





The Combination of the Lactate Dehydrogenase/Hemoglobin Ratio with the PLASMIC Score Facilitates Differentiation of TTP from Septic DIC Without Identification of Schistocytes

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Abstract

In some cases, differentiating thrombotic thrombocytopenic purpura (TTP) from septic disseminated intravascular coagulation (DIC) without measuring ADAMTS13 activity is critical for urgent lifesaving plasma exchange. To investigate whether PLASMIC score without identifying the presence of schistocytes, D-dimer, fibrin/fibrinogen degradation products (FDP), FDP/D-dimer ratio, prothrombin time-international normalized ratio (PT-INR), lactate dehydrogenase (LD), hemoglobin (Hb), and LD/Hb ratio are useful in differentiating patients with TTP from those with septic DIC. Retrospective analysis was conducted on the medical records of the patients with septic DIC (32 patients) or TTP (16 patients). The PLASMIC score and other laboratory measurements all were helpful in differentiating TTP from septic DIC. When dichotomized between high risk (scores 6–7) and intermediate–low risk (scores 0–5), the PLASMIC score predicted TTP with a sensitivity of 75.0% and a specificity of 100%. However, 4 of 16 patients with TTP and 19 of 32 patients with septic DIC showed comparable PLASMIC scores of 4 or 5, making it difficult to distinguish between the two by PLASMIC score alone. Among the measurements examined, the LDH/Hb ratio was the most useful for differentiation. Receiver operating characteristic analysis of the LD/Hb ratio for predicting TTP revealed a cutoff of 53.7 (IU/10 g) (sensitivity 0.94, specificity 0.91). If the LD/Hb ratio was less than 53.7, it was unlikely that the patient had TTP. A combination of the LD/Hb ratio and the PLASMIC score may be useful for distinguishing between TTP and DIC and identifying patients who need rapid plasma exchange or caplacizumab administration.

Keywords

septic DIC, TTP, PLASMIC score, LD/Hb ratio, sepsis

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) resulting from severely diminished activity of the von Willebrand factor (VWF)-cleaving protease ADAMTS13. It is characterized by extensive intravascular thrombosis enriched with platelets, leading to thrombocytopenia, microangiopathic hemolytic anemia, and occasionally organ dysfunction.¹ Timely initiation of plasma exchange is crucial, as TTP is nearly always fatal without intervention,²

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and a deficiency in ADAMTS13 activity serves as a definitive diagnostic criterion.³ However, due to lengthy turnaround times and limited accessibility of the ADAMTS13 assay, initial diagnosis of TTP primarily relies on clinical manifestations. Distinguishing TTP from other forms of TMA, such as hemolytic uremic syndrome (HUS) and atypical HUS, is challenging since these conditions exhibit similar clinical symptoms. To address this issue, Bendapudi et al⁴ developed the PLASMIC score, which utilizes readily available laboratory parameters to identify TTP patients without measuring ADAMTS13 activity. The PLASMIC score has been validated^{5–8} and has demonstrated a remarkably high sensitivity (0.9–0.98) and specificity (0.46–0.92), making it a practical tool for selecting TTP patients from among TMA cases in clinical practice. Nonetheless, in real-world scenarios, clinicians unfamiliar with TTP diagnosis often face difficulties in differentiating TTP from sepsis-induced disseminated intravascular coagulation (DIC). This challenge arises due to the lack of specific laboratory tests for diagnosing DIC and the overlapping clinical manifestations, such as anemia, thrombocytopenia, bleeding, elevated D-dimer levels, multiple organ dysfunction, and occasionally the presence of fragmented red blood cells (schistocytes) seen in both TTP and septic DIC. Consequently, clinicians encounter delays in promptly and accurately identifying TTP patients, thus impeding the timely initiation of plasma exchange. Moreover, the PLASMIC score, employed to select TTP patients among those with TMA, defined by the presence of at least 1% schistocytes and platelet counts below $150 \times 10^3/\mu\text{L}$,⁴ can pose challenges in emergency situations, particularly during nighttime, when determining the presence of at least 1% schistocytes in peripheral blood becomes arduous. Therefore, we decided to investigate the possibility of differentiating TTP from DIC using PLASMIC score and some laboratory measurements without measuring ADAMTS13 activity and confirming schistocytes.

Institutional Review Board approval was obtained for this study (No. 2146).

Study Design and Methods

Patients

This study included consecutive patients admitted to the Department of General Medicine in the Nara Medical University Hospital between December 2012 and February 2018, who were diagnosed with TTP or septic DIC by physicians in the Department of General Medicine. The diagnosis of patients was based on the Japanese Association for Acute Medicine (JAAM) criteria for DIC^{9,10} and the International Society on Thrombosis and Haemostasis (ISTH) consensus on the definition of TTP.³ Retrospective analysis was conducted on the medical records of these patients.

