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ORIGINAL ARTICLE

# A nationwide cross-sectional analysis of thrombotic microangiopathy in the Japan Renal Biopsy Registry (J-RBR)

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## Abstract

**Background** There have been only a few large-scale cohort studies that have reviewed accumulated cases of thrombotic microangiopathy (TMA). The aim of this study was to collect and analyze TMA cases based on the renal biopsy, as a nationwide survey in Japan.

**Methods** In this cross-sectional study, large nationwide data from the Japan Renal Biopsy Registry (J-RBR) were used. Among the patients registered in the J-RBR online system from July 2007 to July 2017, TMA cases were extracted and epidemiological data and clinical findings were investigated.

**Results** Out of the 38,495 patients enrolled in a period of 10 years, 152 (0.39%) cases had been diagnosed with TMA. The patient age was widely distributed, including 9.2%, 66.4%, and 24.3% for children, adults, and the elderly, respectively. There were various causes of TMA. Among them, hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP) (16.4%), connective tissue disease (CTD)-related (17.1%), and drug-induced (16.4%) were frequently observed. The background factors of TMA were different in children and adults. In a comparison between groups consisting of HUS/TTP, CTD-related, and drug-induced, the HUS/TTP group was significantly younger ($p = 0.01$), and the drug-induced TMA group tended to have a high urinary protein positive rate ($p = 0.05$). A comparative analysis according to the age group showed significantly higher serum creatinine levels in the elderly ($p < 0.01$).

**Conclusion** This is the first report of epidemiological and clinical data of biopsy-proven TMA in Japan. The characteristics of TMA with diversity based on the underlying disease and age group were reported.

**Keywords** Thrombotic microangiopathy · Japan renal biopsy registry (J-RBR) · Renal biopsy · Hemolytic uremic syndrome · Thrombotic thrombocytopenic purpura · Connective tissue disease

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## Introduction

Thrombotic microangiopathy (TMA) was originally a pathological diagnosis. The pathological characteristics of TMA are thrombus formation in the microvessels and vascular endothelial injury. Histopathological changes in TMA mainly occur in the glomeruli and blood vessels, and acute and chronic lesions develop over time. However, TMA is also diagnosed according to clinical findings. It is featured by consumptive thrombocytopenia with thrombus formation, microangiopathic hemolytic anemia, and organ disorders. Among them, the frequency of acute kidney injury is high, and there are many cases where renal biopsy is performed.

As a representative disease of TMA, Moschcowitz et al. reported about thrombotic thrombocytopenic purpura (TTP) in 1924 [1], and hemolytic uremic syndrome (HUS) was described by Gasser et al. in 1955 [2]. Furthermore, TMA can develop due to various background factors, such as metabolic disease, drug use, infection, pregnancy, autoimmune disease, transplantation, malignant hypertension, and malignancy. Cases of TMA that develop this way are collectively referred to as secondary TMA [3–5]. Although the causes of TMA are diverse and the number of cases tends to increase, there has been few country-level epidemiological and clinicopathological information about TMA in Japan.

The Japan Renal Biopsy Registry (J-RBR) is a nationwide renal biopsy registry designed as a web-based prospective registry system for recording the pathological, clinical, and laboratory data relevant to all renal biopsies. This study focused on pathologically proven TMA cases by renal biopsy. The aim of this cross-sectional study was to verify the epidemiological and clinical characteristics of TMA cases using the J-RBR database and to provide the results of the first large-scale cohort study in Japan.

## Materials and methods

### J-RBR online system and extraction of subjects

J-RBR is a nationwide, multicenter registry system, which was organized by the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology in 2007 [6]. Individual patient data are recorded on the J-RBR website using the Internet Data and Information Center for Medical Research system of the University Hospital Medical Information Network (UMIN). J-RBR is registered under the Clinical Trial Registry of UMIN (registration number, UMIN000000618), and the study protocol was approved by the Ethics Committee of the Japanese Society of Nephrology in accordance with the Declaration of Helsinki (approval number 51). Written informed consent was obtained from all patients who participated in this study.

In the J-RBR system, data, including basic patient information, clinical diagnosis, renal pathological findings, biochemical features, and urinalysis, are registered. Out of the 38,495 patients enrolled from July 2007 to July 2017, subjects were extracted based on the clinical and pathological diagnosis using the keyword of TMA.

