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Original Article

Retrospective analysis of von willebrand factor and microthrombus formation in septic shock: associations with TTP-like syndrome and sepsis-induced coagulopathy

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Abstract: Objective: Sepsis shock is characterized by endothelial damage and coagulation abnormalities. However, the relationship between von Willebrand factor (vWF), microthrombosis, and various clinical phenotypes such as thrombotic thrombocytopenic purpura (TTP) and sepsis-induced coagulopathy (SIC) has not been fully elucidated. Methods: This retrospective study enrolled 147 patients with septic shock admitted to the ICU in 2023, all of whom underwent vWF antigen testing. The patients were divided into three groups: the TTP-like group, the SIC group, and the control group. Platelet (PLT) indices, vWF levels, SOFA subscores, incidence of organ dysfunction, and 28-day mortality were compared. Correlation analyses and non-parametric tests were performed. Results: The SIC group showed significantly lower nadir PLT counts and higher PLT decline rates compared with the TTP-like and control groups ($P < 0.05$). vWF levels were elevated across all groups and were significantly higher in the TTP-like and SIC groups versus controls ($P < 0.05$). vWF levels correlated negatively with nadir PLT ($r = -0.20$, $P = 0.018$). Both TTP-like syndrome and SIC were associated with high rates of MODS; however, hepatic and renal injury, number of dysfunctional organs, and 28-day mortality were significantly worse in the SIC group ($P < 0.05$). Conclusion: Elevated vWF is associated with diffuse microthrombus formation in septic shock and may serve as a marker of endothelial injury. While both TTP-like syndrome and SIC contribute to organ dysfunction, SIC is associated with more severe organ injury and higher mortality. Prospective studies are needed to validate these findings.

Keywords: Septic shock, von Willebrand factor, TTP-like syndrome, sepsis-induced coagulopathy

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. It remains a major global health burden and is associated with high morbidity and mortality in the intensive care unit (ICU) setting [2, 3]. Among the many pathophysiologic disturbances observed in sepsis, sepsis-induced coagulopathy (SIC) has become recognized as a major contributor to clinical deterioration and an important factor in the development of multiple organ dysfunction syndrome (MODS) [4]. While extensive research has characterized the inflammatory cascade, immune dysregulation, and complement activation mechanisms associated with sepsis, the pathways underlying sepsis-related coagulation dysfunction remain incompletely elucidated. The prevailing explanation primarily attributes this to tissue factor (TF)-driven exogenous coagulation cascade activation, culminating in fibrin clot formation [5]. The framework historically supports early use of anticoagu-

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lants such as heparin or low molecular weight heparin; however, large-scale clinical studies have not confirmed that it reduces mortality, suggesting that other thrombosis mechanisms may be involved, which are not yet well understood [6].

In clinical practice, a significant proportion of sepsis patients develop thrombocytopenia and multiple organ dysfunction syndrome (MODS) without reaching the diagnostic threshold for systemic inflammatory response (SIR), making coagulation function assessment particularly challenging. Emerging evidence indicates that excessive complement activation in sepsis may induce diffuse endothelial damage through the formation of membrane attack complexes (MAC) [7, 8]. Endothelial damage triggers a destructive 'endothelial response', characterized by the sudden release of an abnormally large quantity of ultra-large vascular hemophilia factor (ULVWF) from Weber-Palade bodies. These polymeric fragments strongly interact with platelets, increasing platelet consumption, promoting widespread microvascular thrombosis, impairing perfusion, and ultimately leading to multiple organ dysfunction syndrome (MODS) [9]. Although this hematologic presentation may resemble that of thrombotic thrombocytopenic purpura (TTP), the underlying biological mechanisms are fundamentally different; hence, the entity is described as a "TTP-like syndrome" [10].

Von Willebrand factor (vWF), a key biomarker of endothelial damage, shows sustained elevation in COVID-19, ARDS, and sepsis patients, with higher vWF levels correlating with more severe microthrombosis and organ dysfunction [11-13]. Despite these findings, systematic research on endothelium-damaged microthrombosis in septic shock remains limited. Direct comparisons between patients exhibiting TTP-like features and those meeting septic shock diagnostic criteria are particularly scarce, leaving gaps in our understanding of their distinct clinical characteristics, thrombotic behavior, and prognostic patterns.