ADAMTS13 Activity

The activity of ADAMTS13 and its inhibitor were measured in TTP patients using ADAMTS13-act-ELISA (Kainos, Tokyo, Japan).

The PLASMIC Score, PT-INR, D-Dimer, FDP, FDP/D-Dimer Ratio, LD, and LD/Hb Ratio

The PLASMIC score was calculated using admission data. The study aimed to determine the usefulness of the PLASMIC score in distinguishing TTP from septic DIC, without identifying the presence of schistocytes, and to investigate whether D-dimer, fibrin/fibrinogen degradation products (FDP), FDP/D-dimer ratio, prothrombin time-international normalized ratio (PT-INR), lactate dehydrogenase (LD), and LD/hemoglobin (Hb) ratio levels could aid in differentiating between TTP and DIC. Differences between the two groups were assessed using a *t*-test. Because the receiver operating characteristic (ROC) analysis can define the optimal cut-point value as the value whose sensitivity and specificity are the closest to the value of the area under the ROC curve and the absolute value of the difference between the sensitivity and specificity values is minimum, ROC analysis was conducted to determine the optimal cutoff points for each measurement in predicting TTP. Statistical analyses were performed using Easy R (EZR) version 1.3.6.¹¹

Results

Patients

The study included patients with septic DIC ($n = 32$) and TTP ($n = 16$). All TTP patients had ADAMTS13 activity levels below 0.5% and positive ADAMTS13 inhibitor titers ranging from 0.6 to 28.7 BU/mL (Table 1).

PLASMIC Score

The PLASMIC scores ranged from 2 to 5 points for septic DIC patients and from 4 to 7 points for TTP patients (Figure 1). Among the total of 48 patients, 11 had PLASMIC scores of 6 or 7, indicating a high-risk group, and all of them were TTP patients. When dichotomized into high risk (scores 6–7) and intermediate-low risk (scores 0–5), the PLASMIC score predicted TTP with a sensitivity of 0.75 [95% confidence interval: 0.48 to 0.93], specificity of 1.00 [95% CI: 0.84 to 1.00], positive predictive value (PPV) of 100% [95% CI: 64.0 to 100.0], and negative predictive value (NPV) of 88.9% [95% CI: 73.9 to 96.9]. This implies that patients with a PLASMIC score of 6 or 7 can be diagnosed as having TTP rather than septic DIC, without confirming the presence of schistocytes. When dichotomized into intermediate-high risk (scores 5–7) and low risk (scores 0–4), the PLASMIC score demonstrated a sensitivity of 0.94 [95% CI: 0.70 to 1.00], specificity of 0.75 [95% CI: 0.57 to 0.89], PPV of 65.2% [95% CI: 42.7 to 83.6], and an NPV of 96.0% [95% CI: 79.6 to 99.9]. However, among the cohort of 16 patients diagnosed with TTP, a total of 3 individuals demonstrated a PLASMIC score of 4 or 5 points. In contrast, within the group of 32 patients diagnosed with septic DIC, a substantial 19 patients exhibited an identical PLASMIC score. Consequently, relying solely on the PLASMIC score becomes challenging in practical settings to differentiate TTP patients from those with septic DIC, especially when the PLASMIC score indicates a value of 4 or 5.

Table 1. Characteristics of Patients with TTP and Those with Septic DIC.

