Renal Replacement Therapy

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Clinical characteristics, treatments, and outcomes of thrombotic thrombocytopenic purpura treated with plasma exchange in Japan: a nationwide inpatient database study

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Abstract

Background Plasma exchange (PEX) has been the primary treatment for immune-mediated thrombotic thrombocytopenic purpura (iTTP) since the 1990s. Daily PEX is recommended in international guidelines, but PEX was only reimbursed up to three times weekly under the Japanese national health insurance system until March 2018. This study was conducted to analyze practice patterns and outcomes in patients with TTP in Japan.

Methods We used the Japanese Diagnosis Procedure Combination inpatient database, including data from approximately 1,200 acute care hospitals. We identified all hospitalized adult patients who were diagnosed with TTP on admission from July 2010 to March 2017 and who received at least one PEX during hospitalization, which we defined as TTP treated with PEX. We revealed patient characteristics, treatment patterns, and outcomes.

Results There were 1,559 patients with TTP treated with PEX. The median age was 64 (interquartile range [IQR] 46–74) years. There were slightly more women (59%) than men enrolled into this study. The median PEX frequency within 7 days of the initial PEX was three (IQR 2–5) times. The median total PEX number during hospitalization was six (IQR 3–10), while the median PEX duration was 10 (IQR 4–22) days. The median time from admission to the initial PEX was 4 (IQR 2–11) days. Overall, in-hospital mortality was 32%. Thirty-three percent (144/437) of hospitals reported only one case of TTP during the study period.

Conclusions Our data demonstrated that clinical practice in Japan considerably varied and its standardization is warranted.

Keywords Thrombotic thrombocytopenic purpura, Plasma exchange, Thrombotic microangiopathies, Steroids, Rituximab

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Background

Thrombotic microangiopathy (TMA) is a pathologic diagnosis of vascular damage manifested by arteriolar and capillary thrombosis, but its diagnosis is often clinically made by the presence of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia in appropriate clinical settings [1]. TMA syndromes include a wide array of diseases, including thrombotic thrombocytopenic purpura (TTP), Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome (STEC-HUS), complement-mediated TMA (atypical HUS, aHUS), and rare hereditary disorders.

Immune-mediated TTP (iTTP) is a medical emergency that becomes fatal without proper treatment. iTTP typically follows a progressive course if untreated, and the mortality rate before the 1980s was approximately 90 percent in the acute phase [2].

Plasma exchange (PEX) with fresh frozen plasma (FFP) has been the primary treatment for iTTP since the 1990s [3]. PEX efficacy was initially demonstrated in a randomized clinical trial published in 1991 [4]. The trial randomly assigned patients with TTP, which is defined as microangiopathic hemolytic anemia and thrombocytopenia without another identifiable cause, to receive either PEX or plasma infusion for 7 days. Survival was significantly greater in those assigned to PEX than those assigned to plasma infusion at 6 months (78% versus 63%). Multiple subsequent studies have confirmed the efficacy of PEX in iTTP [5]. Therefore, current national guidelines recommend that all patients with a confirmed diagnosis or a presumptive diagnosis of iTTP should undergo PEX as soon as possible while considering other TMA syndromes and that this treatment should continue until the platelet count recovers to the normal range [6–8].

Daily PEX is recommended by several guidelines, and Rock et al. demonstrated that daily PEX could reduce the mortality of acute TTP [4]. However, in Japan, PEX up to three times a week for a maximum of 12 weeks had been reimbursed under the Japanese universal health insurance system for 30 years prior to March 2018, which might have led to a unique clinical practice pattern in our country. However, no studies have revealed this real-world practice. In contrast to Japan, daily PEX is standard in other countries.

While clinical practice for iTTP treatment in Japan may differ from those in other countries, real-world practice patterns remain unknown. Therefore, we analyzed the practice patterns using a nationwide inpatient database.

