ORIGINAL ARTICLE

ADAMTS-13 Behavior in Thrombocytopenia of Infectious Origin in ICU Patients

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Abstract

Introduction: Thrombocytopenia is a common hematological abnormality in intensive care unit (ICU) patients, with varying incidence across populations. A disintegrin-like metalloproteinase and thrombospondin-like activity motif 13 (ADAMTS-13), a plasma serine protease, plays a crucial role in modulating von Willebrand factor (vWF) activity by cleaving its ultra-large (UL) multimers and preventing excess platelet aggregation. This study aimed to evaluate the association between ADAMTS-13 levels, viral and non-viral (NV) infections, and thrombocytopenia severity.

Materials and methods: This Prospective observational study included adult ICU patients with thrombocytopenia, categorized into viral and non-viral groups. Thrombocytopenia severity was assessed by absolute platelet count on diagnosis day. Statistical analyses evaluated correlations between ADAMTS-13 levels, thrombocytopenia severity, and clinical outcomes, including bleeding episodes, transfusion needs, and overall patient outcomes.

Results: Among 72 patients (30 viral, 42 non-viral), lower ADAMTS-13 activity correlated significantly with thrombocytopenia severity in both groups ($p < 0.05$), with a greater deficiency observed in NV cases. A disintegrin-like metalloproteinase and thrombospondin-like activity motif 13 levels were associated with bleeding episodes, transfusion requirements, and thrombocytopenia progression in both groups but did not predict increased transfusion needs despite lower platelet counts.

Conclusion: This study highlights an association between reduced ADAMTS-13 activity, infection type, and thrombocytopenia severity, especially in NV infections. A disintegrin-like metalloproteinase and thrombospondin-like activity motif 13 (ADAMTS-13) depletion and increased vWF activity may contribute to infection-related thrombocytopenia pathogenesis. These findings suggest that ADAMTS-13 levels could aid in assessing thrombocytopenia severity and prognosis, informing early management strategies and transfusion guidelines.

Clinical significance: This study found that low ADAMTS-13 activity is associated with higher disease severity in both viral and non-viral infections, particularly in NV cases. While thrombocytopenia correlated with reduced ADAMTS-13 activity, it did not lead to increased platelet transfusions.

Keywords: A disintegrin-like metalloproteinase and thrombospondin-like activity motif 13, ICU severity, Non-viral infections, Thrombocytopenia, Prognosis, Viral infections.

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Highlights

Thrombocytopenia is a frequent and severe hematological condition in intensive care unit (ICU) patients, with incidence rates ranging widely based on ICU type and patient demographics. This study investigates the patterns of A disintegrin-like metalloproteinase and thrombospondin-like activity motif 13 (ADAMTS-13) levels in viral and non-viral thrombocytopenia, examining correlations with disease progression, severity, and clinical outcomes.

Introduction

With an incidence ranging from 13 to 65%, thrombocytopenia is one of the most common hematological disorders seen in the intensive care unit (ICU). The prevalence differs among various intensive care units and patient demographics.[1,2] Compared to pediatric and surgical departments, the incidence is higher in adult and medical ICUs.[1,2] A platelet count of less than 1,50,000/µL or a decrease of >50% from the baseline value is considered thrombocytopenia. Different studies use different criteria for identifying thrombocytopenia; some define it as a count of less than 1,00,000/µL.[2]

A serine protease that circulates in plasma and is mainly produced by liver and endothelial cells is called ADAMTS-13.[3,4] von-Willebrand factor (vWF) is stored in alpha granules of platelets

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and Weibel-Palade bodies found in endothelial cells. It is released as ultra-large (UL) multimers by the active endothelium.[5] By attaching to the A2 site of vWF and controlling its activity, ADAMTS-13 can cleave UL polymers of vWF (ULvWF) in circulation into small monomers.[4–6]

A key factor in the pathophysiology of systemic infections is endothelial dysfunction. Thrombotic thrombocytopenic purpura (TTP) disseminated intravascular coagulation, systemic lupus erythematosus, carcinomas, decompensated liver cirrhosis, and a few additional illnesses are anecdotally linked to ADAMTS-13 deficiency. It has been hypothesized that changes in the Microthrombi development, organ failure, and platelet sequestration in circulation are caused by elevated levels of ULvWF and ADAMTS-13.[7,8]

Systemic infections (viral and non-viral) are linked to heightened ADAMTS-13 depletions, which in turn causes a rise in vWF activity (due to elevated ULvWF levels).[9] We aimed to investigate the relationship between viral and non-viral thrombocytopenia and its correlation with disease prognosis and outcomes.

