Observational Study

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Risk factors of trauma-induced thrombotic microangiopathy-like syndrome

A retrospective analysis

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Abstract

Patients with trauma may develop thrombocytopenia. We encountered cases wherein patients experienced symptoms resembling thrombotic microangiopathies (TMAs) following severe trauma. As the condition of these patients did not meet the diagnostic criteria of thrombotic thrombocytopenic purpura and there was no mention of trauma among the several causes of TMAs, it was termed as "trauma-induced thrombotic microangiopathy-like syndrome" (t-TMAS). In this study, we aimed to analyze the risk factors that may affect the incidence of t-TMAS in patients with severe trauma. This retrospective study was conducted in the trauma intensive care unit at the Kyungpook National University Hospital between January 2018 and December 2019. The medical records of 1164 of the 1392 enrolled participants were analyzed. To assess the risk factors of t-TMAS, we analyzed age, sex, mechanism of trauma, abbreviated injury scale (AIS) score, injury severity score (ISS), hematological examination, and red blood cell volume transfused in 24 hours. Among the 1164 patients, 20 (1.7%) were diagnosed with t-TMAS. The univariate analysis revealed higher age, ISS, and myoglobin, lactate, creatine kinase-myocardial band (on admission), creatine phosphokinase, lactate dehydrogenase (LDH), and lactate (day 2) levels in the t-TMAS group than in the non-t-TMAS group. The red blood cell volume transfused in 24 hours was higher in the t-TMAS group than in the non-t-TMAS group. t-TMAS was more common in patients with injuries in the chest, abdomen, and pelvis (AIS score ≥3) than in those with head injuries (AIS score ≥3) alone. The higher the sum of AIS scores of the chest, abdomen, and pelvis injuries, the higher the incidence of t-TMAS. Multivariate analysis revealed age, ISS, and LDH level (day 2) to be independent predictors of t-TMAS. Trauma surgeons should consider the possibility of t-TMAS if thrombocytopenia persists without any evidence of bleeding, particularly among older patients with multiple severe torso injuries who have high LDH levels on day 2. Early diagnosis and treatment of t-TMAS could improve patients' prognosis.

Abbreviations: ADAMTS13 = A Disintegrin and Metalloproteinase with Thrombospondin motifs 13, AIS = abbreviated injury scale, DIC = disseminated intravascular coagulopathy, HD = hemodialysis, HUS = hemolytic uremic syndrome, ISS = injury severity score, KNUH = Kyungpook National University Hospital, LDH = lactate dehydrogenase, PB = peripheral blood, RBC = red blood cell, ROC = receiver operating characteristic, RR = relative risk, RRT = renal replacement therapy, TICU = trauma intensive care unit, TMA(s) = thrombotic microangiopathy(s), TPE = therapeutic plasma exchange, t-TMAS = trauma-induced thrombotic microangiopathy-like syndrome, TTP = thrombotic thrombocytopenic purpura.

Keywords: risk factor, thrombocytopenia, thrombotic microangiopathy, trauma

1. Introduction

Thrombotic microangiopathies (TMAs), although rare in their occurrence, have various forms. Despite their diversity, different TMAs are integrated into one common condition that may be characterized by specific clinical and pathological features. The clinical features include microangiopathic hemolytic anemia, thrombocytopenia, and organ injury.[1] The pathological features include vascular damage that is manifested by arteriolar and capillary thromboses with characteristic abnormalities in the endothelium and vessel wall. The causes of TMA vary, and the names chosen for these syndromes reflect their causes.[2] However, there is no mention of trauma among the several causes of TMA and only a few studies report the incidence of TMA after trauma.[3,4] There have been several patients at our hospital who experienced TMA-like syndrome

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Data availability statement: The datasets generated or analyzed during this study are included in this published article. The corresponding author may provide specified analyses or fully de-identified parts of the dataset upon reasonable request.

All data generated or analyzed during this study are included in this published article [and itssupplementary information files]

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after severe trauma; their clinical courses, including response to treatment, were significantly similar to those of patients with thrombotic thrombocytopenic purpura (TTP), as A Disintegrin and Metalloproteinase with Thrombospondin motifs 13 (ADAMTS13) deficiency-mediated TMA. Thus, at first, we termed this condition "traumatic TTP." However, these patients did not have ADAMTS13 deficiency, as per the definition of TTP. Thus, we developed a new classification system for these patients, termed as "trauma-induced TMA-like syndrome" (t-TMAS).

Thrombocytopenia is a significantly serious problem for patients with severe trauma because most patients with severe traumas also have bleeding. If thrombocytopenia is caused by t-TMAS rather than by continuous bleeding, conventional treatments such as platelet transfusion can adversely affect the prognosis by promoting the formation of arteriolar platelet thrombi. The strategies of treatment are completely different depending on the cause of thrombocytopenia. Therefore, if factors that affect the occurrence of t-TMAS in severe trauma cases can be determined early on, they can aid in the early diagnosis of t-TMAS and ultimately improve patients' prognosis. This study aimed to analyze the characteristics of patients with trauma who experienced t-TMAS during their stay at the hospital and investigate the predictive factors of t-TMAS occurrence.

