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Strong association between insufficient plasma exchange and fatal outcomes in Japanese patients with immune thrombotic thrombocytopenic purpura

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1 Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threading disorder caused by a severe reduction in ADAMTS13 activity. [1, 2] ADAMTS13 is a metalloproteinase, that specifically cleaves von Willebrand factor (VWF). [3] Two types of TTP exist: a congenital form which is caused by mutations in the *ADAMTS13* gene, [4, 5] and an acquired form, namely, immune-mediated TTP (iTTP), which is caused by autoantibody-mediated inhibition of ADAMTS13 activity. [6, 7] In iTTP patients, this inhibition leads to the accumulation of ultra-large VWF multimers (UL-VWFMs), which are highly adhesive to circulating platelets. [2] Severely decreased ADAMTS13 activity induces systemic microvascular thrombosis, caused by VWF-rich platelet thrombi which provokes fatal, ischemic multi-organ failure involving myocardial and cerebral infarction. [8] Prior to the introduction of plasma exchange (PEX) in clinical practice, [9] the mortality rate of TTP was over 90%. [10] PEX with fresh frozen plasma (FFP) appears to have the following effects: 1) ADAMTS13 supplementations, 2) removal of ADAMTS13 autoantibodies, and 3) elimination of UL-VWFMs. [11] However, the mortality rate of iTTP remains approximately 20% even after the introduction of PEX. [9, 12] Currently, corticosteroids and rituximab are commonly used to reduce ADAMTS13 autoantibodies in iTTP. [11] Recently, caplacizumab, an anti-VWF A1 domain nanobody, was approved for iTTP by the European Medicines Agency in 2018 and the US Food and Drug Administration in 2019. [13] However, this drug is unavailable in Japan as of April 2021.

Although some patients with iTTP experience exacerbation caused by an inhibitor booster, [14] there is no evidence on whether many PEX procedures may lead to fatal outcomes. To our knowledge, there are only a few studies describing the association between the number of PEX procedures and sudden death related to TTP attacks. Therefore, we conducted a nationwide retrospective analysis, focusing on the association between the number of plasma exchange procedures and TTP-related death.

2 Materials and Methods

2.1 Patient enrollment

We analyzed plasma samples from patients suspected of having TTP at a nationwide thrombotic microangiopathy (TMA) center for over two decades [15]; 913 patients were diagnosed between 2006 and 2020. As shown in Figure 1, 240 patients with iTTP were eligible for the analysis, and met the following inclusion criteria: (i) developed severe thrombocytopenia (less than 100×10^9/L) due to unknown causes; (ii) had severe reduction of ADAMTS13 activity (less than 10% of normal), in the presence of

ADAMTS13 functional inhibitor (0.5 Bethesda unit/mL or more); (iii) completed over 30 days follow-up, except for deceased cases; (iv) could recall detailed information regarding the treatment including plasma exchange and corticosteroids; and (v) were not candidates for the domestic clinical trial on caplacizumab.

We then divided 240 patients into 3 groups, which included the survival group (n=195), the TTP-related death group (n=32), and the other cause of death group (n=13). TTP-related death was defined as acute death provoked by a persistent TTP episode, and not by any other cause. In addition, we collected pathophysiological findings from autopsies of deceased patients in the TTP-related death group if the information was available.

ADAMTS13 activity and its functional inhibitor were measured using ADAMTS13-act-ELISA (Kainos Laboratories, Tokyo, Japan). [16] For ADAMTS13 activity, we defined that of pooled citrated plasma from healthy volunteers as 100%. Both patients with primary iTTP and iTTP secondary to medications or various underlying diseases such as autoimmune disease, malignancy, and pregnancy were included in this study. Among them, secondary iTTP was identified in 26 (autoimmune disorders: 23, pregnancy: 2, and malignancy: 1), 2 (autoimmune disorders), and no cases, respectively.