Methods

This study was a retrospective nationwide cohort study in Japan. The reporting in this study conforms to the RECORD statement [9]. The Institutional Review Board of The University of Tokyo approved the study (approval number 3501-3; December 25, 2017). No information that allows the identification of individual patients, hospitals, or physicians was obtained. The requirement for informed consent was waived because of the anonymous nature of the data.

Data source

We used the Japanese Diagnosis Procedure Combination (DPC) inpatient database, which includes discharge abstracts and administrative claims data. We obtained these data from approximately 1,200 acute care hospitals that voluntarily contribute to the database in Japan [10]. For 2018, this database covers approximately 70% of all beds for critically ill patients and 50% for acute-phase patients in Japan. The database includes information about age, sex, diagnoses (including primary diagnosis, comorbidities present at admission, and conditions that arose after admission), procedures, and discharge status. In the Japanese DPC inpatient database, diagnoses are recorded using International Classification of Diseases Tenth Revision (ICD-10) codes and written in Japanese text.

Study population

We identified all hospitalized adult patients diagnosed with TMA or congenital or acquired TTP (ICD-10 code M31.1) on admission as a primary diagnosis code from July 2010 to March 2017 and received at least one PEX during hospitalization to exclude as many cases with TMA other than iTTP as possible. We could not confirm the diagnosis of iTTP with ADAMTS13 activity because the ADAMTS13 ELISA test was not approved until April 2018 in Japan and these results were not available in this national DPC data source, which is a limitation of this study. Therefore, we defined these cases as TTP treated with PEX. Classical HUS, atypical HUS, and disseminated intravascular coagulation (DIC) are not included in this population because they have different ICD-10 codes (D59.3, D65). We excluded patients for the following reasons: (1) patients whose primary diagnosis was TMA; (2) those younger than 18 years to evaluate only adult-onset TTP; (3) those who never received PEX during hospitalization; or (4) readmission data when patients with the ICD code M31.1 were admitted more than once during the study period.

Variables

We collected patient characteristics including age, sex, smoking history, Japan Coma Scale on admission [11], comorbidities on admission, ambulance use, and intensive care unit (ICU) admission. We also collected treatment information, including the frequency of PEX within 7 days after the initial PEX, the total number of PEXs during hospitalization, duration of PEX, days from admission to initial PEX, immunosuppressive therapies, and other supportive therapies during hospitalization. Immunosuppressive therapy contained corticosteroids, steroid pulse therapy, and other immunosuppressive drugs including cyclophosphamide, rituximab, cyclosporine, tacrolimus, azathioprine, and vincristine. Other supportive therapies included catecholamine use, oxygen supplementation, mechanical ventilation, red blood cell transfusion, and platelet transfusion.

We collected outcomes of in-hospital mortality, discharge to home, length of hospital stays, and total hospitalization costs.

Statistical analysis

Categorical variables are reported as the count (%), and continuous variables are reported as median with the interquartile range (IQR). All analyses were performed using Stata/MP, version 16.0 (StataCorp, College Station, TX, USA).

Results

There were 1,559 patients with TTP treated with PEX who were included from 437 hospitals (Fig. 1). The median patient age was 64 (IQR 46–74) years. There were slightly more women (59%) than men in the study. Thirty-one percent of patients used an ambulance service. The percentage of patients with alert consciousness, confusion, somnolence, and coma on admission was 76%, 16%, 4%, and 4%, respectively. Significant comorbidities upon admissions were connective tissue disease (14%) and malignancy (8%) (Table 1).

