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Annual trends in atypical haemolytic uremic syndrome management in Japan and factors influencing early diagnosis and treatment: a retrospective study

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Atypical haemolytic uremic syndrome (aHUS) is a rare disorder characterised by complement-mediated thrombotic microangiopathy (TMA). Despite clinical guidelines, the diagnosis and treatment of aHUS in its early stages remains challenging. This study examined the annual trends in aHUS clinical practices in Japan and explored factors influencing early diagnosis and treatment. Using data from the 2011–2020 Diagnosis Procedure Combination database, 3096 cases with the HUS disease code were identified, of which 217 were confirmed as aHUS and treated with eculizumab or plasma exchange. Early initiation, defined as starting eculizumab or plasma exchange within 7 days of admission, was the focus of the study. Our study revealed no significant changes over time in the number of aHUS diagnoses, cases treated with eculizumab, or early initiation cases. Early initiation cases underwent haemodialysis earlier and had ADAMTS13 activity measured earlier, shorter hospital stays, and lower hospitalisation costs than late initiation cases. In conclusion, we found no increase in the number of newly diagnosed aHUS cases or early treatment initiation over time. Early recognition of TMA and differentiation of the causative disease are crucial for identifying potential aHUS cases, which may lead to better patient prognoses.

Keywords Atypical haemolytic uremic syndrome (aHUS), Thrombotic microangiopathy (TMA), Eculizumab, Plasma exchange, A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13), Thrombocytopenia, Haemolytic anaemia

Atypical haemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) caused by abnormal complement activation due to complement-related genetic mutations or autoantibodies against complement regulatory factors[1]. In recent years, the management of aHUS in Japan has improved due to the introduction of anti-complement agents[2] and establishment of specific practice guidelines[3]. However, early diagnosis and treatment of patients with aHUS remains a challenge. The clinical diagnosis of aHUS is made by confirming three non-specific features—thrombocytopenia, haemolytic anaemia and acute kidney injury—as well as by excluding other causes of TMA (Shiga toxin-producing *Escherichia coli* (STEC)-HUS, thrombotic thrombocytopenic purpura (TTP), and secondary TMA). Anti-complement therapy and plasma exchange (PE) are performed at

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the clinical diagnosis stage, without waiting for the results of tests for definitive diagnosis, such as complement-related genes test or anti-CFH antibodies test. This practice flow can be commonly seen in the Japanese and KDIGO Controversies Conference guidelines[4]. However, half of the patients with a clinical diagnosis of aHUS do not have complement-related genetic abnormalities, despite the turnaround time of the genetic tests. While some tests to prove complement activation have been reported, none of the currently available tests are highly specific or sensitive. Thus, although disease-specific treatment with anti-complement drugs has been developed, the diagnostic methods have not been refined.

Regarding epidemiological data, the genetic background, clinical findings, and outcomes of 118 patients with a confirmed diagnosis of aHUS in Japan have been published[5]. While the registry data showed detailed genetic variations, it did not provide information regarding changes in clinical practices or medical costs that would allow a thorough understanding of practice patterns over time and the current difficulties clinicians face in early case identification and treatment initiation. Thus, clinicians in Japan face challenges to make clinical decisions as they do not have complete access to epidemiological data.

Traditionally, PE and plasma infusion have been the only available treatments for aHUS, but the anti-complement agent eculizumab (Ecu) was approved as a new treatment in the United States and Europe in 2011 and in Japan in 2014. Studies mentioning the efficacy of PE on aHUS were only reported until around 2010[6]. Although it can be easily assumed that the disease-specific efficacy of Ecu is superior to PE, no studies have directly and prospectively compared the efficacy of PE and Ecu. According to data from the aHUS Global Registry, PE is still performed in 57% of aHUS cases[7]. Data from a Japanese epidemiological study show that 74% of aHUS patients were treated with PE; however, the reason for this high percentage of PE use is unclear, and the effectiveness of PE as a treatment is not mentioned. Given this reality in clinical practice, the role of PE in the process from the diagnosis of TMA to the definitive diagnosis of aHUS cannot be ignored.

To fully depict clinical practices, real-world data such as disease registry databases, hospital discharge databases, claims databases, and post-marketing surveillance databases are being utilised worldwide[8]. A study from the United States that used a hospital discharge database showed the benefit of early treatment with Ecu in patients with aHUS[9]. In this context, the Diagnosis Procedure Combination (DPC) database is representative of the real-world data in Japan. DPC is Japan's comprehensive medical cost evaluation system, which was introduced in April 2003 to reduce growing national medical costs and improve the efficiency, transparency, standardisation, and quality of medical care[10]. The database contains information on the patient's age, gender, diagnosed diseases, insurance-covered tests and procedures, and discharge status. In addition, information such as whether a test was ordered and the date of the test can be acquired, although specific test results cannot be obtained. Since 90% of tertiary emergency hospitals in Japan participate in the DPC, this database can possibly be used to collect data suitable for epidemiological studies of serious and rare diseases, such as aHUS.