2.2 Immunohistochemistry of thrombi

Serial sections were stained by hematoxylin and eosin (HE) to identify the basic constituents of the thrombi. Immunohistochemistry staining was performed to evaluate the distribution of platelets and fibrin, as described previously. [17] Briefly, formalin-fixed, paraffin-embedded tissues were cut into 5-μm sections, deparaffinized, and rehydrated in a graded series of ethanol. Antigen retrieval was performed by heating the tissue sections using Target Retrieval Solution at pH 6.0 (DAKO Japan, Kyoto, Japan). Anti-IIb/IIIa (Affinity Biologicals, South Bend, Canada), anti-VWF (DAKO), and anti-fibrin (Accurate Chemical and Scientific Corporation, Westbury, NY, USA) antibodies were added to the sections, which were incubated overnight at 4°C. We then used the ImmPRESS reagent kit, Mouse/HRP, or Rabbit/HRP (VECTOR) for VWF and fibrin, and anti-Sheep IgG (Jackson ImmunoResearch, West Grove, PA, USA) for IIb/IIIa according to the instructions of the manufacturer. Reaction products were visualized with 3,3′-diaminobenzidine (DAB) tetrahydrochloride.

2.3 Statistical analysis

We used several statistical methods to analyze the demographic characteristics. Fisher's exact test was applied for categorical data that resulted from classifying objects in two different ways. To compare continuous variables among the three groups, we used the

Kruskal-Wallis test, followed by the Bonferroni method for post hoc analysis. Gray's test was used for analyzing the cumulative incidence of TTP-related death; it dealt with the other cause of death as a competing risk event. The final visit date and the date of clinical relapse were regarded as a censor. All tests were two-tailed, and a P-value of >0.05 was considered statistically significant. This study used the free software "EZR" for statistical analyses, [18] and the clinical data were analyzed in April 2021.

2.4 Ethics statement

This study was approved by the Ethics Committee of the Nara Medical University, and conducted under the tenets of the Declaration of Helsinki. Based on the existing information, we provided patients the chance to opt out.

3 Results

3.1 Participants' Characteristics

Characteristics of the participating patients are shown in Table 1. The age of onset was markedly lower in the survivors than in the other two groups. As for blood examination upon admission of the first TTP incident, there were no significant differences in platelet counts and hemoglobin levels between the three groups. In addition, both ADAMTS13 activity and its inhibitor were similar in all groups. In contrast, the levels of lactate dehydrogenase (LDH), total bilirubin, serum creatinine, and D-dimer in the TTP-related death group were much higher than those in the survivor group, suggesting a strong association between TTP-related death and multiple organ failure at the first presentation. PEX using fresh frozen plasma was performed in 93.8% of those in the survivor group, 75% in the TTP-related death group, and 76.9% in the other cause of death group. The median number of PEX procedures in the TTP-related death group was significantly lower than that in the survivor group; the numbers were 2.5 and 10, respectively. The administration rate of corticosteroids as an immunosuppressor was lower in the TTP-related death group than in other groups (survivors, 96.4%; TTP-related death, 62.5%; and other death, 92.3%). In contrast, the use of rituximab was more frequent in the survivor group than in the other groups (survivors, 40.5%; TTP-related death, 15.6%; other death, 30.7%). The median follow-up periods in the survivor and other cause of death groups were significantly longer than those in the TTP-related group. Regarding underlying disease, the rate of secondary iTTP cases in the death groups were not significantly higher than that of the survivor group.

3.2 TTP-related death

Table 2 provides detailed information regarding the TTP-related death cases. Unfortunately, 9 patients aged below 50 years died. Most of the patients had a fatal course soon after admission to the hospital, and died suddenly after acute bradycardia and hypotension. Autopsy was performed in 10 of 32 deceased patients, and the pathophysiological findings revealed that most of the patients died because of cardiac microvascular occlusion, not in the stem of the coronary artery, but in the peripheral capillary arteries with microbleeding. That is, we could not find thrombi in the large vessels of the heart, suggesting the occurrence of common acute myocardial infarction. These results indicated that death was not caused by massive thrombi in the heart, but by microvascular occlusion. As for multi-organ damage, we also identified similar systemic microvascular thrombi in other organs (e.g., brain, kidney, and lung) based on the autopsy reports.