Disease	Age	Sex	ADAMTS13 activity (%) or underlying disease	Inhibitor titer (BU/mL)	PT-INR	FDP (μ g/mL)	D-dimer (μ g/mL)	FDP/D-dimer ratio	LD (IU/mL)	Hb (g/dL)	LD/Hb (IU/10g)	CK (IU/mL)	PLASMIC score
TTP	72	M	<0.5	2.4	1.4	44.9	22	2.0	2271	4.2	540.7	292	6
TTP	47	F	<0.5	11.4	1.0	17.6	7.2	2.4	1555	7	222.1	90	7
TTP	55	M	<0.5	12.9	1.1	16.3	7.2	2.3	2037	5.7	357.4	216	6
TTP	67	F	<0.5	17.8	1.0	3.2	1.6	2.0	703	8.8	79.9	53	6
TTP	61	M	<0.5	10	1.1	3	1.5	2.0	835	6.8	122.8	60	6
TTP	36	M	<0.5	17.6	1.0	2.7	1.4	1.9	478	8	59.8	35	6
TTP	38	M	<0.5	4.6	1.0	4.8	1.6	3.0	671	12.5	53.7	976	5
TTP	66	M	<0.5	2.9	1.1	32.7	12.6	2.6	2737	14.6	187.5	299	4
TTP	76	F	<0.5	1.2	1.0	3.9	2	2.0	554	7.8	71.0	196	6
TTP	65	F	<0.5	28.7	1.0	4.9	2.4	2.0	429	9.9	43.3	73	5
TTP	49	F	<0.5	4.9	1.1	12.5	4.7	2.7	1554	7.6	204.5	179	6
TTP	26	M	<0.5	0.6	1.0	51.6	20.9	2.5	1910	5.7	335.1	131	6
TTP	74	M	<0.5	6.5	1.1	21.9	9.2	2.4	1451	11.9	121.9	323	5
TTP	85	M	<0.5	1	1.0	12.4	4.8	2.6	901	12.3	73.3	113	6
TTP	65	M	<0.5	2.9	1.1	22.8	9.8	2.3	1498	7.3	205.2	390	6
TTP	88	M	<0.5	2.3	1.1	12.3	4.8	2.6	809	9.6	84.3	58	6
DIC	79	M	GI perforation	NA	1.08	15.9	6.4	2.5	436	8.9	49.0	573	5
DIC	70	M	Iliopsoas abscess	NA	1.17	39.4	17.6	2.2	279	12.2	22.9	187	3
DIC	66	F	Cellulitis	NA	1.29	16.7	7.6	2.2	670	11.8	56.8	1623	4
DIC	57	M	TTS	NA	1.04	32.1	12.4	2.6	1882	17.1	110.1	45510	3
DIC	66	M	UTI	NA	1.5	68.9	35.7	1.9	339	9.2	36.8	103	3
DIC	68	F	TSW infection	NA	1.11	32.2	20	1.6	248	9.8	25.3	60	5
DIC	67	F	Pneumonia	NA	1.37	33	17.9	1.8	488	9.8	49.8	1482	5
DIC	58	F	Pneumonia	NA	2.37	23.5	9	2.6	444	9.5	46.7	122	5
DIC	74	M	Pneumonia	NA	2.18	130.2	56.6	2.3	1040	9.2	113.0	1333	4
DIC	84	M	SPIPF	NA	2.61	56.2	28.5	2.0	695	13.9	50.0	856	2
DIC	82	M	Meningitis	NA	1.06	87.1	38.9	2.2	315	11.9	26.5	99	4
DIC	66	F	Enterocolitis	NA	1.08	191	100	1.9	193	5	38.6	26	5
DIC	65	M	IE	NA	1	17.2	7.1	2.4	408	15.4	26.5	21	5
DIC	74	F	Pneumonia	NA	1.19	35.9	21.4	1.7	318	8.4	37.9	1372	3
DIC	77	F	Acute pancreatitis	NA	1.22	113.7	66.6	1.7	489	14.2	34.4	419	5
DIC	77	M	Ileus	NA	1.32	43.2	25.8	1.7	595	13.4	44.4	3484	3
DIC	68	M	GI perforation	NA	1.09	7.5	3	2.5	344	11.5	29.9	236	3
DIC	87	F	GI perforation	NA	0.97	8.9	4.8	1.9	213	15.4	13.8	62	4
DIC	82	M	Perineal abscess	NA	1.27	621	331	1.9	234	8.8	26.6	764	4
DIC	86	F	SMA thrombosis	NA	1.55	31.5	18.8	1.7	465	13.5	34.4	122	2
DIC	74	M	Deep mycosis	NA	3.01	2.9	1.6	1.8	255	9.6	26.6	34	4
DIC	88	F	NOMI	NA	1.92	35.2	13.5	2.6	419	12	34.9	6758	2
DIC	61	M	Deep mycosis	NA	1.17	16.9	11.2	1.5	256	10.5	24.4	524	3
DIC	81	M	Pneumonia	NA	1.21	16.1	19.7	0.8	300	9	33.3	158	3
DIC	44	F	UTI	NA	2.09	130.2	126.9	1.0	330	8.5	38.8	172	4
DIC	56	F	Meningitis	NA	1.11	5.7	2.7	2.1	346	12.7	27.2	468	4
DIC	67	F	Prosthetic joint infection	NA	1.79	38.8	49.2	0.8	385	9.1	42.3	92	3
DIC	61	F	UTI	NA	1.35	15.8	6.8	2.3	321	10.2	31.5	164	5
DIC	70	F	UTI	NA	1.72	12.2	11.2	1.1	313	8.7	36.0	150	3
DIC	79	F	GI perforation	NA	1.01	11.7	6.7	1.7	127	9.6	13.2	135	4
DIC	80	M	Pneumonia	NA	1.16	75	39.83	1.9	442	13.9	31.8	38	4
DIC	72	M	Hepatic abscess	NA	1.1	73	45.3	1.6	491	14.6	33.6	1376	4

TTP, thrombotic thrombocytopenic purpura; DIC, disseminated intravascular coagulation; M, male; F, female; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin/fibrinogen degradation product; LD, lactate dehydrogenase; Hb, hemoglobin; CK, creatine kinase; GI, gastrointestinal; TSS, toxic shock syndrome; UTI, urinary tract infection; TSW, thoracoabdominal stab wound; SPIPF, streptococcus pneumonia-induced purpura fulminans; SMA, superior mesenteric artery; NOMI, nonocclusive mesenteric ischemia.