In view of these uncertainties, this study aims to describe the characteristics of intravascular thrombosis in septic shock patients with TTP-like syndrome or SIC, and compare their incidence rates, the severity of organ dysfunction, and 28-day mortality. By clarifying the differences between these coagulation phenotypes, we aim to provide clinicians with more abundant diagnostic clues and treatment considerations for managing sepsis-related coagulation disorders.

Materials and methods

Study design and setting

As a retrospective cohort survey, this study was conducted in the intensive care unit of the Second Affiliated Hospital of Kunming Medical University. All patients admitted with septic shock between January 1st and December 31st, 2023, were screened to determine their eligibility. The study focused on investigating the von Willebrand factor antigen levels, platelet behavior trends, and observed thrombus characteristics among patients classified as having TTP-like syndrome, SIC, or neither of the above conditions.

Study population

Inclusion criteria: Participants were considered for enrollment when they met all of the following requirements: ① a diagnosis of septic shock based on the Sepsis-3 framework; ② age between 18 and 80 years; ③ assessment of vWF antigen levels during their ICU admission; ④ availability of complete clinical information and laboratory results.

Exclusion criteria: Individuals were not included in the cohort if any of the conditions below applied: ① pre-existing thrombocytopenia attributed to causes other than sepsis; ② underlying hematologic cancers, hypersplenism, marked hepatic or renal impairment, significant bleeding events, advanced-stage malignancy, or chronic exposure to immunosuppressive agents; ③ pregnancy or breastfeeding; ④ receipt of extracorporeal circulatory support such as intra-aortic balloon counterpulsation or extracorporeal membrane oxygenation; ⑤ absence of essential medical documentation.

Data collection and variables

Clinical and laboratory data were extracted from the electronic medical record system by two independent investigators.

Baseline demographic and clinical variables: Gender, age, blood type, infection site, pre-ICU

liver function (total bilirubin, TBil) and renal function (creatinine, Crea), and infection markers (white blood cell count (WBC), neutrophil percentage (NEUT%), procalcitonin (PCT)).

Laboratory and clinical measurements: The following parameters were collected daily throughout the first seven ICU days: ① vWF antigen level; ② Platelet count (PLT) and platelet decline rate, calculated as: [(initial PLT - lowest PLT)/initial PLT] × 100%; ③ Coagulation indices: international normalized ratio (INR); ④ Organ function parameters: TBil, Crea, oxygenation index (PaO_2/FiO_2), hemodynamics; ⑤ Neurological status: Glasgow Coma Scale (GCS); ⑥ Daily Sequential Organ Failure Assessment (SOFA) subscores (respiratory, circulatory, hepatic, renal, neurological) using the worst values; ⑦ Outcomes: discharge status and 28-day mortality.

Definitions of clinical phenotypes

Thrombocytopenia [14]: Defined as either: absolute platelet count < 100×10^9/L, or relative decline ≥ 30% from baseline.

SIC diagnosis: SIC score [15] components included: ① INR: ≤ 1.2 = 0, > 1.2 = 1, > 1.4 = 2; ② PLT: ≥ 150×10^9/L = 0, < 150×10^9/L = 1, < 100×10^9/L = 2; SOFA score: 0 = 0, 1 = 1, ≥ 2 = 2. SIC was diagnosed when: INR + PLT subtotal > 2, AND total SIC score ≥ 4.

TTP-like syndrome: Defined as the simultaneous presence of thrombocytopenia (absolute or relative), elevated vWF antigen, and MODS (any SOFA subscore ≥ 1) [10, 16].

Control group: Patients with septic shock who did not meet diagnostic criteria for either the TTP-like or SIC groups.

Handling of missing data and outliers

Two investigators independently reviewed the dataset to ensure accuracy and completeness. ① For variables with less than 5% missing data, continuous measurements were filled using median values, while categorical items were imputed with the most frequent category. ② Outliers were examined against the original medical records, and values deemed incompatible with physiological limits were discarded following agreement between reviewers. ③ None of the variables have reached the preset threshold for excessive missing values, so there is no need to exclude them from the analysis.

