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PLASMIC score to aid diagnosis of aHUS: an analysis of C5 inhibitor clinical trials and the PINC AI™ healthcare database

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Abstract

Background Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) that can lead to end organ damage and death without treatment. The ability to rapidly distinguish aHUS from other forms of TMA is key for optimal patient management. The PLASMIC Score was developed to identify individuals with thrombotic thrombocytopenic purpura (TTP), a TMA subtype characterized by severe ADAMTS13 deficiency (< 10%), using 7 commonly available laboratory variables and aspects of the patient's medical history. This study aimed to assess the distribution of PLASMIC Scores in patients with known aHUS, and evaluate the utility of the PLASMIC Score in the diagnostic pathway of aHUS in patients with confirmed TMA.

Methods Data from eculizumab (NCT01194973) and ravulizumab (NCT02949128) clinical trials were utilized to calculate and evaluate PLASMIC Score distribution in aHUS patients. Real-world patient-level data from the PINC AI™ Healthcare Database (PHD) were used to evaluate the performance of the PLASMIC Score in identifying aHUS in patients with documented TMA diagnoses and renal impairment (primary analysis population; $n = 110$), and subsequent sensitivity analyses were performed in alternative populations.

Results A total of 94 aHUS patients from the eculizumab and ravulizumab clinical trials dataset were evaluated; 18/36 (50.0%) and 27/58 (46.6%) patients in the eculizumab and ravulizumab trials, respectively, had a PLASMIC Score of 4, and most patients (~85%) had PLASMIC Scores ≤ 5 (range: 3–5), which were distributed similarly between the trials. Among the 110 patients with undifferentiated TMA (primary analysis) from the PHD, a PLASMIC Score cutoff of ≤ 5 yielded sensitivity, specificity and positive predictive value (PPV) and negative predictive values (NPV) of 86.5%, 71.4%, 92.8% and 55.6%, respectively, for identifying probable aHUS. Similar diagnostic performance was observed at a cutoff value of ≤ 5 in further sensitivity analyses. A cutoff value of ≤ 4 yielded a lower PPV (62.9%), yet a higher NPV (85.7%), with only 3 patients misclassified as TTP.

Conclusion Application of the PLASMIC Score in the aHUS diagnostic pathway may support clinical judgement and ascertain confidence in the earlier identification and subsequent treatment of patients with aHUS, thereby improving patient outcomes.

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Keywords Diagnosis, TTP, aHUS, Eculizumab, Ravulizumab, TMA, PLASMIC score

Background

Thrombotic microangiopathy (TMA) is a rare, life-threatening disease which presents as thrombocytopenia, microangiopathic hemolytic anemia, and organ damage typically affecting the kidneys [1]. Atypical hemolytic uremic syndrome (aHUS) is a form of TMA caused by dysregulation of the alternative complement pathway, resulting in complement complex deposition on endothelial cells and microvascular thrombosis [2, 3].

aHUS is clinically diagnosed by the exclusion of thrombotic thrombocytopenic purpura (TTP) and Shiga toxin-producing *Escherichia coli*-hemolytic uremic syndrome (STEC-HUS), alongside additional laboratory test results, including germline mutations for complement regulatory genes [1]. While these disorders have similar clinical presentations, both the underlying pathophysiology and current standard of care differ. For example, while TTP is characterized by a severe deficiency (< 10%) of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity levels, ADAMTS13 levels are normal (≥ 10%) in patients with aHUS [1]. Furthermore, although plasma exchange (PE) is considered a first-line therapy for TTP, outcomes for patients with aHUS who receive PE or plasma infusion (PI) alone are generally poor [2].

Multiple challenges remain in the aHUS diagnostic pathway, including the complexity of disease presentation and a lack of confirmatory tests [2, 4, 5]. Furthermore, there is limited access to ADAMTS13 testing facilities, and test results take 3–7 days in most hospitals across the US and Europe. As these tests are essential to rule out TTP, diagnoses are often hindered or delayed [6, 7, 8]. Indeed, delayed treatment results in poorer outcomes, including requirement of dialysis, end-stage renal disease, ischemic organ damage and death [4, 5, 9]. Furthermore, early eculizumab initiation has been linked to improved renal recovery in patients with aHUS [4, 10]. The complexity and similarity of these disorders and their diagnoses, alongside a lack of efficacious and targeted treatment options in some settings, highlight the clinical need for methods to guide rapid and appropriate therapeutic decisions and alternative treatment options, to ensure timely initiation of appropriate management strategies.

The PLASMIC Score, a seven-component clinical prediction tool based on commonly available clinical and laboratory values, was developed to quickly predict the probability of severe ADAMTS13 deficiency in patients with TMA and aid physicians in diagnosing TTP [11]. The PLASMIC Score (range 0–7) is calculated by assigning one point when an individual meets each of the parameter thresholds (eTable 1 in Additional File 1); a PLASMIC Score of 6–7 indicates a high probability of ADAMTS13 deficiency and therefore probable TTP [12]. Although the PLASMIC Score has not been widely applied to diagnosing aHUS, a recent case study noted its utility in patients with etiologies of TMA other than TTP [13], and negative predictive values (NPV) ≥ 98% have been found in ruling out patients with TTP [12].

The objective of this retrospective study was to assess the distribution of PLASMIC Scores in patients with confirmed aHUS and evaluate the utility of the PLASMIC Score in the diagnostic pathway of aHUS in patients with confirmed TMA.

