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Multisystem Involvement at Presentation and 30-Day Mortality in Thrombotic Thrombocytopenic Purpura: A 20-Year Retrospective Cohort Study

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Short Title: Organ Burden and Early Mortality in TTP

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Keywords: ADAMTS13; PLASMIC score; Thrombotic microangiopathy; Risk assessment; Retrospective cohort.

Abstract

Background: The extent and pattern of organ involvement at presentation may reflect clinical severity in thrombotic thrombocytopenic purpura (TTP). Their associations with 30-day mortality were assessed in a two-decade cohort.

Methods: This single-centre retrospective cohort included 168 patients treated between 2004 and 2024. Five organ systems were assessed at admission before treatment at the study centre. Associations with 30-day mortality were estimated after adjustment for age, sex, PLASMIC era and pretreatment ADAMTS13 activity <10%.

Results: Fifty-three patients (31.5%) died within 30 days. Each additional involved organ system was associated with higher adjusted odds of death (adjusted odds ratio [aOR] 1.73, 95% confidence interval [CI] 1.30–2.32). Mortality was 43.4% (36/83) with at least three systems involved and 20.0% (17/85) with fewer than three. When severe neurological manifestations and renal involvement coexisted, mortality reached 43.8% (35/80), compared with 4.2% (1/24) when neither was present. Concurrent involvement remained associated with death after adjustment (aOR 3.34, 95% CI 1.66–6.75). Lower platelet count and higher total bilirubin were also associated with mortality in the integrated model.

Conclusions: Greater organ burden and concurrent severe neurological manifestations with renal involvement characterised patients with higher 30-day mortality. Platelet count and total bilirubin provided complementary laboratory information.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening thrombotic microangiopathy (TMA) characterised by severe deficiency of ADAMTS13 activity. Failure to cleave ultra-large von Willebrand factor (VWF) multimers promotes platelet-rich microvascular thrombosis and acute ischaemic organ injury [1, 2]. Although survival has

improved with therapeutic plasma exchange (TPE), glucocorticoids, B-cell-directed therapy, and anti-VWF treatment [3-5], TTP remains a haematological emergency in which deaths may occur within hours to days of presentation [6, 7].

Treatment decisions often precede diagnostic confirmation. Patients typically present with thrombocytopenia and microangiopathic haemolytic anaemia (MAHA), with variable neurological, renal, or gastrointestinal involvement. The classic pentad is uncommon and should not be required to initiate evaluation or treatment. An ADAMTS13 activity level <10% strongly supports the diagnosis, but limited assay availability, delayed turnaround, and post-treatment sampling may reduce its diagnostic utility [8, 9]. Clinicians therefore integrate presenting features, routine laboratory findings, and clinical prediction tools such as the PLASMIC score while confirmatory testing is pending [10-12].

Guidelines recommend prompt initiation of TPE and glucocorticoids when immune-mediated TTP is strongly suspected, with rituximab and other adjunctive treatments used according to disease characteristics, availability, and contemporary practice [9, 13, 14]. However, long-term real-world data describing diagnostic access, treatment patterns, and in-hospital outcomes remain limited, particularly in settings where access to ADAMTS13 testing, TPE, and caplacizumab has varied over time [15-17]. Early recognition and prompt treatment are central to the management of TTP [6].

This two-decade single-centre cohort examined the association of baseline organ burden and the co-occurrence of severe neurological manifestations and renal involvement with 30-day mortality. Platelet count and total bilirubin were assessed as complementary laboratory measures. Temporal differences in presentation, treatment and outcomes were examined secondarily [10].

Methods

Study design and case ascertainment

Consecutive patients with thrombotic thrombocytopenic purpura (TTP) treated at the First Affiliated Hospital, Zhejiang University School of Medicine, between December 2004 and December 2024 were included in this single-centre retrospective cohort. Potential cases were identified using ICD-9-CM and ICD-10-CM codes and adjudicated by medical record review according to contemporary international criteria. Patients younger than 16 years, those seen only for follow-up without a qualifying acute admission, and those with insufficient records for diagnostic adjudication were excluded (Figure 1). Laboratory-confirmed TTP was defined by a compatible thrombotic microangiopathy (TMA) and pretreatment ADAMTS13 activity <10%. Patients without a qualifying pretreatment ADAMTS13 result were clinically adjudicated after alternative TMAs had been excluded. Anti-ADAMTS13 antibody or inhibitor positivity was supportive but not mandatory [8, 9].