Sample size considerations

Since this study adopted a retrospective design, all patients who met the inclusion criteria within the study window period were included. Therefore, there is no need for a formal sample size calculation. Including the entire available cohort helps maintain statistical robustness and reduces the possibility of selection-related bias.

Statistical analysis

The SPSS software (version 27.0) was used for statistical analysis. The selection of tests for continuous and categorical variables was determined by the underlying distribution of each variable.

Summary and group comparisons: For variables that approximately follow a normal distribution, the mean ± standard deviation is used for summarization, and one-way analysis of variance is employed to evaluate differences between groups. When the measurement indicators do not meet the normality assumption, the results are presented as the median ± interquartile range, and the Kruskal - Wallis test is used for group comparisons, with post - hoc analysis conducted when necessary. Categorical variables are described by frequencies and percentages, and differences between groups are evaluated using the chi - square test or Fisher's exact test, with the specific choice depending on the expected cell frequencies.

Correlation and additional analyses: The Spearman rank correlation analysis method was used to detect the relationship between vWF levels and platelet-related parameters. In addition, by evaluating the differences in the SOFA score components and organ dysfunction patterns among the study groups, the clinical variability in the cohort was more clearly defined.

Exploratory multivariable modelling: In multivariate analysis, variables showing potential associations ($P < 0.10$) in univariate assessment and variables of clinical importance were included in the logistic regression model to identify factors associated with 28-day mortality.

Table 1. Baseline characteristics of the three groups

Indicator	TTP-like Group (n = 65)	SIC Group (n = 64)	Control Group (n = 18)	F/H/χ^2 value	*P* value
Age (years, $\bar{x}\pm s$)	57.4±16.3	59.8±12.4	54.1±14.6	1.181	0.310
Male [n (%)]	40 (61.5)	47 (73.4)	12 (66.7)	2.081	0.353
Blood type				8.326	0.215
Type A [n (%)]	25 (40.3)	18 (29.0)	4 (22.2)		
Type B [n (%)]	15 (24.2)	21 (33.9)	5 (27.8)		
Type AB [n (%)]	5 (8.1)	6 (9.7)	0 (0.0)		
Type O [n (%)]	17 (27.4)	17 (27.4)	9 (50.0)		
Infection site [n (%)]				9.366	0.312
Biliary [n (%)]	8 (12.3)	5 (7.8)	2 (11.1)		
Pulmonary [n (%)]	11 (16.9)	11 (17.2)	4 (22.2)		
Abdominal [n (%)]	29 (44.6)	35 (54.7)	10 (55.6)		
Urinary [n (%)]	16 (24.6)	8 (12.5)	2 (11.1)		
Other [n (%)]	1 (1.5)	5 (7.8)	0 (0.00)		
TBil [μmol/L, M (Q_L, Q_U)]	17.0 (11.3, 24.6)	21.0 (13.4, 42.8)	19.5 (10.7, 29.2)	5.923	0.052
Crea [μmol/L, M (Q_L, Q_U)]	79.5 (63.5, 100.8)	84.0 (61.2, 139.2)	86.0 (58.2, 110.5)	0.289	0.866
WBC [×10^9/L, M (Q_L, Q_U)]	14.3 (10.9, 19.6)	11.2 (7.6, 16.2)	14.1 (12.3, 19.5)	5.734	0.057
NEUT% (%, $\bar{x}\pm s$)	89.5±6.8	89.7±6.6	88.0±6.1	0.454	0.636
PCT [μg/L, M (Q_L, Q_U)]	19.5 (3.4, 84.1)	25.6 (6.7, 69.9)	5.5 (0.9, 22.5)	5.891	0.053

Note: Crea = creatinine; NEUT% = neutrophil percentage; PCT = procalcitonin; TBil = total bilirubin; WBC = white blood cell count.

Significance criteria: Unless otherwise specified, all analyses were performed with a two-sided significance level of 0.05.

Ethical considerations

This research protocol has been reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (Approval No.: PJ - 2023 - 102). Since the study is only based on existing clinical records and does not involve direct contact with patients, the committee waived the requirement for informed consent. All data included in the analysis were anonymized before use, and any details that could identify the subjects were removed.

