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Original Article

Dynamic Monitoring of ADAMTS-13 Activity for Differential Diagnosis Across the Spectrum of Sepsis-Associated Thrombotic Microangiopathies

Yi Liu, Fan Lu, Binbin Ji, Wei Song, Hui Shen, Yingjie Xu and Bining Yang.

Emergency Department, The Fourth Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215125, China.

Competing interests: The authors declare no competing interest.

Abstract. ***Background*: In the ICU, distinguishing immune-mediated thrombotic thrombocytopenic purpura (iTTP) from sepsis-associated thrombotic microangiopathy (TMA) is time-critical. We tested whether serial ADAMTS-13 combined with targeted coagulation and inflammation markers improves iTTP risk stratification in a Sepsis-3 ICU cohort and whether a pragmatic rule-out is feasible.**

***Methods*: Prospective single-center study of adults meeting Sepsis-3 with thrombocytopenia and schistocytes ≥ 1% or LDH > 2× ULN within 24 h of ICU admission. ADAMTS-13 activity and VWF: Ag were assayed at 0/24/48/72 h alongside a thrombo-inflammatory panel. We derived a Dynamic ADAMTS-13 Index (DAI), a Coagulation Consumption Index (CCI) anchored to ISTH DIC and fibrinogen/antithrombin III, and an Inflammation Index (IL-6/HBP). The prespecified main rule-out required a ≥ 15% ADAMTS-13 rise by 48 h plus low CCI. A prespecified RCV-anchored sensitivity analysis required ≥ 35% relative rise or ≥ 10 absolute % points plus low consumption. For decision-making, pre-treatment (pre-plasma exchange, PEx) analyses are emphasized. Intent-to-diagnose (care-embedded) analyses are exploratory, and internal validation used a bootstrap optimism correction.**

***Results*: Of 1,274 screened, 330 were included (iTTP = 34). Discrimination improved from baseline ADAMTS-13 (AUROC 0.78) to DAI (0.93), with smaller gains after adding CCI (0.95) and the Inflammation Index (0.96). With the main rule-out (≥ 15% + low CCI) in the intent-to-diagnose analysis, sensitivity was 97.1%, specificity was 86.1%, and NPV was 99.6%. The RCV-anchored sensitivity analysis preserved 100.0% sensitivity and NPV with 76.0% specificity. A 72-h phenotype (ADAMTS-13 < 10% with high IL-6/HBP) was associated with higher 28-day mortality (adjusted HR 2.6).**

***Conclusions*: In Sepsis-3 ICU patients with TMA features, serial ADAMTS-13 testing, along with targeted coagulation/inflammation markers, enhances early iTTP risk stratification and supports a pragmatic rule-out framework. External validation and implementation studies remain essential. These findings also support investment in rapid/automated ADAMTS-13 activity assays and decision-support workflows to enable timely adoption beyond tertiary centers.**

Keywords: ADAMTS 13; Thrombotic thrombocytopenic purpura; Sepsis; Thrombotic microangiopathy; Disseminated intravascular coagulation; Interleukin 6; Heparin binding protein; Diagnostic accuracy.

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Correspondence to: Bining Yang. No. 9 Chongwen Road, Suzhou Industrial Park, Suzhou, Jiangsu Province,215125 China. E-mail: yangbining041@163.com

Introduction. Distinguishing thrombotic thrombocytopenic purpura (TTP) from other sepsis-associated thrombotic microangiopathies (TMAs) is crucial, given the overlapping clinical presentations, particularly when thrombocytopenia and hemolysis coexist in sepsis. TTP is characterized by a severe deficiency in ADAMTS13 activity, leading to the accumulation of ultra-large von Willebrand factor multimers and subsequent platelet aggregation.[1,2] The classic pentad of TTP includes thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, and fever, but this presentation is rare, making diagnosis challenging.[3,4] In sepsis, thrombocytopenia and hemolysis can mimic TTP, but the underlying pathophysiology differs.[5,6] Diagnostic scores like the Coppo and PLASMIC scores have been developed to aid in differentiating TTP from other TMAs, with the Coppo score showing better performance in predicting TTP in intensive care settings.[7] However, these scores are not foolproof, and the availability of ADAMTS13 activity testing is limited in emergency settings, necessitating empirical treatment decisions.[8] Plasma exchange (PEx) is the cornerstone of TTP treatment and must be initiated promptly to improve survival, but it is not beneficial for other TMAs, such as HUS, where complement inhibitor therapy is more appropriate.[1,9] Therefore, the diagnostic ambiguity in sepsis-associated TMAs underscores the need for rapid, accurate differentiation to avoid unnecessary PEx in non-TTP cases and to ensure timely intervention in TTP.[2,10]