Methods

Overall study design

This retrospective study analyzed data in 2 stages: (1) a post-hoc analysis of clinical trial data, and (2) analysis of real-world data from the PINC AI™ Healthcare Database (PHD).

Stage 1: Post-Hoc clinical trial analysis

The eculizumab study (NCT01194973) was a prospective, open-label, multicenter, single-arm clinical trial of adult patients with confirmed aHUS who had received eculizumab in previous clinical trials [14, 15, 16, 17, 18]. The ravulizumab study (NCT02949128) was a multicenter, single-arm trial evaluating the efficacy and safety of ravulizumab in adults with aHUS [19]. A key exclusion criterion for both trials was severe ADAMTS13 activity deficiency (≤ 5%), and no patients with TTP were included in the clinical trials [14, 15, 16, 19].

All patients analyzed were from the safety sets of each trial. PLASMIC Scores were calculated for each patient based on the available clinical data; these patients represented the reference standard of patients with known aHUS. For the ravulizumab trial, all 7 components for calculating PLASMIC Score were available; however, the international normalization ratio (INR) was not measured for patients in the eculizumab trial. The distribution of INR in the ravulizumab trial was therefore used to inform the imputation of this component in the PLASMIC Score calculation (eTable 1).

Stage 2: PINC AI™ healthcare database analysis

The PHD is a large, US, hospital-based, comprehensive, all-payer, charge master database, and a source of de-identified patient information, including inpatient discharges and healthcare utilization data from standard hospital discharge files [20]. The PLASMIC Score was calculated from real-world data of patients in the PHD to

assess its diagnostic performance in identifying patients with probable aHUS.

Study population

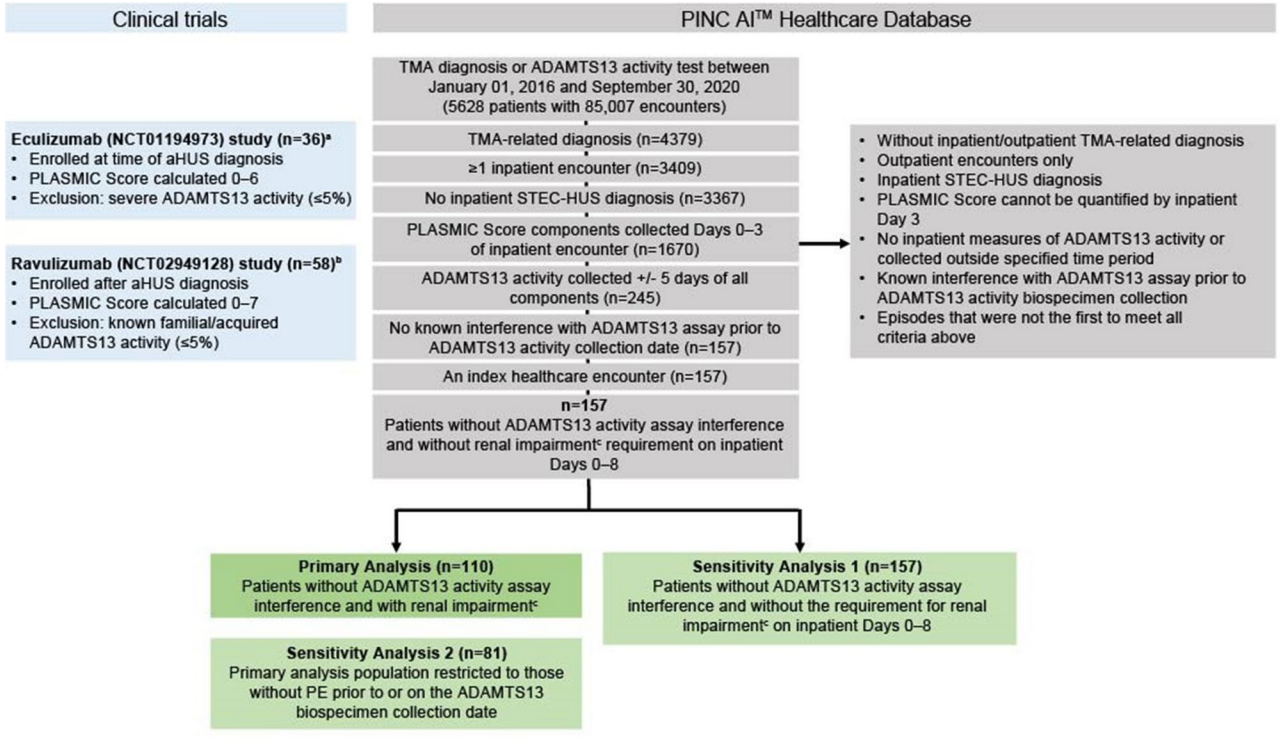
All patients from the database with a TMA diagnosis and ADAMTS13 activity results were screened. Inclusion criteria included: ≥1 inpatient event recorded between January 01, 2016 and September 30, 2020; a TMA-related International Classification of Diseases (ICD)-10 diagnosis code at encounter; and an inpatient healthcare encounter. Patients were excluded if they had a STEC-HUS diagnosis or known interference with ADAMTS13, specifically PE/PI and/or hyperbilirubinemia (total bilirubin > 15 mg/dL), prior to specimen collection for ADAMTS13 activity assay at the inpatient healthcare encounter. The index inpatient encounter was defined as the first encounter which met all of the above criteria. See Additional File 1 for full eligibility criteria.