The results of immunohistochemical analysis of the thrombi found in a representative case (patient number 171 in Table 2) is shown in Figure 2. The patient was a 22-year-old male who had no medical history. After 6 days of symptoms, which included headache, fever, abdominal pain, and cough, he suddenly lost consciousness; he was taken to the hospital, but died after 3 hours without a definitive diagnosis. Therefore, an autopsy was performed, revealing the presence of microthrombi found in several organs such as the brain, heart, lung, liver, kidney, spleen, pancreas, and adrenal glands. Figure 2 shows the results of histological examination of the thrombi in the heart. HE staining showed the presence of microthrombi composed mainly of platelets in the arterioles of the heart. These thrombi stained weakly for fibrin (panel B), and strongly for VWF (panel C) and platelet IIb/IIIa (panel D). These results suggested that the thrombi found in this patient were VWF-rich platelet thrombi, a characteristic finding in patients with acute iTTP.

3.2 Other causes of death

Table 3 presents detailed information regarding the other cause of death group. Seven, four, one, and one patient died due to sepsis, malignancy, liver failure, and subcortical bleeding, respectively. The follow-up period after admission of the first TTP incident varied from case to case in this group. Eight of 13 patients (61.5%) survived more than one year after developing the first TTP episode. Conversely, only one case of early death was noted within 30 days after admission.

3.3 Link between the mortality and the time of PEX

The number of PEX procedures in the three different groups is shown in Figure 3. As

described before, the median number of PEX procedures in the TTP-related death group was significantly smaller than that of the other groups. Approximately 70% of patients in the TTP-related death group underwent only five or fewer PEX procedures owing to sudden death. The main reason for non-receipt of any PEX treatment in some patients was their physical vulnerability, especially in older adult cases; only steroids are often administered in these cases to suppress the production of antibodies.

As shown in the left panel of Figure 4, the one-year cumulative TTP-related mortality rate in all patients (n=240) was 13.3%. Its analysis excluded death caused by other diseases. Interestingly, the deaths caused by a TTP episode occurred within 30 days after admission, and no TTP-related death was seen between 30 days and 1 year after admission. Four groups were classified according to the number of PEX procedures, and the cumulative TTP-related mortality rate of each group was shown in the right panel of Figure 4. The one-year cumulative TTP-related mortality rates in patients receiving no, 1-10, 11-20, and 21 or over sessions of PEX were 32.0%, 18.3%, 5.8%, and 0%, respectively. These results showed that the prognosis of iTTP improves with an increase in the number of PEX procedures.

4 Discussion

In 1924, Moschcowitz first reported iTTP to be a dreadful disease, that leads to fatal systemic microthrombi. [19] The mortality rate of iTTP exceeds 90% unless patients receive the standard therapeutic regimen consisting of PEX using FFP and corticosteroids. [10] Although PEX therapy has contributed significantly to improvements in overall survival in patients with iTTP, the efficacy of corticosteroids is yet to be confirmed in randomized clinical trials. However, physicians expect corticosteroids to suppress the production of ADAMTS13 autoantibodies. Strong evidence has recently been established regarding the efficacy of rituximab therapy in prolonging the remission state in iTTP. [20, 21] However, it requires approximately 10-14 days to obtain an immunosuppressive effect. [22] To date, PEX offers the only direct method for preventing systemic platelet-VWF rich thrombosis, through the removal of UL-VWFMs at the superacute phase. The VWF A1 nanobody, caplacizumab, was also evaluated in the current treatment strategy; [23] the current TTP treatment concept is to reduce abnormal autoantibody production using an adequate immunosuppressor. PEX and caplacizumab were also used to inhibit the interaction between UL-VWFM and platelets.