Materials and Methods

Study Design

The duration of this prospective observational study was one year, from December 2019 to December 2020 at Virinchi Hospital, Hyderabad, and this study was approved by the Institutional Ethics Committee (IEC).

Patient Selection

All adults (aged >18 years) who presented with thrombocytopenia of suspected or proven infectious etiology (The coulter plate count is less than 1,50,000/mm^3) were included in the study. The following were the criteria for exclusion: (A) Individuals having a history of thrombocytopenia produced by heparin (HIT), Idiopathic thrombocytopenic purpura (ITP), or TTP, (B) Patients diagnosed with any hematological condition, (C) Individuals who have been transfused in any way between the commencement of their fever and their presentation, (D) Individuals who test positive for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV), (E) Patients with collagen vascular disease, any autoimmune illness, cancer, either past or current, or chronic liver disease, (F) Patients under antiplatelet or anticoagulants therapy.

Screening for suspected infection was performed based on signs of systemic inflammations (according to the standards set by the Consensus Conference Committee of the Society of Critical Care Medicine). At least three of the four systemic inflammatory response criteria were satisfied by the chosen patients:

- The body temperature is either below 36°C (hypothermia) or >38.5° C (hyperthermia).
- Tachycardia that exceeds the age-appropriate normal by more than two standard deviations.
- A mean respiratory rate that is over two standard deviations higher than the average for the age-group.
- The presence of a confirmed or suspected infection caused the total leukocyte count (TLC) to rise or fall with age.

Case Definition and Ascertainment

"Probable infection-related thrombocytopenia" was the criteria utilized to pick the first cases. It was included based on systemic inflammatory response syndrome (SIRS) criteria, as mentioned below. Patients who tested positive for blood/body fluid culture or gram staining (+/–) or viral markers serology (Dengue-NS1/IgM, COVID-19 RT- PCR/rapid Ag+) were included in the study.

Study Objectives

- To correlate the severity of thrombocytopenia with the level of ADAMTS-13 on the day of diagnosis of thrombocytopenia between the two groups.
- To correlate the initial ADAMTS-13 levels and incidence of bleeding episodes, transfusion requirement, progression of grade of thrombocytopenia and outcome between the two groups.

Data Collection

The blood samples of the individuals who tested positive for viral/non-viral infections were processed for ADAMTS-13 assay at presentation. Details on demographics and clinical parameters were collected. The patients were assessed during the follow-up to evaluate,

- The sequential organ failure assessment [SOFA-(*H*)] and acute physiology and chronic health evaluation (APACHE-II) scores at admission.
- If transfusion support is required (packed red blood cells/ platelets as platelet concentrate/fresh frozen plasma/ cryoprecipitate-worsening/improving-during ICU/hospital stay).
- The progression of thrombocytopenia (worsening/improving during ICU/Hospital stay).
- The outcomes: Mortality, discharged/cured, discharge against medical advice (DAMA).

ADAMTS-13 Assay

Venous blood (3 mL) was extracted from patients using the aseptic technique in tubes that contained 3.2% sodium citrate, an anticoagulant. After the samples were centrifuged, platelet-poor plasma was recovered. Prior to analysis, the specimens were tagged and kept at –80°C. A commercially available chromogenic enzyme-linked immunosorbent test (ELISA) (TECHNOZYM® ADAMTS-13 activity, Technoclone, Vienna, Austria) was used to measure the levels of ADAMTS-13 antigen. An ELISA reader (BIORAD PR S100) operating at 450 nm was used for all tests and readings. According to the manufacturer, ADAMTS-13 activity <0.40 IU/mL (1 IU/mL = 100%) was deemed inadequate. Patients with sufficient antigen levels were contrasted with the group with impaired levels.