Data collection and baseline assessment

Baseline assessments comprised organ involvement documented at admission and the earliest available laboratory measurements, all recorded before TTP treatment at the study centre. ADAMTS13 samples were classified according to their timing relative to treatment, and PLASMIC scores were calculated when all components were available [10, 11]. Organ burden counted involvement of the neurological, renal, cardiac, gastrointestinal and respiratory systems (0–5). Organ involvement was classified from admission findings and relevant investigations. Any neurological manifestation contributed to the organ-burden count, whereas altered consciousness, confusion or coma defined severe neurological involvement for the neurological–renal analysis. Renal involvement included acute or pre-existing kidney dysfunction and urinary abnormalities, including isolated haematuria or proteinuria. The remaining organ systems were assessed from documented clinical findings and investigations. Laboratory data included platelet count, haemoglobin, reticulocytes, schistocytes, lactate

dehydrogenase (LDH), total bilirubin (TBIL), renal indices, coagulation tests and troponin [8, 9, 18]. Pretreatment ADAMTS13 activity <10% and clinically adjudicated TTP formed mutually exclusive diagnostic categories.

Treatments and outcomes

Treatments received during the index admission, including therapeutic plasma exchange (TPE), glucocorticoids, rituximab, other immunosuppressive agents, and supportive care, were abstracted from the medical record. The primary outcome was all-cause death within 30 days of admission. Thirty-day vital status was ascertainable for all 168 patients from the date of index admission. Any recorded death was summarised descriptively in Supplementary Tables S1 and S4. Treatment patterns were analysed descriptively, without estimating comparative treatment effects.

Statistical analysis

Continuous variables are reported as medians (interquartile ranges [IQRs]) and categorical variables as n/N (%). Group comparisons used the Mann–Whitney U, Pearson chi-square or Fisher exact test, as appropriate. Mortality estimates are accompanied by Wilson 95% confidence intervals (CIs). Admissions before 1 January 2017 defined the pre-PLASMIC era, and later admissions defined the PLASMIC era. Associations with 30-day mortality were estimated using logistic regression with robust standard errors, adjusted for age, sex, era and pretreatment ADAMTS13 activity <10%. Organ burden was analysed primarily as a continuous count. Four-category (0–1, 2, 3 and ≥4 systems) and binary (≥3 vs. <3 systems) analyses described the observed risk gradient. Neurological and renal involvement were assessed as mutually exclusive groups and as concurrent involvement. An integrated model added log-transformed platelet count and TBIL, each scaled per standard deviation (SD). A separate model replaced renal involvement with admission acute kidney injury. Benjamini–Hochberg correction was applied to survival and era comparisons according to the variable families

specified in the supplementary table notes. Multivariable models used complete cases. All tests were two-sided, with $p < 0.05$ considered statistically significant. Analyses were performed using IBM SPSS Statistics, version 32.0.

Results

Cohort characteristics and 30-day outcome

Of 189 patients screened, 168 contributed an index admission (Figure 1). Median age was 53 years (IQR 40–65), and 77 patients (45.8%) were male. Pretreatment ADAMTS13 activity was <10% in 153 patients (91.1%). The remaining 15 (8.9%) were clinically adjudicated. The PLASMIC score was available for 94 patients, of whom 78 (83.0%) scored ≥5. Microangiopathic haemolytic anaemia (MAHA) was documented in 139 patients (82.7%), whereas the classic pentad was present in 32 (19.0%). Neurological manifestations occurred in 138 patients (82.1%), including severe manifestations in 126 (75.0%). Renal involvement was recorded in 98 (58.3%), with admission acute kidney injury (AKI) in 47 (28.0%). Cardiac, gastrointestinal and respiratory involvement occurred in 63 (37.5%), 63 (37.5%) and 53 (31.5%). The median number of involved systems was 2 (IQR 1–4), and 83 patients (49.4%) had at least three involved systems. Median platelet count was 12.0×10^9/L (IQR 7.0–22.2), haemoglobin 70.0 g/L (IQR 62.8–87.2), lactate dehydrogenase (LDH) 924.5 U/L (IQR 611.5–1,484.5) and total bilirubin (TBIL) 42.4 μmol/L (IQR 23.6–72.2). Thirty-day vital status was established for all patients, and 53 died (31.5%, 95% CI 25.0–38.9%, Table 1, Supplementary Table S1).