The median PEX administration frequency within 7 days of the initial PEX was three (IQR 2–5) times

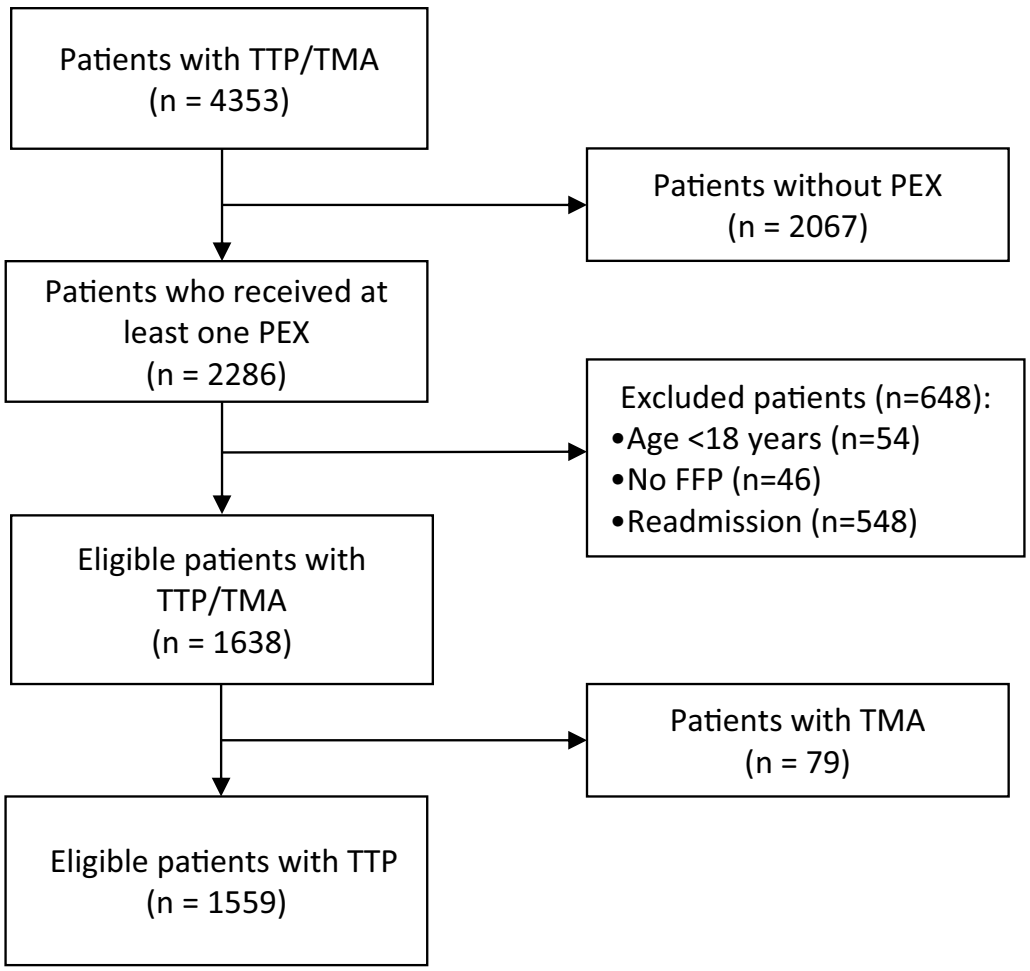

Fig. 1 Flowchart of patient selection. iTTP, immune thrombotic thrombocytopenic purpura; PEX, plasma exchange; FFP, fresh frozen plasma

Table 1 Patient characteristics

	Total (n = 1,559)
Age, years, median (IQR)	64 (46–74)
Male, n (%)	639 (41)
Smoking history, n (%)	
Nonsmoker	885 (57)
Current/past smoker	414 (27)
Unknown	260 (17)
Japan Coma Scale on admission, n (%)	
Alert	1187 (76)
Confusion	245 (16)
Somnolence	62 (4)
Coma	65 (4)
Comorbidities on admission, n (%)	
Coronary artery diseases	11 (1)
Congestive heart failure	112 (7)
Cerebral vascular disease	112 (7)
Dementia	11 (1)
Chronic lung disease	39 (3)
Connective tissue disease	220 (14)
Chronic liver disease	62 (4)
Diabetes	169 (11)
Chronic kidney disease	177 (11)
Malignancy	124 (8)
Acquired immunodeficiency syndrome	2 (0)
Ambulance use, n (%)	481 (31)
ICU admission, n (%)	618 (40)