In this study, we aimed to depict the annual trends in the number of newly diagnosed aHUS cases, to clarify the clinical practices for aHUS in Japan, and to identify the factors that could contribute to early treatment initiation using DPC data. The findings of this study would shed light on the changes in practice patterns before and after the publication of the guidelines and the status of PE treatment in the post-Ecu era.

Results

Baseline characteristics of patients with aHUS and unspecified HUS

The number of patients with ICD (International Statistical Classification of Diseases and Related Health Problems)-10 code "D593", which indicates HUS, was 3,096. Of these, 217 patients were issued the disease name aHUS and were treated with PE or Ecu for the first time (Fig. 1). In total, there were 466 patients with unspecified HUS (Analysis A). Further, we identified 14 of 683 patients in the aHUS and unspecified HUS groups who had the same ZIP code, age, and gender and were admitted and discharged on consecutive days. Thus, these 14 patients were likely transferred from one hospital to another and were double-counted. Nevertheless, it is impossible to identify them as the same patient owing to privacy concerns, and the percentage is very small (approximately 2%). Of the aHUS group, 200 patients were treated within 28 days of admission. We divided them into the early and late initiation groups (Analysis B). Clinical characteristics of patients with aHUS and unspecified HUS are shown in Table 1. Patients in the aHUS group were more likely to receive Ecu (66.8% vs. 7.7%, $P < 0.001$), and the cumulative dose of Ecu was significantly higher in this group than in the unspecified HUS group (1,800 vs. 0, $P < 0.001$). The percentage of PE performed in the aHUS group was significantly lower than that in the unspecified HUS (79.7% vs. 97.4%, $P < 0.001$).

A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity was measured more frequently in the aHUS group than in the unspecified HUS group (22.1% vs. 7.9%, $P < 0.001$). In addition, the aHUS group had more patients who underwent blood purification (60.4% vs. 50.2%, $P = 0.013$) and kidney biopsy (27.6% vs. 15.0%, $P < 0.001$) and had hypertension (27.2% vs. 19.7%, $P = 0.029$) than the unspecified HUS group.

In terms of clinical outcomes, patients in the aHUS group had longer hospital stays (44 vs. 35 days, $P = 0.001$), higher hospitalisation costs (760 vs. 393 million JPY, $P < 0.001$), and more readmissions than those in the unspecified HUS group (48.8% vs. 29.2%, $P < 0.001$). Of the 106 readmissions that were treated with any therapy, 22 (20.75%) were treated with Ecu, 34 (32.08%) with PE, and 50 (47.17%) with both.

Annual trends in aHUS treatment in Japan

Eight patients were diagnosed with aHUS between 2011 and 2013, before the implementation of insurance coverage for Ecu. The number of patients with aHUS notably increased to 31 in 2014, but the annual number of aHUS patients did not change significantly between 2014 and 2019 (Table 2). No significant annual trend was observed in terms of the ratio of early vs. late initiation, as well as between Ecu-first and PE-first groups.