Clinical and laboratory associations with 30-day mortality

Organ burden distinguished patients who died from survivors (median 3 vs. 2 systems, $p < 0.001$, Supplementary Table S2). In the primary adjusted analysis, each additional involved system was associated with higher odds of 30-day death (aOR 1.73, 95% CI 1.30–2.32, p <

0.001, Table 3). Absolute mortality increased from 17.0% with 0–1 systems and 23.7% with two to 42.1% with three and 44.4% with at least four (Table 2). In the secondary three-system grouping, 36 of 83 patients (43.4%) with at least three involved systems died, compared with 17 of 85 (20.0%) with fewer than three (aOR 3.86, 95% CI 1.74–8.56, $p < 0.001$, Tables 2 and 3).

Beyond the number of affected systems, their composition was associated with outcome. Severe neurological manifestations were documented in 47 of 53 patients who died (88.7%) versus 79 of 115 survivors (68.7%, $p = 0.005$), and renal involvement in 40 (75.5%) versus 58 (50.4%, $p = 0.002$, Supplementary Table S2). Mortality across the mutually exclusive neurological–renal groups ranged from 1 of 24 patients (4.2%) with neither feature to 35 of 80 (43.8%) with both. It was 12 of 46 (26.1%) with severe neurological manifestations alone and 5 of 18 (27.8%) with renal involvement alone (Table 2). Concurrent involvement remained associated with 30-day death after adjustment (aOR 3.34, 95% CI 1.66–6.75, $p < 0.001$, Table 3). The corresponding association was similar when admission AKI replaced broader renal involvement (aOR 3.37, 95% CI 1.56–7.28, $p = 0.002$, Supplementary Table S3).

Baseline laboratory findings also differed by 30-day outcome. Compared with survivors, nonsurvivors had lower platelet counts (median, 8.0 vs. 14.0 $\times 10^9$/L, $p < 0.001$) and higher TBIL (52.8 vs. 35.0 μmol/L, $p < 0.001$), LDH, creatinine and troponin. All five differences remained significant after Benjamini–Hochberg adjustment (adjusted $p \leq 0.030$, Supplementary Table S2). In the integrated model, concurrent severe neurological manifestations and renal involvement remained associated with 30-day death (aOR 3.10, 95% CI 1.48–6.49, $p = 0.003$). Higher log-transformed platelet count was associated with lower odds of death (aOR per SD 0.53, 95% CI 0.31–0.90, $p = 0.019$), while higher log-transformed TBIL was associated with greater odds (aOR per SD 1.76, 95% CI 1.16–2.66, $p = 0.007$, Table 3).

Case mix, treatment, and outcomes across PLASMIC eras

The pre-PLASMIC and PLASMIC-era cohorts comprised 74 and 94 patients. Pretreatment ADAMTS13 activity <10% was recorded in 70 (94.6%) and 83 (88.3%), respectively ($p = 0.155$). The later cohort had more renal involvement (68.1% vs. 45.9%, $p = 0.004$), admission AKI (39.4% vs. 13.5%, $p < 0.001$) and involvement of at least three systems (68.1% vs. 25.7%, $p < 0.001$). Critical or intensive care admission was also more frequent (71.3% vs. 41.9%, $p < 0.001$, Supplementary Table S4). Therapeutic plasma exchange (TPE) was administered to 115 patients (68.5%) overall, without a significant era difference (72.3% vs. 63.5%, $p = 0.222$). In contrast, glucocorticoid use increased from 56.8% to 86.2%, rituximab from 9.5% to 33.0% and intravenous immunoglobulin from 14.9% to 44.7% (all $p < 0.001$). Thirty-day mortality was similar between eras (30.9% vs. 32.4%,$p = 0.827$, Supplementary Table S4).

Discussion

At presentation, mortality rose with the number of involved organ systems, and the three-system grouping separated patients with approximately 20% from those with more than 40% 30-day mortality. The neurological–renal analysis identified a specific pattern within this broader burden: concurrent severe neurological manifestations and renal involvement marked the highest observed mortality. The association was similar when renal involvement was restricted to acute kidney injury (AKI), while platelet count and total bilirubin (TBIL) contributed further information in the integrated model.