The pathobiological rationale for a dynamic, panel-based strategy in managing TTP and differentiating it from sepsis-related thrombotic microangiopathy or disseminated intravascular coagulation lies in the distinct mechanisms and clinical trajectories of these conditions. TTP is primarily characterized by a severe deficiency of ADAMTS13, an enzyme responsible for cleaving ultra-large von Willebrand factor (ULVWF) multimers, which, if left uncleaved, lead to microvascular thrombosis and the clinical manifestations of TTP, such as thrombocytopenia and microangiopathic hemolytic anemia.[11-13] This deficiency is often due to autoimmune inhibition, resulting in persistently low ADAMTS13 activity, which is a hallmark of TTP.[14,15] In contrast, sepsis-related thrombotic microangiopathy or disseminated intravascular coagulation involves transient suppression of ADAMTS13 activity, accompanied by surges in VWF and a consumption coagulopathy, alongside endothelial and inflammatory activation, marked by elevated levels of interleukin-6 (IL-6), heparin-binding protein (HBP), and serum amyloid A (SAA).[16,17] These inflammatory markers help differentiate the trajectory of sepsis-related thrombotic microangiopathy or disseminated intravascular coagulation from TTP.[18] Therefore, a serial measurement of ADAMTS13 activity, along with a thrombo-inflammatory panel, is crucial to capture the kinetics and phenotype of these conditions. This approach allows for the differentiation between the persistent enzymatic deficiency seen in TTP and the transient, inflammation-driven changes observed in sepsis-related thrombotic microangiopathy or disseminated intravascular coagulation, thereby guiding appropriate therapeutic interventions.[19,20]

Our primary objective was to determine whether dynamic ADAMTS-13 profiling, with stepwise addition of a coagulation consumption and a parsimonious inflammation index, improves iTTP risk stratification within the ISTH framework among Sepsis-3 ICU patients relative to a single baseline ADAMTS-13. Secondary objectives were to evaluate a pre-treatment rule-out defined at 48 h using an RCV-anchored ADAMTS-13 rise (≥35% or ≥10 % points) plus a clinically anchored low-consumption profile, and to quantify associations with ΔSOFA and 28-day mortality, while assessing robustness to heparin and lupus anticoagulant.

Methods

Study design. We conducted a prospective, single-center diagnostic-accuracy study at The Fourth Affiliated Hospital of Soochow University (March 2023–February 2024) focused on Sepsis-3 patients with thrombocytopenia (platelets $<100\times10^9$/L) and either schistocytes ≥1% or LDH >2× ULN, enrolled ≤24 h. All index tests were prespecified and processed blinded to final adjudication. The study addresses differential diagnosis and risk stratification in Sepsis-3 ICU patients with suspected thrombotic microangiopathy, not all comers with TMA. The protocol conformed to the Declaration of Helsinki and was approved by the ethics committee of the Fourth Affiliated Hospital of Soochow University. All participants provided written informed consent prior to any study procedures.

Participants. Eligible patients met Sepsis-3 and had thrombocytopenia (platelets $<100\times10^9$/L) plus either schistocytes ≥1% on an ICSH-compliant smear or LDH >2× the upper limit of normal. Patients were excluded if therapeutic plasma exchange (PEx) occurred before baseline sampling, congenital TTP was known or strongly suspected, advanced hepatic failure precluded interpretation of factors, or pre-analytical quality criteria were not met.

Index tests and sampling schedule. ADAMTS-13

activity (FRETS-VWF73) and VWF:Ag were obtained at 0/24/48/72 h, together with a thrombo-inflammatory panel (Prothrombin Time Test and INR [PT/INR], APTT, fibrinogen, thrombin time [TT], antithrombin III [AT-III], D-dimer, Fibrin degradation products [FDP], anti-factor Xa [anti-Xa], and baseline lupus anticoagulant [LA], alongside CRP, PCT, IL-6, HBP, and SAA at all timepoints). Because standard care proceeded in parallel, we prospectively recorded PEx start times. For dynamic indices and the rule-out, we defined an evaluable pre-treatment window ending at the earliest of 48 h or the time of PEx initiation. Heparin intensity was continuously monitored by anti-Xa assay, and LA testing followed ISTH/ICSH procedures (screen–mix–confirm) with anticoagulant-interference mitigation.