Sample Size Estimation

Although the prevalence of thrombocytopenia in our intensive care unit was 25% for the previous 2 years, the sample size was determined using the total incidence of the condition. Thus, 72 was the projected sample size (*n*). The study's power was 80%.

Statistical Analysis

Whereas categorical data were represented by numbers and frequencies (%), continuous variables were represented by mean ± SD. Analysis of variance (ANOVA) and the student's *t*-test were used to examine the continuous variables. The categorical variables were compared using the Chi-squared (χ^2) test. Correlations between two continuous variables were assessed using Pearson's test. When the two-tailed *p*-value was less than 0.05, statistical significance was determined. All analyses were conducted using IBM's SPSS program, version 22.

Results

A total of 72 patients were involved in the study and were grouped as viral ($n = 30$) and non-viral (NV) ($n = 42$) based on their infectious nature. About 54 patients (75%) were males and were predominant in both groups. The distribution of age and gender did not significantly differ between the two groups. For both groups, the ADAMTS-13 activity assay was conducted. The viral group's mean ADAMTS-13 levels (37.7 ± 24.2) were substantially greater than those of the NV group (26.14 ± 16.05) ($p < 0.05$) (Table 1).

The mean group's ADAMTS-13 levels were shown to be statistically negligible when compared to the grades of severity of thrombocytopenia (Table 2).

The relationship between the ADAMTS-13 assay and APACHE-II and SOFA-(*H*) scoring systems measured on day 1 in group showed a negative correlation ($r = -0.408$ and -0.178). In group V, APACHE-II scores and ADAMTS-13 levels were significantly correlated ($p < 0.05$), but not significantly correlated with SOFA-(*H*) scores ($p > 0.05$). The correlation coefficients for group NV were $r = -0.257$ and -0.311. The ADAMTS-13 levels showed a significant association with SOFA-(*H*) scores ($p < 0.05$) but insignificant with APACHE-II scores ($p > 0.05$) (Table 3).

The mean ADAMTS-13 assay of the two groups with bleeding manifestations was insignificant ($p = 0.205$ and $p = 0.250$). Additionally, the need for transfusions was statistically insignificant ($p = 0.097$ and $p = 0.210$) (Table 4).

In group V, the mean ADAMTS-13 level was significantly higher in the survivors compared to the deceased ($p = 0.04$), while group NV's results showed no discernible difference ($p = 0.19$) (Table 5).

Group NV's thrombocytopenia progression showed a notable improvement ($p = 0.007$) whereas it was statistically insignificant in group V ($p = 0.14$) (Table 6).

Table 1: Patient demographics and ADAMTS-13 activity assay levels (sub-group analysis between viral and non-viral groups)

S. No	*Parameter*	*Viral (n = 30)*	*Non-viral (n = 42)*	*p-value*
1.	Age, (mean ± SD)	51.13 ± 14.77	57.9 ± 15.9	0.072
2.	Sex, *n* (%)			
	• Male	22 (73.3)	32 (76.2)	0.78
	• Female	8 (26.7)	10 (23.8)	
3.	ADAMTS-13 activity assay levels	37.7 ± 24.2	26.14 ± 16.05	0.017*

The *p*-value with *indicates that the result is statistically significant, meaning the observed difference or correlation is unlikely to have occurred by random chance.

Table 2: Comparison of the ADAMTS-13 values with severity of thrombocytopenia with infectious nature

	Grade of thrombocytopenia			
Parameter	*Mild*	*Moderate*	*Severe*	*p-value*
ADAMTS-13				
• Viral	41.88 ± 12.18	31.58 ± 21.71	41 ± 19.8	0.54
• Non-viral	32.8 ± 16.2	23.19 + 15.28	18 ± 18.38	0.15

Table 3: Correlation of ADAMTS-13 assay values with APACHE-II and SOFA-(*H*) scores in both groups

Infection type	*ADAMTS-13 activity assay*	*APACHE-II*	*SOFA-(H)*
Viral ($n = 30$)	Pearson correlation	–0.408*	–0.178
	p-value	0.025	0.347
Non-viral ($n = 42$)	Pearson correlation	–0.257	–0.311*
	p-value	0.100	0.045

The *p*-value with *indicates that the result is statistically significant, meaning the observed difference or correlation is unlikely to have occurred by random chance.