Earlier TTP cohorts have associated age, cerebral involvement, haemodynamic instability and biochemical markers of tissue injury with adverse outcomes [7, 16, 17, 19]. By measuring involvement across five organ systems, this study characterises cumulative clinical burden alongside a defined neurological–renal pattern. The classic pentad was documented in only 19.0% of patients, and platelet count and TBIL remained associated with mortality when analysed with the neurological–renal phenotype.

Clinical presentation and management differed across the PLASMIC eras. The later cohort had

more multisystem and renal involvement and more frequent critical care admission, alongside greater use of glucocorticoids and rituximab. Thirty-day mortality remained similar across periods despite these changes in case mix and treatment practice.

The 31.5% 30-day mortality observed here exceeds estimates from the French and United States registries [7, 19]. A Chinese emergency cohort reported 38.5% mortality during follow-up, and the Brazilian registry reported 15.3% in-hospital mortality [16, 17]. These estimates reflect different outcome periods and case mixes. This cohort largely predates caplacizumab-based management. Trial and real-world evidence has since supported its role in limiting acute TTP-related complications [5, 14, 20, 21], making contemporary validation of organ-burden associations important.

By examining both the number and the pattern of organ systems involved, this study identifies a clinical severity profile associated with early mortality in TTP. Greater organ burden and the co-occurrence of severe neurological manifestations and renal involvement marked higher 30-day risk, while platelet count and total bilirubin contributed complementary laboratory information. These findings bring readily available admission features into a more integrated assessment of short-term risk. The retrospective, single-centre design and changes in care over two decades should be considered when interpreting the results, and the observed separation at three involved systems requires assessment in contemporary cohorts.

Conclusions

In this retrospective TTP cohort, 30-day mortality increased with the number of organ systems involved at admission. Coexisting severe neurological manifestations and renal involvement characterised the group with the highest observed mortality, while platelet count and TBIL provided complementary laboratory information. These findings support early risk assessment based on both the extent and pattern of organ involvement.

List of abbreviations

ADAMTS13 A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13

AKI Acute kidney injury

aOR Adjusted odds ratio

CI Confidence interval

ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification

ICD-10-CM International Classification of Diseases, Tenth Revision, Clinical Modification

IQR Interquartile range

LDH Lactate dehydrogenase

MAHA Microangiopathic haemolytic anaemia

OR Odds ratio

SD Standard deviation

TBIL Total bilirubin

TMA Thrombotic microangiopathy

TPE Therapeutic plasma exchange

TTP Thrombotic thrombocytopenic purpura

VWF Von Willebrand factor

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital, Zhejiang University School of Medicine (approval No. IIT20250330A) and was conducted in accordance with the Declaration of Helsinki. The same board waived the

requirement for written informed consent because the study retrospectively analysed de-identified clinical data.

Consent for publication

Not applicable. The manuscript contains no identifiable individual-level information.

Availability of data and materials

The patient-level data analysed in this study are not publicly available because of patient confidentiality and institutional restrictions. De-identified aggregate data supporting the reported results are available from the corresponding author upon reasonable request, subject to institutional and ethics approval.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' Contributions

H.T., X.P.Z., Y.L., and L.Y. designed the study. Y.L. and L.Y. developed the methodology, curated and analysed the data, and drafted the manuscript. X.P.Z., Y.L., and L.Y. collected the data. H.T., X.P.Z., R.L., and X.Z. critically revised the manuscript. H.T., X.P.Z., and R.L. supervised the study. All authors read and approved the final manuscript.