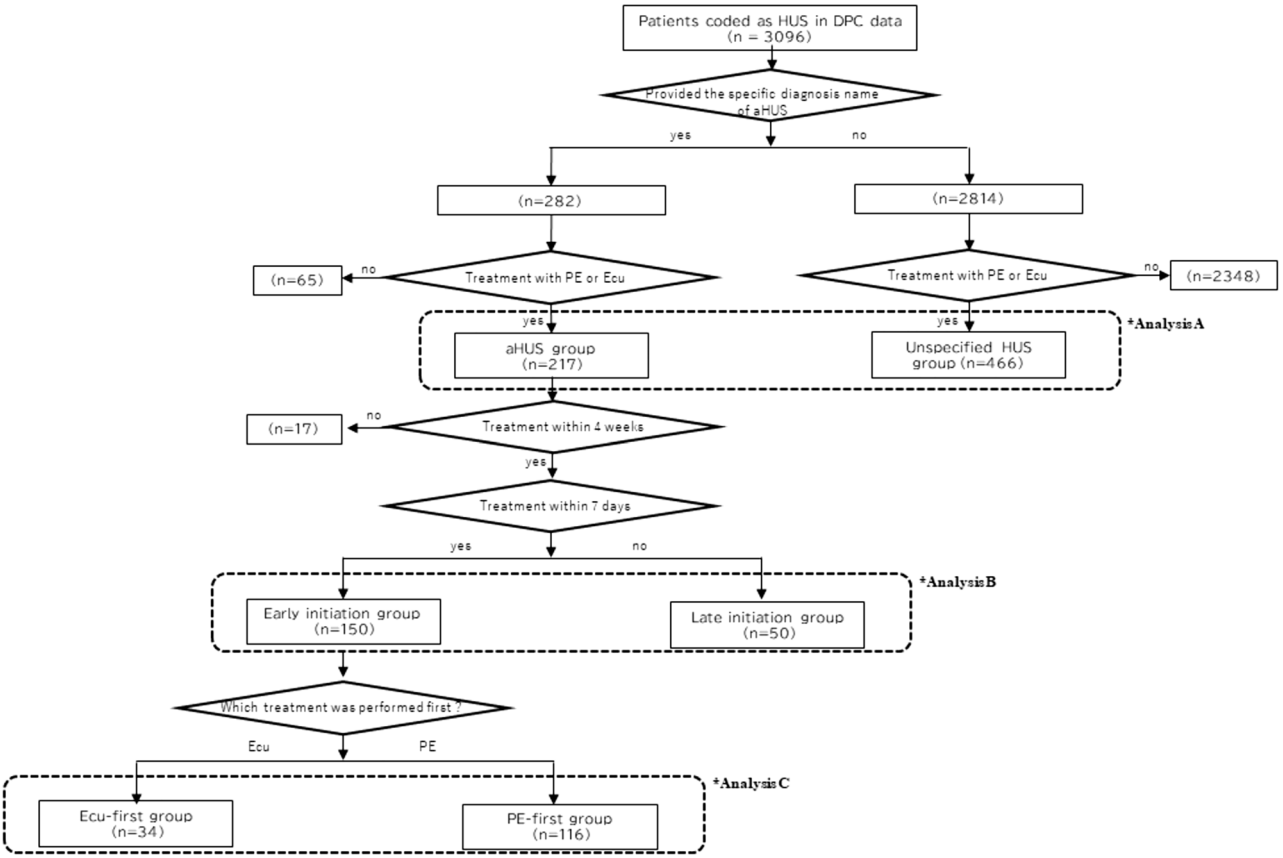

Figure 1. Flowchart of study participants. The aHUS group was defined as a group of cases in which the disease name "aHUS" was described and the patients were treated with PE or Ecu. First, we compared the characteristics of aHUS group patients with those of unspecified HUS group patients (Analysis A). Subsequently, we compared the characteristics between those who were treated early (the early initiation group) and those who were treated late (the late initiation group) (Analysis B). In the early initiation group, the Ecu-first group (patients whose treatment was initiated with eculizumab) and PE-first group (those whose treatment was initiated with PE) were compared (Analysis C). aHUS, atypical hemolytic uremic syndrome; DPC, Diagnosis Procedure Combination; PE, plasma exchange; Ecu, eculizumab.

No annual changes in hospitalisation costs, length of stay, or in-hospital mortality were observed. A total of 42 (19.4%) patients received dialysis immediately before discharge from the hospital, and no significant annual trend was observed in this context. However, readmissions significantly decreased over time (P for trend = 0.008).

Treatment and timing of patients with aHUS

The early initiation group had a shorter time from admission to the start of blood purification therapy (3 vs. 12 days) and a shorter time from admission to ADAMTS13 activity measurement (1 vs. 14 days) than the late initiation group. The early initiation group also had lower hospitalisation costs (6.20 vs. 9.12 million JPY) and a shorter length of stay (36.5 vs. 55 days) compared with the late initiation group. The total dose of glucocorticoids administered was lower in patients belonging to the early initiation group (615 vs. 2104 mg, P = 0.013). Although there was no significant difference in the percentage of patients tested for ADAMTS13 activity, those in the early initiation group were more likely to be tested earlier (Table 3). Multivariable analysis also showed that the length of hospitalisation in the early initiation group was shorter than that in the late initiation group by 21.4 (5.98–36.8) days. There were no significant differences in activities of daily living (ADL) improvement, death during hospitalisation, readmission, or dialysis up to 2 days before discharge (Table 4).

We also compared 150 patients in the early initiation group after dividing them into the Ecu-first and PE-first groups. The results showed that the Ecu-first group included younger patients (18 vs. 59.5 years, P < 0.001) and had a smaller proportion of patients on blood purification (29.4% vs. 65.5%, P < 0.001), shorter days to initiation of blood purification (3 vs. 12 days, P < 0.001), and lower total dose of prednisolone (0 vs. 1365 mg, P < 0.001) than the PE-first group. In addition, the Ecu-first group had significantly shorter hospital stays (20 vs. 43 days, P < 0.001) and lower hospitalisation costs (620 vs. 912 million, P = 0.008) than the PE-first group (Table 5).

