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ORIGINAL ARTICLE

Clinical dissection of thrombotic microangiopathy

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Abstract Differential treatment strategies are applied in thrombotic microangiopathy (TMA) according to the sub-classifications. Hence, it is worthwhile to overview clinical manifestations and outcomes of overall TMA patients according to sub-classifications. We analyzed TMA patients whose serum lactate dehydrogenase levels >250 IU/L, with the presence of schistocytes in their peripheral blood smear, or with typical vascular pathologic abnormalities in their renal biopsy. We compared clinical manifestations including overall survival (OS) and renal survival according to TMA causes. A total of 117 TMA patients (57 primary and 60 secondary TMA) were analyzed. Renal symptom was the most common manifestation in whole patients, while renal function at diagnosis was worst in pregnancy-related TMA group. Primary TMA patients had more frequent CNS symptom and hematologic manifestation compared to secondary TMAs. Among secondary TMAs, pregnancy- and HSCT-related TMA patients showed prevalent hemolytic features. During 150.2 months of follow-up, 5-year OS rate was 64.8%. Poor prognostic factors included older age, combined hematologic and solid organ malignancies, lower hemoglobin levels, and lower serum albumin levels. There was no significant difference in OS between primary and secondary TMAs. Seventy-eight percent of patients experienced AKI during TMA. Five-year death-censored renal survival rate was poor with only 69.2%. However, excellent renal outcome was observed in pregnancy-associated TMA. TMA showed various clinical manifestations according to their etiology. Notably, both OS and renal survival were poor regardless of their etiologies except pregnancy-associated TMA. Physicians should differentiate a variety of TMA categories and properly manage this complex disease entity.

Keywords Thrombotic microangiopathy · Clinical manifestation · Hemolytic uremic syndrome

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Introduction

Thrombotic microangiopathy (TMA) is a disease defined by various clinical features including thrombocytopenia, microangiopathic hemolytic anemia, and pathologic features such as endothelial damage, and arteriolar and capillary thrombosis in the endothelium and vessel wall [1] of end organs [2]. Thrombotic thrombocytopenia purpura (TTP) is caused by the disruption of von Willebrand factor (vWF) multimer processing [3] and atypical hemolytic uremic syndrome (aHUS)

caused by uncontrolled complement activation [4], which are representative of the disease entity of TMA. Recently, TMA has been classified into nine categories according to initiating factors, a hereditary component, and pathophysiologic mechanism [1]. In addition, there are many other types of TMA triggered by drug toxicities, bacterial toxins, autoantibodies, uncontrolled malignancies, pregnancies, and malignant hypertension.

With the advent of sub-classifications of TMA based on the understanding of TMA pathophysiology, recent studies have focused on molecular mechanisms in the disease development or features of specific types of TMA. However, the sub-classification of TMA in clinical practice is not always evident within a short time mostly due to limitations in certain laboratory tests. Hence, presumed TMA patients are classified according to readily available lab tests and their symptoms at first sight. Patients with TMA may present with various symptoms including cerebral dysfunction, acute kidney injury (AKI), gastrointestinal symptoms, bleeding diathesis, and symptoms related to anemia. For this regard, detailed description of clinical manifestations of whole TMA patients and analysis according to specific TMA etiology is still valuable. The analysis of the clinical feature of the whole TMA patients is also important, because TMA patients are treated by physicians with diverse specialties including hematology, nephrology, and gastroenterology.

However, not many studies regarding the clinical features of all types of TMA have been performed previously. Therefore, we decided to describe the clinical features of overall TMA based on their etiologies. We aimed to (1) determine the difference in main clinical manifestations among diverse types of TMA, (2) investigate the difference between primary and secondary TMA, and (3) investigate patients and renal outcomes in overall TMAs. Our goal was to provide epidemiologic data and a guide for the diagnosis and classification of TMA according to the clinical manifestations.

Materials and methods

Study design and population

A retrospective analysis was conducted including patients who were diagnosed as having TMA from January 2005 to October 2015 at a tertiary hospital in Korea. Diagnostic criteria for TMA included (1) elevated serum lactate dehydrogenase (LDH) level over 250 IU/L (reference range 110 to 225 IU/L) and the presence of schistocytes in peripheral blood smear (PBS), or (2) typical vascular pathologic abnormalities involving renal arterioles and glomerular capillary walls in their percutaneous renal biopsy specimen. Patients were excluded if they were aged <18 years or had clinical symptoms and signs more indicative of disseminated intravascular coagulopathy rather than TMA according to clinicians' detailed review (Fig. 1).

Classification of TMA

To clarify clinical characteristics of the TMA subgroups considering the various pathogenesis, we followed the classification from previous review paper [1] and consensus article published in 2017 [5]. First, we divided all patients into

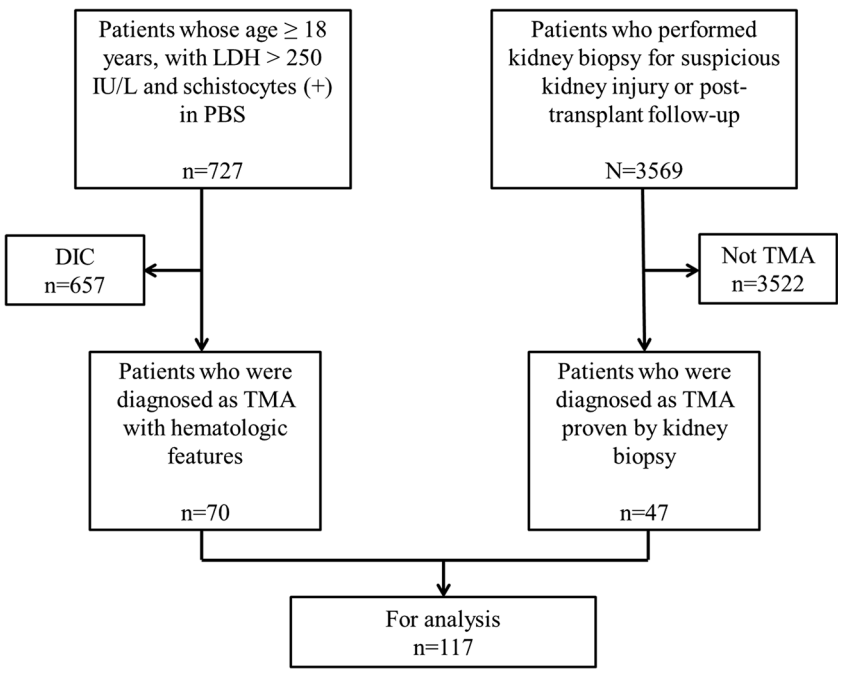

Fig. 1 Retrospective cohort design and study flow chart. *LDH* lactate dehydrogenase, *PBS* peripheral blood smear, *DIC* disseminated intravascular coagulopathy; *TMA* thrombotic microangiopathy