Tragic outcomes even occur in young adult patients with iTTP for over two decades. The present study revealed the relationship between sudden death and the total number of PEX

procedures. First, the TTP-related death group had higher levels of LDH and serum creatinine compared to the other two groups during their first presentation, suggesting that iTTP-related organ damage caused by ischemic microthrombi may contribute to sudden death. Contrastingly, there were no significant differences in the platelet counts, hemoglobin level, or ADAMTS13 parameters among the three groups (Table 1). In general, severe iTTP cases at the first presentation would be assumed to develop multi-organ damage. Further studies are required to reveal why patients with similar platelet counts, hemoglobin levels, and ADAMTS13 parameters have widely varying clinical outcomes ranging from remission in a few following PEX, to sudden death. Second, a small number of PEX procedures were associated with a greater risk of TTP-related death, whereas some mild cases achieved remission after a couple of PEX procedures. In our report, 12 mild cases were successfully treated by combinations of 1 or 2 of the following: steroids, FFP infusion, and intravenous immunoglobulin infusion. Conversely, most severe cases were not able to receive an adequate number of PEX procedures until remission was achieved. They also did not receive effective immunosuppressors with sufficient PEX treatments owing to a rapid impairment of cardiac function (Table 1). As previously reported by the international clinical study on caplacizumab, [13,24] when used along with the standard regimen of PEX and corticosteroids, the agent significantly reduced thrombotic events and deaths during the superacute phase. In this context, caplacizumab could have provided significant benefits for the patients who experienced sudden deaths in our cohort, if it had been available for use in the clinical setting. There were no reported cases of death in the patients who had undergone many PEX procedures due to exacerbation of the first TTP episode. Finally, the valuable autopsies in the TTP-related death cases provided robust evidence to suggest that most cases died owing to cardiac microvascular occlusion. This localization of pathogenic thrombi must depend on the ability of UL-VWFM to adhere to circulating platelets, which are found mostly in the capillaries. [24, 25] As shown in Figure 2, these thrombi found in an acute attack of iTTP, were mainly composed of VWF and platelets.

This study has several limitations. Our registry is based on the clinical data reported by each physician only in cases where they request for ADAMTS13 analysis in iTTP patients; more than 30 days of follow-up is found in a relatively small number of participants. Moreover, the follow-up periods differed considerably among physicians. Detailed data regarding the clinical response to PEX and immunosuppressors were not available in most cases. Some physicians performed consecutive PEX procedures, while others administered PEX every other day. The real problem lies in that consecutive PEX was not permitted by the Japanese health insurance system until April 2018. Hence, the

same numbers of PEX procedures did not always represent the same therapeutic regimen. As there were a smaller number of secondary iTTP cases in our cohort, it was impossible to conclude whether the underlying disorder may have contributed to the unfavorable outcomes. Lastly, we could not obtain the results of cardiac troponin levels as a prognostic parameter indicative of cardiac damage, as most patients die suddenly of acute cardiogenic hypofunction caused by microvascular thrombi. [26, 27]. The current TTP guidelines in Japan recommend the measurements of cardiac troponin levels during acute TTP episodes. [11] However, the practice of routine checking of cardiac troponin levels does not appear to be prevalent across Japan

This study focused on the association between sudden death caused by acute TTP episodes and the number of PEX procedures. No patient with TTP-related death died after receiving over 20sessions of PEX. In contrast, most TTP-related deaths occurred before patients received a sufficient number of PEX procedures. As reported in clinical studies, [13, 28] caplacizumab is a promising novel agent for TTP treatment, as it can save patients from sudden death. Further studies are required for obtaining sufficient evidence on whether sudden death could be avoided by the use of caplacizumab.

AUTHORSHIP DETAILS

M. Kayashima. treated the patients, collected patient data, and wrote the manuscript; K. S. designed the study concept, analyzed data, and wrote the manuscript; I. H., J. K., and K. H. performed the histological analysis; M. Kubo., E. H., and M. H. collected patient data; M. M. directed the study and wrote the manuscript.

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CONFLICTS OF INTEREST

M. Matsumoto is a member of the clinical advisory board of Takeda Yakuhin and Sanofi. He is also an inventor of the ADAMTS13 act-ELISA. The remaining authors declare no competing financial interests.

Figure legends

Figure 1. Patient selection

Among 913 patients diagnosed with TMA at our institute between 2006 and 2020, 240 met the inclusion criteria listed. These participants were classified into three groups: the survivor, TTP-related death, and other cause of death groups.

Figure 2. Immunohistochemical analysis of the thrombi found in the heart of patients with iTTP (patient No. 171)

Histological findings in the heart of patient no. 171 using hematoxylin and eosin (HE) staining show intravascular thrombi (panel A). These thrombi stained weakly for fibrinogen/fibrin (panel B), while they stained strongly for von Willebrand factor (VWF) (panel C) and platelet IIb/IIIa.