Laboratory methods and quality control. Citrate plasma was obtained via venipuncture or new arterial lines, maintained at 2–8 °C, double-centrifuged, and assayed within manufacturer stability windows. Residual specimens were stored at −80 °C with ≤1 freeze–thaw cycle for batched cytokines. ADAMTS-13 and VWF assays were run with internal controls and external quality assurance. Inter-assay CVs were recorded across runs. Since unfractionated heparin prolongs TT/APTT, TT was interpreted only when anti-Xa <0.10 IU/mL; if anti-Xa ≥0.10 IU/mL, a reptilase time (or high-concentration TT) was obtained to adjudicate fibrinogen function independent of heparin. LA testing used dRVVT and an LA-sensitive APTT in a screen–mix–confirm sequence with heparin neutralization and avoidance or validated removal of DOACs. Schistocytes were quantified per ICSH recommendations by expert morphologists.

Derived indices and operational definitions. We computed the VWF:ADAMTS-13 ratio, ISTH-DIC and SIC scores, and a Coagulation Consumption Index (CCI) (standardized composite of PT/INR, D-dimer/FDP, reverse-signed fibrinogen, platelets, antithrombin III, factor V). The Dynamic ADAMTS-13 Index (DAI) combined the patient-specific slope (from mixed-effects models) and log-AUC(0–72 h), estimated within the pre-treatment window when applicable. The Inflammation Index (II) averaged z-scores of log(IL-6) and log(HBP).

The prespecified main rule-out required a ≥15% relative rise in ADAMTS-13 by 48 h and a low-consumption profile defined by ISTH-DIC < 5, fibrinogen ≥ 2.0 g/L, and antithrombin III ≥ 70%. Because a 15% change can approach analytical/biologic variation, we prespecified an RCV-anchored sensitivity analysis requiring ≥ 35% relative rise or ≥ 10 absolute %-points by 48 h plus the same low-consumption profile. The reference standard classified iTTP per ISTH definitions (severe ADAMTS-13 deficiency and inhibitor/anti-ADAMTS-13 when available, plus clinical response), acknowledging non-independence with index tests.

Outcomes and diagnostic reference standard. The primary outcome was TTP discrimination across a stepwise model ladder: Model 1 (M1) used baseline ADAMTS-13; M2 substituted DAI; M3 added CCI; and M4 added II. The secondary diagnostic outcome was a pragmatic rule-out defined as ≥15% relative rise in ADAMTS-13 by 48 h, together with low CCI, chosen to maximize clinical feasibility; because 15% can fall within analytical/biologic variation, we prespecified a stricter sensitivity analysis requiring ≥35% relative rise or ≥10 absolute %-points by 48 h plus low CCI. Prognostic outcomes included 28-day all-cause mortality and ΔSOFA over 0–72 h. The reference standard for iTTP combined clinical adjudication with severe ADAMTS-13 deficiency (<10%) and, when available, inhibitor/anti-ADAMTS-13 IgG and response to PEx. The non-TTP group comprised sepsis-associated TMA/DIC after exclusion of complement-mediated TMA and STEC-HUS.

Statistical analysis. Group contrasts used Wilcoxon and χ^2/Fisher tests with Hodges–Lehmann differences/odds ratios and FDR control. Repeated measures were modeled with mixed-effects (group, time, interaction; random intercepts), with slopes/AUCs extracted within the pre-treatment window when applicable. The model ladder (M1 baseline ADAMTS-13; M2 DAI; M3 DAI + CCI; M4 DAI + CCI + II) was deliberately parsimonious (≤ 3 predictors in M4). AUROC/AUPRC, Brier score, DeLong comparisons, calibration, and decision-curve analysis were reported. Internal validation used a 1,000-sample bootstrap optimism correction.

For the rule-out, performance in the intent-to-diagnose cohort is descriptive/exploratory. The pre-treatment estimand, restricted to patients untreated through 48 h (censoring at PEx start), is the target for decision-making. Corresponding analyses are emphasized where feasible.