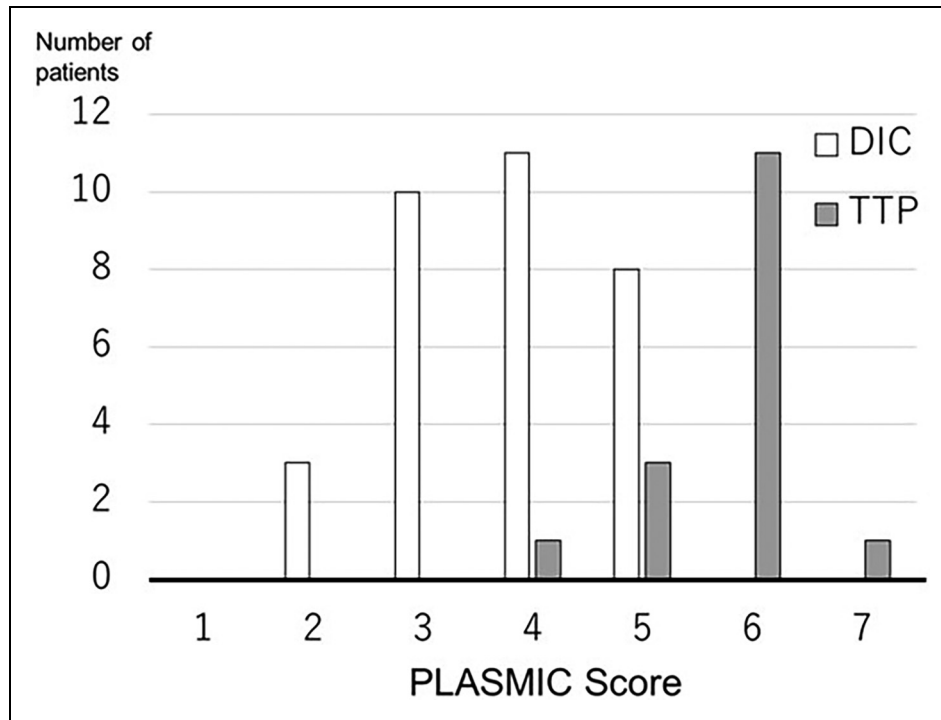


Figure 1. PLASMIC scores of patients with septic DIC or TTP. The open bar represents the distribution of the PLASMIC score in septic DIC patients, and the closed bar represents the distribution of the PLASMIC score in TTP patient. Abbreviations: DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura.

D-Dimer, FDP, and FDP/D-Dimer Ratio

The mean value of D-dimer in patients with TTP was 7.11 $\mu\text{g}/\text{mL}$, which was not significantly lower than that observed in patients with septic DIC (36.4 $\mu\text{g}/\text{mL}$, $t=0.06$) as shown in Figure 2a. ROC analysis demonstrated an AUC of 0.80 [95% CI: 0.67 to 0.93] for the D-dimer in diagnosing TTP, with a cutoff point of 9.8 (sensitivity 0.81 [95% CI: 0.54 to 0.96], specificity 0.69 [95% CI: 0.50 to 0.84]). Similarly, the mean value of FDP in TTP patients was 16.7 $\mu\text{g}/\text{mL}$, which did not significantly differ from the value in septic DIC patients (63.7 $\mu\text{g}/\text{mL}$, $t=0.10$) as shown in Figure 2b. The AUC of the FDP in ROC analysis for TTP diagnosis was 0.75 [95% CI: 0.65 to 0.90], with a cutoff point of 22.8 (sensitivity 0.81 [95% CI: 0.54 to 0.96], specificity 0.63 [95% CI: 0.44 to 0.79]). Additionally, we calculated the FDP/D-dimer ratio and compared it between TTP and septic DIC patients. The average FDP/D-dimer ratio for TTP patients was 2.33, significantly higher than that observed in patients with septic DIC (1.89, $t=0.003$) as shown in Figure 2c. The AUC of the FDP/D-dimer ratio in ROC analysis for TTP diagnosis was 0.78 [95% CI: 0.65 to 0.91], with a cutoff point of 1.93 (sensitivity 1.00 [95% CI: 0.71 to 1.00], specificity 0.56 [95% CI: 0.38 to 0.74]).