### Collection of clinical findings

Baseline characteristics, including clinical and pathological features at the time of renal biopsy, were obtained from the J-RBR database. The clinical parameters evaluated were age, sex, body mass index, systolic and diastolic blood pressure, medical history of hypertension and diabetes mellitus, serum total protein and albumin levels, serum total cholesterol level, serum creatinine level, estimated glomerular filtration rate (eGFR), glycosylated hemoglobin level, qualitative tests of urinary protein and occult blood, and urinary protein–creatinine ratio. The background factors of TMA were classified into 9 types (HUS/TTP, connective tissue disease [CTD], drug-induced, hematopoietic stem cell transplantation, kidney transplantation, hypertension, liver transplantation, malignancy, and pregnancy) in consideration of the clinical diagnosis, remarks column, and free comments [6]. At the start of the J-RBR database system, diagnostic tools to distinguish Shiga toxin-producing pathogenic *Escherichia coli* (STEC)-HUS, TTP, and complement-related HUS (atypical HUS [aHUS]) had not been established. The comprehensive diagnosis labeled HUS/TTP was adopted [6]. Cases in which the cause of TMA could not be identified were classified as unknown.

### Subgroup analysis of clinical features

Subjects were stratified according to the cause of TMA and age group, and subgroup analyses were performed. In the analyses, according to the background factors of TMA, they were classified into three groups: HUS/TTP, CTD-related TMA, and drug-induced TMA. The age-related analysis was divided into three groups: child (< 18 years), adult (18–64 years), and elderly (≥ 65 years). Clinical findings were compared in each group.

### Statistical analysis

Clinical data were presented as medians with interquartile ranges or numbers denoting percentages. Differences among

the three groups were analyzed using the Kruskal–Wallis test (for continuous variables) or chi-square test (for categorical variables). Statistical significance was set at a $p$ value < 0.05. All statistical tests were performed using Stata software version 14.0 (StataCorp LLC, College Station, TX, USA).

## Results

### Clinical characteristics of extracted patients

Among 38,495 patients registered in the J-RBR online system for a period of 10 years, from July 2007 to July 2017, 152 (0.39%) cases had been pathologically diagnosed with TMA. Figure 1 shows the results. Out of the 157 cases extracted using the keyword of TMA, diabetic nephropathy and focal segmental glomerulosclerosis with lesions partially similar to TMA were excluded. In addition, 3 cases with lesions suspected TMA, but no definitive diagnosis were excluded.

Clinical baseline data at the time of renal biopsy of the 152 patients diagnosed with TMA are shown in Table 1. Table 1 presents the median, percentage, and minimum and maximum values. Some parameters have missing values, and the total number of observations is also shown. The age distribution was 3–84 years, and the median age was 50 years. For sex difference, men accounted for 49.3% of the individuals. Of the patients, 75.4% had hypertension, and the median systolic and diastolic blood pressure was 135 and 80 mmHg, respectively. In the biochemical examination findings, the median serum total protein, serum albumin, and serum total cholesterol levels were 6.3 g/dL, 3.6 g/dL, and 192.5 mg/dL, respectively. Regarding renal function, the median serum creatinine level was 1.55 mg/dL, with a minimum of 0.2 and a maximum of 15.90. The median eGFR was 37.6 mL/min/1.73 $m^2$, with < 30 mL/min/1.73 $m^2$ in 42.1% of patients and < 15 mL/min/1.73 $m^2$ in 18.4%. The urinary protein test was positive (1 + or more) in 78.3% of patients, with 2 + being the largest, accounting for 30.9%. In the 70 patients whose proteinuria quantification results were registered, the median urinary protein was 2.25 g/g creatinine, and 29 (41.4%) patients had nephrotic range proteinuria. Urinary occult blood was positive in 51.3% of patients.