Results

Baseline characteristics

A total of 147 patients with septic shock met the criteria for analysis and were divided into three groups: the TTP-like group (n = 65), the SIC group (n = 64), and the control group (n = 18). Baseline characteristics, including demographic characteristics, main infection sites, and liver and kidney functions before ICU admission, showed no significant differences among the groups. Infection-related laboratory values such as white blood cell count, neutrophil percentage, and procalcitonin were also similar among the cohorts (all $P > 0.05$). In summary, these results indicate that the groups were comparable at baseline, allowing for meaningful comparisons of subsequent coagulation and endothelial injury markers (**Table 1**).

Platelet kinetics and vWF levels

During the first week of ICU admission, platelet parameters and vWF antigen concentrations differed markedly among the groups. The nadir platelet count demonstrated a distinct stepwise pattern, with the SIC group exhibiting the lowest values, followed by the TTP-like group and then the controls ($P < 0.001$). PLT decline rate also demonstrated a progressive worsening pattern: SIC > TTP-like > control ($P < 0.001$). vWF antigen levels were elevated in all three groups compared with the normal reference range (50-160%), with significantly higher levels in both the TTP-like and SIC groups than in controls ($P < 0.05$) (see **Table 2**).

There was no statistically important difference in vWF levels between the TTP-like and SIC

Table 2. Comparison of lowest PLT, PLT decline rate, and vWF antigen expression

Indicator	TTP-like Group (n = 65)	SIC Group (n = 64)	Control Group (n = 18)	F/H value	*P* value
PLT [×10^9/L, M (Q_L, Q_U)]	117.0 (62.5, 153.5)	44.0 (10.2, 73.8)	204.0 (129.0, 298.5)	63.374	< 0.001
PLT decline rate [%, M (Q_L, Q_U)]	48.2 (38.5, 64.3)	68.6 (51.8, 85.8)	17.1 (-6.0, 27.4)	41.311	< 0.001
vWF [U/dL, $\bar{x}$ ±s]	333.4±82.5	318.8±94.0	267.61±79.4	3.992	0.021

Note: PLT = platelet; vWF = von Willebrand factor.

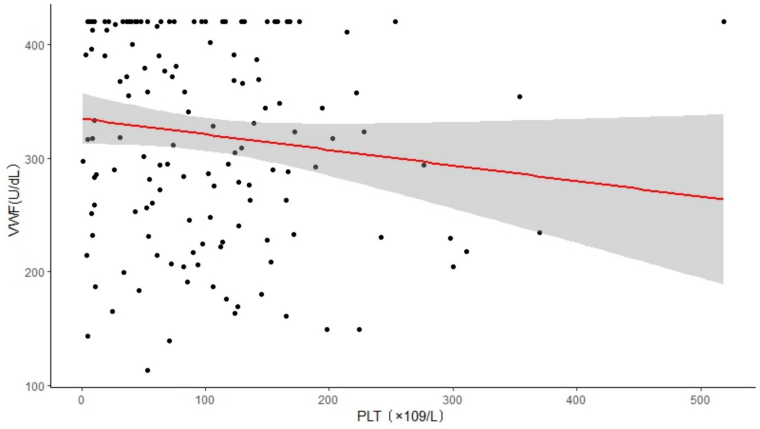

Figure 1. Scatter plot of the relationship between lowest PLT and vWF. Note: vWF = von Willebrand factor; PLT = platelet.

Table 3. Correlation analysis of lowest PLT and vWF antigen expression

Indicator	r value	*P* value
vwf	-0.20	0.018

Note: vWF = von Willebrand factor; PLT = platelet.

groups, suggesting that endothelial activation occurred to a similar extent in both phenotypes. These observations support a strong association between endothelial injury, vWF release, and platelet consumption in septic shock.

Correlation between vWF and platelet count

Spearman correlation analysis demonstrated a significant negative association between the lowest PLT count and vWF antigen level (r = -0.20, *P* = 0.018) (see **Figure 1** and **Table 3**). This relationship suggests that greater endothelial injury and vWF release correspond to more severe thrombocytopenia, reinforcing the mechanistic link between microthrombus formation and platelet consumption.