2. Methods

2.1. Data collection

We retrospectively examined 1392 patients who were admitted to the trauma intensive care unit (TICU) at Kyungpook National University Hospital (KNUH) from January 2018 to December 2019. Data on demographics, mechanism of trauma, volume of red blood cells (RBCs) transfused within 24 hours, laboratory findings, injury severity score (ISS), and abbreviated injury scale (AIS) score were collected prospectively. The results of serum laboratory tests that were performed at the time of admission, on the second day of hospitalization, and at the time of t-TMAS diagnosis, were analyzed.

2.2. Exclusion criteria

The patients who were discharged or died within 3 days from admission, those aged ≤17 years, or those who experienced non-acute traumatic events, such as chronic subdural hematoma, were excluded from the study. Additionally, patients who were transferred to our trauma center from another hospital after 24 hours were excluded (Fig. 1).

2.3. Diagnostic criteria of t-TMAS

The diagnostic criteria of t-TMAS in this study were as follows: history of recent acute traumatic events, persistent thrombocytopenia not improved by platelet transfusion after adequate hemostasis, hematological findings similar to those of microangiopathic hemolytic anemia (presence of schistocytes on peripheral blood [PB] smear examination, low haptoglobin level, high lactate dehydrogenase [LDH] level, and high bilirubin level on serum tests), and ruling out other conditions that could cause TMAs or produce schistocytes (disseminated intravascular coagulopathy [DIC], sepsis, drug-mediated TMA, hemolytic uremic syndrome [HUS], and complement-mediated TMA).[2]

2.4. Diagnostic algorithm of t-TMAS in KNUH

When the platelet count was sustained below the level of 100,000/μL for 3 days and when there was no response despite platelet transfusion after adequate hemostasis using conservative treatment and endovascular or surgical procedures, the possibility of DIC and sepsis was ruled out. In cases with normal laboratory profiles excluding DIC or sepsis, the possibility of t-TMAS was suspected and platelet transfusion was restricted unless absolutely necessary. Next, the assessment of the level of LDH and PB smear were performed immediately. If the level of LDH was higher than the normal value (<250 U/L), especially in cases with higher values than before, we strongly suspected the possibility of t-TMAS. When schistocytes were present on the PB smear, several other tests were performed to rule out other causes of TMA; Coombs test was performed to exclude autoimmune or drug mediated hemolytic anemia; C3 and C4 measurements were performed to exclude complement-mediated TMA; anti-nuclear antibody test was conducted to exclude autoimmune diseases such as lupus nephritis and acute scleroderma; stool culture was obtained to exclude HUS due to Shiga toxin-secreting bacterial infection; coagulation factor bundle was assessed to exclude coagulation factor deficiency; haptoglobin test was performed to confirm hemolytic anemia; and ADAMTS13 level was evaluated to confirm TTP. Consultation with a hematologist was conducted for the confirmation of diagnosis and the administration of methylprednisolone. Subsequently, when all other causes of TMA were ruled out, t-TMAS was diagnosed, and therapeutic plasma exchange (TPE) was immediately initiated (Fig. 2).

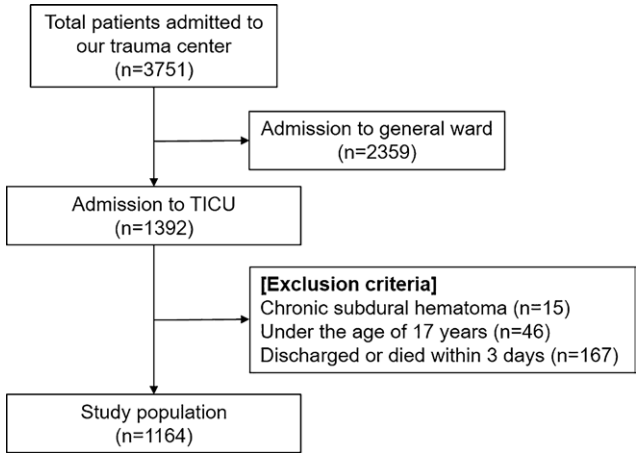


Figure 1. Flowchart depicting the patient selection procedure. TICU = trauma intensive care unit.

2.5. Classification of trauma severity

The degree of trauma severity was described based on the ISS and AIS. ISS is a validated tool used by specialists to quantify, in an objective and comparable manner, the overall severity of traumatic injuries sustained by an individual. To calculate ISS, each traumatic injury is assigned an AIS[5] score for the corresponding region of the body (head, face, chest, abdomen, extremities [including the pelvis], and external regions); the sum of the squares of the 3 highest AIS scores is the ISS.[6] The AIS score is generally assigned to each injury based on its location in 6 regions of the body, namely, the head (including neck and cervical spine), face, chest (including the thoracic spine), abdomen (including the lumbar spine), extremities (including the pelvis), and external regions. However, we classified the AIS into the head, neck, C-spine, chest, T-spine, abdomen, L-spine, pelvis, extremities, and external regions to accurately reflect the damage at each anatomical region. Moreover, in case of multiple injuries in the same anatomical region, the sum of AIS scores was calculated by adding each AIS score in the same region to give weight.