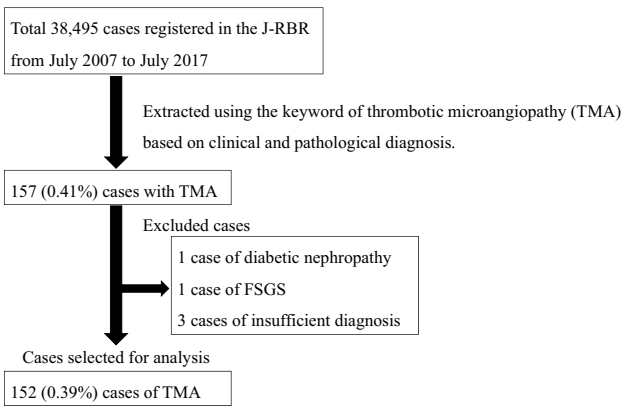


**Fig. 1** Extraction of TMA cases analyzed in this study. *FSGS*, focal segmental glomerulosclerosis; *J-RBR*, Japan Renal Biopsy Registry

Details of the onset age are presented in Fig. 2. There were 14 children (9.2%) aged < 18 years and 101 adults (66.4%) between the ages of 18 and 64 years. Thirty-seven elderly patients aged ≥ 65 years were included and accounted for 24.3% of the total number of patients. Age was widely distributed from < 10 years to > 80 years. Among them, the largest group (30 patients, 19.7%) consisted of individuals aged between 60 and 69 years.

Background diseases causing TMA are shown in Table 2. There were various causes of TMA. Of the total, 26 cases (17.1%) were CTD-related TMA, and 25 cases (16.4%) were HUS/TTP and drug-induced TMA. Regarding cases in which the classification of collagen disease was described, there were 4 cases of systemic lupus erythematosus (SLE), 4 cases of antiphospholipid antibody syndrome (APS), 3 cases of systemic sclerosis (SSc), and 1 case of mixed connective tissue disease. The drugs that caused TMA were gemcitabine in 5 patients, bevacizumab in 3, calcineurin inhibitor in 3, pazopanib in 1, and adalimumab in 1. There were 52 cases (34.2%) classified as unknown because the cause of TMA could not be identified.

### Comparative evaluation based on the cause of TMA

Differences in clinical findings according to the background factor of TMA were compared among the three groups: HUS/TTP, CTD-related TMA, and drug-induced TMA. As a result, the HUS/TTP group was significantly younger ($p = 0.01$), and the CTD-related TMA group had significantly more women ($p < 0.05$). The drug-induced TMA group had higher serum creatinine levels and lower eGFR compared to the other two groups, although there was no significant difference among the three groups. The urinary protein positive ratio tended to be higher in the drug-induced TMA group ($p = 0.05$) (Table 3).

### Comparison of clinical features among children, adults, and elderly individuals

A comparative analysis of the clinical findings at the time of renal biopsy in the three groups, consisting of children, adults, and elderly individuals, was performed. Systolic and diastolic blood pressures were significantly lower in children ($p < 0.01$), and the prevalence of hypertension and diabetes mellitus was significantly higher in the elderly patients ($p = 0.01$ and $p < 0.01$, respectively). Of

**Table 1** Clinical characteristics of TMA at the time of renal biopsy

| | Median [IQR], *n* (%) | Range | *n* |
|---|---|---|---|
| Age at renal biopsy (years) | 50 [35–64] | 3–84 | 151 |
| Gender, male | 75 (49.3) | | 152 |
| BMI (kg/m$^2$) | 21.2 [18.9–23.4] | 12.6–34.9 | 152 |
| Systolic blood pressure (mmHg) | 135 [120.5–150] | 91–246 | 128 |
| Diastolic blood pressure (mmHg) | 80 [70–91] | 37–165 | 128 |
| Hypertension | 95 (75.4) | | 126 |
| Diabetes mellitus | 21 (19.4) | | 108 |
| Laboratory parameters | | | |
| Serum total protein (g/dL) | 6.3 [5.6–6.8] | 3.9–8.2 | 152 |
| Serum albumin (g/dL) | 3.6 [2.8–4.0] | 1.4–4.9 | 151 |
| Total cholesterol (mg/dL) | 192.5 [152–240] | 51–526 | 138 |
| Serum creatinine (mg/dL) | 1.55 [1.03–2.51] | 0.20–15.9 | 144 |
| eGFR (mL/min/1.73 m$^2$) | 37.6 [20.1–56.2] | 3.2–154.2 | 151 |
| eGFR less than 30 mL/min/1.73 m$^2$ | 64 (42.1) | | 152 |
| eGFR less than 15 mL/min/1.73 m$^2$ | 28 (18.4) | | 152 |
| HbA1c (%) | 5.4 [4.9–5.7] | 3.7–7.5 | 83 |
| Urinary protein | | | |
| (−) | 21 (13.8) | | 152 |
| (±) | 12 (7.9) | | 152 |
| (1 +) | 32 (21.1) | | 152 |
| (2 +) | 47 (30.9) | | 152 |
| (3 +) | 30 (19.7) | | 152 |
| (4 +) | 10 (6.6) | | 152 |
| Proteinuria (g/gCr) | 2.25 [1.30–5.43] | 0.00–65.25 | 70 |
| Nephrotic range proteinuria | 29 (41.4) | | 70 |
| Urinary occult blood | | | |
| (−) | 47 (30.9) | | 152 |
| (±) | 27 (17.8) | | 152 |
| (1 +) | 23 (15.1) | | 152 |
| (2 +) | 26 (17.1) | | 152 |
| (3 +) | 29 (19.1) | | 152 |