Variables	aHUS n = 217	Unspecified HUS n = 466	P-value
Baseline characteristics			
Age, year	49 (27–67)	53 (24–71)	0.20
Male sex	106 (48.8)	196 (42.1)	0.096
Barthel Index on admission	90 (0–100)	100 (30–100)	0.053
Hypertension documented during hospitalization	59 (27.2)	92 (19.7)	**0.029**
Medical procedures performed during hospitalization			
Percutaneous kidney biopsy	60 (27.6)	70 (15.0)	**< 0.001**
Measurement of ADAMTS13*	48 (69.6)	37 (51.4)	**0.027**
Days to measurement of ADAMTS13*	2 (1–12.5)	3 (1–11)	0.63
Blood purification	131 (60.4)	234 (50.2)	**0.013**
Days to commencement of blood purification	4 (2–12)	4 (2–10)	0.57
Blood purification continued up to 2 days before discharge	42 (19.4)	67 (14.4)	0.098
Plasma exchange	173 (79.7)	454 (97.4)	**< 0.001**
Days to initiation of plasma exchange	4 (2–11)	4 (2–7)	0.81
Eculizumab (Ecu)	145 (66.8)	36 (7.7)	**< 0.001**
Days to Ecu initiation	12 (7–25)	11.5 (4.5–27)	0.86
Dose of Ecu, mg	1800 (0–4200)	0 (0–0)	**< 0.001**
Dose of prednisolone, mg	1025 (25–4370.5)	675 (20–4095.25)	0.34
Hospitalization outcome			
Hospitalization costs, JPY	760 (399–1388)	393 (249–625)	**< 0.001**
Duration of hospitalization, days	44 (24–82)	35 (20–63)	**0.001**
In-hospital mortality	43 (19.8)	97 (20.8)	0.76
Readmission	106 (48.8)	136 (29.2)	**< 0.001**
Change in Barthel Index	0 (0–5)	0 (0–25)	0.15

Table 1. Characteristics, procedures, and outcomes of patients with aHUS and unspecified HUS (Analysis A). *Data regarding ADAMTS13 were available in 2018 and 2019, Since measurement of ADAMTS13 was covered by health insurance in the middle of the year 2018. Continuous variables are expressed as mean (standard deviation) or median (interquartile range) and categorical variables as numbers (%). Emboldened letters of P-value mean statistically significant (P < 0.05). aHUS, atypical hemolytic uremic syndrome; HUS, hemolytic uremic syndrome; JPY, Japanese yen; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; RRT, renal replacement therapy.

	2014	2015	2016	2017	2018	2019	Total	P for trend
Numbers of patients	31	33	32	44	31	38	209†	NA
Ecu initiation	25 (80.7)	20 (60.6)	22 (68.8)	31 (70.5)	19 (61.3)	27 (71.1)	151 (69.6)	0.59
Days to Ecu initiation days	12 (7–46)	12 (6–18)	12.5 (7–25)	11 (4–28)	15 (8–35)	9(6–23)	12 (7–25)	0.79
Early treatment initiation	19 (61.3)	26 (78.8)	22 (68.8)	33 (75.0)	20 (64.5)	26 (68.4)	150 (69.1)	0.98
Death within hospitalization duration	6 (19.4)	6 (18.2)	3 (9.4)	9 (20.5)	12 (38.7)	6 (15.8)	43 (19.82)	0.42
Blood purification continued up to 2 days before discharge	7 (22.6)	5 (15.2)	5 (15.6)	7 (15.9)	7 (22.6)	10 (26.3)	42 (19.4)	0.44
Readmission	18 (58.1)	15 (45.5)	21 (65.6)	24 (54.6)	9 (29.0)	12 (31.6)	106 (48.9)	**0.008**
Duration of hospitalization, days	70 (30–92)	44 (28–63)	49.5 (33–84)	36 (21–78)	35 (23–83)	43 (25–80)	44 (24–82)	0.17
Hospitalization cost, JPY	1250 (432–2000)	744 (397–1180)	995 (378–1530)	649 (385–1040)	793 (392–1390)	742 (478–1050)	759 (399–1390)	0.28

Table 2. Annual trends in clinical practices for patients with aHUS. Emboldened letters of *P*-value mean statistically significant (*P < 0.05*). Continuous variables are expressed as mean (standard deviation) or median (interquartile range) and categorical variables as numbers (%). NA, not applicable; PE, plasma exchange; Ecu, eculizumab; JPY, Japanese yen. †Owing to the scarce data for 2011–2013, annual trend Tables and trend tests were performed on 209 cases for 2014–2019.