Study analysis

The primary analysis was conducted in all individuals who fulfilled the eligibility criteria outlined above, and who had evidence of renal impairment, defined as serum creatinine above the upper limit of normal within 8 days of presentation (Fig. 1). Two sensitivity analyses were performed by adjusting population eligibilities: Sensitivity Analysis 1 removed the requirement of renal impairment evidence from the primary analysis cohort, and Sensitivity Analysis 2 removed patients who had ADAMTS13 activity test collection on the same day they received PE.

Study variables

The threshold of PLASMIC Scores varied from 1 to 7. For each threshold value from 1 to 7, patients with a PLASMIC Score equal to, or lower than, this were considered as probable aHUS patients. The ground truth of probable aHUS was defined as having the following: a TMA diagnosis, lack of evidence of STEC-HUS, and an ADAMTS13 activity level ≥ 10%. Sensitivity, specificity, positive predictive value (PPV), and NPV were calculated to assess the performance of utilizing the PLASMIC Score to aid the diagnosis of aHUS at each cutoff point, varying from 1 to 7. The area under the curve (AUC) was calculated to further assess the capabilities of the PLASMIC Score [21].



[a]NCT01194973, An Open-label, Multi-center Clinical Trial of Eculizumab in Adult Patients with Atypical Hemolytic-uremic Syndrome.
[b]NCT02949128, Study of ALXN1210 in Complement Inhibitor Treatment-Naïve Adult and Adolescent Participants with Atypical Hemolytic Uremic Syndrome (aHUS).
[c]Renal impairment defined as serum creatinine > upper limit of normal within Days 0 to 8 of the index healthcare encounter.
Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; PE, plasma exchange; RI, renal impairment; STEC-HUS, Shiga-toxin producing E. coli–HUS; TMA, thrombotic microangiopathy.

Fig. 1 Diagram of patients included in this Study

Statistical analysis

Descriptive analysis of categorical variables was conducted for PHD patients. For continuous measures, means and standard deviations (SD) were calculated, while median values (IQR) are reported for ADAMTS13 levels, length of inpatient stay, and age. Statistical comparisons of median ADAMTS13 levels between PLASMIC Score groups (0–5 vs. 6–7) were performed using Wilcoxon rank sum tests, while Chi-squared tests were performed to compare the proportion of patients in different groups with ADAMTS13 activity level below 10%.

Statistical analyses were performed using SAS v9.4 (SAS: Cary, NC, USA) and Microsoft Excel (Microsoft: Redmond, WA, USA). For further details on the statistical analysis please see Additional File 1.

Results

Stage 1: Post-Hoc clinical trial analysis

Patient characteristics

Patient eligibility for this study is depicted in Fig. 1. We included 36 and 58 aHUS patients from the eculizumab and ravulizumab trials, respectively (patient characteristics are reported in eTable 2).

PLASMIC scores and ADAMTS13 activity levels

Across PLASMIC Score components, platelet count and creatinine thresholds were met by the fewest patients in the eculizumab and ravulizumab trials (3/36 [8.3%] and 9/58 [15.5%] met platelet count, and 8/38 [22.2%] and 9/58 [15.5%] met creatinine thresholds, respectively) (eTable 2). An INR < 1.5 and no history of active cancer or cancer therapy in the past year were the most common factors contributing to the PLASMIC Score (≥ 98.3% of patients scored 1 on each component, eTable 2). In total, 18/36 (50.0%) aHUS patients in the eculizumab trial, and 27/58 (46.6%) aHUS patients in the ravulizumab trial, had a PLASMIC Score of 4 (Fig. 2). The majority of aHUS patients from both trials had scores that fell between 3 and 5 (31/38, 86.1%, in the eculizumab trial and 52/58, 87.9%, in the ravulizumab trial). Across the trials, 12/94 (12.8%) aHUS patients had a PLASMIC Score ≥ 6; further details on these patients are presented in eTable 3.

Mean (SD) ADAMTS13 activity levels were similar across the trials, reported as 80.7% (18.76) and 82.5% (33.1) in the eculizumab and ravulizumab trials, respectively; in patients with a PLASMIC Score of ≥ 6 ($n = 12$), mean (SD) ADAMTS13 activity level was 74.6% (24.8) in the eculizumab trial ($n = 5$) and 80.5% (37.3) in patients from the ravulizumab trial ($n = 6$). Median ADAMTS13 activity levels were also similar across the clinical trial patients (eTable 2). No patient had an ADAMTS13 activity level below 10%; a single ravulizumab trial patient with a PLASMIC Score of 7 had an ADAMTS13 activity level of 110% (eTable 2).

Stage 2: Real-World PHD data

Analysis cohorts

At the time of the analysis, there were 5628 patients with 85 007 encounters in the PHD with a TMA diagnosis and an ADAMTS13 activity test (Fig. 1). Overall, 110 patients comprised the primary analysis population, 157 patients were used in Sensitivity Analysis 1 (renal impairment not required), and 81 patients in the primary analysis who did not receive PE on the day of ADAMTS13 specimen collection were included in Sensitivity Analysis 2.