Values are shown as either a median with an interquartile range (IQR) or a number denoted as a percentage (%)

*BMI*, body mass index; *Cr*, creatinine; *eGFR*, estimated glomerular filtration rate; *Hb*, hemoglobin; *TMA*, thrombotic microangiopathy

the elderly patients with TMA, 90.6% had hypertension. In the elderly group, the median serum albumin level was as low as 3.2 g/dL, and the median serum creatinine level was as high as 1.91 mg/dL ($p < 0.01$). The eGFR was < 30 mL/min/1.73 m$^2$ in 62.2% of elderly patients. There was significantly lower proteinuria in the adult group ($p = 0.02$). With relation to the underlying factors of TMA in each age group, HUS/TTP was most frequently observed in the children. The cause of TMA was diverse in the adult and elderly groups, and the composition of factors was similar (Table 4).

## Discussion

In Japan, the results of national survey on TMA in the field of pediatrics and kidney transplantation were reported [7, 8], but there are still few studies on TMA. This is the first nationwide cross-sectional analysis on biopsy-proven TMA. The causes of TMA are becoming more complex, and it is meaningful to survey the actual state in Japan. In 2013, Japanese diagnostic criteria for aHUS were created, and TMA was classified into three categories: STEC-HUS,

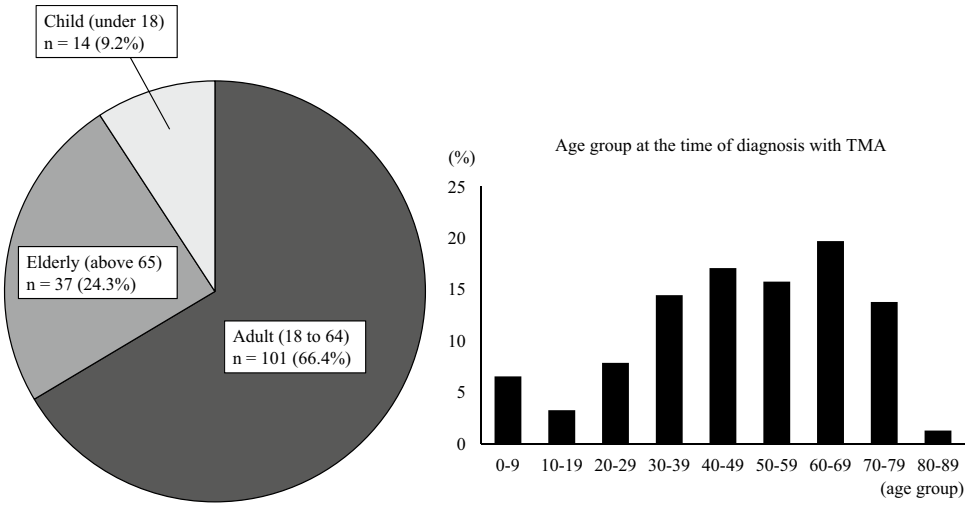


**Fig. 2** The percentages of children, adults, and elderly individuals with TMA were 9.2%, 66.4%, and 24.3%, respectively. When stratified according to the age group, patients aged 60–69 were the largest. *TMA*, thrombotic microangiopathy