Organ dysfunction profiles

Comparisons of organ injury patterns revealed distinct clinical expressions between the TTP-like and SIC phenotypes (see **Table 4**). Respiratory, circulatory, and neurological dysfunction occurred with similar frequencies in both groups (*P* > 0.05). Hepatic and renal dysfunction were significantly more common in the SIC group (both *P* < 0.05). The mean number of dysfunctional organs was also higher in patients with SIC (*P* < 0.001). Although the incidence of MODS approached 100% in both groups, the severity and burden of organ failure were greater in the SIC phenotype, suggesting a more advanced or widespread thromboinflammatory process.

SOFA subscores

Analysis of the worst SOFA subscores showed that higher respiratory, hepatic, and renal subscores in the SIC group (all *P* < 0.05). No significant difference in circulatory or neurological subscores (*P* > 0.05). These findings are consistent with the organ injury analysis and indicate that SIC is associated with more profound impairment of oxygenation, bilirubin metabolism, and renal function compared with TTP-like syndrome (see **Table 5**).

Clinical outcomes

The duration of ICU hospitalization showed no appreciable variation between the two cohorts (*P* > 0.05; **Table 6**). In contrast, outcome measures diverged notably, with the TTP-like group demonstrating a markedly greater likelihood of being discharged alive (*P* < 0.001). In-hospital mortality and 28-day mortality were markedly higher in the SIC group (both *P* < 0.01). Taken together, the findings indicate that while TTP-like syndrome and SIC both involve microvascular thrombosis and multi-organ impairment,

Table 4. Organ injury in TTP-like and SIC groups

Indicator	TTP-like Group (n = 65)	SIC Group (n = 64)	χ^2/t value	*P* value
Respiratory injury [n (%)]	65.0 (100.0)	64.0 (100.0)	-	-
Circulatory injury [n (%)]	61 (93.8)	62 (96.9)	0.159	0.690
Hepatic injury [n (%)]	33 (50.8)	44 (68.8)	4.333	0.037
Renal injury [n (%)]	27 (41.5)	40 (62.5)	5.676	0.017
Neurological injury [n (%)]	7 (10.8)	9 (14.1)	0.322	0.570
Number of injured organs [$\bar{x}\pm s$]	3.0±0.8	3.5±0.8	-3.873	< 0.001
MODS [n (%)]	65 (100.0)	63 (98.4)	0.001	0.994

Note: MODS = multiple organ dysfunction syndrome.

Table 5. Worst SOFA sub-scores in TTP-like and SIC groups

Indicator	TTP-like Group ($\bar{x}\pm s$)	SIC Group ($\bar{x}\pm s$)	T value	*P* value
Respiratory system	2.4±0.7	2.8±0.9	-2.682	0.008
Circulatory system	2.7±1.3	3.1±1.3	-1.599	0.112
Hepatic system	0.9±1.0	1.6±1.1	-3.852	< 0.001
Renal system	0.7±1.0	1.2±1.4	-2.599	0.011
Neurological system	0.2±0.1	0.2±0.1	0.293	0.770

Note: SOFA = sequential organ failure assessment.

Table 6. Prognostic outcomes in TTP-like and SIC groups

Indicator	TTP-like Group	SIC Group	Z/t value	*P* value
ICU stay [days, M (Q_L, Q_U)]	5.0 (30, 7.0)	4.0 (3.0, 8.5)	-0.311	0.756
Outcome			13.078	< 0.001
Discharge [n (%)]	62 (95.4)	46 (71.9)	-	-
Death [n (%)]	3 (4.6)	18 (28.1)	-	-
28-day death [n (%)]	5 (7.7)	19 (29.7)	10.302	0.001

patients with SIC tend to experience more pronounced organ failure and markedly poorer survival.