primary and secondary TMAs. Secondary TMA was defined when there were definite causes of TMA, including hematopoietic stem cell transplantation (HSCT), transplantation (TPL) of solid organs, malignant neoplasms, pregnancy, autoimmune diseases, and malignant hypertension. The remaining patients were classified as having primary TMA. Primary TMA syndromes included a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency-mediated TMA (thrombotic thrombocytopenic purpura, TTP), Shiga toxin-mediated TMA (Shiga toxin hemolytic uremic syndrome, ST-HUS), drug-mediated TMA, and hemolytic uremic syndrome with non-infectious cause (HUS-NI). Except for ST-HUS and drug-mediated TMA, we sorted other primary TMA based on ADMATS13 activity of 10%; patients whose ADAMTS13 activity was <10% were classified as having TTP [6], and the remaining patients were classified as having HUS-NI. Patients in whom the ADAMTS13 activity was not measured were classified in the primary TMA undetermined group.

Evaluation and measurements

Information about initial clinical manifestations was reviewed via electronic medical record (EMR). We classified clinical manifestation at diagnosis into five symptoms: hematologic symptoms including dizziness or bleeding, renal symptoms such as decreased urine output or edema, gastrointestinal symptoms including abdominal pain or diarrhea, symptoms of the central nervous system (CNS) such as altered mentality, seizure, or sided weakness and other symptoms such as fever. Fever was based on a body temperature more than 37.7 °C.

Clinical variables such as age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS) at diagnosis, body weight and height, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission, comorbidities including diabetes mellitus (DM), hypertension, ischemic heart disease, heart failure, liver cirrhosis, chronic lung disease, brain infarction or hemorrhage, hematologic malignancies, solid organ malignancy, and autoimmune diseases were obtained from EMR.

Regarding hematologic features, we collected a hemogram (white blood cell count (reference range 4–10 × 10^3/uL), hemoglobin (Hb) (reference range 12–16 g/dL), and platelet (PLT) count (reference range 130–400 × 10^3/uL)), plasma Hb (reference range 0–5 mg/dL), haptoglobin (reference range 30–180 mg/dL), and coagulation profiles (reference range 9.8–12.9 s for prothrombin time (PT), 26.7–37.6 s for activated partial thromboplastin time (aPTT), 192–411 mg/dL for fibrinogen) at the time of diagnosis. Schistocytes in PBS were classified into two groups (yes or no), regardless of the number of schistocytes in high-power field. ADAMTS13 was measured by using the sodium dodecyl sulfate-agarose gel electrophoresis with its activity at one central laboratory in Korea [7].

We also collected chemistry profiles, including the levels of blood urea nitrogen (BUN) (reference range 10–26 mg/dL), serum creatinine (reference range 0.7–1.4 mg/dL), total protein (reference range 6–8 g/dL), albumin (reference range 3.3–5.2 g/dL), complement component 3 (C3) (reference range 70–150 mg/dL), and complement component 4 (C4) (reference range 10–35 mg/dL) at the diagnosis. Renal function was calculated using the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula. The presence of albuminuria was defined as more than two positive in the urine dipstick.

Baseline serum creatinine was defined as the lowest serum creatinine level within 3 months before TMA diagnosis. If there was no serum creatinine level within 3 months, we expanded the duration until 6 months before TMA diagnosis. Baseline renal function was classified into five categories: normal, chronic kidney disease (eGFR 15–60 mL/min/1.73 m^2), end-stage renal disease (ESRD, eGFR <15 mL/min/1.73 m^2), transplanted kidney, and unknown renal function. AKI was defined as an increase in the serum creatinine level by 0.3 mg/dL or more within 48 h, or an increase in the serum creatinine to 1.5 times or more than the baseline value [8] within 7 days after admission. For evaluating AKI, patients who were ESRD or had unknown renal function were excluded. In kidney TPL recipients, we regarded AKI event as delayed graft function or delayed renal function improvement.

Outcomes

Overall survival (OS) was defined as the time from the date of diagnosis of TMA to the date of death or the last follow-up. Death data was obtained from EMR review and the Korean Statistical Information Service (KOSIS) data. Renal survival was defined as renal function deterioration to ESRD who was depended on maintenance renal replacement therapy (RRT). ESRD data was collected from EMR or the Korean Society of Nephrology (KSN) ESRD registry. We excluded patients with known ESRD status and those who died within 3 months (early death) in renal survival analysis. Death with a functioning kidney was included as maintenance of renal function in the analysis of renal survival. We defined the relapse as cases which required retreatment such as plasmapheresis or steroid for an evidence of hemolysis or target organ damage as aggravated renal function.

Statistical analysis

To identify the difference among each subgroup of TMA, we analyzed baseline characteristics. For descriptive statistics, continuous variables were presented as a mean ± SD, and categorical variables are expressed as a proportion and frequency. To

compare the difference between primary and secondary TMAs, we used the Student *t* test and Wilcoxon rank-sum test to analyze continuous variables and the chi-square test and the Shapiro-Wilk test to analyze categorical variables.

OS was estimated using the Kaplan-Meier (KM) method. The Cox proportional hazard regression model was used to assess risk factors that affect OS. If a variable does not satisfy the proportional hazard assumption, we considered it to be with stratification rather to include in the model directly. Multivariable model included variables that were significant in $P < 0.10$ level in univariate analysis or clinically meaningful regardless of *P* value. Renal survival were also estimated using the KM method. Because we excluded early death and defined the beginning of maintenance RRT from 3 months after diagnosis, the minimum of renal survival should be 3 months. All reported *P* values are two-sided and considered significant if $P < 0.05$. All statistical analyses were performed using STATA, version 12 (StataCorp LP, College Station, TX, USA).

Results

Classification of overall patients with TMA (277)

Among a total of 117 TMA patients, 57 patients (48.7%) had primary TMA. As only 30 patients measured ADAMTS13, there were only 6 TTP patients (10.5%) with decreased ADAMTS13 levels. More than half of patients ($n = 31$, 54.4%) were classified as primary TMA undetermined. Ten patients developed drug-induced TMAs as follows: 5 mitomycin-C, 1 gemcitabine, 1 oxaliplatin, 1 imatinib, 1 sunitinib, and 1 hydroxychloroquine.