**Table 2** Causative diseases of TMA cases confirmed by renal biopsy

| Underlying diseases associated with TMA ($n = 152$) | $n$ (%) |
|---|---|
| Connective tissue disease | 26 (17.1) |
| HUS/TTP | 25 (16.4) |
| Drug-induced | 25 (16.4) |
| Hematopoietic stem cell transplantation | 9 (5.9) |
| Kidney transplantation | 6 (3.9) |
| Hypertension | 4 (2.6) |
| Liver transplantation | 2 (1.3) |
| Malignancy | 2 (1.3) |
| Pregnancy | 1 (0.7) |
| Unknown | 52 (34.2) |

The causes of TMA were classified into 9 types, including secondary factors: HUS/TTP, connective tissue disease, drug-induced, hematopoietic stem cell transplantation, kidney transplantation, hypertension, liver transplantation, malignancy, and pregnancy. Cases that did not identify the underlying disease of TMA were considered unknown

*HUS*, hemolytic uremic syndrome; *TMA*, thrombotic microangiopathy; *TTP*, thrombotic thrombocytopenic purpura

related to Shiga toxin; TTP, with remarkable decrease of a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) activity; and aHUS [9, 10]. Overseas, Scully et al. defined aHUS in 2014, and cases excluding STEC-HUS, TTP, and secondary TMA with various underlying diseases were treated as aHUS [3]. Thereafter, clinical guides for aHUS were published in Japan, and TMA was divided into four categories: STEC-HUS, TTP, aHUS, and secondary TMA [4, 5]. As a cause of aHUS, complement-related congenital gene abnormalities, such as complement factor B, H, and I, membrane cofactor protein, C3, and thrombomodulin have been identified. In addition, acquired autoantibody to complement factor H has been found. In recent years, it has been reported that complement-related gene abnormalities also exist in secondary TMA [11]. The complement activation may be induced in the background diseases of secondary TMA, and a new concept of secondary aHUS has also been proposed [12, 13]. Thus, there have been various changes regarding the TMA classification, and a unified opinion has not yet been established. With these backgrounds, J-RBR has been operating with new registration categories and systems since January 2018. This study used data from J-RBR up until 2017. At the present time, it is valuable to analyze data for the past 10 years according to the conventional classification.

Bayer et al. have reported the results of a large-scale, retrospective study on etiology and clinical outcomes of 564 clinically diagnosed cases of TMA [14]. In their study, TTP and aHUS were defined as primary TMA, and TMA triggered by other causes, including STEC-HUS, was defined as secondary TMA. Interestingly, 5.9% of the cases were primary TMA, and the remaining 94.1% were secondary TMA. The total frequency of the three types, TTP, STEC-HUS, and aHUS, which are representative diseases of TMA, was 12.1%. Regarding the causes of secondary TMA, pregnancy, malignancy, infection, and drug use were the main subjects. As another feature, it was reported that cases with multiple causes of TMA were significantly more frequent in secondary TMA. Concerning the onset age, 3.0% were children aged < 18 years, and 20.9% were elderly patients aged > 60 years. The median serum creatinine level at the onset of TMA was 1.2 mg/dL, and proteinuria was observed in 68.4% of patients. Although the comparison to this study is less accurate due to differences in terms of diagnostic methods of TMA, case selection criteria, race, and facility, the high frequency of secondary TMA caused by various factors was similar. The age at TMA onset was widely distributed, and the proportion of elderly patients was similar, but our study included more children. In the baseline clinical findings, advanced kidney injury and high proportion of