Variables	Early initiation n = 150	Late initiation n = 50	P-value
Age, year	49 (20–68)	49 (39–68)	0.34
Male sex	73 (48.7)	25 (50.0)	0.87
Duration of hospitalization, days	36.5 (21–69)	55 (31–95)	**0.002**
Change in Barthel Index	0 (0–17.5)	0 (0–0)	0.06
Total cost of hospitalization, JPY	620 (360–1127)	912 (536–1607)	**0.008**
In-hospital mortality	24 (16.0)	12 (24.0)	0.20
Readmission	75 (50.0)	24 (48.0)	0.81
Measurement of ADAMTS13*	33 (71.7)	10 (43.5)	0.255
Days to measurement of ADAMTS13*	1 (1–2)	14 (12–19)	**< 0.001**
Blood purification	86 (57.3)	36 (72.0)	0.066
Days to initiation of blood purification	3 (2–6)	12 (5–15)	**< 0.001**
Early ICU admission	45 (30.0)	11 (22.0)	0.275
Days to initiation of PE or Ecu	2(1–4)	13 (11–18)	**< 0.001**
PE	86 (57.3)	36 (72.0)	0.066
Days to initiation of PE	2 (1–4)	13 (11–17)	**< 0.001**
Ecu	98 (65.3)	32 (64.0)	0.86
Days to Ecu initiation	7 (4–15)	22.5 (16–27.5)	**< 0.001**
Total dose of Ecu during hospitalization, mg	1500 (0–3600)	1800 (0–4800)	0.57
Total dose of prednisolone during hospitalization, mg	615 (0–3870)	2104 (267.5–4720)	**0.013**

Table 3. Comparison between early and late initiation groups (Analysis B). Continuous variables are expressed as mean (standard deviation) or median (interquartile range) and categorical variables as numbers (%). Emboldened letters of P-value mean statistically significant ($P < 0.05$). aHUS, atypical hemolytic uremic syndrome; HUS, hemolytic uremic syndrome; PE, plasma exchange; Ecu, eculizumab; JPY, Japanese yen; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ICU, intensive care unit. *Data regarding ADAMTS13 were available in 2018 and 2019, since measurement of ADAMTS13 was covered by health insurance in the middle of the year 2018.

Dependent variables	Point estimates	P-value
Linear regression analysis	Coefficients (95% CI)	
Duration of hospitalization, days	-21.4 (-36.8–-5.98)	**0.002***
Total cost of hospitalization, JPY	-0.29 (-0.56–-0.02)	**0.008***
Logistic regression	Odds ratios (95% CI)	
Death during hospitalization duration	0.60 (0.27–1.35)	0.22
Readmission	1.10 (-0.56–2.0)	0.84
Blood purification continued up to 2 days before discharge	0.71 (0.31–1.63)	0.42

Table 4. Multivariable regression analysis comparing early versus late treatment initiation. Point estimates compared early versus late initiation. The reference is late initiation. Multivariable regression analyses are adjusted for age, sex, and blood purification. *Statistically significant ($P < 0.05$).

Discussion

This study demonstrated the clinical practices for aHUS over approximately a decade, during which the guidelines for aHUS were published and Ecu was approved in Japan. Our study showed that early initiation with either PE or Ecu was associated with a shorter length of hospital stay and reduced medical expenses. Early blood purification and measurement of ADAMTS13 activity were associated with early treatment initiation. Our findings provide a temporal trend of clinical practice in patients with aHUS before and after the introduction of guidelines and Ecu. Moreover, we were also able to identify several associated problems with aHUS.

Compared with a previous registry study of 118 cases diagnosed with aHUS over 18 years in Japan[5], our study was larger in scale and included a total of 217 cases diagnosed over 9 years from all over Japan. However, the number of potential aHUS patients might have been far higher. Previous reports have estimated that the annual incidence of aHUS is 2–3 per million[11], which means that approximately 200–300 patients would potentially be diagnosed with aHUS annually in Japan. Hence, the estimated number of patients over a 9-year study period would be 1800–2700. The data from this study shows that even the sum of unspecified HUS and aHUS cases did not correspond with the number of cases that can be inferred from the previous reports.

The number of aHUS diagnoses and the number of patients receiving Ecu have not changed significantly since 2014, the year after the Ecu was approved for insurance. On the other hand, the number of patients readmitted to hospital decreased. This may be because maintenance treatment with Ecu for patients with a confirmed diagnosis