Results. Of 1,274 patients screened, 330 were enrolled within 24 h of ICU admission and completed the index-test schedule, 34 (10.3%) were adjudicated as iTTP, and 296 as non-TTP sepsis-associated TMA/DIC (**Figure 1**). Baseline profiles showed the anticipated divergence between iTTP and sepsis-associated coagulopathy (**Table 1**). iTTP patients were younger (mean difference −11 years, 95% CI −17 to −5, p=0.002, FDR q=0.006) and had more severe thrombocytopenia (18 vs 56×10^9/L, p<0.001, q<0.001), higher LDH (830 vs 610 U/L, p=0.002, q=0.006), and markedly lower

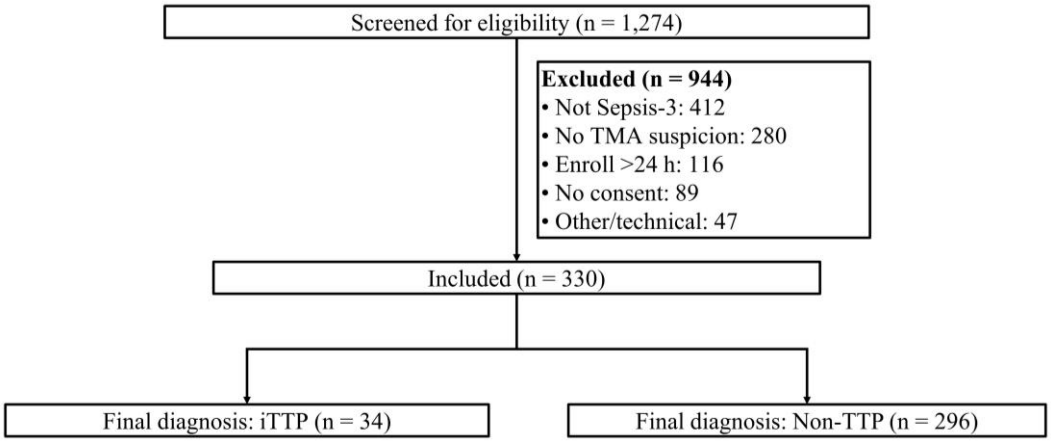

Figure 1. Screening, eligibility, and analysis populations. Of 1,274 patients screened, 330 were included ≤24 h (iTTP = 34; non-TTP = 296).

Table 1. Baseline characteristics by final diagnosis.

Characteristic	iTTP (n=34)	Non-TTP (n=296)	Difference/Effect	p value	FDR q
Age, years (mean ± SD)	49 ± 16	60 ± 14	−11 (95% CI −17 to −5)	0.002	0.006
Female sex, n (%)	20/34 (58.8%)	115/296 (38.9%)	OR 2.3 (1.1–4.8)	0.030	0.070
Platelets, 109/L	18 (12–24)	56 (39–75)	−31 (−38 to −24)	<0.001	<0.001
LDH, U/L	830 (720–950)	610 (520–760)	+190 (+110 to +280)	0.002	0.006
Hemoglobin, g/dL	8.0 (7.3–8.7)	8.8 (7.9–9.7)	−0.8 (−1.3 to −0.3)	0.006	0.012
Schistocytes, %	2.6% (1.8–3.4)	1.5% (1.1–2.1)	+0.9 (+0.5 to +1.3)	<0.001	<0.001
Direct antiglobulin (Coombs) positive, n (%)	1/34 (2.9%)	10/296 (3.4%)	OR 0.8 (0.1–6.5)	0.880	0.890
PT/INR	1.1 (1.0–1.2)	1.4 (1.2–1.6)	−0.3 (−0.4 to −0.2)	<0.001	<0.001
APTT, s	31 (28–34)	38 (33–46)	−7 (−10 to −4)	<0.001	<0.001
Fibrinogen, g/L (Clauss)	3.3 (2.9–3.8)	2.1 (1.5–2.6)	+1.2 (+0.9 to +1.5)	<0.001	<0.001
D-dimer, mg/L FEU	1.8 (1.1–3.0)	4.5 (2.8–6.9)	−2.2 (−3.1 to −1.3)	<0.001	<0.001
Antithrombin III, %	88% (79–97)	62% (51–76)	+22 (+17 to +28)	<0.001	<0.001
ADAMTS-13 activity, %	7% (5–9)	28% (18–38)	−19 (−23 to −15)	<0.001	<0.001
VWF:Ag, %	235% (200–285)	275% (220–340)	−30 (−60 to 0)	0.020	0.040
VWF:ADAMTS-13 ratio	33 (26–41)	12 (8–17)	+19 (+15 to +23)	<0.001	<0.001
ISTH-DIC score	2 (1–3)	5 (3–6)	−3 (−4 to −2)	<0.001	<0.001
SIC score	2 (1–3)	4 (3–5)	−2 (−2 to −1)	<0.001	<0.001
Anti-Xa, IU/mL	0.00 (0.00–0.05)	0.15 (0.00–0.30)	−0.11 (−0.16 to −0.06)	<0.001	<0.001
Heparin exposure, n (%)					
None (<0.10 IU/mL)	24/34 (70.6%)	170/296 (57.4%)	—	0.140	0.200
Prophylactic (0.10–0.30)	8/34 (23.5%)	86/296 (29.1%)	—	—	—
Therapeutic (>0.30)	2/34 (5.9%)	40/296 (13.5%)	—	—	—
Lupus anticoagulant positive, n (%)	3/34 (8.8%)	26/296 (8.8%)	OR 1.0 (0.3–3.4)	0.999	0.999