**Table 3** Comparison of clinical features at renal biopsy according to background disease of TMA

| | HUS/TTP ($n=25$) | Connective tissue disease ($n=26$) | Drug-induced ($n=25$) | $p$ value |
|---|---|---|---|---|
| | Median [IQR], $n$ (%) | Median [IQR], $n$ (%) | Median [IQR], $n$ (%) | |
| Age at renal biopsy (years) | 39 [13–55.5] | 53 [41–66] | 58 [50–66] | 0.01* |
| Gender, male | 11 (44.0) | 5 (19.2) | 13 (52.0) | 0.04* |
| BMI (kg/m$^2$) | 19.5 [16.0–21.3] | 19.3 [18.0–21.6] | 21.6 [18.9–23.3] | 0.12 |
| Systolic blood pressure (mmHg) | 125 [110–145] | 139 [132–142] | 142 [127–155] | 0.08 |
| Diastolic blood pressure (mmHg) | 74.5 [68–87] | 82 [70–94] | 82 [74–90] | 0.39 |
| Hypertension | 15 (65.2) | 20 (87.0) | 15 (79.0) | 0.21 |
| Diabetes mellitus | 3 (17.6) | 2 (11.1) | 5 (26.3) | 0.49 |
| Laboratory parameters | | | | |
| Serum total protein (g/dL) | 6.5 [5.9–6.7] | 6.0 [5.6–7.0] | 6.1 [5.3–6.7] | 0.82 |
| Serum albumin (g/dL) | 3.7 [3.1–4.2] | 3.3 [2.8–3.9] | 3.6 [2.8–4.0] | 0.33 |
| Total cholesterol (mg/dL) | 171 [148–229] | 195.5 [156–217] | 203.5 [166–248.5] | 0.55 |
| Serum creatinine (mg/dL) | 1.24 [0.80–3.82] | 1.28 [0.92–2.30] | 1.71 [1.16–2.01] | 0.68 |
| eGFR (mL/min/1.73 m$^2$) | 45.5 [11.8–67.2] | 40.0 [20.1–58.2] | 35.3 [23.4–58.9] | 0.91 |
| eGFR less than 30 mL/min/1.73 m$^2$ | 10 (40.0) | 10 (38.5) | 10 (40.0) | 0.99 |
| eGFR less than 15 mL/min/1.73 m$^2$ | 7 (28.0) | 6 (23.1) | 3 (12.0) | 0.36 |
| Urinary protein-positive | 15 (60.0) | 16 (61.5) | 22 (88.0) | 0.05 |
| Urinary protein 3 + or 4 + | 6 (24.0) | 5 (19.2) | 7 (28.0) | 0.76 |
| Proteinuria (g/gCre) | 1.76 [1.09–3.55] | 1.82 [1.30–6.90] | 2.00 [1.21–4.38] | 0.90 |
| Nephrotic range proteinuria | 2 (28.6) | 5 (45.5) | 6 (31.6) | 0.69 |
| Urinary occult blood-positive | 10 (40.0) | 16 (61.5) | 16 (64.0) | 0.17 |

*BMI*, body mass index; *Cr*, creatinine; *eGFR*, estimated glomerular filtration rate; *HUS*, hemolytic uremic syndrome; *IQR*, interquartile range; *TMA*, thrombotic microangiopathy; *TTP*, thrombotic thrombocytopenic purpura

*$p<0.05$

proteinuria in our cohort might have been correlated with bias, accumulating TMA cases diagnosed by renal biopsy.

In the results of this study, CTD and drug-induced were frequently the causes of secondary TMA. Among CTD, SLE, APS, and SSc were identified as background factors of secondary TMA. To date, there have been several reports of TMA in SLE [15, 16]. Complications of renal TMA correlated with poor renal prognosis [15]. Scleroderma renal crisis (SRC) is a serious condition that affects 2–15% of patients with SSc [17]. Typical cases with severe hypertension in SRC are often diagnosed clinically; however, renal biopsy can be a clue for diagnosis in normotensive renal crisis without hypertension [18]. Although APS is characterized by thrombosis, TMA has been reported as a nonthrombotic condition [19]. Antiphospholipid antibodies reportedly play a role in endothelial cell damage in TMA associated with APS [20].

Recently, kidney injury caused by anticancer drugs has been regarded as a problem. Even in our study, renal TMA related to antineoplastic drugs was often recognized. Direct endothelial cell injury and vascular endothelial growth factor (VEGF) inhibition are roughly classified as the mechanisms of drug-induced TMA [21]. Gemcitabine and calcineurin inhibitors have been reported as representative agents of the former [22, 23]. In contrast, the latter include monoclonal antibody against VEGF [24–26] and tyrosine kinase inhibitor [27, 28]. According to the present results, drug-induced TMA tended to have a higher median serum creatinine level at the time of renal biopsy as compared to HUS/TTP and CTD. Drug-induced TMA is less likely to develop into systemic TMA [27], and it may be related to perform a renal biopsy in the acute phase. The high urinary protein positive rate in the drug-induced TMA group may reflect epithelial cell damage related to the drug in addition to endothelial injury [25, 27]. Through this study, it was also clarified that the cause was not identifiable for many cases of TMA diagnosed pathologically. The pathogeneses of these unknown cases of TMA need to be elucidated by further research.