Figure 3. Link between outcome and PEX procedures

The horizontal and vertical axes show the number of PEX procedures and the number of patients, respectively. Twenty-two of 32 patients in the TTP-related death group received merely five or fewer PEX procedures owing to sudden death.

Figure 4. The one-year cumulative TTP-related mortality rate

The left panel shows the one-year cumulative TTP-related mortality rate. Most deaths occurred within 30 days. The right panel represents the one-year cumulative TTP-related mortality rate stratified by the number of PEX procedures; none, 1 to 10, 11 to 20, and more. Less than ten PEX procedures do not save the patients with iTTP from sudden death.

Table 1. Comparison of demographic parameters between survivors and non-survivors

	Survivor (n=195)	TTP-related death (n=32)	Other death (n=13)	p-value
Age (years)	54 (37.5-67)	64.5 (49-74)	77 (69-81)	<0.001
Sex (Female/Male)	117/78	18/14	4/9	0.12
Blood testing on admission				
Platelet counts (10^9/L)	10 (7-15)	11 (7-16)	9 (8-12))	0.63
Hemoglobin (g/dL)	7.7 (6.5-9.2)	8.0 (7.1-9.2)	7.8 (7.3-9.9)	0.51
LDH (U/mL)	975 (695-1326)	1637 (1003-2637)	958.5 (742-1132)	<0.001
Total bilirubin (mg/dL)	2.8 (2.2-4.33)	4.23 (2.65-5.85)	2.6 (2.1-2.9)	0.014
serum creatinine (mg/dL)	0.86 (0.66-1.13)	1.285 (0.90-1.735)	1.06 (0.74-1.47)	<0.001
D-dimer (μg/mL)	3.77 (1.52-6.3)	9.2 (5.4-13.5)	7.6 (4.25-9.5)	<0.001
ADAMTS13 activity (%)	<0.5 (<0.5-<0.5)	<0.5 (<0.5-<0.5)	<0.5 (<0.5-<0.5)	0.50
ADAMTS13 inhibitor (BU/mL)	2.7 (1.5-5.4)	3.25 (1.85-5.5)	3.3 (1.3-4.2)	0.62
Treatment				
PEX (number of patients)	183	24	10	0.001
PEX (number of times)	10 (5-16)	2.5 (0.75-7.25)	5 (3-17)	<0.001
Corticosteroids (number of patients)	188	20	12	<0.001
Rituximab (number of patients)	79	5	4	0.019
Follow-up duration (days)	770 (241-1810)	5 (2.75-10)	719 (61-933)	<0.001

Data are reported as median (25% - 75%).

Abbreviations; LDH: lactate dehydrogenase, BU: Bethesda Unit, PEX: plasma exchange

Table 2. Characteristics of patients in the thrombotic thrombocytopenic purpura-related death group