Table 4: ADAMTS-13 assay values in relation to bleeding complications and transfusion requirements in both groups

S. No	*Parameter*	*Present*	*Absent*	*p-value*
1.	Bleeding complications			
	• Viral	27.42 ± 20.93	22.07 ± 13.02	0.20
	• Non-viral	40.8 ± 24.65	28.17 ± 17.07	0.25
2.	Transfusion requirement			
	• Viral	26.5 ± 22.77	40.5 ± 24.17	0.21
	• Non-viral	20 ± 11.4	28.9 ± 17.2	0.09

Table 5: Subgroup analysis of patient outcomes in both groups in relation with ADAMTS-13 assay values

	Outcome		
Parameter	*Survival*	*Mortality*	*p-value*
ADAMTS-13			
• Viral	43.57 ± 24.5	22.17 ± 14.35	0.04
• Non-viral	28.84 ± 16.85	28.17 ± 17.07	0.19

Table 6: Comparison of the progression of thrombocytopenia levels in both groups by ADAMTS-13 assay levels

	Progression of thrombocytopenia (POT)		
Parameter	*Improved*	*Worsened*	*p-value*
ADAMTS-13			
Viral	41.6 ± 24.06	27 ± 22.55	0.14
Non-viral	30.75 ± 15.72	16.92 ± 12.71	0.007*

The *p*-value with *indicates that the result is statistically significant, meaning the observed difference or correlation is unlikely to have occurred by random chance.

Discussion

Even though our study comprises a smaller sample size, this is the first study to correlate ADAMTS-13 in adult patients. levels between viral (group-V) and NV (group-NV) infection groups and associated with the severity of thrombocytopenia. In this study, we analyzed ADAMTS-13 levels with parameters such as APACHE-II/SOFA-(*H*) scoring systems, bleeding manifestations, transfusion requirement, progression of thrombocytopenia and clinical outcomes (Fig. 1).

A total of 72 patients presented with proven or suspected infectious etiology (viral/non-viral) as a cause of thrombocytopenia were involved in this study. Among them, 30 cases were viral infections such as dengue (n = 10), hepatitis-A (n = 2) and COVID-19 (n = 18). The remaining 42 cases had microbiological documentation of sepsis/septic shock and others like pneumonia (n = 18), pyelonephritis (n = 11) and catheter-related infections (n = 13). *Pseudomonas aeruginosa* (n = 7), *Streptococcus pneumonia* (n = 5), *Streptococcus species* (n = 5), *Staphylococcus aureus* (n = 4), and *miscellaneous* (n = 7) pathogens, including *Klebsiella pneumonia* (n = 2), *Acinetobacter baumannii* (n = 1), and no growth media (n = 6) (only gramme stain evidence), were among the pathogens involved.

Trends of ADAMTS-13 Levels

A disintegrin-like metalloproteinase and thrombospondin-like activity motif 13 activity was shown to be decreased in both groups (group V and NV). The NV group experienced a substantial decrease in comparison to the viral group (p = 0.017). In a Swedish study conducted.[10] About 40 sepsis cases were compared with 40 identically aged and gendered healthy controls. They found that ADAMTS-13 had much lower levels in sepsis cases than controls. They have also shown in a study that sepsis and low ADAMTS-13 levels are significantly correlated.[11] There was a similar reduction in ADAMTS-13 levels in viral infections like Dengue and COVID-19 reported in two studies.[12,13]

We have compared disease severity with APACHE-II and SOFA-(*H*) scoring systems. It showed a significant negative correlation with ADAMTS-13 levels (p = 0.045) among the scores in group NV. A study also showed a similar correlation in septic shock patients, but these results contrasted those who showed no correlation between the two measures.[14,15] Patients with higher mean ADAMTS-13 levels in our study had fewer bleeding manifestations and transfusion requirements, but were not statistically significant in comparison between both groups. Patients with a declining platelet count trend had significantly lower mean ADAMTS-13 levels compared to those who showed an improving trend in the group of NV (p = 0.007). Within the population under investigation, ADAMTS-13 levels showed a declining trend with severity of thrombocytopenia between the groups, but were statistically insignificant. Two French studies also reported similar results of thrombocytopenia in sepsis patients.[15,16] This might be due to low ADAMTS-13 levels, increasing the ULvWF secondary to infection and host inflammation.