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Figure legends

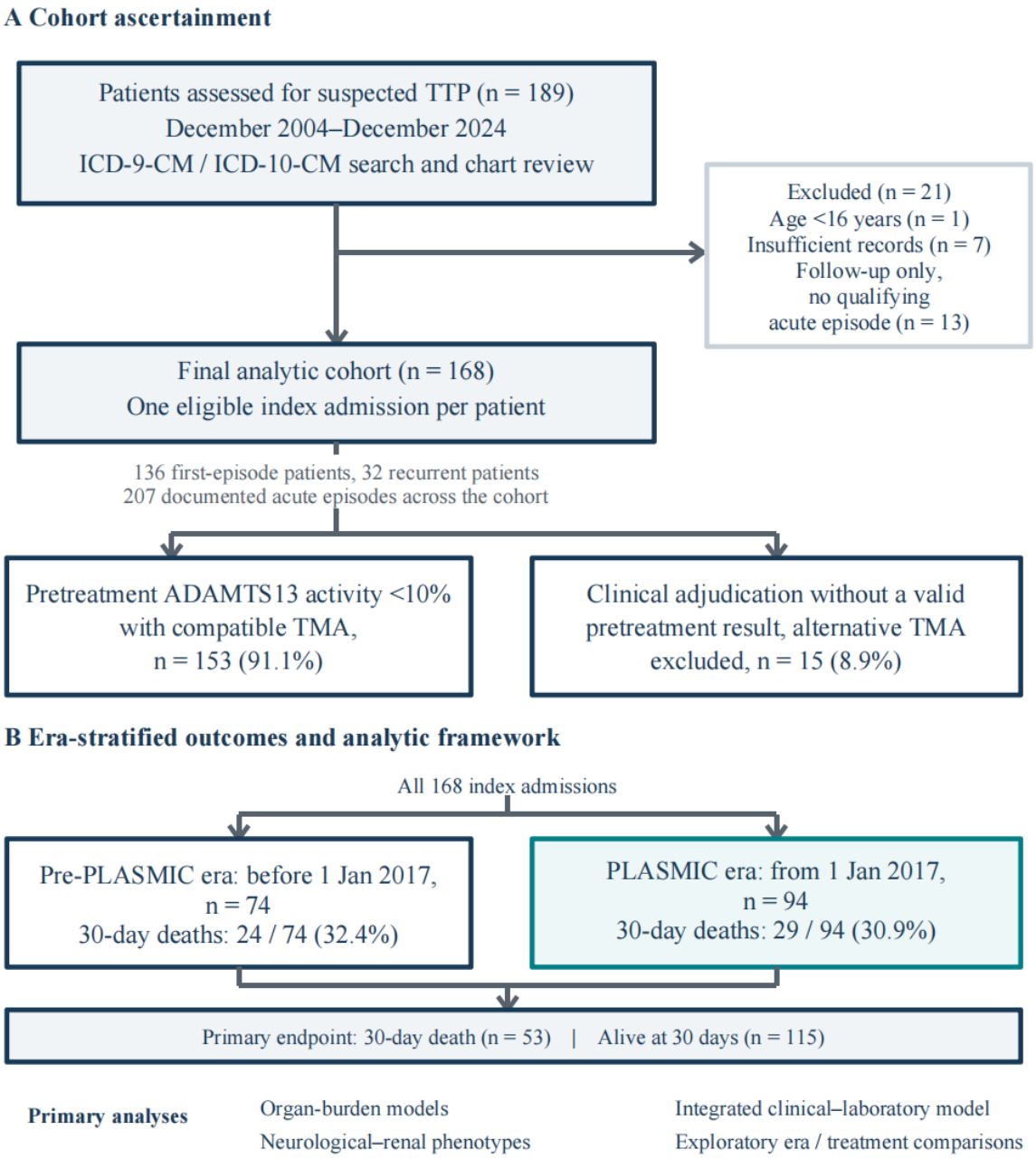


Figure 1. Cohort selection, diagnostic classification, and 30-day outcomes.
(A) Of 189 patients assessed between December 2004 and December 2024, 168 were included after 21 exclusions. Pretreatment ADAMTS13 activity <10% was documented in 153 patients. The remaining 15 were clinically adjudicated after exclusion of alternative thrombotic microangiopathies. (B) The pre-PLASMIC and PLASMIC eras included 74 patients (24 deaths within 30 days) and 94 patients (29 deaths within 30 days). Each patient contributed one index admission.

Table 1. Clinical and laboratory characteristics and 30-day outcome of the TTP cohort