PLASMIC score distributions and ADAMTS13 activity levels

Characteristics of the primary analysis cohort are presented in Tables 1 and 83/110 (75.4%) patients in this cohort scored between 0 and 5, and 27/110 (24.6%)

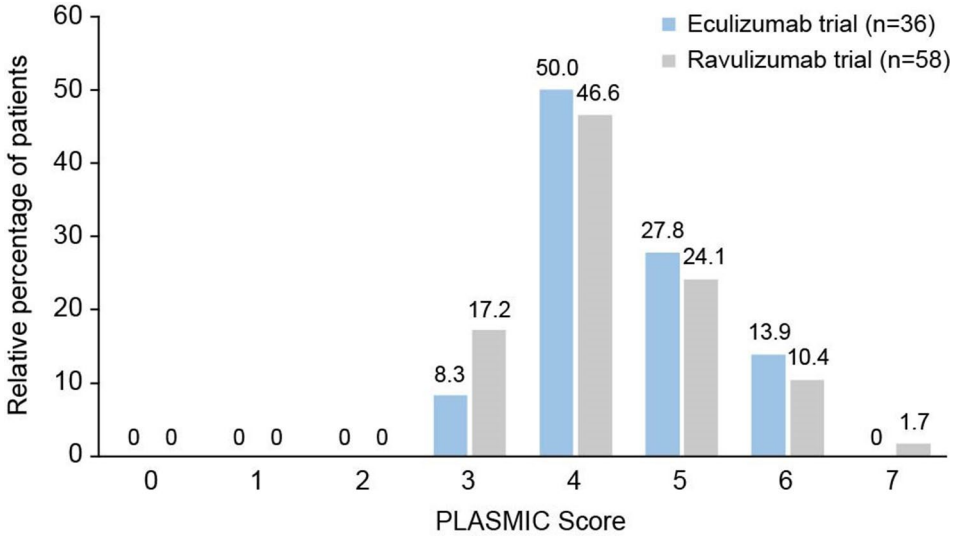


Fig. 2 PLASMIC score distributions in patients from Eculizumab and Ravulizumab clinical trials with aHUS

Table 1 Characteristics of patients in primary analysis from the PINC AI™ database (*n* = 110)

Characteristics	Overall	ADAMTS13 activity		PLASMIC score groups	
		< 10%[e]	≥ 10%[f]	0 to 5	6 to 7
	(*n* = 110)	(*n* = 21)	(*n* = 89)	(*n* = 83)	(*n* = 27)
Demographics					
Age at the index visit, median (Q1, Q3) years	56 (36,68)	48 (36,56)	57 (37,70)	56 (37,70)	52 (31,64)
Race/Ethnicity, *n* (%)					
White	45 (40.9)	16 (76.2)	29 (32.6)	32 (38.6)	13 (48.1)
Black	57 (51.8)	5 (23.8)	52 (58.4)	44 (53)	13 (48.1)
Other	8 (7.3)	0 (0)	8 (9)	7 (8.4)	1 (3.7)
Male	52 (47.3)	7 (33.3)	45 (50.6)	45 (54.2)	7 (25.9)
Index visit characteristics					
Discharge year, *n* (%)					
2016	12 (10.9)	4 (19.0)	8 (9.0)	8 (9.6)	4 (14.8)
2017	18 (16.4)	5 (23.8)	13 (14.6)	13 (15.7)	5 (18.5)
2018	22 (20.0)	2 (9.5)	20 (22.5)	17 (20.5)	5 (18.5)
2019	37 (33.6)	6 (28.6)	31 (34.8)	29 (34.9)	8 (29.6)
2020	21 (19.1)	4 (19.0)	17 (19.1)	16 (19.3)	5 (18.5)
Length of index inpatient visit, median (Q1, Q3) days	10 (6,17)	9 (6,15)	10 (6,17)	10 (6,18)	10 (4,15)
Treatment at the index visit, *n* (%)					
Plasma exchange / plasma infusion	51 (46.4)	16 (76.2)	35 (39.3)	34 (41.0)	17 (63.0)
Prior to the ADAMTS13 biospecimen collection date	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
On the ADAMTS13 biospecimen collection date	29 (26.4)	13 (61.9)	16 (18.0)	18 (21.7)	11 (40.7)
Eculizumab	7 (6.4)	1 (4.8)	6 (6.7)	4 (4.8)	3 (11.1)
Ravulizumab	20 (18.2)	2 (9.5)	18 (20.2)	17 (20.5)	3 (11.1)
Renal and hematological measures at the index inpatient visit, median (Q1, Q3)					
LDH, U/L[a]	677 (404,1575)	1367 (827.5,1856)	551 (363,1316)	550 (355,1056)	1647 (1059,2174.5)
Platelet count, x 10^9 / L[b]	45 (16,77)	13 (10,22)	54 (27,84)	54 (31,85)	13 (10,22)
Hemoglobin, %[a]	7.6 (6.4,9.3)	7.3 (5.8,9.5)	7.7 (6.6,9.3)	7.6 (6.7,9.1)	7.8 (6.3,9.5)
Serum creatinine, mg / dL[c]	2.3 (1.4,4.2)	1.1 (1.0,1.6)	2.9 (1.5,5.0)	2.9 (1.5,5.4)	1.5 (1.0,1.8)
Received dialysis	1.6 (1.2,2.9)	1.1 (1.0,1.6)	1.9 (1.3,3.3)	1.9 (1.3,3.3)	1.2 (1.0,1.8)
Did not receive dialysis	5.2 (2.6,7.7)	1.7 (1.0,2.3)	5.4 (3.0,7.9)	5.4 (3.0,8.2)	1.9 (1.2,4.0)
Dialysis use, n (%)	36 (32.7)	2 (9.5)	34 (38.2)	32 (38.6)	4 (14.8)
Serum creatinine > upper limit of normal, n (%)[d]	110 (100)	21 (100)	89 (100)	83 (100)	27 (100)
Estimated glomerular filtration rate, mL / min / 1.73m^{2} footnote c	31.6 (14.7,57.8)	68.6 (54.0,88.7)	23.7 (12.2,46.2)	23.2 (11.3,47.0)	55.3 (35.6,82.2)