PT-INR

The mean value of PT-INR in patients with TTP was 1.06, significantly lower than that observed in patients with septic DIC

(1.42, $t=0.008$) as shown in Figure 2d. ROC analysis indicated an AUC of 0.84 [95% CI: 0.71 to 0.96] for PT-INR in diagnosing TTP, with a cutoff point of 1.07 (sensitivity 0.81 [95% CI: 0.54 to 0.95], specificity 0.84 [95% CI: 0.67 to 0.95]).

LD and LD/Hb Ratio

The mean value of LD in patients with TTP was 1275 U/L, which was significantly higher than that observed in patients with septic DIC (440 U/L, $t<0.001$) as shown in Figure 2e. ROC analysis unveiled an impressive AUC of 0.92 [95% CI: 0.85 to 1.0] for the LD in facilitating TTP diagnosis, with a discerning cutoff point of 554 (sensitivity 0.88 [95% CI: 0.62 to 0.98], specificity 0.84 [95% CI: 0.67 to 0.95], PPV 73.7% [95% CI: 48.8 to 90.9], and an NPV 93.1% [95% CI: 77.2 to 99.2]).

Moreover, we calculated and compared the LD/Hb ratio between TTP patients and those with septic DIC. The average of the LD/Hb ratio for TTP patients stood remarkably higher at 173, a significant contrast to that of DIC (39.0, $p<0.001$), as illustrated in Figure 2f. ROC analysis indicated an AUC of 0.96 [95% CI: 0.91 to 1.0] for the LD/Hb ratio in TTP diagnosis (Table 2), with an impactful cutoff point of 53.7 (IU/10 g) (sensitivity 0.94 [95% CI: 0.70 to 1.00], specificity 0.91 [95% CI: 0.75 to 0.98], PPV 83.3 [95% CI: 58.6 to 96.4], NPV 96.7% [95% CI: 82.8 to 99.9]). Thus, the LD/Hb ratio demonstrated superiority in differentiating TTP from septic DIC. Remarkably, among the 16 patients diagnosed with TTP, all but one displayed an LD/Hb ratio equal to or exceeding 53.7

