LU, CPS, WHD, and RSM contributed to study design, review and analysis of data, and editing of the report. AMB, JMG, and SV were responsible for generating data comparing the prediction score with standard clinical assessment. RSM, PKB, AF, MBM, AL, LS, VU, LU, and AH collected data. PKB, SH, SWW, and RSM did the statistical analysis.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Cristina M Brueggeman for her assistance with this project. This work was supported by the Luick Family Fund of the Massachusetts General Hospital and the American Society of Hematology HONORS Program (AL). JMG was supported by a National Heart, Lung, and Blood Institute training grant (5T32CA009172-39).

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