Among 60 secondary TMA patients, autoimmune disease was the most common cause of TMA, followed by organ TPL, HSCT, malignant HTN, malignancy, and pregnancy. Autoimmune disease included systemic lupus erythematosus ($n = 9$), anti-neutrophil cytoplasmic antibodies-associated vasculitis ($n = 3$), anti-phospholipid syndrome ($n = 2$), dermatomyositis ($n = 2$), and systemic sclerosis ($n = 1$). Solid organ TPL was comprised of kidney ($n = 11$), liver ($n = 4$), and liver-kidney co-transplantation ($n = 1$). As we defined malignancy-related TMA as the paraneoplastic TMA due to uncontrolled disease activity rather than chemotherapeutic agents, 5 patients (1 myeloproliferative neoplasm, 1 hepatocellular carcinoma, 1 breast cancer, 1 gastrointestinal stromal tumor, and 1 Castleman disease) were classified as malignancy-related TMA, not as drug-induced TMA patients, even if they received chemotherapy. Four women developed TMA during their pregnancies, including 2 with hemolysis, elevated serum LDH levels, lower PLT counts (HELLP) syndrome, and 1 patient was diagnosed with pregnancy-induced hypertension.

Table 1 Classification of overall TMA population and clinical manifestations

Classification	Number	Percent	Hematologic Sx (+)(dizziness, bleeding)	Renal Sx (+)(decreased urine output, edema)	GI Sx (+)(abd pain, diarrhea)	CNS Sx (+)(altered mentality, seizure, weakness)	Other Sx (+)(fever)
Primary TMA	57		26 (45.6)	31 (54.4)	12 (21.1)	25 (43.9)	14 (24.6)
TTP	6	10.5	5 (83.3)	1 (16.7)	1 (16.7)	4 (66.7)	4 (66.7)
ST-HUS	1	1.8	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)
HUS-NI	9	15.8	4 (44.4)	4 (44.4)	3 (33.3)	1 (11.1)	1 (11.1)
Primary TMA undetermined	31	54.4	15 (48.4)	19 (61.3)	7 (22.6)	19 (61.3)	9 (29.0)
Drug-induced TMA	10	17.5	2 (20.0)	6 (60.0)	0 (0.0)	1 (10.0)	0 (0.0)
Secondary TMA	60		27 (45.0)	41 (68.3)	11 (18.3)	14 (23.3)	10 (16.7)
HSCT	10	16.7	10 (100.0)	4 (40.0)	4 (40.0)	7 (70.0)	2 (20.0)
OrganTPL	16	26.7	1 (6.3)	11 (68.8)	0 (0.0)	1 (6.3)	0 (0.0)
Malignancy	5	8.3	3 (60.0)	3 (60.0)	1 (20.0)	1 (20.0)	1 (20.0)
Pregnancy	4	6.7	2 (50.0)	4 (100.0)	1 (25.0)	0 (0.0)	1 (25.0)
Autoimmune disease	17	28.3	10 (58.8)	13 (76.5)	3 (17.6)	5 (29.4)	6 (35.3)
Malignant HTN	8	13.3	1 (12.5)	6 (75.0)	2 (25.0)	0 (0.0)	0 (0.0)

Abbreviations: *TMA* thrombotic microangiopathy, *Sx* symptoms, *GI* gastrointestinal, *CNS* central nervous system, *TTP* thrombotic thrombocytopenia purpura, *ST-HUS* Shiga toxin-associated hemolytic uremic syndrome, *HUS-NI* hemolytic uremic syndrome with non-infectious cause, *HSCT* hematopoietic stem cell transplantation, *OrganTPL* organ transplantation, *HTN* hypertension

Table 2 Patient characteristics according to the cause of thrombotic microangiopathy (TMA)

Variables	Detail	Number	Total	Primary TMA (n = 57)	Secondary TMA (n = 60)	P*
Age at diagnosis	Median (range)	117	56 (17–82)	61 (23–82)	52.5 (17–78)	**0.002**
	≥60		50 (42.7)	30 (52.6)	20 (33.3)	**0.035**
	<60		67 (57.3)	27 (47.4)	40 (66.7)	
Sex	Male, n (%)	117	60 (51.3)	23 (40.4)	37 (61.7)	**0.021**
	Female, n (%)		57 (48.7)	34 (59.6)	23 (38.3)	
ECOG performance status	<2, n (%)	113	70 (61.4)	33 (58.9)	37 (63.8)	0.594
	≥2, n (%)		44 (38.6)	23 (41.1)	21 (36.2)	
Comorbidity	Yes, n (%)	117	90 (76.9)	39 (68.4)	51 (85.0)	**0.033**
Each comorbidity	Diabetes mellitus, n (%)		21 (17.9)	10 (17.5)	11 (18.3)	0.911
	Hypertension, n (%)		43 (36.8)	20 (35.1)	23 (38.3)	0.716
	IHD or heart failure, n (%)		10 (8.5)	3 (5.3)	7 (11.7)	0.324
	Chronic liver disease, n (%)		7 (6.0)	1 (1.7)	6 (10.0)	0.115
	Chronic lung disease, n (%)		4 (3.4)	2 (3.5)	2 (3.3)	0.999
	Brain infarct or hemorrhage, n (%)		9 (7.7)	5 (8.8)	4 (6.7)	0.739
	Hematologic malignancy, n (%)		19 (16.2)	7 (12.3)	12 (20.0)	0.258
	Solid organ malignancy, n (%)		16 (13.7)	10 (17.5)	6 (10.0)	0.235
	Autoimmune disease, n (%)		16 (13.4)	3 (5.3)	13 (21.7)	**0.014**
Baseline renal function	Normal kidney, n (%)	117	55 (47.0)	27 (47.4)	28 (46.7)	**0.013**
	Chronic kidney disease, n (%)		19 (16.2)	11 (19.3)	8 (13.3)	
	End-stage renal disease, n (%)		4 (3.4)	2 (3.5)	2 (3.3)	
	Transplanted kidney, n (%)		11 (9.4)	0 (0.0)	11 (18.3)	
	Unknown kidney function, n (%)		28 (23.9)	17 (29.8)	11 (18.3)	
Blood pressure at diagnosis						
SBP	Mean (SD)	115	133.4 (26.1)	131.2 (27.0)	135.3 (25.3)	0.409
DBP	Mean (SD)	115	79.7 (16.3)	76.4 (16.7)	82.8 (15.4)	**0.035**
Hemogram at diagnosis						
WBC	Mean (SD)	117	8.9 (6.2)	9.4 (6.5)	8.5 (5.8)	0.434
Hb	Mean (SD)	117	9.1 (2.0)	8.6 (1.6)	9.5 (2.3)	0.019
PLT	Mean (SD)	117	94.9 (92.7)	69.5 (56.3)	119.1 (112.5)	0.003
Presence of schistocyte in PB smear	Yes, n (%)	103	84 (81.5)	47 (87.0)	37 (75.5)	0.132
	No, n (%)		19 (18.5)	7 (13.0)	12 (24.5)	
ADAMTS13	Decreased, n (%)	30	6 (5.1)	6 (10.5)	0 (0.0)	**0.011**
	Normal or increased, n (%)		24 (20.5)	14 (24.6)	10 (16.7)	
	Not tested, n (%)	87	87 (74.4)	37 (64.9)	50 (83.3)	
LDH	Mean (SD)	90	926.7 (992.8)	1006.8 (1079.4)	826.5 (875.8)	0.395
Haptoglobin	Mean (SD)	79	45.1 (80.4)	39.9 (85.1)	51.5 (74.8)	0.529
Plasma Hb	Mean (SD)	72	24.1 (32.4)	31.4 (42.4)	15.9 (10.9)	**0.043**
PT	Mean (SD)	112	13.9 (4.4)	14.2 (5.6)	13.5 (2.9)	0.381
aPTT	Mean (SD)	114	37.8 (17.9)	37.4 (19.8)	38.2 (16.1)	0.803
Fibrinogen	Mean (SD)	115	323.2 (137.3)	295.9 (139.5)	345.0 (130.7)	**0.034**
C3	Mean (SD)	63	93.0 (32.3)	86.9 (27.5)	98.6 (35.6)	0.155
C4	Mean (SD)	62	20.8 (9.9)	19.1 (8.8)	22.4 (10.7)	0.201
BUN	Mean (SD)	117	46.8 (25.2)	44.5 (25.2)	49.0 (25.1)	0.334
MDRD-GFR at diagnosis	Mean (SD)	117	35.0 (29.5)	31.1 (27.3)	38.7 (31.4)	0.170
	<15, n (%)		38 (32.5)	22 (38.6)	16 (26.7)	0.384
	15≤, <60, n (%)		57 (48.7)	25 (43.9)	32 (53.3)	
	≥60, n (%)		22 (18.8)	10 (17.5)	12 (20.0)	