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy

[a] As measured prior to the ADAMTS13 activity collection

[b] As measured on index encounter Days 0 to 3

[c] Mean of measures on index encounter Days 0 to 8

[d] Any measure on index encounter Days 0 to 8

[e] Consistent with a diagnosis of thrombotic thrombocytopenic purpura

[f] Indicates a TMA other than thrombotic thrombocytopenic purpura

scored 6–7 (eFigure 1). Within the group with PLASMIC scores 0–5, no patients had a score of 0, 2 patients had a score of 1 and 3 patients had a score of 2 (eFigure 1). Patients scoring 0–5 were similar in age to those scoring 6–7 (56 vs. 52 years old) and of similar ethnicities, but more patients scoring 0–5 were male (45/83 [54.2%] vs. 7/27 [25.9%]; Table 1). Among PLASMIC Score components, platelet count and creatinine criteria were met by the fewest patients, 41/110 (37.3%) and 58/110 (52.7%), respectively, while no history of solid organ or stem cell transplant and an INR < 1.5 were met by the most patients, 104/110 (94.5%) and 94/110 (85.5%), respectively (Table 2).

In total, 89/110 patients in the primary analysis cohort had ADAMTS13 activity ≥ 10%, which when combined with other eligibility criteria (TMA diagnosis, lack of evidence of STEC-HUS) satisfied ground truth for a diagnosis of aHUS. Of the 110 primary analysis patients, 21 had an ADAMTS13 activity < 10% (indicative of TTP), and 27 patients had a PLASMIC Score ≥ 6; of these patient

Table 2 PLASMIC score and ADAMTS13 activity characteristics of patients in primary analysis from the PINC AI™ database (*n* = 110)

Characteristics	Overall	ADAMTS13 activity		PLASMIC Score	
		< 10%[e]	≥ 10%[f]	0 to 5	6 to 7
	(*n* = 110)	(*n* = 21)	(*n* = 89)	(*n* = 83)	(*n* = 27)
PLASMIC Score components, *n* (%)					
Platelet count < 30×10^9 / L[a]	41 (37.3)	18 (85.7)	23 (25.8)	18 (21.7)	23 (85.2)
Hemolysis[a, b]	64 (58.2)	19 (90.5)	45 (50.6)	39 (47)	25 (92.6)
No active cancer in the past year	68 (61.8)	11 (52.4)	57 (64.0)	45 (54.2)	23 (85.2)
No history of solid organ or stem cell transplant	104 (94.5)	21 (100)	83 (93.3)	77 (92.8)	27 (100)
Mean corpuscular volume < 9×10^{-14} L[a, c]	72 (65.5)	14 (66.7)	58 (65.2)	50 (60.2)	22 (81.5)
International Normalization Ratio < 1.5[a]	94 (85.5)	20 (95.2)	74 (83.1)	68 (81.9)	26 (96.3)
Creatinine < 2.0 mg / dL[d]	58 (52.7)	20 (95.2)	38 (42.7)	32 (38.6)	26 (96.3)
ADAMTS13 activity level, %[a]					
Median (Q1, Q3)	57.5 (35, 83)	5 (5, 5)	67 (48, 85)	64 (46, 84)	5 (5, 55)

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; SD, standard deviation

[a] Lowest measure available within the appropriate time frame

[b] Hemolysis was defined as indirect bilirubin > 2 mg/dL (34.2 µmol/L) or reticulocyte count > 2.5% or undetectable haptoglobin

[c] Equivalent to < 90 fL

[d] Equivalent to 176.8 µmol/L

[e] Consistent with a diagnosis of thrombotic thrombocytopenic purpura

[f] Indicates a TMA other than thrombotic thrombocytopenia purpura

subgroups most patients (> 95%) had a serum creatinine of < 2.0 mg/dL and received a point for this PLASMIC parameter. Median (Q1, Q3) ADAMTS13 activity levels were higher in patients with PLASMIC Scores 0–5 (64% (46, 84)) than in patients with PLASMIC Scores 6–7 (5% (5, 55)) ($P < 0.0001$; Table 2). The distribution of ADAMTS13 activity levels above and below 10% also differed significantly by PLASMIC Score (0–5 vs. 6–7) ($P < 0.0001$; eTable 4).

Diagnostic performance

In the primary analysis, an AUC of 0.8371 was derived from the sensitivity and specificity values at each PLASMIC Score value from 1 to 7 (Fig. 3). A PLASMIC Score cutoff value of 5 (indicative of aHUS) resulted in a sensitivity of 86.5% and specificity of 71.4% (Table 3). Among the 89 patients that satisfied the ground truth for probable aHUS, 77/89 (86.5%) were correctly classified as aHUS at the cutoff score of 5, while the remaining 12/89 (13.5%) patients had a PLASMIC Score ≥ 6. Among the 21 patients with ADAMTS13 activity level < 10% (indicative of TTP), 15/21 (71.4%) patients were correctly classified as TTP at the cutoff score of 5, and the remaining 6 (28.6%) patients had a PLASMIC Score ≤ 5. In contrast, at the PLASMIC Score cutoff value of 4, 56/89 (62.9%) patients were correctly classified as aHUS, while 33 patients were not; 18/21 (85.7%) patients were correctly classified as TTP, while 3 were not. Further, when the cutoff was set at a PLASMIC Score of 6, although 8 more patients were correctly classified as aHUS (85/89; 95.5%), only six of 21 (28.6%) patients were correctly classified as TTP. The sensitivity-specificity curve data indicate that a patient is likely to have aHUS if their PLASMIC Score is calculated as ≤ 5.