ADAMTS-13 activity (7% vs 28%, p<0.001, q<0.001), resulting in a substantially higher VWF:ADAMTS-13 ratio (33 vs 12, p<0.001, q<0.001). Non-TTP patients exhibited the DIC phenotype with higher PT/INR and APTT, lower fibrinogen and AT-III, higher D-dimer, and higher ISTH-DIC and SIC scores (all p<0.001, q<0.001), consistent with consumption coagulopathy. Heparin exposure by anti-Xa categories was more frequent in non-TTP, while LA prevalence was identical (8.8%, p=0.999).

Longitudinal modeling demonstrated distinct kinetics by diagnosis (**Figure 2**). ADAMTS-13 activity in iTTP remained severely depressed with minimal change from baseline to 72 h (mean 7% [95% CI 6–8] to 8% [7–9]), whereas non-TTP recovered from 28% (26–30) to 41% (39–43), yielding a significant group×time interaction

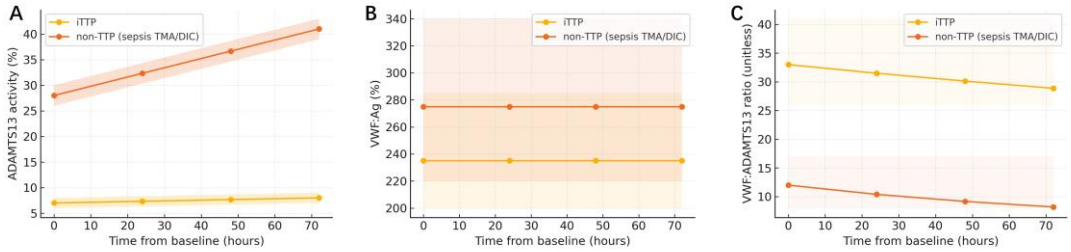

Figure 2. A), ADAMTS-13 activity trajectories (0–72 h) with 95% CIs; iTTP remains severely low while non-TTP shows recovery. **B),** VWF: Ag trajectories (0–72 h). **C),** VWF: ADAMTS13 ratio: persistently high in iTTP; declining in non-TTP. Mixed-effects estimates are overlaid with pointwise 95% CIs.

Table 2. Diagnostic model performance.

Metric	M1	M2	M3	M4
AUROC (95% CI)	0.78 (0.70–0.86)	0.93 (0.88–0.97)	0.95 (0.92–0.98)	0.96 (0.93–0.99)
ΔAUROC vs previous (p, FDR q)	—	+0.15 (p<0.001, q<0.001)	+0.02 (p=0.021, q=0.032)	+0.01 (p=0.048, q=0.048)
AUPRC	0.42	0.66	0.72	0.75
Brier score	0.098	0.061	0.058	0.057
Calibration intercept (95% CI)	−0.12 (−0.29 to 0.04)	−0.02 (−0.12 to 0.08)	−0.01 (−0.10 to 0.07)	0.00 (−0.09 to 0.08)
Calibration slope (95% CI)	0.82 (0.66–0.98)	0.98 (0.86–1.10)	1.01 (0.90–1.11)	1.02 (0.92–1.12)
Net benefit at pt=10%	0.055	0.137	0.145	0.149
Validation AUROC (optimism-corrected)	0.77	0.92	0.94	0.95
Validation Brier	0.100	0.064	0.060	0.059
EPP (predictors)	34.0 (1)	34.0 (1)	17.0 (2)	11.3 (3)