Table 2 (continued)

Variables	Detail	Number	Total	Primary TMA (n = 57)	Secondary TMA (n = 60)	P*
Total protein	Mean (SD)	117	5.7 (0.9)	5.8 (1.0)	5.6 (0.9)	0.177
Albumin	Mean (SD)	118	3.1 (0.6)	3.3 (0.6)	3.0 (0.6)	**0.045**
Presence of albuminuria	Yes, n (%)	118	69 (59.0)	36 (63.2)	33 (55.0)	0.370
AKI	Yes, n (%)	85	66 (77.7)	27 (71.1)	39 (83.0)	0.189

Abbreviations: *TMA* thrombotic microangiopathy, *ECOG* Eastern Cooperative Oncology Group, *IHD* ischemic heart disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WBC* white blood count, *Hb* hemoglobin, *PLT* platelet, *PB* peripheral blood, *LDH* lactate dehydrogenase, *PT* prothrombin time, *aPTT* activated partial thromboplastic time, *C3* complement 3, *C4* complement 4, *BUN* blood urea nitrogen, *MDRD* Modification of Diet in Renal Disease, *eGFR* estimated glomerular filtration rate, *AKI*, acute kidney injury*P*<0.05 as bolded value

Clinical symptoms of overall TMA patients

The most common clinical manifestation was renal symptom, followed by hematologic and CNS symptom in overall TMA patients. Renal symptoms were the most common in organ TPL-, pregnancy-, and malignant hypertension-related TMA. Drug-induced TMA mainly showed renal symptoms, whereas neither GI nor CNS symptoms were indicative. CNS symptom was present more in primary (43.9%) than in secondary TMAs (23.3%). However, in secondary TMA's, the presence of CNS symptom varied according to etiology, where 70% of HSCT-related TMA patients had CNS symptoms, whereas none of pregnancy- and malignant hypertension-associated TMA had CNS symptoms. Patients diagnosed as TTP commonly developed hematologic manifestations and fever. In secondary TMA, all HSCT-related TMA patients showed hematologic symptoms. These results are summarized in Table 1.

Baseline characteristics of overall TMA patients

Table 2 summarizes the baseline characteristics of the total participants across the classification of TMA. More than half of TMA patients were younger than 60 years old (57.3%), were men (51.3%), had good performance status (<2) (61.4%), and had at least one comorbidity (76.9%).The most common comorbidity was hypertension (36.8%). Among patients with known baseline renal function, half of patients (n = 55, 47%) had preserved baseline renal function. Preexisting renal impairment was present in 34 (29.1%) patients including 19 (16.2%) CKD, 4 (3.4%) ESRD, and 11 (9.4%) kidney allograft. Patients who did not know their baseline renal function was 28 (23.9%). At the time of diagnosis, 38 (32.5%) patients had advanced renal dysfunction with an eGFR <15 mL/min/1.73 m^2. More than 50% (n = 69) of TMA patients presented albuminuria in urinary dipstick. Among 85 non-ESRD patients with known renal function, more than two-thirds (n = 66, 77.7%) experienced AKI at diagnosis. The prevalence of AKI was not different between primary and secondary TMAs (P = 0.189). Among primary TMA patients, 1 ST-HUS (100%), 3 aHUS (75.0%), 15 primary TMA undetermined (75.0%), 8 drug-induced TMA (88.9%) underwent AKI, whereas none of TTP patients did. Most of secondary TMA patients, especially HSCT-, malignancy-, pregnancy-, and HTN-related TMA patients, underwent AKI (Table 3).

Except for 14 patients in whom the PBS was not tested, 84 (81.5%) had schistocytes in their PBS. ADAMTS13 was measured only 30 (25.7%) patients, 20 of 57 (35.1%) primary TMA patients, and 10 of 60 (16.7%) secondary TMA patients. Among the 14 patients who classified primary TMA, 9 patients were categorized as HUS-NI and 5 patients were included in drug-induced TMA. Although the mean levels of C3 and C4 were preserved within normal range, decreased C3 and C4 levels were found in 13 (20.3%) and 8 (12.7%) patients, respectively. Plasmapheresis had been used for 60 patients (51.3%) in order to manage with TMA. None of the patients received eculizumab. Among 60 patients who were treated with plasmapheresis, we found that 5 (8.3%) patients were given retreatment (Supplementary Table 1).