Variables	Ecu-first n = 34	PE-first n = 116	P-value
Age, year	18 (5–44)	59.5 (32–69)	**< 0.001**
Male sex	20 (58.8)	53 (45.7)	0.18
Duration of hospitalization, days	20 (9–31)	43 (26–78)	**< 0.001**
Total cost of hospitalization, JPY	620 (360–1127)	912 (536–1607)	**0.008**
In-hospital mortality	5 (14.7)	19 (16.4)	0.81
Readmission	17 (50.0)	58 (50.0)	1.00
Measurement of ADAMTS13*	4 (11.8)	29 (25.0)	0.10
Days to measurement of ADAMTS13*	2 (1.5–9.5)	1 (1–2)	0.25
Blood purification	10 (29.4)	76 (65.5)	**< 0.001**
Days to initiation of blood purification	3 (2–6)	12 (5–15)	**< 0.001**
Blood purification continued up to 2 days before discharge	3 (8.8)	23 (19.8)	0.14
PE	3 (8.8)	116 (100)	**< 0.001**
Days to initiation of PE	4 (3–5)	2 (1–4)	0.13
Ecu	34 (100)	64 (55.2)	**< 0.001**
Days to Ecu initiation	2.5 (2–4)	11 (7.5–18)	**< 0.001**
Total dose of Ecu during hospitalization, mg	2400 (900–4800)	900 (0–3600)	**0.005**
Total dose of prednisolone during hospitalization, mg	0 (0–97.5)	1365 (105.5–4295)	**< 0.001**

Table 5. Comparison between Ecu -first and PE-first in Early initiation group (Analysis C). Continuous variables are expressed as mean (standard deviation) or median (interquartile range) and categorical variables as numbers (%). Emboldened letters of P-value mean statistically significant ($P < 0.05$).

of aHUS stabilised their condition and allowed for continued treatment in an outpatient setting. Once the diagnosis of aHUS is confirmed, initiating Ecu as a disease-specific treatment is not difficult. Nevertheless, the reason why the number of cases treated with Ecu has not increased is not because of the Ecu itself but rather because of the difficulty in diagnosing aHUS. One possible reason for this may be that the diagnostic flow and treatment strategies suggested in the clinical guidelines are not refined and straightforward. To address this problem, the diagnostic process of aHUS has been divided into three phases: Phase 1, recognition of TMA; Phase 2, clinical diagnosis of aHUS; and Phase 3, definitive diagnosis of aHUS.

In Phase 1, microangiopathic haemolytic anaemia (often accompanied by thrombocytopenia, anaemia, identification of schistocyte and decreased haptoglobin) and major organ damage (primarily kidney failure) allow the physician to recognise TMA. However, since blood investigation results were not available for this study, it was not possible to confirm whether TMA cases were accurately incorporated. Thus, we analysed the initiation of blood purification therapy as a surrogate indicator of renal dysfunction, which is a frequent complication of TMA, to analogise whether clinicians recalled the possibility of TMA.

In phase 2, entities such as (STEC)-HUS, TTP, and secondary TMA must be excluded to arrive at the clinical diagnosis of aHUS. Measurement of ADAMTS13 activity is performed at the beginning of phase 2 to differentiate TTP and is therefore a surrogate marker of TMA recognition. The lack of TMA recognition is reflected in the low frequency of testing for ADAMTS13 activity in patients belonging to the late initiation group. All clinicians should be aware of the concept of TMA, as Phases 1 and 2 may involve any category of healthcare setting and not just tertiary hospitals.

In Phase 3, complement-related gene testing and measurement of anti-Complement Factor H (CFH) antibody tests are performed to confirm the diagnosis of aHUS. During the data collection period of this study, the abovementioned tests were not covered by insurance and, therefore, were not used. However, to reach Phase 3, we must ensure that Phases 1 and 2 are completed. In cases with severe kidney injury requiring blood purification therapy, clinicians may have been more likely to recognise TMA (Phase 1) and measure ADAMTS13 activity to rule out TTP (Phase 2), which may lead to early treatment initiation. Several studies have advocated the efficacy of early treatment initiation for aHUS, but they have focused only on the early initiation of anti-complement drugs[9,12]. However, in the present study, PE was performed in approximately 80% of patients with aHUS. In addition, PE in the aHUS group was started 8 days earlier than Ecu (4 vs. 12), and PE-first was more common than Ecu-first (23% vs. 77%) in the early initiation group, indicating a tendency for PE to be pre-emptively performed. Therefore, analysing not only Ecu but also PE as an initial treatment was justified.

In the era before the advent of anti-complement drugs, PE played a central role in the treatment of aHUS. Norris et al. found that plasma therapy resulted in partial remission (haematologic remission and residual renal function) or better in approximately 70% of aHUS cases, whereas end-stage renal failure occurred in 27.3% (72/264 patients) and death in 3.8% (10/264)[5]. One possible reason for the poor long-term prognosis is that PE is difficult to perform long-term with respect to allergy caused by plasma infusion and infection at the site of vascular access implantation. The decrease in the proportion of readmissions in the annual trend chart could be due to the introduction of Ecu, which may make maintenance treatment easier. Apheresis guidelines published in several countries do not positively recommend PE for the treatment of aHUS, limiting its use to the stage when anti-complementary drugs are not available or when TTP cannot be ruled out[12,13]. However, in the acute phase, we believe that PE is a non-negligible bridging therapy before anti-complement therapy: the replenishment of

complement regulating factors and the removal of anti-CFH antibodies (for only positive cases). Therefore, it is justified to analyse not only Ecu but also PE as initial therapy.