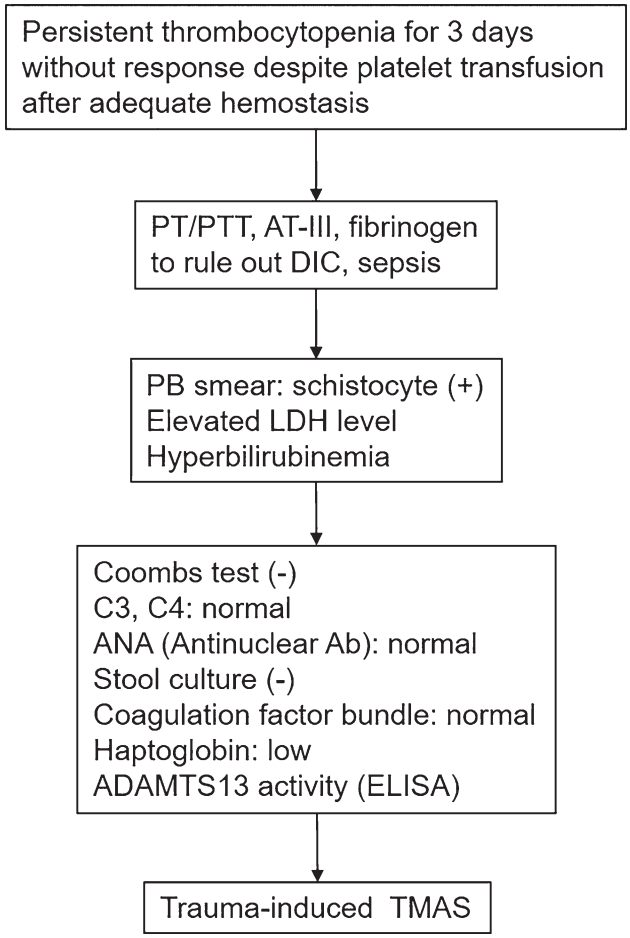


Figure 2. Diagnostic algorithm of trauma-induced thrombotic microangiopathy-like syndrome. ADAMTS13 = A Disintegrin and Metalloproteinase with Thrombospondin motifs 13, AT = antithrombin, DIC = disseminated intravascular coagulopathy, ELISA = enzyme linked immunosorbent assay, LDH = lactate dehydrogenase, PB = peripheral blood, PT = prothrombin time, PTT = partial thromboplastin time, TMAS = thrombotic microangiopathy-like syndrome.

2.6. Treatment of t-TMAS at KNUH

When the patient was diagnosed with t-TMAS, TPE with or without methylprednisolone was administered as the first-line treatment as soon as possible. Methylprednisolone alone was administered if the patient refused TPE or when the patient was hemodynamically unstable. The endpoint of TPE was the time when the platelet count exceeded 150,000/μL and LDH level was normalized. In patients with acute renal failure, renal replacement therapy (RRT) in the form of continuous RRT was initiated, which was replaced with conventional hemodialysis (HD) when the patient's condition stabilized.

2.7. Statistical analysis

Patients were divided into the TMAS and non-TMAS groups for comparative analysis of variables. Statistical analysis was performed using a commercial software (SPSS for Windows, version 22.0, SPSS, Inc., Chicago, IL). Data were evaluated for normality before statistically analyzing them using the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as absolute numbers and/or percentages. Normally distributed continuous variables were compared using the Student *t* test, and non-normally distributed variables were analyzed using the Mann–Whitney *U* test. Categorical variables were analyzed using either the Pearson chi-squared test or Fisher exact test, as appropriate. To analyze the relative risk (RR), among the continuous variables that were statistically significant in the univariate analysis, continuous variables with an area under the curve of 0.75 or more in the receiver operating characteristic curve were converted to categorical variables. The receiver operating characteristic curve was plotted to obtain an optimal cut-off value for the volume of transfused RBCs within 24 hours, age, and the level of LDH on day 2 based on Youden index (Fig. 3). The association between parameters recorded in our database and the incidence of t-TMAS was tested by performing binary logistic regression analysis. To avoid overfitting, only those factors that were significantly associated ($P < .05$) with the main outcome were used to build multivariate forward stepwise logistic regression models to determine if they were independent predictors of t-TMAS. For all statistical tests, P values <.05 were considered significant.