Comparisons between primary and secondary TMAs

Table 2 compared clinical phenotypes between primary and secondary TMAs. Primary TMA patients were older (vs. 52.5 years, P = 0.002), were predominantly women (59.6 vs. 38.3%, P = 0.021), and had fewer comorbidity (68.4 vs. 85.0%, P = 0.033) than those with secondary TMA. They showed more predominant hematologic manifestations including lower PLT count (P = 0.003), lower Hb level (P = 0.019), higher plasma Hb level (P = 0.043), and lower fibrinogen level (P = 0.034) compared to secondary TMA patients. There were no definite differences in serum LDH and haptoglobin levels between the two groups.

Different from the hematologic manifestations, there was no difference in renal manifestations such as the serum BUN

Table 3 Differences according to the specific causes among secondary TMA group

Variables	Detail	HSCT (*n* = 10)	Organ TPL (*n* = 16)	Malignancy (*n* = 5)	Pregnancy (*n* = 4)	Autoimmune (*n* = 17)	Malignant hypertension (*n* = 8)
Age at diagnosis	Median (range)	58.5 (38–68)	52.5 (23–75)	58 (37–78)	35 (30–39)	51 (17–75)	47.5 (26–70)
Sex	Male, *n* (%)	6 (60.0)	14 (87.5)	4 (80.0)	0 (0.0)	7 (41.2)	6 (75.0)
	Female, *n* (%)	4 (40.0)	2 (12.5)	1 (20.0)	4 (100.0)	10 (58.8)	2 (25.0)
ECOG performance status	<2, *n* (%)	1 (11.1)	16 (100.0)	1 (20.0)	2 (50.0)	10 (62.5)	7 (87.5)
	≥2, *n* (%)	8 (88.9)	0 (0.0)	4 (80.0)	2 (50.0)	6 (37.5)	1 (12.5)
Blood pressure at diagnosis							
SBP	Mean (SD)	109.2 (11.2)	147.3 (17.1)	131.6 (37.0)	158.0 (41.9)	128.1 (20.3)	150.1 (13.2)
DBP	Mean (SD)	74 (8.0)	86.3 (12.1)	77.6 (22.8)	96.0 (15.6)	81.6 (15.0)	85.9 (20.3)
Hemogram at diagnosis							
WBC	Mean (SD)	4.6 (2.5)	9.4 (6.4)	8.4 (7.5)	11.1 (3.1)	9.9 (7.2)	7.7 (1.0)
Hb	Mean (SD)	9.4 (1.7)	9.7 (0.8)	8.5 (3.0)	8.7 (1.4)	9.0 (3.0)	11.2 (2.7)
PLT	Mean (SD)	25.6 (10.9)	137.5 (83.1)	146.8 (248.8)	66.5 (36.1)	122.8 (116.1)	200.1 (45.8)
Presence of schistocyte in PB smear	Yes, *n* (%)	10 (100.0)	4 (40.0)	4 (80.0)	4 (100.0)	13 (86.7)	2 (40.0)
	No, *n* (%)	0 (0.0)	6 (60.0)	1 (20.0)	0 (0.0)	2 (13.3)	3 (60.0)
LDH	Mean (SD)	895.4 (513.8)	376.3 (327.6)	1398.6 (2127.5)	1582.8 (348.4)	623.7 (441.2)	347.0 (102.5)
Haptoglobin	Mean (SD)	8.1 (2.7)	62.3 (110.5)	62.0 (92.9)	8.5 (3.0)	72.1 (75.6)	166.5 (89.8)
Plasma Hb	Mean (SD)	25.6 (6.9)	6.2 (3.0)	16.2 (16.2)	17.6 (11.4)	13.5 (10.2)	13.7 (9.1)
PT	Mean (SD)	17.3 (3.2)	11.7 (1.9)	14.1 (1.3)	13.2 (1.0)	13.5 (2.3)	11.8 (1.4)
aPTT	Mean (SD)	38.5 (5.9)	31.7 (8.1)	41.9 (8.5)	36.4 (6.0)	45.4 (27.5)	34.4 (4.6)
Fibrinogen	Mean (SD)	241.7 (105.2)	324.1 (75.9)	271.2 (68.2)	391.5 (77.4)	428.5 (163.8)	401.9 (79.5)
C3	Mean (SD)	64 (NA)	86.7 (22.1)	106.7 (28.9)	106.5 (3.5)	95.8 (46.8)	116.5 (17.1)
C4	Mean (SD)	17 (NA)	21.2 (5.6)	21.3 (6.7)	36.0 (0.0)	18.5 (13.1)	30.0 (3.9)
BUN	Mean (SD)	64.3 (33.9)	49.2 (18.4)	47.0 (46.2)	49.0 (5.4)	45.3 (22.4)	38.8 (16.0)
MDRD-GFR	Mean (SD)	44.3 (17.2)	34.8 (33.8)	46.2 (41.6)	16.3 (6.1)	31.5 (25.3)	61.1 (43.4)
	<15, *n* (%)	0 (0.0)	6 (37.5)	1 (20.0)	2 (50.0)	5 (29.4)	2 (25.0)
	15≤, <60, *n* (%)	8 (80.0)	7 (43.7)	3 (60.0)	2 (50.0)	10 (58.8)	2 (25.0)
	≥60, *n* (%)	2 (20.0)	3 (18.8)	1 (20.0)	0 (0.0)	2 (11.8)	4 (50.0)
Total protein	Mean (SD)	5.2 (1.0)	5.5 (0.7)	6.3 (0.7)	5.3 (1.3)	5.6 (1.0)	5.9 (0.9)
Albumin	Mean (SD)	3.0 (0.5)	3.1 (0.4)	3.7 (0.7)	2.9 (0.7)	2.6 (0.5)	3.4 (0.8)
Presence of albuminuria	Yes, *n* (%)	3 (30.0)	7 (43.7)	3 (60.0)	3 (75.0)	11 (64.7)	6 (75.0)
AKI	Yes, *n* (%)	10 (100.0)	11 (68.7)	2 (100.0)	4 (100.0)	9 (75.0)	3 (100.0)

Abbreviations: *TMA* thrombotic microangiopathy, *HSCT* hematopoietic stem cell transplantation, *OrganTPL* organ transplantation, *HTN* hypertension, *ECOG* Eastern Cooperative Oncology Group, *IHD* ischemic heart disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WBC* white blood count, *Hb* hemoglobin, *PLT* platelet, *PB* peripheral blood, *LDH* lactate dehydrogenase, *PT* prothrombin time, *aPTT* activated partial thromboplastic time, *C3* complement 3, *C4* complement 4, *BUN* blood urea nitrogen, *MDRD* Modification of Diet in Renal Disease, *eGFR* estimated glomerular filtration rate, *AKI* acute kidney injury

level, MDRD-eGFR, and dipstick albuminuria between the two groups.