Characteristic	Overall (n = 168)
Demographic and diagnostic characteristics	
Age, years, median (IQR)	53 (40–65)
Male sex	77/168 (45.8)
Clinical phenotype and organ involvement	
Microangiopathic haemolytic anaemia	139/168 (82.7)
Haemolysis	142/168 (84.5)
Haemorrhagic manifestations	108/168 (64.3)
Any neurological involvement	138/168 (82.1)
Severe neurological involvement	126/168 (75.0)
Renal involvement	98/168 (58.3)
Acute kidney injury	47/168 (28.0)
Cardiac involvement	63/168 (37.5)
Gastrointestinal involvement	63/168 (37.5)
Respiratory involvement	53/168 (31.5)
Involved organ systems, median (IQR)	2 (1–4)
Classic pentad documented	32/168 (19.0)
≥3 involved organ systems	83/168 (49.4)
PLASMIC score and ADAMTS13	
PLASMIC score available	94/168 (56.0)
PLASMIC score ≥5 among scored patients	78/94 (83.0)
ADAMTS13 activity < 10%	153/168 (91.1)
Laboratory investigations	
Platelet count, $\times 10^9$/L, median (IQR)	12.0 (7.0–22.2)
Haemoglobin, g/L, median (IQR)	70.0 (62.8–87.2)
Lactate dehydrogenase, U/L, median (IQR)	924.5 (611.5–1484.5)
Reticulocytes, %, median (IQR)	4.85 (2.60–9.20) [n=158]
Total bilirubin, μmol/L, median (IQR)	42.4 (23.6–72.2)
Creatinine, μmol/L, median (IQR)	83.0 (65.8–103.0)
Troponin, ng/mL, median (IQR)	0.05 (0.02–0.15)
Outcome	
30-day death	53/168 (31.5, 95% CI: 25.0–38.9)

Values are median (IQR) or n/N (%), with N denoting available observations. Incomplete laboratory sample sizes are shown in brackets. PLASMIC ≥5 is based on scored patients. Organ burden counts five systems assessed at admission before treatment at this hospital. The mortality proportion includes a Wilson 95% confidence interval (CI).

Abbreviations: CI, confidence interval; IQR, interquartile range; TTP, thrombotic thrombocytopenic purpura.

Table 2. Absolute 30-day mortality by organ burden and neurological–renal involvement

Risk stratum	30-day deaths, n/N	Mortality, %	Wilson 95% CI, %
Organ burden: three-system grouping			
<3 involved organ systems	17/85	20.0	12.9–29.7
≥3 involved organ systems	36/83	43.4	33.2–54.1
Organ burden: four-category definition			
0–1 involved organ systems	8/47	17.0	8.9–30.1
2 involved organ systems	9/38	23.7	13.0–39.2
3 involved organ systems	16/38	42.1	27.9–57.8
≥4 involved organ systems	20/45	44.4	30.9–58.8
Severe neurological manifestations and renal involvement			
Neither feature	1/24	4.2	0.7–20.2
Severe neurological involvement alone	12/46	26.1	15.6–40.3
Renal involvement alone	5/18	27.8	12.5–50.9
Concurrent severe neurological and renal involvement	35/80	43.8	33.4–54.7

Deaths are n/N within each stratum, with Wilson 95% confidence intervals (CIs). Organ burden counts five systems assessed at admission before treatment at this hospital. Renal involvement includes urinary abnormalities and renal dysfunction recorded at admission. Any neurological manifestation contributes to the count. The mutually exclusive neurological‑renal groups require severe manifestations. Each organ-burden grouping represents the same 168 patients and 53 deaths.

Table 3. Adjusted associations of organ burden, neurological–renal involvement, and laboratory measures with 30-day mortality

Variable	Adjusted OR (95% CI)	p value
Model A: Continuous organ burden		
Involved organ systems, per system	1.73 (1.30–2.32)	<0.001
Model B: At least 3 involved organ systems		
≥3 involved organ systems	3.86 (1.74–8.56)	<0.001
Model C: Concurrent severe neurological and renal involvement		
Concurrent severe neurological and renal involvement	3.34 (1.66–6.75)	<0.001
Model D: Integrated clinical and laboratory model		
Concurrent severe neurological and renal involvement	3.10 (1.48–6.49)	0.003
ln(platelet count), per 1 SD increase	0.53 (0.31–0.90)	0.019
ln(total bilirubin), per 1 SD increase	1.76 (1.16–2.66)	0.007

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression with robust standard errors (n=168). All models adjusted for age, sex, PLASMIC era and pretreatment ADAMTS13 activity <10% (n = 153). Model A treats organ burden as a continuous count. Model B compares ≥3 with <3 involved systems. Model C compares concurrent severe neurological manifestations and renal involvement with all other patients. Model D adds natural-log-transformed platelet count and total bilirubin, each per standard-deviation (SD) increase, to Model C. P values were not adjusted for multiple comparisons.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 03SupplementaryTables.docx