The results of our study indicate that TMA develops widely from children to elderly individuals, and causes of TMA differ with age. It became clear that the cause of TMA is more complicated in adults than in children. The majority of childhood-onset TMA cases were HUS/TTP, with less secondary TMA. In addition, among secondary TMA, CTD-related cases were common. In a cohort study including 258 Japanese pediatric patients with

**Table 4** Comparison of clinical findings and causes of TMA based on age group

| | Child (under 18) ($n=14$) Median [IQR], $n$ (%) | Adult (18–64) ($n=101$) Median [IQR], $n$ (%) | Elderly (above 65) ($n=37$) Median [IQR], $n$ (%) | $p$ value |
|---|---|---|---|---|
| Age at renal biopsy (years) | 5 [3–10] | 45 [36–54] | 71 [67–74] | |
| Gender, male | 6 (42.9) | 52 (51.5) | 17 (45.9) | 0.74 |
| BMI (kg/m$^2$) | 15.8 [14.6–16.5] | 21.6 [19.7–23.5] | 21.1 [18.9–24.4] | 0.01 > * |
| Systolic blood pressure (mmHg) | 108 [100–114] | 136 [122.5–147.5] | 140 [127–160] | 0.01 > * |
| Diastolic blood pressure (mmHg) | 68 [46–78] | 86 [74.5–96] | 75 [68–80] | 0.01 > * |
| Hypertension | 4 (44.4) | 62 (72.9) | 29 (90.6) | 0.01* |
| Diabetes mellitus | 0 (0.0) | 9 (12.3) | 12 (40.0) | 0.01 > * |
| Laboratory parameters | | | | |
| Serum total protein (g/dL) | 6.7 [6.2–7.0] | 6.2 [5.5–6.8] | 6.1 [5.5–7.1] | 0.31 |
| Serum albumin (g/dL) | 4.1 [3.7–4.4] | 3.6 [2.8–3.9] | 3.2 [2.8–3.8] | 0.01 > * |
| Total cholesterol (mg/dL) | 215 [164–254] | 197.5 [149.5–248] | 176 [160–205] | 0.34 |
| Serum creatinine (mg/dL) | 0.50 [0.23–0.92] | 1.52 [1.10–2.52] | 1.91 [1.17–3.32] | 0.01 > * |
| eGFR (mL/min/1.73 m$^2$) | 62.2 [52.2–115.8] | 38.4 [23.0–55.5] | 27.6 [14.8–45.7] | 0.01 > * |
| eGFR less than 30 mL/min/1.73 m$^2$ | 1 (7.1) | 40 (39.6) | 23 (62.2) | 0.01 > * |
| eGFR less than 15 mL/min/1.73 m$^2$ | 0 (0.0) | 18 (17.8) | 10 (27.0) | 0.08 |
| Urinary protein-positive | 9 (64.3) | 78 (77.2) | 32 (86.5) | 0.21 |
| Urinary protein 3 + or 4 + | 4 (28.6) | 23 (22.8) | 13 (35.1) | 0.34 |
| Proteinuria (g/gCr) | 3.99 [2.76–13.66] | 1.71 [1.23–3.90] | 4.53 [2.00–6.90] | 0.02* |
| Nephrotic range proteinuria | 3 [60.0] | 16 [34.8] | 10 [52.6] | 0.28 |
| Urinary occult blood-positive | 5 (35.7) | 53 (52.5) | 20 (54.1) | 0.47 |