Comparisons between the subgroups of secondary TMA

The baseline characteristics of patients with secondary TMA were compared according to the specific cause of TMA (Table 3). Pregnancy-related TMA patients were youngest in six different groups. Solid organ TPL-related TMA patients had better performance status than those related to HSCT- or malignancy-associated TMAs. The blood pressure was higher in pregnancy- and hypertension-associated TMA, whereas HSCT- or autoimmune-associated TMA patients were not. Both pregnancy- and HSCT-related TMA patients showed prevalent hemolytic features, including lower PLT counts, higher serum LDH levels, higher plasma Hb levels, and lower haptoglobin levels. Renal function at the time of diagnosis was worst in pregnancy-related TMA group (16.3 ± 6.1 mL/min/1.73 m^2).

Overall survival and associating factors

During the 150.2 months of follow-up, the crude mortality was 41.9% (n = 49). Five-year OS rate was 64.8%, and the median OS of all TMA patients was 96.8 months (Fig. 2). Twenty-five (43.9%) and 24 (40.0%) deaths occurred in primary and secondary TMAs, respectively. Specifically, 10 (100%) deaths occurred in HSCT-related TMA, 7 (70%) deaths in drug-related TMA, and 8 (47.1%) deaths in autoimmune disease-related TMA. All pregnancy-associated TMA patients remained alive. About half of AKI patients (n = 31, 47.0%) died.

Table 4 summarizes the result of univariate and multivariable Cox regression analysis for death. In univariate analysis, older age more than 60 years, poor ECOG performance status (≥2), hematologic and solid organ malignancies, SBP higher than 140 mmHg, higher WBC count (≥10 × 10^3/uL), lower Hb levels (<9 g/dL), lower PLT counts (<50 × 10^3/uL), higher serum LDH levels (≥ 500 IU/L), longer PT and aPTT, and lower serum albumin levels (<3 g/dL) were associated with elevated risk for all-cause death. The cause of TMA failed to affect OS (P = 0.554). After stratifying baseline renal function because it did not satisfy the assumption for proportionality, age at diagnosis, hematologic malignancy and solid organ malignancy, SBP, WBC count, Hb, PLT count, LDH, PT, and albumin were included in multivariable analysis. Finally, older age (adjusted HR 2.99, 95% confidence interval (CI) 1.33–6.74, P = 0.008), hematologic malignancy (adjusted HR 5.12, 95% CI 1.47–17.89, P = 0.010), solid organ malignancy (adjusted HR 5.68, 95% CI 1.74–18.59, P = 0.004), lower Hb levels (adjusted HR 3.02, 95% CI 1.18–7.72, P = 0.021), and lower albumin levels (adjusted HR 2.86, 95% CI 1.09–7.54, P = 0.033) were significantly influenced on overall survival in TMA patients.

Renal outcomes of TMA

After excluding 10 patients who died earlier than 3 months, we analyzed 75 patients for estimation of renal survival. Among them, 17 patients (22.7%) progressed to ESRD state or received kidney TPL. The 5-year renal survival rate was 69.2%. The median renal survival had not reached in overall TMA patients during the follow-up period (Fig. 3). For 75 patients with information of maintenance renal replacement treatment, 32 underwent plasmapheresis and only 5 (15.6%)

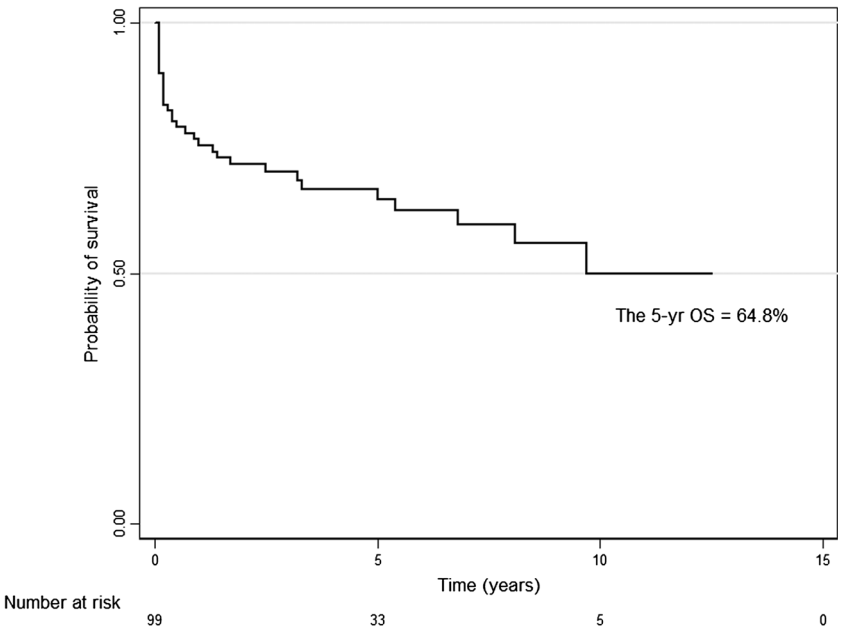

Fig. 2 Overall survival of overall TMA patients. *TMA* thrombotic microangiopathy, *yr* year, *OS* overall survival. OS was defined as the time from the date of diagnosis to the date of death or the last follow-up