PE is more likely to be performed early in clinically diagnosed aHUS cases due to etiologic and diagnostic process reasons. The etiologic reason is the possibility that TTP cannot be ruled out until the measurement results of ADAMTS13 activity are available. Another reason is that the C3 I1157T variant, a genetic variant of aHUS that is relatively responsive to PE, is common in the Japanese population[14], and PE can be performed at several tertiary care facilities in Japan. Interestingly, even in the treatment of readmission cases, PE had a higher rate than Ecu, which may have also been unique to the Japanese population. There was no evidence that PE was preferred because of the high prevalence of meningitis (only 1 in 106 readmission cases were given antibiotics for more than 2 weeks with meningitis as the disease name). Reasons for the diagnostic process that PE is more likely to be performed ahead of Ecu include the complexity of aHUS disease and the lack of knowledge and experience of physicians. Ecu, a disease-specific treatment, is difficult to use in the early stages unless there is a strong diagnostic basis, such as family history. Therefore, PE is often used as a pre-emptive treatment until the results of genetic and anti-CFH antibody tests are available.

In this study, the proportion of PE was higher in the late-initiation group than in the early-initial group, and corticosteroids (which were rarely given to patients with aHUS) were used more frequently, suggesting that the late-initiation group included more cases with difficult diagnosis. In the early initiation group, patients in the Ecu-first group was younger than those in the PE-first group, had a lower proportion of those on haemodialysis, and used less corticosteroids, suggesting that patients who could be administered Ecu early had fewer complications and were easier to diagnose. Therefore, it would be short-sighted to interpret the results of lower hospitalisation costs and shorter length of stay in the Ecu-first group too favourably towards Ecu. However, we believe that in cases with fewer comorbidities and less difficulties in diagnosis, such as in children, Ecu-first interventions should be performed earlier and more aggressively than that in the past.

Multivariable analysis showed that early treatment initiation was associated with 21 fewer days of hospitalisation than late treatment initiation, with more than 11 days difference in the treatment starting date. In addition, hospitalisation costs were also reduced by approximately 26% in the early treatment initiation group. Thus, the DPC data demonstrated that early initiation was associated with shorter hospital stays and lower hospitalisation costs.

Although the establishment of practice guidelines and introduction of Ecu were expected to increase clinicians' awareness of aHUS and accelerate the timing of therapeutic intervention, the percentage of patients in the early-initiation group did not actually increase. Further disease awareness is warranted for both aHUS and TMA, which would be the preliminary stage.

This study had a few limitations. First, owing to the retrospective design of the study, the association between the timing of treatment initiation and clinical outcomes was not causal. However, our main objective was to describe the current clinical practices for aHUS and not the efficacy of medical interventions. Our study clearly demonstrated that early initiation of PE or anti-complement therapy was associated with favourable clinical outcomes. Second, we used disease codes and documented disease names to classify aHUS cases, which may cause selection bias. The possibility that the unspecified HUS group included undiagnosed aHUS could not be ruled out. Nevertheless, it is unlikely that our results or discussion would be significantly changed even if all 7.7% of this unspecified HUS group were aHUS patients, because the difference in the proportion of Ecu use between the aHUS and unspecified HUS groups was large (66.8 vs. 7.7%). Excluding untreated cases may have also led to the exclusion of aHUS cases that resolved spontaneously. However, the topic of interest for clinicians is the diagnosis and therapeutic intervention in severe cases. Thus, our study still adheres to the main aim of our study using DPC data, which is to provide realistic clinical practice data that can be used as a reference for clinicians who are involved actively in the ongoing care of patients with severe TMA.

Additionally, some duplicate cases may have been present due to transfers from other facilities. However, their proportion was so small that it would not substantially affect the results of this study. Third, laboratory test results, including platelet counts and levels of haemoglobin, LDH, or serum creatinine, were not available in the database. Therefore, we could not judge the severity of the cases. However, the items and dates of laboratory testing performed were available, which allowed us to evaluate the clinical practices followed by the physicians. Finally, the results of genetic variants were not available since genetic testing for the disease was not covered by health insurance during the period of data acquisition. Phase 3 was considered to be beyond the scope of the present study. We are currently conducting a prospective study of aHUS and unexplained TMA cases consulted by hospitals throughout Japan. We are waiting for the results of long-term prognosis and genetic tests in this registry to be available.