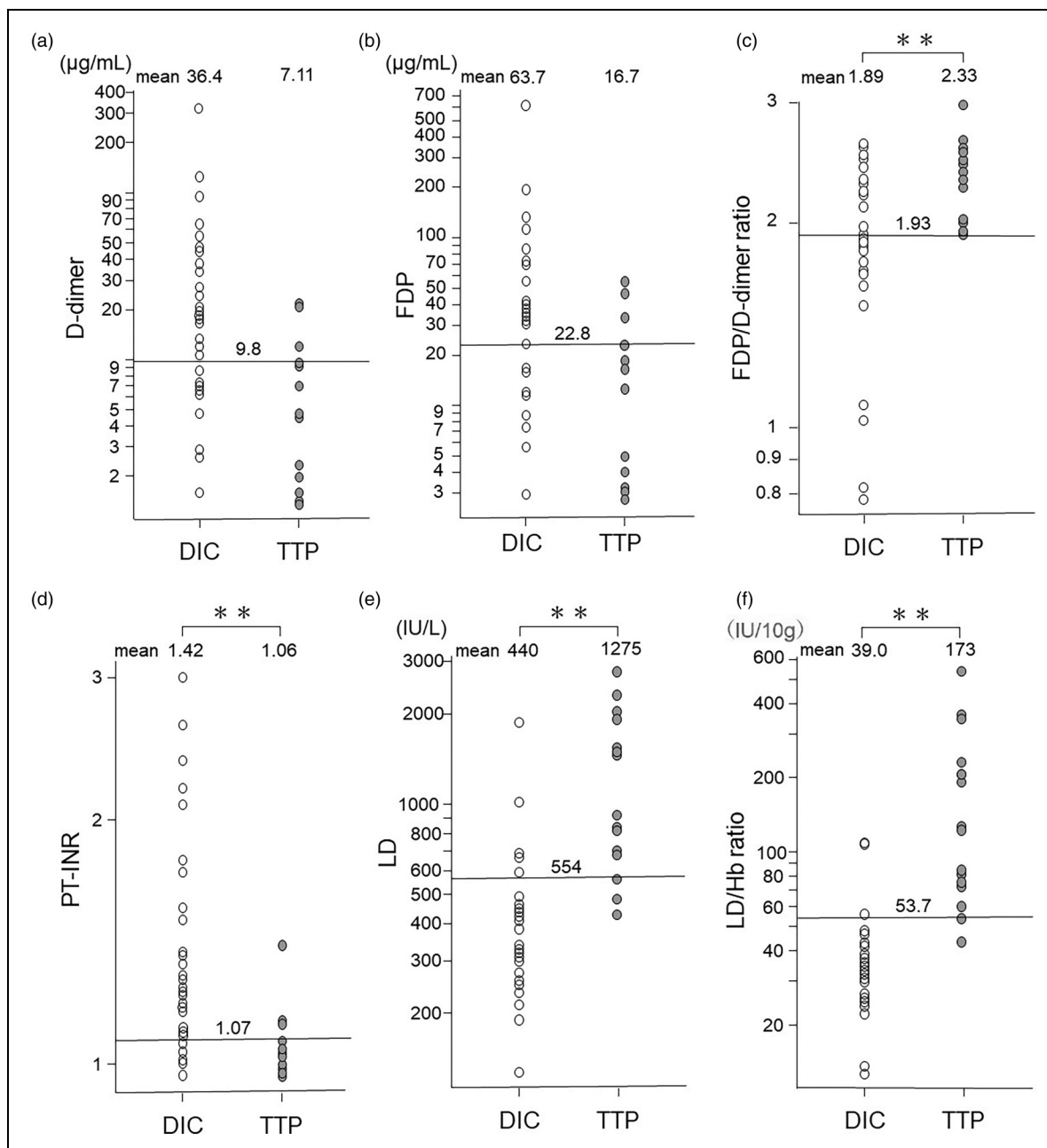


Figure 2. Distribution of the values of D-dimer (a), FDP (b), FDP/D-dimer ratio (c), PT-INR (d), LD (e), and LD/Hb ratio (f) in patients with septic DIC and those with TTP. The number written at the top of the figure for each measurement is the mean value for each group. The long horizontal lines in each figure are the cutoff values for identifying TTP patients for each measurement. D-dimer and FDP were not significantly different between septic DIC and TTP, but FDP/D-dimer ratio, PT-INR, LD, and LD/Hb ratio were significantly different between the two groups. The LD/Hb ratio values showed the least overlap between the two groups. Abbreviations: FDP, fibrin/fibrinogen degradation products; LD/Hb, lactate dehydrogenase/hemoglobin; TTP, thrombotic thrombocytopenic purpura; DIC, disseminated intravascular coagulation; AUC, area under the curve; ROC, receiver operating characteristic.

(IU/10 g). The exception, a truly exceptional case, exhibited an LD/Hb ratio of 43.3 (IU/10 g), alongside a PLASMIC score of 5, ADAMTS13 activity below 0.5%, an inhibitor titer of 2 BU/mL, and a platelet count of $3.0 \times 10^4/\mu\text{L}$, indicative of a severe manifestation of TTP. Nonetheless, this particular patient presented no signs of renal dysfunction, showed low levels of hemolysis throughout the disease course, and even had only

slight positivity in urine occult blood during the diagnostic phase before treatment, which might elucidate the relatively modest values of LD and LD/Hb ratio. Hence, we confidently deemed an LD/Hb ratio of 53.7 (IU/10 g) or higher as the decisive threshold for TTP diagnosis.

Intriguingly, all septic DIC patients with a PLASMIC score of 5 exhibited an LD/Hb ratio lower than 53.7, strongly

Table 2. Performance Metrics of Various Measurements for Identifying TTP.

	Cut off point	AUC	95%CI	sensitivity	95%CI	specificity	95%CI
D-dimer	9.8	0.80	0.67–0.93	0.81	0.54–0.96	0.69	0.50–0.84
FDP	22.8	0.75	0.61–0.90	0.81	0.54–0.96	0.63	0.44–0.79
FDP/D-dimer	1.93	0.78	0.65–0.91	1.00	0.71–1.00	0.56	0.38–0.74
PT-INR	1.07	0.84	0.71–0.96	0.81	0.54–0.95	0.84	0.67–0.95
LD	554	0.92	0.85–1.00	0.88	0.62–0.98	0.84	0.67–0.95
LD/Hb	53.7	0.96	0.91–1.00	0.94	0.70–1.00	0.91	0.75–0.98

suggesting the potential use of the LD/Hb ratio alongside the PLASMIC score to discriminate between TTP and septic DIC patients. Furthermore, within the septic DIC cohort, the three patients displaying LD/Hb ratios surpassing 53.7 (IU/10 g) manifested serum creatine kinase (CK) levels exceeding 1000 IU/L, while none of the TTP patients demonstrated CK levels surpassing 1000 IU/L (Table 1).