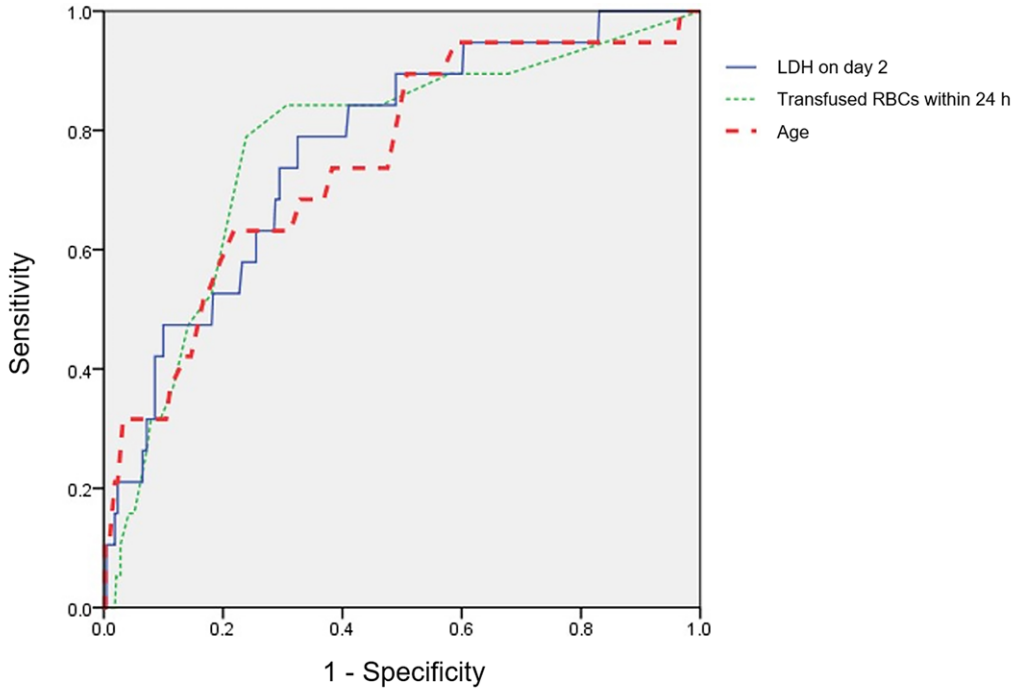
This retrospective study was approved by the KNUH Institutional Review Board (KNUH 2020-07-005). As all data were anonymized and the study posed no significant risks and was retrospective, the requirement for written informed consent was waived.

3. Results

From January 2018 to December 2019, 3751 patients were admitted to our trauma center, of whom 1392 were admitted to the TICU. Among those admitted to the TICU, after excluding patients who did not meet the inclusion criteria, 1164 patients were enrolled. Twenty of the 1164 patients were diagnosed with t-TMAS according to the above-mentioned diagnostic criteria. These accounted for 0.53% of the 3751 patients admitted due to trauma and 1.72% of the 1164 patients admitted to the TICU.

Of these patients, 14 (70%) were men, and the mean age was 71 years. Regarding the clinical features of 20 patients diagnosed with t-TMAS, digital necrosis was noted in 10 patients (50%), alteration of mental status in 11 (55%), and non-infectious fever in 9 (45%) at the time of diagnosis of t-TMAS. Seventeen (85%) patients required RRT owing to acute renal failure, and 5 of the 12 surviving patients transitioned to a state of chronic renal failure and required HD even after discharge. The ADAMTS13 test was performed for 19 patients, of whom 4 had ADAMTS13 deficiency (activity < 40%) and one had ADAMTS13 activity ≤10% (diagnostic criteria of TTP[7]). Digital necrosis was noted in 10 patients (50%), alteration of mental status in 11 (55%), and non-infectious fever in 9 (45%). TPE with or without methylprednisolone was administered in 17 patients for an average of 5.9 ± 4.3 days, and 3 patients who refused to undergo TPE were treated with methylprednisolone only. Among the 20 patients who received first-line treatment (TPE or methylprednisolone), 18 achieved remission. The condition of the patient who was unresponsive to TPE improved after the administration of rituximab, a monoclonal antibody against CD20 (Tables 1 and 2).

When comparing the t-TMAS (n = 20) and non-t-TMAS (n = 1144) groups, there was no difference in the sex ratio between the 2 groups. Age and ISS were significantly higher in the t-TMAS group than in the non-t-TMAS group. Penetrating trauma was absent in the t-TMAS group. Levels of myoglobin, lactate, and creatine kinase-myocardial band were significantly higher in the t-TMAS group at admission and those of creatine phosphokinase, LDH, and lactate were significantly higher in the t-TMAS group on day 2 than in the non-t-TMAS group. The volume of RBCs transfused within 24 hours after admission was significantly higher in the t-TMAS group than in the non-t-TMAS group. Analysis of the severity of injury according to the site of injury revealed that the patients with t-TMAS had significantly more injuries with AIS ≥3 in the chest, abdomen,



Variable	AUC	p-value	95% CI	Cut-off value	Sensitivity	Specificity
LDH on day 2	0.770	0.000	0.669–0.872	500 U/L	73.7 %	69.8 %
Transfused RBCs within 24 h	0.772	0.000	0.662–0.883	5 units	78.9 %	76.1 %
Age	0.750	0.000	0.635–0.866	65 years	68.4 %	67.1 %

Figure 3. Receiver operating characteristic (ROC) curve. AUC = area under the curve, CI = confidence interval, LDH = lactate dehydrogenase, RBC = red blood cell.