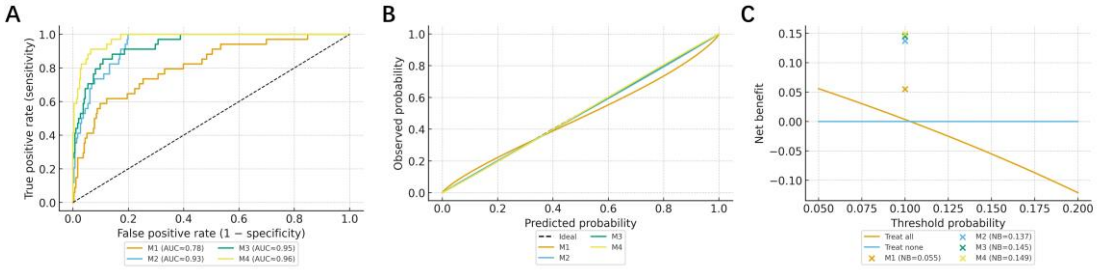

Figure 3. A), ROC curves for M1–M4. Diagonal indicates no-information line. **B),** Calibration lines using reported intercepts/slopes for M1–M4; dashed line is perfect calibration. **C),** Decision-curve analysis across 5–20% thresholds; net benefit highest for M4.

(p<0.001). VWF:Ag was high in both groups but modestly higher in non-TTP (group effect p=0.014), and the VWF:ADAMTS-13 ratio declined over time in non-TTP while remaining markedly elevated in iTTP (group×time p<0.001) (**Figure 2**).

Within Sepsis-3 ICU patients with thrombocytopenia and microangiopathic hemolysis features, discrimination improved stepwise from M1 (baseline ADAMTS-13, AUROC 0.78 [0.70–0.86]) to M2 (DAI, 0.93 [0.88–0.97], Δ=0.15 vs M1, p<0.001), with smaller incremental gains for M3 (0.95 [0.92–0.98], Δ=0.02, p=0.021) and M4 (0.96 [0.93–0.99], Δ=0.01, p=0.048), and acceptable calibration and decision-curve net benefit (**Table 2, Figure 3**). As DAI includes dynamic information that can be influenced by post-baseline care, we estimated slopes/AUCs within the pre-treatment window where data permitted. Where not, dynamic effects are interpreted as monitoring/prognostic signals rather than pre-treatment diagnostic information. Internal validity was assessed with bootstrap optimism correction (1,000 resamples).

Using the prespecified main rule-out (≥ 15% ADAMTS-13 rise by 48 h plus low CCI), the intent-to-diagnose analysis yielded 97.1% sensitivity, 86.1% specificity, and 99.6% NPV (**Table 3**). In a prespecified RCV-anchored sensitivity analysis (≥ 35% relative rise or ≥ 10-point rise by 48 h plus low consumption), sensitivity and NPV were 100.0% with 76.0% specificity (**Table 3**). Because some high-probability iTTP patients initiated PEx before 48 h, these care-embedded estimates cannot be interpreted as pre-treatment diagnostic performance. Pre-treatment analyses are prioritized for decision-making and are presented where data permit. Subgroup patterns were

Table 3. Rule-out strategy performance and sensitivity analyses.
A. Sensitivity analyses for alternative "rise" thresholds (still requiring low CCI).

Threshold	TP	FP	TN	FN	Sens, % (95% CI)	Spec, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, %
≥20%	33	48	248	1	97.1% (85.1–99.5)	83.8% (79.2–87.5)	40.7% (30.7–51.6)	99.6% (97.8–99.9)	85.2%
≥30%	34	65	231	0	100.0% (89.8–100.0)	78.0% (73.0–82.4)	34.3% (25.7–44.1)	100.0% (98.4–100.0)	80.3%
≥35% or ≥10 %-points	34	71	225	0	100.0% (89.8–100.0)	76.0% (70.8–80.5)	32.4% (24.2–41.8)	100.0% (98.3–100.0)	78.5%

B. Subgroup performance (main definition: ≥15% + low CCI).

Subgroup	n (iTTP / non-TTP)	Sens, % (95% CI)	Spec, % (95% CI)	PPV, %	NPV, %
Anti-Xa: none (<0.10 IU/mL)	24/170	95.8% (79.8–99.3)	90.0% (84.6–93.7)	57.5%	99.4%
Anti-Xa: prophylactic (0.10–0.30)	8/86	100.0% (67.6–100.0)	83.7% (74.5–90.0)	36.4%	100.0%
Anti-Xa: therapeutic (>0.30)	2/40	100.0% (34.2–100.0)	75.0% (59.8–85.8)	16.7%	100.0%
LA positive	3/30	100.0% (43.8–100.0)	80.0% (62.7–90.5)	33.3%	100.0%
LA negative	31/266	96.8% (83.8–99.4)	86.8% (82.3–90.4)	46.2%	99.6%

C. Main analysis (N=330; iTTP = 34; non-TTP = 296).

Metric	Value (95% CI)
TP/FP/TN/FN	33/41/255/1
Sensitivity, %	97.1% (85.1–99.5)
Specificity, %	86.1% (81.7–89.6)
PPV, %	44.6% (33.8–55.9)
NPV, %	99.6% (97.8–99.9)
Accuracy, %	87.3% (83.2–90.4)
LR+/LR−	7.01/0.03

consistent across anti-Xa strata and lupus anticoagulant status (**Table 3**).