Patient no.	Onset Age	Sex	Follow-up date	Number of PEXs	Autopsy	AD13 activity	AD13 inhibitor	PLT	Hb	LDH	T-Bil	sCr
7	26	F	**1**	1	NA	<0.5	4.5	20	5.5	3327	7.1	0.7
8	74	F	21	6	NA	<0.5	20	6	NA	NA	2.2	1
13	87	M	**4**	0	NA	<0.5	2.6	11	7.6	NA	4.23	1.15
14	56	F	**8**	5	NA	<0.5	4.5	16	6.8	1515	5.5	1.6
16	86	F	**6**	2	NA	<0.5	1.1	13	7.8	NA	7	0.77
20	34	F	**1**	0	NA	<0.5	1.2	11	4.9	5720	5.2	1.49
22	41	F	**1**	0	NA	<0.5	1	12	4.3	1532	5.7	1.28
23	71	M	24	5	NA	2.8	1.7	7	7.6	930	2.6	1.54
24	49	F	**1**	1	NA	7	0.5	4	8.1	NA	4.9	1.97
50	34	F	**10**	8	NA	<0.5	5.8	21	6	2536	1.9	1.22
52	65	M	**3**	2	Performed	<0.5	2.7	11	10	2263	5.5	2.84
53	58	M	11	11	NA	<0.5	2.7	14	7.8	NA	2.7	1.26
62	61	M	**9**	8	Performed	<0.5	5	14	6.8	835	2.8	1.46
68	74	M	**1**	0	NA	<0.5	2.4	7	8.1	4427	13.1	1.4
72	74	F	**1**	1	NA	5.9	1.9	9	8	1902	2.3	1.4
73	55	M	23	13	Performed	<0.5	1.1	11	8	983	2.8	0.9
74	77	F	20	10	Performed	<0.5	15.2	9	7.7	1022	2.2	0.63
110	74	F	**4**	3	Performed	<0.5	9.1	15	13.5	2864	NA	2.2
114	61	F	26	12	NA	<0.5	14.6	4	7.3	1224	2.7	0.59
124	69	M	**6**	5	NA	<0.5	8	6	7.6	1530	6	1.9
129	86	F	**9**	0	NA	<0.5	1.3	18	11.7	944	3.7	0.9
135	66	M	**4**	4	Performed	<0.5	2.9	7	14.6	2737	6.5	3.36
141	64	F	**4**	1	NA	<0.5	2.9	9	8.3	1882	4.9	1.03
171	22	M	**1**	0	Performed	<0.5	7.5	39	4.4	12318	5.6	1.68
182	81	F	20	12	Performed	<0.5	2	4	9.7	922	2.8	1.29
185	46	F	**3**	0	NA	<0.5	5.1	14	6.9	1591	1.77	0.65
205	69	F	**3**	1	NA	0.8	4.8	16	11.2	1637	6.5	0.79
213	62	M	**10**	7	NA	<0.5	3.6	4	9.5	2454	6.3	0.88
220	88	M	**2**	0	NA	<0.5	6.8	15	8.7	500	1.7	1.23
232	49	F	**9**	9	Performed	<0.5	5.1	19	8.9	2966	2.1	2.17
234	47	M	**3**	1	Performed	<0.5	5.4	4	13.5	2418	2.9	3.71
241	65	M	**9**	5	NA	7.1	0.8	7	8.3	271	7.6	5.33

Abbreviations; NA: not available, PEX: plasma exchange, AD13: ADAMTS13, PLT: platelet count, Hb: hemoglobin, T-Bil: total bilirubin, sCr: serum creatinine.

Table 3. Characteristics of patients in the other cause of death group

Patient no.	Onset Age	Sex	Follow-up date	Number of PEXs	Cause of death	AD13 activity	AD13 inhibitor	PLT	Hb	LDH	T-Bil	sCr
2	61	M	3344	21	Sepsis	<0.5	5.5	0.9	7.8	403	2.3	0.74
41	78	M	719	7	Sepsis	<0.5	1.3	0.9	14.3	684	1.6	1.13
51	81	F	21	0	Sepsis	<0.5	3.3	0.5	8.9	NA	NA	2.6
56	64	M	480	3	Sepsis	<0.5	4.9	0.4	9.9	NA	NA	0.7
57	82	F	54	0	Subcortical bleeding	<0.5	15.4	0.4	7.3	1028	2.7	0.43
79	69	M	933	4	Liver failure caused by liver cirrhosis	<0.5	3.3	1.5	4.6	NA	2.4	1.54
94	82	M	61	19	Sepsis	<0.5	3.7	0.8	7.4	1166	1.9	1.3
138	77	F	777	0	Malignancy	<0.5	1	0.8	7.4	741	1.7	0.58
144	77	M	1029	5	Malignancy	1.7	2.6	1.6	10.1	744	4.8	0.77
146	72	M	741	5	Malignancy	<0.5	1	1.8	7.3	1229	2.6	1.47
154	72	M	1135	13	Malignancy	<0.5	2	0.8	8.6	1934	3.1	1.06
161	66	F	66	35	Sepsis	<0.5	4.2	1.2	6.7	1016	2.7	0.9
235	85	M	52	17	Sepsis	<0.5	1	1	12.3	901	3.7	1.78

Abbreviations; NA: not available, PEX: plasma exchange, AD13: ADAMTS13, PLT: platelet count, Hb: hemoglobin, T-Bil: total bilirubin, sCr: serum creatinine.