Discussion

This study mainly found that in patients with septic shock and thrombocytopenia, the expression of von Willebrand factor (vWF) antigen was elevated, and the lowest platelet count was negatively correlated with the vWF antigen level. In sepsis, endothelial injury leads to the excessive release of ultra-large vWF multimers (ULVWF), exceeding the cleavage ability of its cleaving metalloproteinase ADAMTS13. Together with the action of proteases and inflammatory mediators, it results in the relative deficiency of ADAMTS13 activity and expression, which further promotes the recruitment and activation of ULVWF, consumes platelets to form microthrombi [15, 17, 18]. This process is called endotheliopathy-associated vascular microthrombotic disease (EA-VMTD) [10]. The study shows that elevated vWF is one of the key markers for the diagnosis of EA-VMTD. This study found that the levels of vWF in the TTP-like syndrome group and the SIC group were significantly higher than those in the control group, and the incidence rates of TTP-like syndrome and SIC were similar (both about 44%), suggesting that diffuse microthrombosis exists in both. Moreover, the vast majority of SIC patients also had the characteristics of TTP-like syndrome, indicating that patients with septic shock often have fibrin thrombus formation on the basis of microthrombi. The incidence rates of MODS in both groups were extremely high (nearly 100%), and the mortality rate in the TTP-like group was close to 8%, indicating that intravascular microthrombi can cause severe organ function damage and even death, and the formed platelet microthrombi are not easily lysed. This result deserves clinical attention.

Related studies have also found that the degree of thrombocytopenia is closely related to organ dysfunction and mortality, supporting the key role of microthrombus formation in the course of sepsis [19]. The damage to the respiratory, liver, and kidney functions in the TTP-like group was slightly milder than that in the SIC group, and the overall prognosis and mortality were slightly better than those in the SIC group. This indicates that the "large thrombi" formed by microthrombi, fibrin thrombi, and blood cells under the action of adhesion molecules in the SIC group are more difficult to lyse than microthrombi. In terms of the distribution of organ damage, both groups mainly had damage to the respiratory and circulatory systems, and the nervous system was less affected, which may be related to endothelial heterogeneity and the difference in organotropism of pathogens [16, 20, 21].

This study suggests that vWF antigen detection can serve as a potential biomarker for endothelial damage and microthrombus formation in patients with sepsis, which is helpful for the early identification of TTP-like syndrome. Given the high incidence of TTP-like syndrome in septic shock and its potential progression to SIC, clinical monitoring and intervention for such patients should be strengthened. Early identification of the microthrombus formation stage may provide a critical time window for improving the prognosis of sepsis [22].

The advantage of this study lies in its focus on the role of vWF in sepsis-induced thrombocytopenia. Meanwhile, it comparatively analyzes the clinical and laboratory characteristics of TTP-like syndrome and SIC, providing a new perspective for understanding the coagulation and endothelial disorders in sepsis. However, this study is a single-center observational analysis with a limited sample size and does not cover the impact of therapeutic interventions on the dynamic changes of vWF and prognosis.

In the future, multicenter and large-sample studies should be conducted to verify the predictive value and diagnostic cut-off of vWF in sepsis-related thrombotic diseases. Further exploration should be carried out on the mechanism of action of the ADAMTS13-vWF axis in the pathology of sepsis, and whether treatment strategies targeting this pathway (such as recombinant ADAMTS13 and vWF-targeted drugs) can improve the prognosis of patients. Meanwhile, by combining multi-omics technology and dynamic monitoring, it is expected to clarify the key links of microthrombosis formation in the progression from sepsis to MODS, providing a basis for individualized anticoagulation and endothelial protection therapy.

Conclusions

This study preliminarily suggests that vWF can serve as a potential biomarker for endothelial injury and microthrombus formation in septic shock, and predict the severity of microthrombus and "macrothrombus" formation. Meanwhile, the study observed that TTP-like syndrome is associated with the risk of MODS and death, and patients with SIC tend to have more severe organ damage and a higher mortality rate. These findings provide clues for understanding the pathophysiology of coagulation disorders in sepsis.

Limitations and future directions: Given the limited sample size and single-center design of this study, caution should be exercised when extrapolating the results. Future studies should prospectively validate the predictive value of vWF for thrombotic events through larger-scale cohorts and further explore the specific mechanisms by which SIC affects prognosis.

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Disclosure of conflict of interest

None.

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