and pelvis compared with the non-t-TMAS group. Notably, the incidence of t-TMAS was significantly lower in patients with injuries in the head with AIS ≥3 (Table 3). The RR of t-TMAS occurrence was increased in patients with injuries of AIS ≥3 in the chest, pelvis, and abdomen (RR, 4.23; 95% confidence interval [CI]: 1.64–10.92; P = .001; RR, 3.91 [95% CI: 1.53–9.97], P = .002; and RR, 2.77 [95% CI: 1.02–7.49], P = .038, respectively). Furthermore, the risk of t-TMAS was higher in patients who were transfused with ≥5 units of RBCs, in patients who were aged over 65 years, and in those with LDH level ≥500 U/L on day 2 (RR, 22.34 [95% CI: 7.54–65.94], P < .001; RR, 3.70 [95% CI: 1.43–9.56], P = .004; RR, 5.97 [95% CI: 2.19–16.26], P < .001, respectively). However, the RR of t-TMAS occurrence was lower in patients with injuries with AIS ≥3 in the head and AIS < 3 in other sites (RR, 0.13 [95% CI: 0.02–0.98], P = .019) (Table 4).

On multivariate analysis, age, ISS, and LDH level on day 2 were found to be independent predictors for the development of t-TMAS (Table 5).

4. Discussion

TMA, first described by Symmers in 1952,[8] is defined as a lesion of vessel wall thickening (mainly arterioles or capillaries) with swelling or detachment of endothelial cells from the basement membrane, accumulation of fluffy material in the subendothelial space, intraluminal platelet thrombosis, and partial or complete obstruction of the vessel lumen.[9] TMA is a life-threatening condition and a case of medical emergency. Hematological features such as thrombocytopenia and hemolytic anemia are almost always present in patients with TMA lesions, which reflect the consumption of platelets and disruption of RBCs in the microvasculature.

George and Nester classified TMAs into 9 disorders and are described as primary TMA syndrome, for which there is evidence supporting a defined abnormality as probable cause.[2] The nomenclature chosen for these syndromes reflects their cause. However, common names, such as TTP for ADMATS13 deficiency-mediated TMA and HUS for Shiga toxin-mediated TMA, are more familiar. The presence of a causal abnormality, such as ADAMTS13 deficiency or a complement mutation, may not be clinically expressed until a condition, such as pregnancy, surgery, or an inflammatory disorder, precipitates an acute TMA episode.[2]

TTP, the most commonly occurring TMA, is characterized by a deficiency of von Willebrand factor cleaving protease (i.e., ADAMTS13). ADAMTS13 cleaves the multimers of von Willebrand factor secreted by a vascular endothelial cell. However, in ADAMTS13-deficient individuals, large multimers of von Willebrand factor are not cleaved resulting in an increased risk of platelet aggregation in small vessels.[1] Historically, TTP is characterized by a pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms, and renal failure. TTP requires rapid diagnosis and urgent treatment.

In our experience, several patients with severe trauma develop TMA, with their clinical course similar to that of TTP; however, they did not satisfy the condition of ADAMTS13 deficiency. Thus, it is controversial to diagnose these patients with TTP. Therefore, we defined their diagnosis as t-TMAS in this study. Although similar to TTP, t-TMAS has some differences. First, TTP is more common in patients aged 32 to 59 years,[10] whereas t-TMAS is more prevalent in older patients. Second, the incidence of TTP is more common in women than in men,[10] whereas our analysis in patients with t-TMAS revealed that there was no significant difference between the sexes. Third, the rate of incidence of acute renal failure was higher in patients

Table 1

Clinical findings and outcomes of patients with trauma-induced thrombotic microangiopathy-like syndrome.

No.	Sex	Age, yrs	ISS	Trauma mechanism	Hospital stay, d	Fever	Mental fluctuation	Digital necrosis	RRT	Transition to CRF	TPE	Remission	Mortality (cause of death)
1	F	71	17	Blunt	65						+	+	
2	M	86	4	Blunt	29	+	+		+		+	+	+ (AMI)
3	F	87	22	Blunt	70		+		+	+	+	+	
4	F	84	16	Blunt	52		+	+	+		+	+	
5	M	76	27	Blunt	8		+		+		+	-	+ (MOF, Cbr. infarct)
6	M	65	29	Blunt	88	+		+	+		+	+	
7	M	57	25	Blunt	37		+		+	+	+	+	
8	M	83	25	Blunt	25		+	+	+	+	+	+ (Rituximab)	+ (Sepsis)
9	M	89	21	Blunt	36			+				+	
10	M	58	22	Blunt	97	+	+		+	+		+	
11	M	70	16	Blunt	72	+		+	+		+	+	
12	M	63	38	Blunt	73	+	+	+	+	+	+	+	
13	F	21	34	Blunt	209			+	+		+	+	
14	M	58	33	Blunt	65	+		+	+	+	+	+	
15	M	77	27	Blunt	20			+	+	+	+	+	+ (Pneumonia)
16	F	74	22	Blunt	66			+	+	+	+	+	+ (Pneumonia)
17	M	54	24	Blunt	43		+		+		+	+	
18	F	87	9	Blunt	85	+			+		+	+	
19	M	89	43	Blunt	24		+		+			+	
20	M	74	25	Blunt	58	+					+	+	

Cbr. = cerebral, CRF = chronic renal failure, F = female, ISS = injury severity score, M = male, MOF = multi-organ failure, No. = patient number, RRT = renal replacement therapy, TPE = therapeutic plasma exchange.