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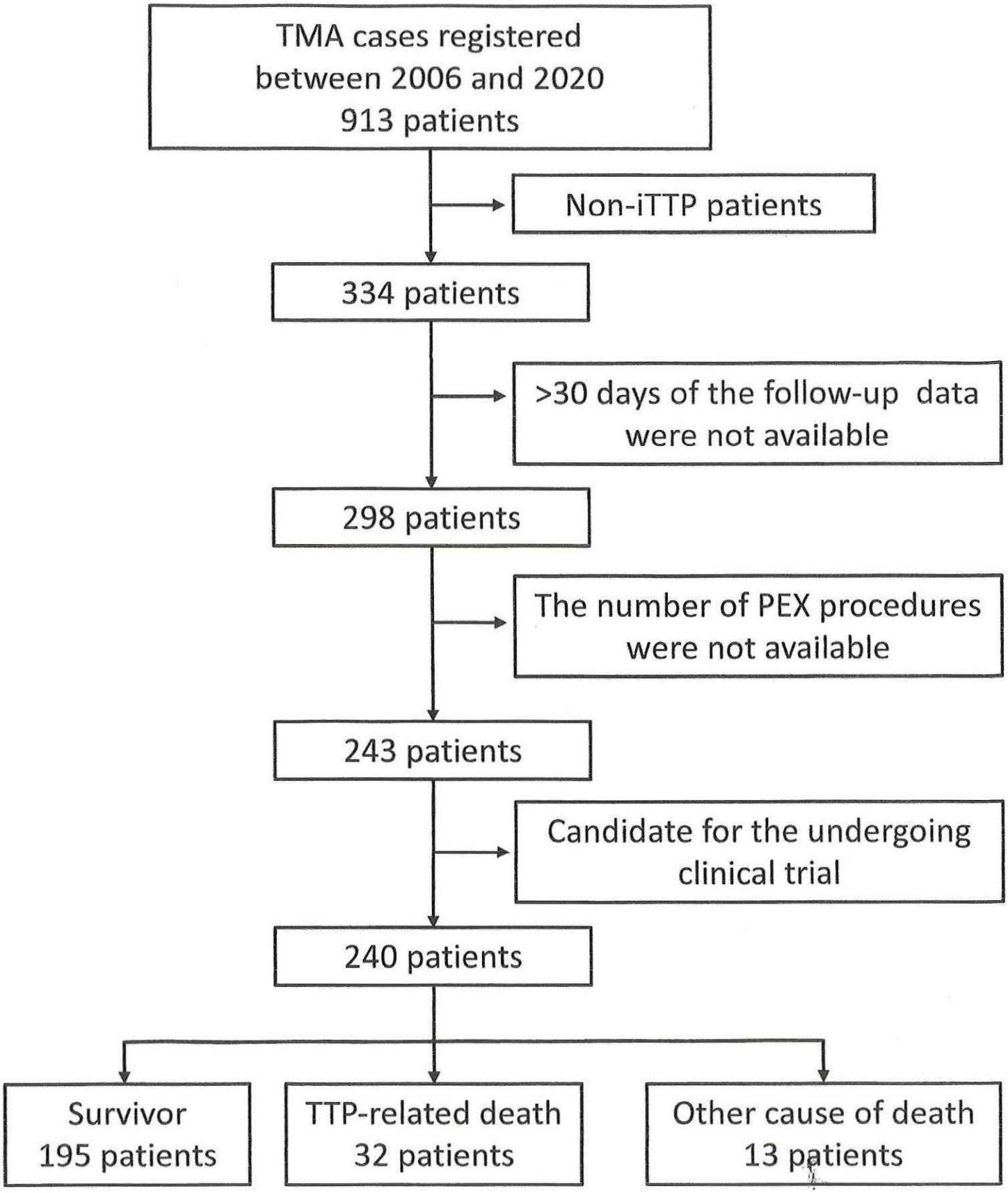

TMA cases registered
between 2006 and 2020
913 patients
Non-iTTP patients
334 patients
>30 days of the follow-up data
were not available
298 patients
The number of PEX procedures
were not available
243 patients
Candidate for the undergoing
clinical trial
240 patients
Survivor
195 patients
TTP-related death
32 patients
Other cause of death
13 patients

Figure 1.