IQR interquartile range, *ICU* intensive care unit

(Fig. 2A). The median total number of PEXs during hospitalization was six (IQR 3–10) (Fig. 2B). The median PEX duration was 10 (IQR 4–22) days (Fig. 2C), and the median time from admission to the initial PEX was 4 (IQR 2–11) days. Twenty-four percent of the patients received an initial PEX on the day of admission, and 28% received initial PEX on day 10 or later after admission (Fig. 2D). Among 437 hospitals where PEX was provided for patients with TTP, 33% (144/437) of hospitals reported only one case of TTP during the study period (Fig. 2E).

The percentage of patients who received corticosteroids and steroid pulse therapy was 93% and 66%, respectively (Table 2). The percentage of patients who received second-line immunosuppressive therapies including cyclophosphamide, rituximab, cyclosporine, tacrolimus, azathioprine, and vincristine was 14%, 10%, 8%, 5%, 3%, and 1%, respectively.

Forty percent of the patients required admission to the ICU. For other supportive therapies, 67% received oxygen supplementation, 34% received catecholamines, and 30% required mechanical ventilation during hospitalization (Table 2). Additionally, all patients received FFP, 76% of the patients received a red blood cell transfusion, and 40% of the patients received a platelet transfusion.

The overall in-hospital mortality was 32% (Table 3). Fifty-two percent of the patients were successfully discharged home, and the rest were discharged to rehabilitation or nursing facilities. The median length of hospital stay was 46 (IQR 25–78) days. The median total healthcare cost expenditure was $41,247 (IQR $24,264–$63,997) US dollars.

Discussion

Using a nationwide inpatient database in Japan, we identified 1,559 patients with TTP who received at least one PEX during hospitalization. We found a unique practice pattern of PEX and a high mortality rate for patients with TTP treated with PEX in Japan. Our study revealed that in-hospital mortality (32%) was unexpectedly higher than that reported in previous studies. For example, the Oklahoma TTP-HUS Registry reported a mortality of approximately 13% [12], while the UK TTP Registry reported 8.5% [13], the French TMA Reference Center reported 12% [14], and the Milan TTP Registry from Italy reported 5% mortality [15]. Our present study also showed that 40% of the patients required ICU care, and 30% required mechanical ventilation, suggesting that more patients developed critical illness than in other countries. Unfortunately, we could not determine the cause of such severe conditions. The high mortality, as well as the high percentage of severe disease, might have several explanations and should be interpreted with caution, which is discussed below. First, there was a significant delay in diagnosis and initiation of PEX (median 4 days after admission). It is known that a delay in initiating PEX is associated with a worse prognosis [16]. Second, our study's inclusion and exclusion criteria are different from those of other studies. For example, both the recent US and UK studies used the ADAMTS13 activity to identify patients. A limitation of our study is that our national DPC database does not include ADAMTS13 data. Therefore, given the proportion of patients with comorbidities, such as connective tissue disease and malignancy, our study likely included patients with secondary TMA, which is defined as MAHA and thrombocytopenia caused by other systemic disorders and requires therapy directed at the underlying disorder. The Japanese Society for Apheresis has developed a registry of diseases for which apheresis, including plasma exchange, is used as a therapeutic option. Future studies using this national registry are expected to overcome the challenges encountered in our study.