At the 72-h landmark, the high-risk phenotype, defined a priori as ADAMTS-13 <10% at 72 h together with IL-6 and/or HBP at 72 h ≥ the 75th percentile of the cohort at 72 h, was associated with worse 28-day survival than all others (29.2% vs 15.2% mortality, log-rank p=0.006) (**Figure 4**). In Cox models adjusted for age, sex, and baseline SOFA, the high-risk phenotype conferred an HR of 2.6 (95% CI 1.3–5.2, p=0.007), proportional hazards assumptions were not violated (global Schoenfeld p=0.22), and mixed-effects models showed greater SOFA worsening from 0–72 h in the high-risk group (p=0.002).

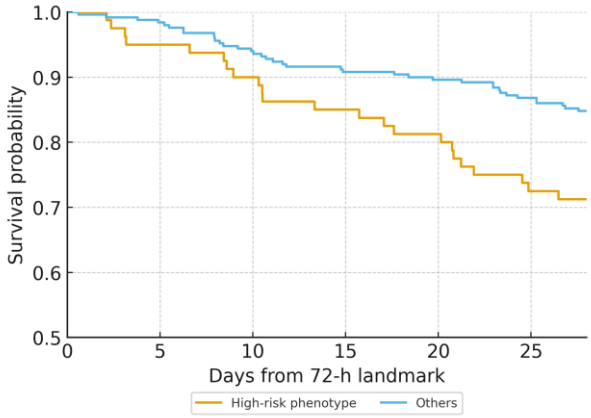

Figure 4. Kaplan–Meier survival from the 72-h landmark comparing high-risk phenotype vs others; annotation shows adjusted HR and p-values; numbers at risk provided.

Discussion. In this Sepsis-3 ICU cohort with TMA features, moving from a single baseline ADAMTS-13 measure to dynamic profiling produced a substantial gain in iTTP discrimination, with incremental improvements after adding a parsimonious coagulation index and a two-analyte inflammation index, while maintaining calibration and net benefit. The pragmatic rule-out achieved 97.1% sensitivity and 99.6% NPV in the care-embedded analysis, and an RCV-anchored threshold (≥35% or ≥10%, points) preserved 100% sensitivity/NPV at the expected cost to specificity, supporting a safety-first option when the consequences of missed iTTP are high. A 72-h high-risk phenotype was associated with higher 28-day mortality and greater SOFA worsening, underscoring the biological plausibility that early enzymatic and endothelial-inflammatory signals capture clinically meaningful risk.

In our ICU cohort, iTTP showed the expected pathognomonic pattern, severe and persistent ADAMTS-13 deficiency with minimal 72-h recovery, whereas sepsis-associated thrombotic microangiopathy

or disseminated intravascular coagulation exhibited partial suppression with progressive ADAMTS-13 recovery alongside a sustained VWF surge, yielding a markedly higher and more persistent VWF:ADAMTS-13 ratio in iTTP. These trajectories align with guideline definitions that anchor iTTP to ADAMTS-13 activity <10% and inhibitory autoantibodies, whereas sepsis is characterized by endothelial activation and consumptive coagulopathy rather than isolated ADAMTS-13 loss.[21,22] Experimental and clinical studies in sepsis further show that VWF release and relative ADAMTS-13 deficiency track organ dysfunction and mortality, supporting the biologic coherence of our dynamic-index approach and the prognostic salience of the ratio.[23-25] The inflammatory context, IL-6, HBP, and SAA explain why our high-risk phenotype was enriched for death and worsening SOFA.[26-28] Finally, our smear threshold aligns with ICSH recommendations across TMAs and supports the initial suspicion of microangiopathy.[29]