Discussion

In the realm of practical clinical scenarios, differentiating between patients with TTP and those afflicted with septic DIC often poses a challenging task. This difficulty arises due to the unavailability of immediate results for ADAMTS13 activity and the presence or absence of schistocytes in peripheral blood, particularly during emergency situations and nighttime hours. However, a rapid differential diagnosis is necessary to enable prompt plasma exchange to save the lives of patients with TTP. The primary distinction between septic DIC and TTP lies in the fact that septic DIC patients have serious infections and fibrin thrombi throughout the body, whereas TTP patients have no serious underlying disease and platelet thrombi throughout the body. However, identifying the presence of a serious infection is sometimes surprisingly difficult in actual clinical practice as it may be overshadowed by other potential causes such as connective tissue diseases or malignancies. Moreover, the early stages of a severe infection can manifest with TTP-like pathological features. Intriguingly, an experimental porcine model of septic DIC induced by intraperitoneal injection of lipopolysaccharide revealed that as early as 12 h after injection, platelet thrombi, rather than fibrin clots, were frequently observed in the kidneys, effectively simulating a TTP-like condition.¹² After that sustained stimulation to vascular endothelium and macrophages by lipopolysaccharide may consequently trigger the coagulation system and lead to DIC. These experimental findings highlight the occasional difficulty, even at the pathological level, in distinguishing between septic TTP and septic DIC. Moreover, surprisingly, the D-dimer values, indicating fibrin thrombus formation, in patients with TTP in actual clinical practice usually are all elevated than normal as shown in Table 1. Considering the above, we decided to investigate whether the PLASMIC score, which was developed to select TTP patients among TMAs that have more than 1% of schistocytes and platelets less than 150,000/ μ L, would be useful in differentiating TTP patients from septic DIC patients.

Several diagnostic criteria exist for septic DIC, including those formulated by the International Society on Thrombosis and Haemostasis (ISTH),¹³ the Japanese Society of Thrombosis and Hemostasis (JSTH), and the Japanese Association for Acute Medicine (JAAM).^{9,10} In our study, we employed the diagnostic criteria established by JAAM, as it is specifically designed to detect DIC at an earlier or milder stage compared to the criteria of ISTH and JSTH. Consequently, it may have the potential to identify abnormal coagulation patterns resembling TTP in the early phase of septic DIC, which may present a condition that can make us hesitate to distinguish between the two in clinical practice.

Among the cohort of 16 patients diagnosed with TTP, a total of 13 individuals were classified within the high PLASMIC score category, exhibiting a score of 6 or higher. Strikingly, none of the patients affected by septic DIC were found to belong to this specific group. This observation suggested that the positive predictive value is 100%, indicating the possibility that the patient has TTP when a patient shows a PLASMIC score of 6 or higher. Importantly, these findings highlight that employing a PLASMIC score of 6 or 7, without necessitating the evaluation of schistocytes, not only enables the identification of TTP patients within the spectrum of TMAs but also allows for the reliable differentiation between TTP and septic DIC cases. However, it is worth noting that a notable proportion of septic DIC patients (19 out of 32 cases) and TTP patients (3 out of 16 cases) presented with a PLASMIC score of 4 or 5. This poses a considerable challenge in accurately distinguishing between these two groups when solely based on the PLASMIC score alone.

In addition to the PLASMIC score, which measurements are useful in differentiating TTP from septic DIC was examined. All measurements except D-dimer and FDP were significantly different between the two groups. Although Vincent et al¹⁴ reported that abnormal coagulation profile including the D-dimer level can differentiate DIC from TMAs; surprisingly, none of the TTP patients had D-dimer within normal limits. Therefore, it was challenging to differentiate between TTP and DIC based solely on the presence or absence of elevated D-dimer or FDP levels. However, it was considered that when the D-dimer level was above 9.8 μ g/mL or the FDP level was above 22.8 μ g/mL, the likelihood of TTP was low. Additionally, the FDP/D-dimer ratio was calculated and compared between the two groups. This approach was motivated by the understanding that during hyperfibrinolysis, the FDP/

D-dimer ratio tends to increase.¹⁵ Consequently, it was hypothesized that plasminogen activator inhibitor 1 secreted from an injured vascular endothelium caused by sepsis in patients with septic DIC would suppress fibrinolysis¹⁶ and exhibit a lower FDP/D-dimer ratio, providing a means for discrimination between the two groups. Indeed, the FDP/D-dimer ratio was significantly higher in the TTP group, and no TTP cases were observed with an FDP/D-dimer ratio below 1.93. Therefore, an FDP/D-dimer ratio below 1.93 was considered indicative of the absence of TTP. The PT-INR showed a greater AUC and a higher negative predictive value than this FDP/D-dimer ratio indicated that a PT-INR exceeding 1.07 rendered it improbable for a patient to have TTP. This observation suggests that despite the presence of elevated D-dimer levels in individuals with TTP, signifying the occurrence of fibrin thrombus formation, the extent of fibrin thrombus formation in TTP patients may be insufficient to precipitate a consumptive reduction in coagulation factors which prolong PT-INR.