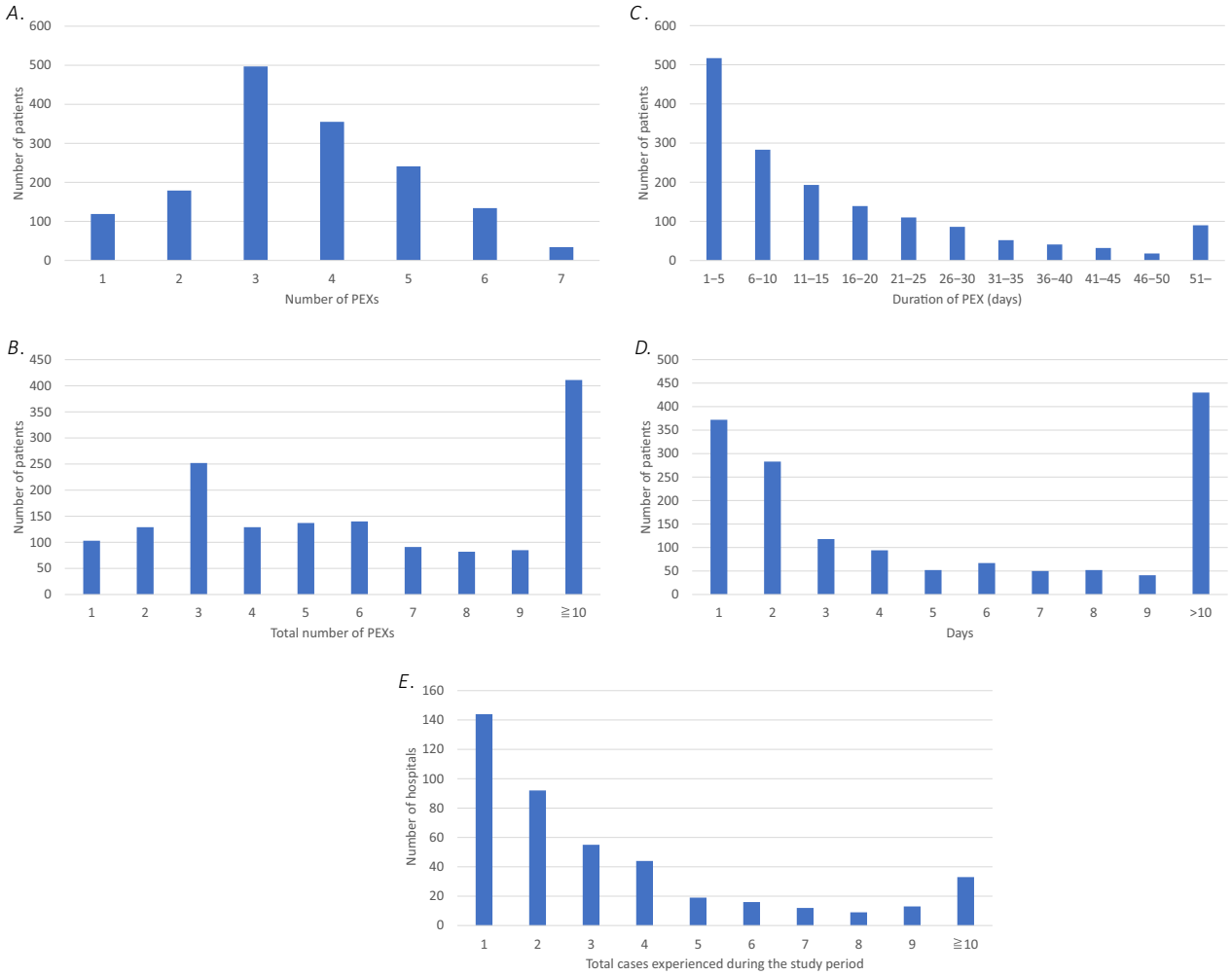

Fig. 2 **A** Frequency of PEX within 1 week after the initial PEX; **B** Total number of PEXs during hospitalization; **C** Duration of PEX; **D** Interval days from admission to initial PEX; **E** Total cases reported at each hospital during the study period. PEX, plasma exchange