The stepwise model gains we observed, moving from baseline ADAMTS-13 (M1) to dynamic ADAMTS-13 (M2), then adding a Coagulation Consumption Index (M3) and a parsimonious Inflammation Index (M4), support embedding serial ADAMTS-13 plus a focused panel early in ICU workflows to sharpen iTTP discrimination and prevent overuse of plasma exchange. Importantly, guideline-concordant care requires not delaying urgent iTTP therapy in high-probability presentations. Dynamic testing primarily refines decisions in sepsis-dominant, low-to-intermediate probability cases.[21,22] Our pragmatic rule-out delivered 97.1% sensitivity and 99.6% NPV with robustness across anti-Xa strata and LA status, complementing Sepsis-3 definitions and ISTH DIC/SIC frameworks for coagulopathy phenotyping.[30-32] Implementation should include systematic anti-Xa monitoring to quantify heparin exposure, interpret thrombin time only when anti-Xa is low or confirm with reptilase time, and follow ISTH SSC procedures for LA testing.[33-35] When ADAMTS-13 results are pending, PLASMIC remains useful for pre-test triage but should be contextualized against dynamic enzyme data and the focused panel.[36,37] Serial ADAMTS-13 with a focused coagulation/inflammation panel can be embedded early in ICU workflows to sharpen iTTP discrimination and potentially reduce unnecessary plasma exchange, while flagging a high-risk phenotype for intensified care. Broad deployment of a serial ADAMTS-13 strategy depends first on establishing an institutional pathway for rapid ADAMTS-13 activity reporting for Sepsis-3 ICU patients with TMA features. Where this prerequisite is not yet met, the approach we tested can be implemented in stages. 1) Obtain ADAMTS-13 at presentation (0 h) and repeat at 48 h, and apply the prespecified rule-out using routine coagulation markers (ISTH-DIC <5, fibrinogen ≥2.0 g/L, AT-III ≥70%) together with a ≥15% rise in ADAMTS-13 (or the prespecified RCV-anchored rise as a safety-first option). This tier intentionally avoids complex indices and is designed to be feasible for early adoption. 2), Where serial testing is established, incorporate dynamic ADAMTS-13 information and coagulation consumption signals to refine classification in sepsis-dominant, low-to-intermediate probability presentations, while recognizing that high-probability iTTP remains a "treat-now" diagnosis. 3) Add a parsimonious inflammation signal to support risk phenotyping and prognosis. In settings with informatics support, trajectories/indices can be automatically computed within the laboratory information system or EHR, minimizing additional clinician burden.

Limitations of this study include the single-center setting and a modest iTTP case count, which limited power to detect small incremental gains; potential assay and turnaround constraints that may affect workflow generalizability; and residual confounding despite anti-Xa/LA adjustments. In centers without same-day ADAMTS-13 availability, early decisions will still rely on clinical probability and empiric therapy. Therefore, implementation studies focusing on time-to-result and laboratory workflows are a prerequisite to generalizability. Although we used a 72-h landmark to avoid immortal-time bias in prognosis analyses, this design can exclude very early deaths and will require confirmation in broader populations. Additionally, a ≥15% rise in ADAMTS-13 may reflect analytical/biologic variation, which we addressed by stricter sensitivity thresholds, but that should be externally validated. Future work should prioritize multicenter external validation with assay-specific recalibration where needed, build real-time/near-patient assay pathways and decision-support to operationalize serial ADAMTS-13 plus a focused panel, and conduct health-economic studies quantifying plasma-exchange averted, time-to-treatment, and safety.

Taken together, these findings support embedding dynamic ADAMTS-13, along with a focused coagulation/inflammation panel, into early ICU workflows to enhance diagnosis and risk stratification across sepsis-associated TMAs, enable a pragmatic rule-out pathway that may reduce unnecessary plasma exchange, and inform targeted escalation for high-risk patients, pending multicenter implementation and economic evaluation.

Ethics approval and consent to participate. The protocol conformed to the Declaration of Helsinki and was approved by the ethics committee of the Fourth Affiliated Hospital of Soochow University. All participants provided written informed consent prior to any study procedures.

Data availability statement. Data sets generated during the current study are available from the corresponding author on reasonable request.

Author Contribution Statement. The authors confirm contribution to the paper as follows: study conception and design: B.Y.; data collection: Y.L., F.L., B.J., W.S., H.S., Y.X.; analysis and interpretation of results: Y.L., F.L., B.J., W.S., H.S., Y.X.; draft manuscript preparation: Y.L., F.L., B.J., W.S., H.S., Y.X., B.Y. All authors reviewed the results and approved the final version of the manuscript.

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