Sensitivity analyses

PLASMIC Score distributions and ADAMTS13 activity levels among patients in Sensitivity Analyses 1 and 2 were similar to those from the primary analysis (eFigure 1 and eTable 5).

In Sensitivity Analysis 1, a PLASMIC Score of 5 was similarly able to identify patients with probable aHUS compared with the primary analysis (sensitivity 85.5% in Sensitivity Analysis 1 compared with 86.5% of patients in the primary analysis; Table 3). In Sensitivity Analysis 2, sensitivity was 89.0%, whereas the likelihood that negative test results reflected true negative cases (NPV) was only 50.0% (Table 3).

Discussion

This study leveraged patient data collected in clinical trial and real-world settings to evaluate the usability of the PLASMIC Score in the diagnostic pathway for aHUS, a disorder in which diagnosis is commonly challenging. The PLASMIC Score was designed for use in patients with known TMA to rapidly assess the probability of severe ADAMTS13 deficiency. In 2 clinical trials of patients diagnosed with aHUS, a PLASMIC Score ≤ 5 was observed in most patients (86.1% and 87.9% in eculizumab and ravulizumab trials, respectively), and the most common score was 4 (50.0% and 46.6% in eculizumab and ravulizumab trials, respectively). Similarly, the real-world data showed that the majority (86.5%) of aHUS patients in the primary analysis scored ≤ 5, which was further supported by the high sensitivity and PPV values

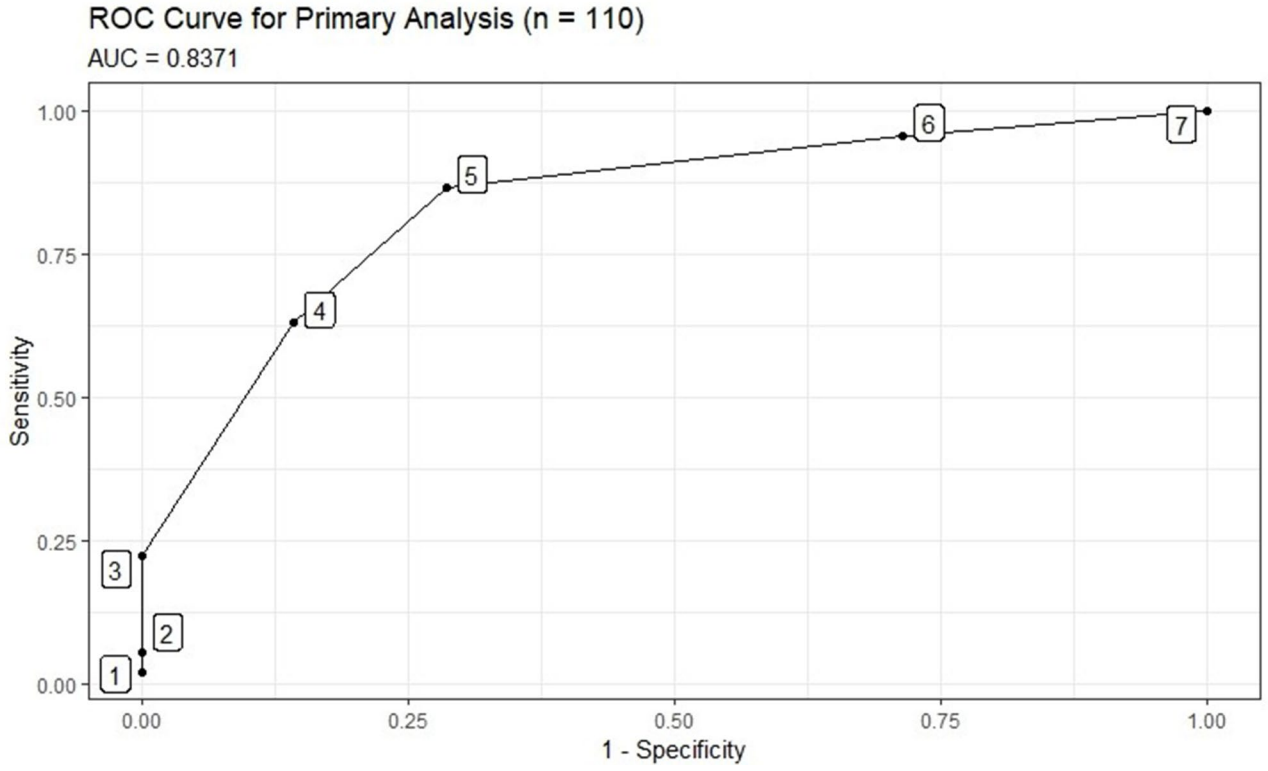


Fig. 3 Receiver operating curve (ROC) for patients in primary analysis from the PINC AI™ database (*n* = 110). A ROC was derived from the sensitivity and specificity values at each PLASMIC Score from 1–7, with the AUC value (0.8371) confirming the prognostic predictive value of the PLASMIC Score at a cutoff value of 5. AUC, area under curve; ROC, receiver operating characteristic

Table 3 Diagnostic performance for identifying aHUS at PLASMIC score cutoff ≤ 5 in the PINC AI™ database population