Table 2

Laboratory findings of patients with trauma-induced thrombotic microangiopathy-like syndrome at the time of diagnosis.

No. Normal range	BUN, mg/dL <20	Cr, mg/dL <1.2	Platelet (10^3/μL) 130–400	LDH, U/L <250	Schistocyte, % 0	Haptoglobin, mg/dL 30–200	Bilirubin (total/direct), mg/dL <1.20/0.01–0.30	ADAMTS13 activity, % >40
1	46	1.01	64	708	2–3	<10	1.73/1.01	98
2	16.1	1.9	40	915	3	13	9.19/6.75	106
3	21.6	1.22	42	519	1–2	<10	4.08/3.04	97
4	39.5	2.05	56	1430	4	<10	1.9/0.76	86
5	23	1.6	52	1265	9	<10	7.95/5.56	50
6	27.5	1.17	28	617	2–3	<10	2.51/0.9	95
7	31.7	3.02	38	3020	13-14	<10	1.05/0.46	54
8	36.7	1.77	20	587	2–3	<10	6.58/4.73	49
9	18.9	0.51	55	475	1–2	<10	1.92/0.79	Not checked
10	22.1	2.08	54	1737	2–3	<10	8.22/7.48	46
11	8.6	2.02	18	1352	2–3	<10	11.44/9.39	0
12	38.9	1.82	24	3509	5–6	<10	3.74/2.01	28
13	38.8	3.86	19	1139	2–3	<10	3.94/2.61	34
14	72.7	3.00	64	4117	13	<10	41/37.03	60
15	30.5	2.64	46	698	4–5	<10	10/7.51	43
16	25.2	1.83	48	1073	3	<10	2.71/1.01	53
17	54.2	3.41	25	1405	2–3	<10	1.63/0.87	63
18	28.8	0.94	19	321	1	31	1.10/0.64	41
19	29.8	1.61	40	583	1	39	6.97/4.82	71
20	69.8	3.15	42	1709	2–3	<10	1.94/0.86	62

ADAMTS13 = A Disintegrin and Metalloproteinase with Thrombospondin motifs 13, BUN = blood urea nitrogen, Cr = creatinine.

with t-TMAS than in those with TTP; among the formers, 85% patients required RRT, and 5 of the 12 surviving patients developed chronic renal failure, resulting in the need for permanent HD, whereas this rarely occurs in the latter group.[11] However, the incidence rate of acute renal failure in t-TMAS was similar to that observed in patients with complement-mediated TMA and Shiga toxin-mediated TMA.[2] This difference is mainly due to extensive microvascular thrombosis in the kidneys of patients with TTP, as opposed to injury to residual renal cells and endothelial cells in addition to microvascular thrombosis in other TMAs.[2,12] These variations in the clinical manifestations of TMA syndromes emphasize the need for greater understanding of the mechanisms of the disease.[2] Therefore, t-TMAS is considered to have such a cause; however, further studies using renal biopsy are warranted to understand the underlying mechanism of t-TMAS.

In patients with multiple severe traumas, thrombocytopenia is a significantly serious problem. Therefore, prompt platelet transfusion is required to prevent unexpected bleeding, and the control of active bleeding is essential to prevent consumptive thrombocytopenia. However, in the case of thrombocytopenia caused by t-TMAS, platelet transfusion further promotes the formation of arteriolar platelet thrombi, which exacerbates organ injury; for this reason, platelet transfusion should be minimized and used only when absolutely necessary.[13] Therefore, if the diagnosis of t-TMAS is delayed, inappropriate treatment

Table 3

Comparison of characteristics between groups with or without trauma-induced thrombotic microangiopathy-like syndrome using univariate analysis.