| Child (under 18) | | Adult (18–64) | | Elderly (above 65) | |
|---|---|---|---|---|---|
| $n=14$ | $n$ (%) | $n=101$ | $n$ (%) | $n=37$ | $n$ (%) |
| HUS/TTP | 9 (64.3) | Connective tissue disease | 17 (16.8) | Drug-induced | 9 (24.3) |
| Connective tissue disease | 4 (28.6) | Drug-induced | 16 (15.8) | Connective tissue disease | 8 (21.6) |
| Unknown | 1 (7.1) | HUS/TTP | 12 (11.9) | HUS/TTP | 4 (10.8) |
| | | Hematopoietic stem cell transplantation | 8 (7.9) | Hematopoietic stem cell transplantation | 1 (2.7) |
| | | Kidney transplantation | 6 (5.9) | Liver transplantation | 1 (2.7) |
| | | Hypertension | 4 (4.0) | Malignancy | 1 (2.7) |
| | | Liver transplantation | 1 (1.0) | Unknown | 13 (35.1) |
| | | Malignancy | 1 (1.0) | | |
| | | Pregnancy | 1 (1.0) | | |
| | | Unknown | 35 (34.7) | | |

*BMI*, body mass index; *Cr*, creatinine; *eGFR*, estimated glomerular filtration rate; *HUS*, hemolytic uremic syndrome; *IQR*, interquartile range; *TMA*, thrombotic microangiopathy; *TTP*, thrombotic thrombocytopenic purpura

*$p<0.05$

TMA, STEC-HUS, and TTP accounted for the majority of 70.2%, with similar results [7]. The causes of TMA in children were simpler, indicating that there was less need to consider various factors, such as drug use, hypertension, and malignancy. In an age-related comparison, renal function was lower in adults and the elderly compared to children. The ratio of HUS/TTP, generally characterized by severe thrombocytopenia with difficulty in invasive procedures, was obviously higher in children than adults and the elderly. There is a possibility that the duration from disease onset to renal biopsy was shorter in adults and the elderly than in children, and the timing of renal biopsy may have affected renal function. Among them, serum creatinine levels were significantly higher, especially in the elderly. TMA-induced renal injury results from impaired microcirculation [25]. In the acute phase, a decrease in glomerular filtration due to enlargement of endothelial cells and tubular injury induced by hypoxia and ischemia contribute to the pathophysiology. The prevalence of hypertension and diabetes was significantly higher in the

elderly, suggesting that TMA-associated renal damage was promoted based on the potential glomerular ischemia and endothelial damage.

There are several limitations of this study as follows: (1) clinically defined TMA and pathologically proven TMA are not always consistent. We analyzed the limited data of J-RBR that did not include clinically diagnosed TMA cases, in which renal biopsy was not performed. Therefore, these analyses may not reflect overall TMA in Japan. (2) Clinical data related to TMA, such as platelet count, hemoglobin, and lactate dehydrogenase (LDH), were not available because they were not included in the J-RBR registration system. (3) The clinical data registered in the J-RBR system were limited, and detailed information related to clinical diagnosis was not available. (4) Since the J-RBR categorization was a comprehensive diagnosis of HUS/TTP, it was difficult to analyze STEC-HUS, TTP, and aHUS separately. (5) Depending on the degree of thrombocytopenia, the timing of renal biopsy may be different among patients. (6) The pathological diagnosis of TMA was performed at each facility, and the detailed process leading to the diagnosis could not be understood. (7) The pathological data registered in the J-RBR system were limited, and we could not perform a detailed analysis on the pathological features. (8) This study is a cross-sectional study, and longitudinal analysis including clinical prognosis is necessary for sufficient verification of TMA in Japan.

In summary, this study provides the results of the first large-scale cohort study on epidemiological data and clinical findings of pathologically proven TMA cases in Japan using the J-RBR database. Our studies demonstrated that TMA has various causes, with a higher frequency of secondary TMA, including CTD-related and drug-induced. The characteristics of clinical findings based on the underlying disease of TMA and age group were shown. There are various limitations in our study; however, it is meaningful to record valuable national data over the decade of 2007–2017 to recognize the current state of TMA in our country. Further studies require TMA-related clinical findings including platelet, hemoglobin, and LDH and detailed pathological features, such as glomerular lesions, interstitial fibrosis and tubular atrophy, and vascular abnormalities. In addition, it is necessary to investigate the correlation between clinical, pathological, and treatment parameters and clinical prognosis.

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## Compliance with ethical standards

**Conflict of interest** The authors have no conflicts of interest to declare.

**Ethical standards** The ethical committee of the Japanese Society of Nephrology comprehensively examined and approved the study protocol.

**Informed consent** Informed consent was obtained from all participants included in this study.

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