Table 4 Factors affecting overall survival

		Univariate analysis			Multivariable model[a]		
Variables	Detail	HR	95% CI	*P**	HR	95% CI	*P**
Cause of TMA	Secondary (vs primary)	0.84	0.47–1.49	0.554	(Not entered)		
Age at diagnosis	≥60 (vs <60)	3.32	1.81–6.08	**<0.001**	2.99	1.33–6.74	**0.008**
Sex	Male (vs female)	0.99	0.56–1.75	0.967	(Not entered)		
ECOG performance status	≥2 (vs <2)	2.56	1.41–4.65	**0.002**	2.10	0.86–5.16	0.103
Comorbidity	Yes (vs no)	3.00	1.18–7.58	**0.021**	(Not entered)		
Each comorbidity	Diabetes mellitus (vs no)	1.42	0.72–2.80	0.306	(Not entered)		
	Hypertension (vs no)	0.70	0.37–1.31	0.264	(Not entered)		
	IHD or heart failure (vs no)	1.74	0.69–4.43	0.243	(Not entered)		
	Chronic liver disease (vs no)	0.29	0.04–2.10	0.220	(Not entered)		
	Chronic lung disease (vs no)	1.72	0.56–5.90	0.317	(Not entered)		
	Brain infarct or hemorrhage (vs no)	0.95	0.34–2.66	0.925	(Not entered)		
	Hematologic malignancy (vs no)	4.79	2.52–9.11	**<0.001**	5.12	1.47–17.89	**0.010**
	Solid organ malignancy (vs no)	1.89	0.94–3.82	**0.074**	5.68	1.74–18.59	**0.004**
	Autoimmune disease (vs no)	0.50	0.18–1.40	0.189	(Not entered)		
Blood pressure at diagnosis							
SBP	≥140 (vs <140)	0.56	0.30–1.03	**0.064**	0.48	0.16–1.49	0.206
DBP	≥90 (vs <90)	0.59	0.31–1.18	0.111	(Not entered)		
Hemogram at diagnosis							
WBC	≥10,000 (vs <10,000)	1.82	1.01–3.26	**0.045**	2.34	0.80–6.88	0.121
Hb	<9 (vs ≥9)	2.23	1.24–4.03	**0.008**	3.02	1.18–7.72	**0.021**
PLT	<50,000 (vs ≥50,000)	2.21	1.24–3.94	**0.007**	0.87	0.31–2.47	0.798
LDH	≥500 (vs <500)	1.98	0.98–4.02	**0.058**	1.70	0.70–4.13	0.244
Haptoglobin	Low (vs normal or high)	0.90	0.40–2.00	0.796	(Not entered)		
Plasma Hb	High (vs normal or low)	1.47	0.44–4.91	0.533	(Not entered)		
PT	High (vs normal or low)	1.94	1.01–3.74	**0.047**	1.35	0.51–3.54	0.546
aPTT	High (vs normal or low)	1.85	1.02–3.34	**0.043**	(Not entered)		
Fibrinogen	Low (vs normal or high)	0.84	0.45–1.56	0.589	(Not entered)		
Albumin	<3 vs (≥3)	2.19	1.23–3.91	**0.008**	2.86	1.09–7.54	**0.033**
Presence of albuminuria	Yes (vs no)	1.46	0.80–2.67	0.219	(Not entered)		

Abbreviations: *TMA* thrombotic microangiopathy, *HR* hazard ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *IHD* ischemic heart disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WBC* white blood count, *Hb* hemoglobin, *PLT* platelet, *PB* peripheral blood, *LDH* lactate dehydrogenase, *PT* prothrombin time, *aPTT* activated partial thromboplastic time

[a] Multivariable model included age at diagnosis, ECOG performance status, comorbidity (hematologic, solid organ malignancy), WBC, Hb, PLT, LDH, PT sec, albumin, stratified with baseline renal function (CKD+ESRD+TPL vs normal vs unknown)

of them suffered from the maintenance of renal replacement treatment.

Discussion

Most previous studies regarding TMA have focused on specific TMA subtypes. Notably, we aimed to present the overall clinical picture of all TMA patients regardless of subtypes. We included both TMA patients who were diagnosed by kidney biopsy and were diagnosed by hematological manifestations. There are various classification criteria of TMA and widely utilized categories [5] including TTP and HUS (ST-HUS and complement-mediated HUS) by ADAMTS13 activity are difficult to be applied in the setting in which ADAMTS13 results are not immediately obtained. Although ADAMTS13 activity and complement levels are important for the classification of TMA [5], we intended to provide clinical phenotypes to physicians to help rapid TMA diagnosis even before the acquisition of ADAMTS13 levels or pathologic test results, which usually takes a time in clinical practice. Moreover, although renal manifestation is one of the important symptoms in TMA patients, studies regarding renal outcome in TMA have been lacking until recently. Accordingly, we performed a detailed

clinical analysis, including renal outcome, in overall patients with TMA.

In our study, CNS symptoms were prevalent in TTP and HSCT-related TMA patients. This finding was consistent with that of previous studies in TTP patients [9, 10] and in HSCT-related TMA [11]. Although the glomerular endothelium is the main target of TMA, endothelial cells in the CNS microvasculature are often damaged in TTP patients. Among HSCT-related TMA patients, acute uncontrolled TMA-associated hypertension and CNS hemorrhage are the frequent causes of CNS manifestations [12].

Renal manifestations were the most common in both primary and secondary TMA patients. This implies that clinician should suspect a diagnosis of TMA if patients have only renal symptoms without definite cause. In our study, the renal manifestation of aHUS accounted for only 44.4%, which was relatively lower, compared with other primary TMA. We assume that due to recent advance in knowledge regarding TMA, we diagnose aHUS patients earlier when they present only hematologic manifestations. When we focus on AKI among renal manifestations, the prevalence of AKI varies from 0 to 90% among different types of TMA. The renal involvement of TMA is known to be common in most TMA patients. Exception is a TTP [1], while extensive microvascular thrombi found in the TTP patient's kidney [13]. We assume that different pathogenesis of TMA may be one explanation for this phenomenon. The main pathogenesis of TTP is vascular thrombosis caused by PLT dysfunction and they have predominant hematologic manifestation, whereas other types of TMA primarily injure endothelial cells or resident renal cells before they develop PLT dysfunction. For example, vascular endothelial growth factor (VEGF) inhibitors suppress constitutive expression and secretion of VEGF by podocytes, and they subsequently break down glomerular integrity [14]. Other anti-cancer drugs such as mitomycin-C, gemcitabine, or calcineurin inhibitors directly injure glomerular endothelial cells [15, 16]. aHUS is also characterized by endothelial swelling and detachment, the subendothelial accumulation of proteins and cell debris, and the thickening of the renal arterioles and capillaries. In aHUS, endothelial cells were one of the primary target of over-activated, uncontrolled complement systems [17, 18].

When we compared primary and secondary TMAs, primary TMA had dominant hematologic manifestations compared to secondary TMA except for HSCT-related TMA. However, we found that there was no significant difference in patients' survival between primary and secondary TMAs. This finding is inconsistent with results from a retrospective review that enrolled 137 patients in Canada and reported that patients with secondary TTP or HUS died more than those with primary TTP or HUS (13 vs. 33%, $P = 0.007$) [19]. We assume this inconsistence originates from the study population; the Canadian group only analyzed patients with TTP and HUS, whereas we analyzed all patients with TMA.