We compared the ADAMTS-13 levels with patient outcomes in both groups. In group V, the mean of the discharged group's ADAMTS-13 activity was noticeably greater than the patient's deceased (i.e., dead) (group V, p = 0.040). It was reported that decreased ADAMTS-13 activity is an important mortality risk factor in the Saudi population.[16] The current study could not establish a statistically significant predictive value for mortality with changes in ADAMTS-13 activity, unlike the other studies which have established a positive correlation.[14,17]

Limitations

The sample size was very small, as it was calculated according to the total number of thrombocytopenia patients admitted to MICU in our hospital. This might be the reason for less/no statistical correlation in comparison between both groups. A comparison of ADAMTS-13 activity with other causes of thrombocytopenia-associated

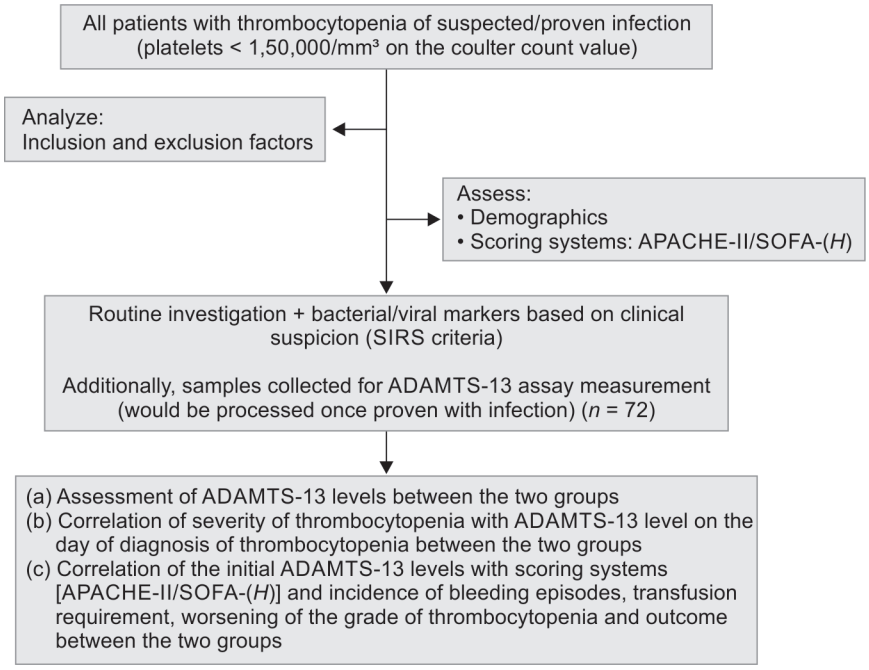

Fig. 1: Study algorithm

infections was not carried out in our study. A more comprehensive study comparing and correlating all causes of thrombocytopenia including lower ADAMTS-13 activity, with a larger sample size is needed.

Conclusion

In this study, lower ADAMTS-13 activity correlated positively with both viral and non-viral infections' disease severity. However, the degree of deficiency was more pronounced in NV infections. The correlation between APACHE-II scores, SOFA scores and ADAMTS-13 activity was less prominent in viral infections. Generally, a dropping platelet count with resultant clinically significant bleeding episodes usually triggers a platelet transfusion. In this study, the transfusion requirements did not differ among patients with normal and lower ADAMTS-13 activity. Therefore, it is likely that while ADAMTS-13 activity correlates with disease severity, including the degree of thrombocytopenia, the activity parse does not result in more frequent platelet transfusions.

Clinical Significance

In this study, we found that both viral and non-viral infections are linked to increased illness severity when ADAMTS-13 activity is low, particularly in NV cases. While thrombocytopenia correlated with reduced ADAMTS-13 activity, it did not lead to increased platelet transfusions. Thus, ADAMTS-13 activity impacts severity but not transfusion frequency.

Authors Contributions

VDKG: Methodology, resources, project administration, writing-original draft; SS: Conceptualization, supervision; NA: Validation; RR: Writing-review and editing; MN: Investigation software.

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