In conclusion, early recognition of TMA and early diagnosis of clinical aHUS were insufficient, irrespective of the introduction of anti-complement agents and the establishment of specific practice guidelines. Enlightening physicians about these entities will promote a rapid, definitive diagnosis of aHUS and early therapeutic intervention.

Methods

Study population and patient selection

This retrospective cohort study was conducted using the DPC data between April 1, 2011 and March 31, 2020. We enrolled patients who were registered with the disease code of haemolytic uremic syndrome (HUS) (ICD-10 code: D593) as the primary disease, secondary disease, or the disease for which most of the medical resources were invested. Subsequently, we defined patients with aHUS as those who had been provided a specific aHUS disease name, were hospitalised, and were treated with PE or Ecu for the first time. Patients with HUS other than aHUS were classified as those with unspecified HUS. Patients with other diagnoses who were treated with Ecu,

including paroxysmal nocturnal haemoglobinuria, neuromyelitis optica, and myasthenia gravis, were excluded from the study.

To examine the effect of early treatment, patients with aHUS who received treatment within 7 days of admission were defined as the early initiation group, and those who were administered treatment after 8–28 days of admission were defined as the late initiation group, and the two groups were compared. We excluded cases with aHUS wherein treatment was started after 28 days or later, as we considered them exceptional cases. The rationale for defining 7 days as early was based on previous studies, which reported that aHUS patients who started treatment with Ecu within 7 days experienced an improvement in platelet count and anaemia[12]. In the early initiation group, the Ecu-first and PE-first groups were compared.

Measurements

The following information were collected from the database: sex, age at admission, date of admission and discharge, in-hospital mortality, hypertension (including hypertensive emergencies and malignant hypertension) during hospitalisation, readmission, total medical expenses during hospitalisation expressed in Japanese yen, which is equivalent to approximately US$0.01, and improvement in ADL scores. Improvement in ADL score was defined as the difference in Barthel Index[13] before and after hospitalisation.

Regarding laboratory investigations, although actual test results were not available in the present study, we examined whether ADAMTS13 activity was measured and how many days had passed between the date of admission and the measurement. ADAMTS13 activity is an essential diagnostic test for TTP, one of the differential diagnoses for TMA[14]. Data regarding ADAMTS13 activity were available in 2018 and 2019 since the measurement of ADAMTS13 activity was covered by health insurance in the middle of the year 2018. We also examined whether and when a percutaneous kidney biopsy was performed as a sign of kidney injury.

In the context of treatment, we investigated whether the patient was on blood purification or PE and whether, when, and how much Ecu or glucocorticoids were administered. The cases in which treatment was initiated with Ecu were defined as Ecu-first, and the cases in which treatment was initiated with PE were defined as PE-first. Cases in which both treatment modalities were started on the same day were defined as Ecu-first. To determine the proportion of patients who ultimately required kidney replacement therapy after discharge, we ascertained whether they had been on dialysis for up to 2 days before discharge.

Statistical analysis

For descriptive analysis, Student's t-test or Wilcoxon rank sum test was performed for continuous variables and Chi-square test for categorical variables. The following trend tests were conducted to assess the annual trend: The Cochran-Armitage trend test was used when the outcome variable was binary and the explanatory variable was ordinal or numeric. The Jonckheere-Terpstra trend test was used when the outcome variable was continuous. However, owing to the scarce data for 2011–2013, a trend test was performed with data from 2014 to 2019 after the introduction of Ecu.

Multiple regression analysis was performed for hospitalisation costs, duration of hospitalisation, and change in the Barthel Index. Logistic regression analysis was performed for death during hospitalisation and readmission. These analyses were adjusted for age, sex, and whether blood purification was performed. Since blood purification was performed in patients with severe conditions such as kidney failure, we considered blood purification a proxy for severe kidney disease and thus added it to the covariates. Hospitalisation costs were log-transformed as they violated the assumptions of linear regression. All statistical analyses were conducted using Stata, version 17.0 (StataCorp LP, College Station, TX, USA). Statistical significance was set at $P < 0.05$.

Ethics declarations

The study was performed following the tenets of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the University of Tokyo [approval number: 3501-(3), dated December 25, 2017]. Since all data were de-identified, the requirement for patient informed consent was waived by the committee.

Data availability

Owing to personal information protection laws, our data are not freely available. The data underlying this article will be shared upon reasonable request to the corresponding author.

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Author contributions

Y.T. and T.I. substantially contributed to the study conceptualization. N.M., R.K., H.M., K.F., and H.Y. significantly contributed to data analysis and interpretation. N.K. and S.M. organized this research project and interpreted the results. Y.T. substantially contributed to the manuscript drafting. All authors critically reviewed and revised the manuscript draft and approved the final version for submission.

Competing interests

Shoichi Maruyama received lecture fee from Alexion Pharmaceuticals, Inc.

Additional information

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