Additionally, our study revealed a unique practice pattern of PEX in Japan, which also could have contributed to the higher mortality. The median frequency of PEX within 7 days of the initial PEX was only three times, which shows a disparity between real-world clinical practice in Japan and the guidelines in other countries. Furthermore, 28% of patients started PEX more than 10 days after admission, which is later than we originally expected, suggesting that there was difficulty in diagnosing TTP at local hospitals. In the USA and EU, TMA centers have TTP medical experts, while our study revealed that more than 400 hospitals accepted patients with TTP, and approximately 30% of these hospitals reported only one case of TTP during the study period. These data suggest that each hospital does not have enough experience with TTP. However, the Japanese healthcare system is trying to build centers for specific intractable diseases, and Nara Medical University is currently the leading TMA center in the country. The future development of new diagnostic and treatment methods is expected in cooperation with the research group of the Ministry of Health, Labor, and Welfare.

We found that the median total number of PEXs during hospitalization was six while the median duration of PEX was 10 days, suggesting a non-daily schedule of PEX in this cohort. However, other countries have reported that PEX was performed daily and the median duration of daily PEX was around 7–10 days [17, 18]. The non-daily schedule in our cohort did not affect treatment duration. Since April of 2018, daily PEX until normalization of platelet counts for 2 days has been approved for reimbursement by the universal health insurance system in Japan. Future studies need to examine how this affects PEX patterns and patient prognosis.

When additional treatments were examined, the use of second-line immunosuppressive therapies in Japan was

Table 2 Immunosuppressive therapy and other supportive therapies during hospitalization

	Total (n = 1,559)
Corticosteroids, n (%)	1447 (93)
Steroid pulse therapy, n (%)	1031 (66)
Immunosuppressants, n (%)	501 (32)
Cyclophosphamide	212 (14)
Rituximab	149 (10)
Cyclosporine	127 (8)
Tacrolimus	76 (5)
Azathioprine	43 (3)
Vincristine	22 (1)
Other supportive therapies, n (%)	
Catecholamine use	523 (34)
Oxygen supplementation	1046 (67)
Mechanical ventilation	472 (30)
Fresh frozen plasma	1559 (100)
Red blood cell transfusion	1184 (76)
Platelet transfusion	626 (40)

Table 3 Outcomes

	Total (n = 1,559)
In-hospital mortality, n (%)	498 (32)
Discharge to home, n (%)	824 (53)
Length of hospital stay, days, median (IQR)	46 (25, 78)
Total healthcare cost, USD, median (IQR)	$41,247 ($24,264, $63,997)

IQR interquartile range, *USD* United States dollars

found to be limited. Conversely, rituximab is commonly used as a first-line therapy in the USA and EU. Rituximab was officially approved to treat iTTP in February 2018 in Japan, but it was not approved during the study period [19].

Conclusions

This retrospective study assessed real-world clinical practice for patients with TTP treated with PEX in Japan using the nationwide inpatient database. Our data demonstrated that the clinical practice in Japan considerably varied, and its standardization is warranted.

Abbreviations

PEX Plasma exchange
iTTP Immune-mediated thrombotic thrombocytopenic purpura
IQR Interquartile range
TMA Thrombotic microangiopathy
MAHA Microangiopathic hemolytic anemia
STEC-HUS Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome
FFP Fresh frozen plasma
DPC Diagnosis procedure combination
ICD-10 International classification of diseases tenth revision
DIC Disseminated intravascular coagulation
ICU Intensive care unit

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Author contributions

Y. Yamada, H. Ohbe, H. Yasunaga, H. Nakamoto and Y. Miyakawa made a substantial contribution to concept and design, analysis and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests

YM received research fund from Sanofi and worked as a medical advisor for Zenyaku Kogyo.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The Institutional Review Board of The University of Tokyo approved the study (approval number 3501-3; December 25, 2017). No information that allows the identification of individual patients, hospitals, or physicians was obtained. The requirement for informed consent was waived because of the anonymous nature of the data.

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