Diagnostic parameter	Primary Analysis *n* = 110	Sensitivity Analysis #1 *n* = 157	Sensitivity Analysis#2 *n* = 81
Sensitivity, % (95% CI)	86.5 (79.4–93.6) [77 / 89]	85.5 (78.9–92.0) [94 / 110]	89.0 (81.9–96.2) [65 /73]
Specificity, % (95% CI)	71.4 (52.1–90.8) [15 / 21]	63.8 (50.1–77.6) [30 / 47]	100 [8 / 8]
PPV, % (95% CI)	92.8 (87.2–98.3) [77 / 83]	84.7 (78.0–91.4) [94 / 111]	100 [65 / 65]
NPV, % (95% CI)	55.6 (36.8–74.3) [15 / 27]	65.2 (54.5–79.0) [30 / 46]	50.0 (25.5–74.5) [8 / 16]

Abbreviations: aHUS, atypical hemolytic uremic syndrome; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

Diagnostic performance for identifying aHUS at the PLASMIC Score cutoff of ≤ 5 in the primary analysis and sensitivity analyses patients from the PINC AI™ Database population

observed at the PLASMIC Score cutoff value of 5, with 77/89 (86.5%) patients correctly identified as patients with aHUS; although NPV at this cutoff was 55.6%. While a PLASMIC Score ≤ 4 detected a smaller number of probable aHUS patients compared with a PLASMIC Score ≤ 5, our data at this cutoff threshold indicate a low risk for misdiagnosing TTP, consistent with previous reports [11]. This study supports the use of the PLASMIC Score to assist clinical judgement and ascertain confidence in the diagnosis of aHUS (including ruling out TTP), and thereby better inform early treatment decisions. Clinical assessment for aHUS should include exclusion of other common forms of TMA (e.g., TTP and STEC-HUS), as well as other conditions which may contribute to microangiopathic hemolytic anemia (such as cancer or diffuse intravascular coagulation). Further, while the likelihood of patients with intermediate PLASMIC scores (4 or 5) subsequently presenting with severe ADAMTS13 deficiency requiring therapeutic plasma exchange is minimal, it is not non-existent. Therefore, it is recommended that healthcare professionals should use clinical judgement alongside current TTP guidelines in cases with intermediate PLASMIC scores.

Our results are comparable to those of previous studies that have validated the use of the PLASMIC Score to diagnose TTP [12, 22, 23]. Moreover, when the PLASMIC Score cutoff was dichotomized to a high-risk score (6–7) versus low-intermediate risk (0–5) in a prior study it predicted severe ADAMTS13 deficiency with similarly high accuracy [12]. The same study showed that in patients with high-risk PLASMIC Scores (i.e., high chance of being TTP), PE treatment was associated with significantly improved survival, while low-risk patients

did not appear to respond to PE; these data support the use of the PLASMIC Score to differentiate probable aHUS cases from TTP according to PE treatment response [12]. Our data indicate that patients with probable aHUS fall within a range of PLASMIC Scores distinct from those with TTP and, together with the existing literature, strengthen the evidence for its use to distinguish between TTP and aHUS in a real-world setting. Further, the proportion of individuals with severe ADAMTS13 deficiency differed significantly between patients with a PLASMIC Score of 0–5 vs. 6–7 *(P* < 0.0001). Importantly, we assessed all scores and our analyses suggest that severe ADAMTS13 activity levels are rarely observed in patients with a PLASMIC Score ≤ 5 and practically never in those with a score of ≤ 4, consistent with prior reports [11]. These observations support the capability of the PLASMIC Score as a tool to identify cases of probable aHUS without substantial risk of misclassifying TTP patients who require urgent therapy with PE.

Several studies have assessed modifications to the PLASMIC Score to improve its utility in diagnosing TTP. Substitution of INR with neurological symptoms increased the specificity of the PLASMIC Score in ruling out TTP [24]. Further, the addition of one point when proteinuria level was < 1.2 g/g of creatininuria increased the predictive performance of the PLASMIC Score for TTP [25]. In our study, platelet counts and creatinine component thresholds were exceeded by the fewest patients, which is likely related to the required thresholds for each variable; a platelet count $< 30 \times 10^9$/L and creatinine values of < 2.0 mg/dL may therefore be more applicable to TTP than aHUS. Further studies may be needed to determine the role of individual PLASMIC Score components. It is also important to consider studies such as that from Liu et al. [26] which found that the PLASMIC score has a reduced sensitivity for diagnosis of TTP in older individuals (≥ 40 years), which was attributed to higher platelet counts and serum creatinine in this group. A similar elevation of platelet counts and serum creatinine has not been described in elderly patients with aHUS. Furthermore, the median age in our study was 56 years, above the age where sensitivity/specificity of the PLASMIC score dropped. However, it is worth clinician's considering this possibility when screening older individuals.

Prompt diagnosis of aHUS is crucial to enable earlier treatment initiation, which has been shown to improve patient outcomes and lower healthcare resource utilization, including reduced dialysis rates and PE use [4, 10, 16, 19]. A survey reporting responses from 254 clinicians found that laboratory result delays are one of the major challenges of an aHUS diagnosis, in addition to the absence of a single diagnostic test and the heterogeneity of disease presentation [27]. The rapid diagnosis of aHUS remains an unmet medical need due to the poor clinical outcomes associated with late diagnosis; a screening test with a high PPV, such as the PLASMIC Score, is thus warranted and appropriate [28]. The lower NPV value observed in Sensitivity Analysis 2 may be explained by the small number of encountered non-aHUS cases in this cohort. Furthermore, use of the PLASMIC Score may streamline aHUS diagnoses, as the laboratory components are relatively easy to obtain, which may be particularly helpful in countries with limited resources for diagnosing TMA disorders [29].