Factors	Non-t-TMAS group (n = 1144)	t-TMAS group (n = 20)	P-value
Sex [female], %	283 (24.7)	6 (30.0)	.604
Mechanism of trauma [penetrating], %	47 (4.1)	0 (0.0)	1.000
Age, yrs	58.2 ± 17.9	71.0 ± 16.8	.000*
ISS	18.4 ± 9.9	23.9 ± 9.2	.007*
On arrival CPK, U/L	839.3 ± 3705.6	811.5 ± 945.5	.065*
LDH, U/L	466.9 ± 375.5	826.9 ± 1078.9	.170*
Myoglobin, ng/mL	1120.6 ± 1675.7	3043.7 ± 3153.4	.000*
Lactate, mmol/L	3.2 ± 2.5	5.8 ± 4.4	.002*
D-dimer, μg/mL	45.7 ± 45.3	74.2 ± 53.2	.124*
CK-MB, ng/mL	13.2 ± 68.8	15.3 ± 15.8	.003*
Day 2 CPK, U/L	2510.0 ± 6841.3	2706.2 ± 1872.5	.004*
LDH, U/L	518.4 ± 575.1	1192.5 ± 1301.3	.000*
Myoglobin, ng/mL	875.3 ± 1606.3	2924.7 ± 3608.2	.063*
Lactate, mmol/L	2.5 ± 2.3	4.1 ± 4.4	.033*
Transfused RBC within 24 h (units)	2.4 ± 4.2	8.7 ± 5.4	.000*
AIS (head) =3	489 (42.7%)	4 (20.0%)	.041
AIS (chest) =3	400 (35.0%)	14 (70.0%)	.001
AIS (abdomen) =3	120 (10.5%)	5 (25.0%)	.054
AIS (pelvis) =3	109 (9.5%)	6 (30.0%)	.010
AIS (extremity) =3	166 (14.5%)	3 (15.0%)	1.000
AIS (C-spine) =3	86 (7.5%)	1 (5.0%)	1.000
AIS (T-spine) =3	31 (2.7%)	0 (0%)	1.000
AIS (L-spine) =3	33 (2.9%)	1 (5.0%)	.450
AIS (head =3, others	331 (28.9%)	1 (5.0%)	.019
Sum AIS (head)	3.56 ± 4.68	1.75 ± 3.26	.085*
Sum AIS (chest)	2.30 ± 3.29	5.05 ± 4.22	.001*
Sum AIS (abdomen)	0.93 ± 1.88	2.35 ± 3.27	.004*
Sum AIS (pelvis)	0.52 ± 1.22	1.55 ± 2.19	.005*
Sum AIS (extremity)	2.00 ± 3.51	2.50 ± 3.35	.313*

AIS = abbreviated injury scale, CK-MB = creatine kinase-myocardial band, CPK = creatinine phosphokinase, ISS = injury severity score, LDH = lactate dehydrogenase, TMAS = thrombotic microangiopathy-like syndrome.

*Statistical significance was assessed using the Mann–Whitney *U* test.

Table 4

Estimated relative risks for trauma-induced thrombotic microangiopathy-like syndrome.

Covariates	*P*-value	Relative risk	95% CI
AIS (chest) =3	.001	4.23	1.637–10.917
AIS (abdomen) =3	.038	2.77	1.024–7.494
AIS (pelvis) =3	.002	3.91	1.532–9.976
[Table_Body]AIS (head =3, others	.019	0.13	0.018–0.981
Age =65 years	.004	3.70	1.433–9.564
Transfused RBC within 24 h =5 units		22.34	7.545–65.939
LDH on day 2 =500 U/L		5.97	2.192–16.255

AIS = abbreviated injury scale, CI = confidence interval, LDH = lactate dehydrogenase.

Table 5

Logistic regression analysis for the risk factors associated with trauma-induced thrombotic microangiopathy-like syndrome.

Risk factor	*P*-value	Odds ratio	95% CI
Age		1.161	1.075–1.254
ISS	.001	1.269	1.107–1.454
LDH on day 2	.011	1.002	1.001–1.003

CI = confidence interval, ISS = injury severity score, LDH = lactate dehydrogenase.

may worsen the patient prognosis. The incidence of t-TMAS was found to be significantly low in this study (1.72% of the severe trauma patients admitted to the TICU at KNUH); moreover, diagnosis of t-TMAS is challenging. It is difficult to suspect this disease in patients with multiple severe injuries who develop thrombocytopenia owing to various causes. Hence, the treatment of t-TMAS is often delayed. If the occurrence of t-TMAS could be predicted during the initial evaluation of patients with severe trauma, it would be helpful in early diagnosis.

The underlying pathogenesis of TMA is considered to be endothelial cell injury due to several causes (Shiga toxin, quinine, chemotherapy agents, calcineurin inhibitor, malignant hypertension).[14] Furthermore, we believe that direct mechanical injury to the endothelium by a massive blunt trauma may induce TMA. Several studies have described the cause of post-traumatic or postoperative TMA as direct damage to endothelial cells of vessels. Injured endothelial cells from a major trauma or extensive surgery may result in decreased thrombomodulin synthesis, enhanced induction of tissue factor, and production of unusually large von Willebrand factor multimers.[15] It was hypothesized that a direct massive blunt injury induces the vessel endothelium to produce high level of unusually large von Willebrand factor multimers, which are higher than the level that can be processed by ADAMTS13.[4] Moreover, decreased thrombomodulin would lead to an inefficient protein C-dependent anticoagulant pathway, and an increased tissue factor supply would cause activation of factor VII. Both events would cause intravascular thrombosis.[4,15] In our study, the incidence of t-TMAS was higher in patients with excessive bleeding owing to severe injuries in the chest, abdomen, and pelvis with an AIS score ≥3. All patients with t-TMAS in the current study had experienced blunt traumas, and when traumatic brain injury was the main injury, there were few patients with t-TMAS. These results suggest that the more severe the injury of the endothelial cells of vessels owing to blunt trauma, the higher the incidence of t-TMAS. In addition, these findings could support the pathogenesis of t-TMAS suggested by several previous researchers,[4,15] and explain the lack of ADAMTS13 deficiency in patients with t-TMAS.