Within the secondary TMA subgroup, it is interesting that HSCT- and pregnancy-related TMA showed similar hematologic manifestations, although their clinical outcomes were dramatically different. As previous reports showed [20, 21], the mortality rate of HSCT-related TMA patients was very high in this study. However, all the pregnancy-related TMA patients survived. This finding might be explained by the reversibility of the preceding cause. HSCT-related TMA cannot reverse the cause, whereas pregnancy-related TMA can be resolved with delivery. Moreover, patients who received

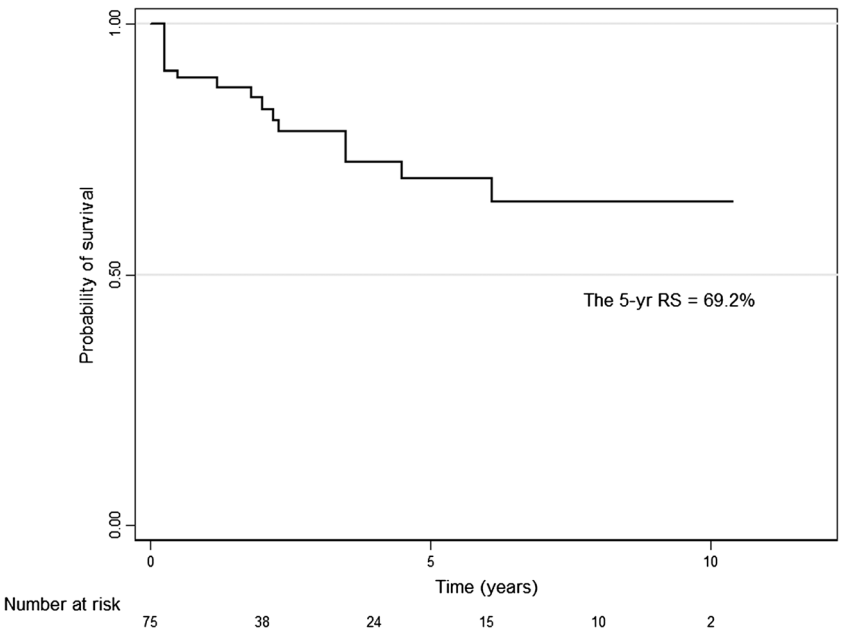

Fig. 3 Renal survival of overall TMA patients. *TMA* thrombotic microangiopathy; *yr* year, *RS* renal survival. RS was defined as the time from the date of diagnosis of TMA to the date of maintenance hemodialysis. Patients with early death were excluded, and the minimum of renal survival should be 3 months

HSCT are older and have higher comorbidity, compared with young pregnant women. They usually have poor general conditions due to heavy cytotoxic and immunosuppressive treatments before HSCT and/or infectious complications.

Although it is reported that the use of many therapeutic agents improve OS in TMA patients [9, 22, 23], little has been known as demographic and clinical factors associated with OS. In our study, we found that older age, anemia, and hypoalbuminemia are significantly poor prognostic factors for OS. Although these overall TMA patients are heterogeneous because they received different treatments, we suggest that physicians might pay attention to patients with these risk factors.

Notably, we showed the overall renal survival of TMAs. In fact, a few studies examined various rates of long-term renal failure in specific TMA populations [24]. In a retrospective analysis of 92 patients diagnosed as having TTP, 15% required dialysis and 6% finally progressed to ESRD [25]. Worse outcome that only a half of survivors recovered renal function was reported in patients with aHUS [26]. However, to our knowledge, it is the first to present renal survival in overall TMA patients, not focusing on specific TMA subgroups. We found that the long-term renal survival was dismal. Almost 70% of total patients finally lost their kidney function. This is significantly higher ESRD progression rate than diabetes [27, 28] and various glomerulonephritis [29–32], well-known causes of ESRD [33]. These findings enable clinicians to guess the estimate of renal survival in clinical setting, regardless of the cause of TMA. Recently, complement inhibitors such as eculizumab (Soliris®; Alexion Pharmaceuticals, Inc., Cheshire, CT, USA) have made progress in TMA treatment with a favorable effect on long-term renal survival in TMA patients including aHUS and HSCT-related TMA [23, 34, 35]. We believe dismal renal outcome would be improved through various methods including pharmacologic therapies and plasma-based therapies in a near future.

There are several limitations in this study. First, patients who underwent ADAMTS13 and complement level testing were limited to recently diagnosed patients, and sorting all patients with primary TMA into TTP and aHUS was not possible. Because not all the patients tested ADAMTS13 level, there is potential bias that some secondary TMA according to our criteria might be misclassified. Nevertheless, ADAMTS13 activity differs between our TMA classification entities. For example, in our study, all the secondary TMA patients ($n = 10$) who measured ADAMTS13 activity showed normal or elevated level, similar to a previous study reporting that severe ADAMTS13 deficiency was rarely observed in secondary TMA [36]. In the future, as technology continues to develop, measurements of ADAMTS13 will be much faster and easier enough to solve this technical issue. Second, because the underlying disease could be have an effect on survival, it is difficult to define TMA-specific mortality. Third, because kidney biopsies were not performed in all patients, we could not calculate the prevalence of actual renal involvement of TMA. Although the GFR or proteinuria is used as a potential indicator for renal involvement, the most straightforward way is to confirm pathological renal involvement in biopsy specimen. However, most patients diagnosed as having TMA by hematologists did not undergo a kidney biopsy ($n = 65/69$ patients, 94.2%). We assume that thrombocytopenia, which hampers a kidney biopsy, could be an explanation for the infrequent kidney biopsy in patients treated by hematologists. Considering the unfavorable long-term renal outcome in patients with TMA, further efforts are warranted to understand renal involvement in TMA using a kidney biopsy. Fourth, although we analyzed >100 patients with TMA, the number of patients with specific TMA category was not large, hampering the analysis with statistical significance in some variables. Fifth, because ST-HUS is frequently diagnosed in pediatric patients, this entity is not well described in our adult patient study. Moreover, because we did not routinely test EHEC PCR for all the patients suspecting TMA, some patients without diarrhea classified as HUS-NI or primary TMA undetermined might be misclassified because ST-HUS occasionally presents without diarrhea. However, ST-HUS is a very rare disease in adults, only with a few case reports [37] in Korea. Lastly, we did not evaluate the effect of plasmapheresis for TMA patients because of the limited number of patients who received it.

In conclusion, we integrated overall clinical manifestations and patients/renal outcomes in various types of TMA patients. Clinical phenotypes were diverse according to the cause of TMA. Unfortunately, however, their patients and renal outcomes were poor regardless of their TMA etiologies, except pregnancy-associated TMA. Our study may help physicians understand overall manifestations of TMA and diagnose promptly based on clinical suspicions.

Compliance with ethical standards This study was approved by the institutional review board at our institution (number: H-1509-070-703). All procedures were performed in accordance with the principles of the Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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