A key strength of this study was the utilization of both clinical trial and real-world patient data from a large database, which yielded similar results. The small proportion of patients with probable aHUS selected from real-world data (2.5–3.5% of patients with TMA) reflects the application of strict inclusion criteria, such as the presence of schistocytes in peripheral blood, to ensure accurate probable aHUS case identification, despite it being accepted that their absence does not exclude the diagnosis of aHUS.

There are also some limitations of this study. First, the study is retrospective: analysis of real-world data from the PHD relied on the accuracy of diagnosis codes and laboratory results recorded for patients. Thus, there was the potential for coding discrepancies across hospitals. Second, there was no ICD-10 diagnosis specific to aHUS during the PHD data window (January 01, 2016 to September 30, 2020), which would have aided a more precise ground truth definition of aHUS. Third, patients could not be tracked across hospitals, and disease history may not be available in current hospital records. Fourth, data were collected from patients with known TMA only; the PLASMIC Score and conclusions drawn from this study may not be applicable to broader patient populations. While efforts were undertaken to use appropriate eligibility criteria, e.g., renal impairment indicators, the PLASMIC Score was only validated in patients with known TMA, and its use in other patient populations may be inappropriate. Additionally, in the trial of eculizumab (NCT01194973) INR measurements were not available for the patients and the INR distribution from the ravulizumab trial was used to impute this data; this could potentially lead to overestimation in the calculation of the PLASMIC score for the eculizumab trial. Finally, computerized algorithms utilized to determine PLASMIC Scores and other clinical information may differ from real-time methods that clinicians use, particularly in time-sensitive situations. Results from these analyses also may not be generalizable in clinical scenarios that differ due to geographical differences in clinical practice or patient presentation.

Overall, these data indicate that a patient with confirmed TMA and renal impairment is likely to have aHUS

if their PLASMIC Score is calculated as ≤ 5, particularly if they have a score of 3–5. The PLASMIC Score could therefore become a valuable addition to the aHUS diagnostic toolkit, as confirming a diagnosis is notoriously challenging. Supplementing clinical judgement with the PLASMIC Score could ascertain confidence in an aHUS diagnosis, and thereby assist treatment decisions, prompt earlier interventions, and improve overall patient outcomes.

Abbreviations

ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
aHUS	Atypical hemolytic uremic syndrome
eGFR	Estimated glomerular filtration rate
HUS	Hemolytic uremic syndrome
ICD	International classification of diseases
INR	International normalized ratio
LDH	Lactate dehydrogenase
NPV	Negative predictive value
PE	Plasma exchange
PI	Plasma infusion
PHD	Premier healthcare database
PPV	Positive predictive value
RI	Renal impairment
ROC	Receiver operating curve
SD	Standard deviation
STEC-HUS	Shiga toxin-producing Escherichia coli-hemolytic uremic syndrome
TTP	Thrombotic thrombocytopenic purpura
TMA	Thrombotic microangiopathy

Supplementary Information

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Supplementary Material 1

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Author contributions

FRE and JNB contributed to the acquisition, analysis and interpretation of the data, including the statistical analysis, and were involved in the drafting and critical review of the manuscript. MGU and AIA contributed to the interpretation of the data, and were involved in the drafting, revisions, and critical review of the manuscript. AC, CG, IT, CL and YW contributed to the conception and design of this study, interpretation of the data included, and were involved in the drafting and critical review of the manuscript. All authors read and approved the final manuscript.

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Data availability

Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://www.alexionclinicaltrialtransparency.com/data-requests/. Patient-level data from the PINC AI™ database used in this study were obtained on a contractual basis. The data sets generated are not publicly available owing to their proprietary nature.

Declarations

Human ethics and consent to participate

The patient-level data included in this study were evaluated and approved by the Institutional Review Board or Independent Ethics Committee, and the study was conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines.

Consent to publish

All participants provided informed consent prior to enrolling in the clinical trials included in this study; due to the de-identified nature of the PINC AI™ database, consent was not required for these patients.

Competing interests

Miguel Giovanni Uriol-Rivera is a consultant of Alexion, AstraZeneca Rare Disease, including expert testimony fees; a receipt of honoraria from Alexion, AstraZeneca Rare Disease, has participated in advisory boards for Alexion, AstraZeneca Rare Disease and has also received honoraria from GlaxoSmithKline. Frank R Ernst was an employee of CTI Clinical Trial and Consulting Services, Inc, who were contracted by Alexion, AstraZeneca Rare Disease, at the time of the study. John N Booth III was an employee of CTI Clinical Trial and Consulting Services, Inc, who were contracted by Alexion, AstraZeneca Rare Disease to conduct the current study, at the time of the study. Àngels Comas is a current employee and stakeholder of Alexion, AstraZeneca Rare Disease. Christoph Gasteyger is a current employee and stakeholder of Alexion, AstraZeneca Rare Disease. Ioannis Tomazos was an employee of Alexion, AstraZeneca Rare Disease at the time this study was conducted. Ching Lum was an employee of Alexion, AstraZeneca Rare Disease at the time this study was conducted. Yan Wang is a current employee and stakeholder of Alexion, AstraZeneca Rare Disease. Ana I Ávila has received honoraria from, and participated in advisory boards for Alexion, AstraZeneca Rare Disease, and is a recipient of honoraria from GlaxoSmithKline.

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