In patients with severe trauma, thrombocytopenia owing to bleeding is a significantly common symptom. As severe thrombocytopenia in acute traumatic patients increases the risk of serious consequences such as cerebral hemorrhage, it needs immediate intervention. However, if thrombocytopenia persists despite platelet transfusion and there is no evidence of ongoing bleeding, subsequent treatment decisions can be challenging for surgeons, particularly in cases where thrombocytopenia is accompanied by acute renal failure. In such situations, survival can be improved by diagnosing t-TMAS and administering TPE promptly, considering t-TMAS to be the cause of thrombocytopenia. This is evident from the fact that the survival rate of patients with TTP was 10% previously but was improved to 78% when TPE was administered.[16] The patients in our study achieved a 95% remission rate and 75% survival rate through active and prompt treatment.

This study has some limitations. First, t-TMAS is a new term that has not been presented previously and is defined by the author arbitrarily; therefore, consensus between expert groups on this new classification is required. We believe that trauma can induce t-TMAS through the above-mentioned mechanism and further study will unmask the pathogenesis of this clinical category. Second, in patients with suspected t-TMAS, diagnosis and treatment of t-TMAS were performed according to a predetermined algorithm, and data on patients were collected prospectively; however, the same tests were not performed in all patients who were admitted to the TICU. Third, the number of subjects was significantly small. Fourth, this study was a retrospective analysis. Hence, selection bias is inevitable. Therefore, future studies in a larger cohort are required to corroborate these results.

5. Conclusion

If thrombocytopenia persists without any evidence of bleeding, and if older patients with multiple severe torso injuries have high LDH levels on day 2, trauma surgeons should consider the possibility of t-TMAS. This would lead to rapid diagnosis and treatment, thereby improving patient's prognosis.

Author contributions

Kyoung Hoon Lim conceived of and designed the study. Kyoung Hoon Lim and Sung Hoon Cho contributed the primary data. Kyoung Hoon Lim performed the data analysis. Kyoung Hoon Lim, Jinyoung Park, and Sung Hoon Cho cared for patients. Kyoung Hoon Lim and Jinyoung Park contributed to interpretation of results. Kyoung Hoon Lim contributed to writing-original draft. All authors revised the draft for important intellectual content. All authors read and approved the final manuscript submitted for publication.
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References

[1] Moake JL. Thrombotic microangiopathies. N Engl J Med 2002;347:589–600.
[2] George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med 2014;371:654–66.
[3] Lim KH, Park J. Thrombotic thrombocytopenic purpura after blunt traumatic liver injury. Am J Emerg Med 2016;34:939.e3–4.
[4] Ikegami K, Yamagishi T, Tajima J, et al. Post-traumatic thrombotic microangiopathy following pelvic fracture treated with transcatheter arterial embolization: a case report. J Med Case Rep 2018;12:216.
[5] Gennarelli TA, Wodzin E. Abbreviated Injury Scale 2005: Update 2008. Barrington, IL: Association for the Advancement of Automative Medicine; 2008.
[6] Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14:187–96.
[7] Sadler JE. What's new in the diagnosis and pathophysiology of thrombotic thrombocytopenic purpura. Hematology Am Soc Hematol Educ Program 2015;2015:631–6.
[8] Symmers WS. Thrombotic microangiopathic haemolytic anaemia (thrombotic microangiopathy). Br Med J 1952;2:897–903.
[9] Remuzzi G. RP, Bertani T. Thrombotic Microangiopathies, in Renal Pathology: With Clinical and Functional Correlations. 1994; Lippincott Company.
[10] Mariotte E, Azoulay E, Galicier L, et al. Epidemiology and pathophysiology of adulthood-onset thrombotic microangiopathy with severe ADAMTS13 deficiency (thrombotic thrombocytopenic purpura): a cross-sectional analysis of the French national registry for thrombotic microangiopathy. Lancet Haematol 2016;3:e237–45.
[11] George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood 2010;116:4060–9.
[12] Hosler GA, Cusumano AM, Hutchins GM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are distinct pathologic entities. A review of 56 autopsy cases. Arch Pathol Lab Med 2003;127:834–9.
[13] Goel R, Ness PM, Takemoto CM, Krishnamurti L, King KE, Tobian AA. Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality. Blood 2015;125:1470–6.
[14] Goldberg RJ, Nakagawa T, Johnson RJ, Thurman JM. The role of endothelial cell injury in thrombotic microangiopathy. Am J Kidney Dis 2010;56:1168–74.
[15] Eskazan AE, Buyuktas D, Soysal T. Postoperative thrombotic thrombocytopenic purpura. Surg Today 2015;45:8–16.
[16] Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 1991;325:393–7.