There are various reports on LD levels in patients with TTP, and LD levels are considered very important in TTP. One is that the mortality rate increases when LD levels are 10 times higher than normal.¹⁷ Another is that substituting LD for the hemolysis indicator in the PLASMIC score has been reported as diagnostically useful, albeit with lower specificity.¹⁸ Moreover, Zhao et al¹⁹ considered that LD might be a potent element for the early diagnosis of TTP; however, they did not ascertain the usefulness of LD values in differentiating TTP from septic DIC. The present study demonstrated that the LD value showed greater AUC than D-dimer, FDP, FDP/D-dimer ratio, or PT-INR to identify TTP patients. Furthermore, the LD value has higher sensitivity and specificity, so that patients with LD values below 554 IU/L did not seem to be TTP patients. LD is present in various tissues, including the heart, red blood cells, liver, kidneys, brain, lungs, and skeletal muscles, and is elevated in many diseases. But elevated LD in patients with TTP may be due to hemolysis. Hence, in order to obtain a more representative measure of hemolysis severity in TTP, we employed the ratio of LD to Hb levels. As can be seen in Figure 1f, the LD/Hb ratio values showed the least overlap between TTP and septic DIC patients, and the ROC analysis showed a surprisingly high AUC of 0.96 in Table 2, which was considered excellent for selecting TTP patients. At a cutoff point of 53.7 IU/10 g, the sensitivity and specificity were 0.94 and 0.91, respectively. Furthermore, the NPV of the LD/Hb ratio for TTP was remarkably high at 96.7%, suggesting that an LD/Hb ratio below 53.7 IU/10 g effectively rules out TTP. The PLASMIC score incorporates the presence or absence of hemolysis, but as a measure of the degree of hemolysis, the LD/Hb ratio may provide additional information for a TTP diagnosis. Notably, the LD/Hb ratio was 53.7 IU/10 g or greater in 15 out of 16 TTP patients (all but 1 exceptional case mentioned in the results), whereas only 3 septic DIC patients with PLASMIC scores of 3 or 4 showed LD/Hb ratios above 53.7 IU/10 g. The cause of the elevated LD/Hb ratio in these septic DIC patients is likely due to rhabdomyolysis because they had an increased level of CK, which is

common in sepsis,²⁰ rather than hemolysis. Furthermore, the CK levels in these patients were over 1000 IU/ml, suggesting that if the cause of the elevated LD level is due to rhabdomyolysis, the condition may require an elevated CK above 1000 for the LD/Hb ratio to be above 53.7 IU/10 g.

From the above, we believe that the PLASMIC score and LD/Hb ratio can be used together to differentiate patients with TTP from those with septic DIC. In essence, irrespective of the presence or absence of schistocyte, when a patient exhibits a PLASMIC score ranging from 6 to 7, they can be classified as suffering from TTP. Moreover, even with a score falling between 4 and 5, if the LD/Hb ratio surpasses 53.7 IU/10 g and CK levels remain within the normal range, there is a strong likelihood of TTP manifestation. Naturally, by consulting other PT-INR values and FDP/D-dimer ratios as well, we can confidently ascertain the presence of TTP in patients as shown in this study.

There are several limitations to this study. The sample size is small and it is a retrospective study. Future prospective studies with larger sample sizes are needed. Although the septic DIC patients in this study had a variety of underlying diseases, LD and Hb may vary with an underlying diseases and should be investigated in septic DIC patients with more underlying diseases. However, in contrast to assessing ADAMTS13 levels or identifying the presence of schistocytes, the PLASMIC score and certain aforementioned laboratory test outcomes, notably the LD/Hb ratio, can be readily obtained from any clinical laboratory. These measurements hold the potential to distinguish TTP patients from those with septic DIC and encourage for prompt plasma exchange or caplacizumab administration.²¹

Conclusion

The combination of the LD/Hb ratio with the PLASMIC score may be useful to distinguish between TTP and septic DIC and to identify patients with TTP who need rapid plasma exchange.

Author Contributions

NN and KY performed data and sample collection, statistical analysis, interpretation of the results, and writing of the manuscript. NY, AK, AS, SS, HK, RY, SO, KS, MM, and HF performed data and sample collection. KY and KN designed the research, interpreted the results, and wrote the paper.



Declaration of Conflicting Interests


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