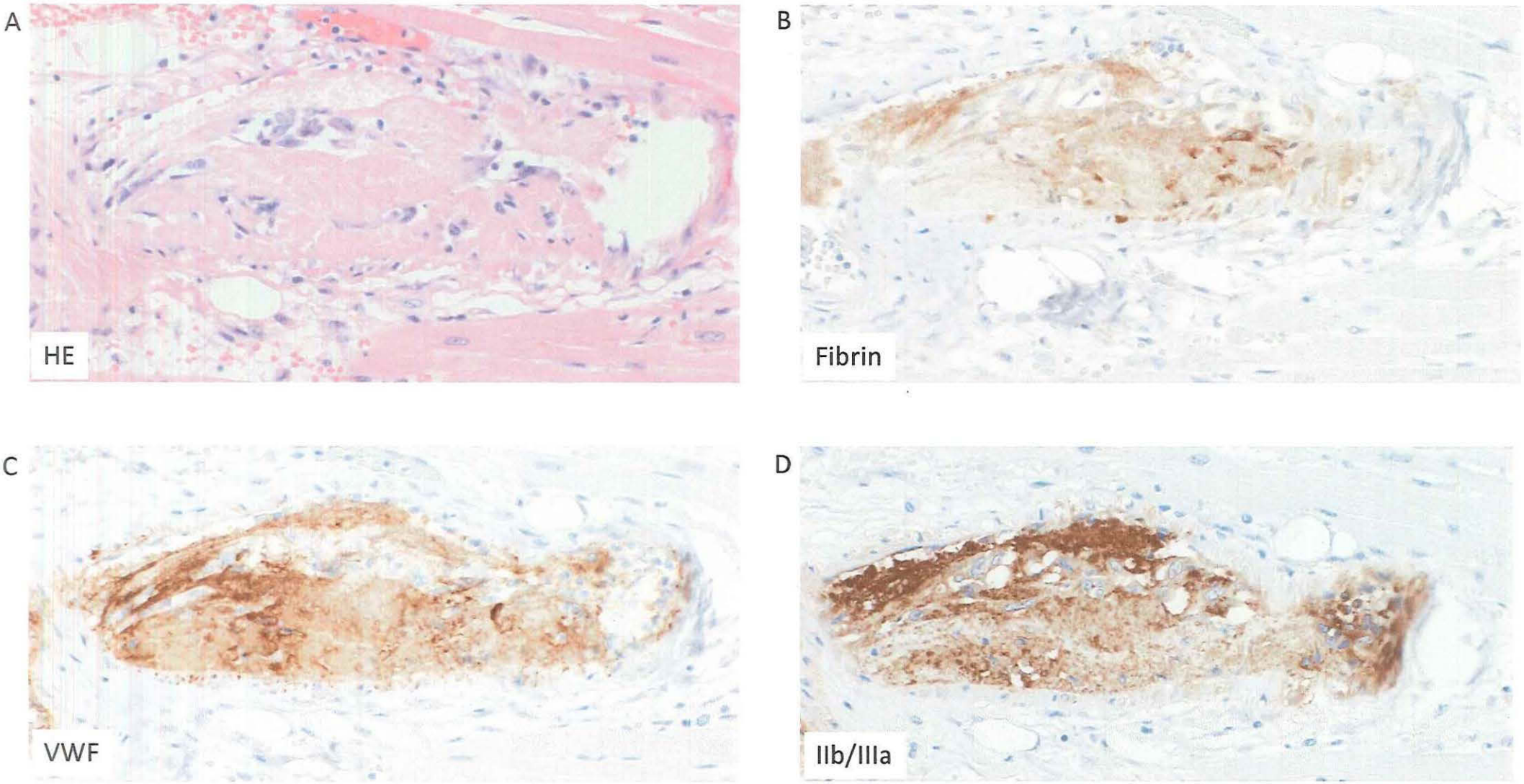


Figure 2

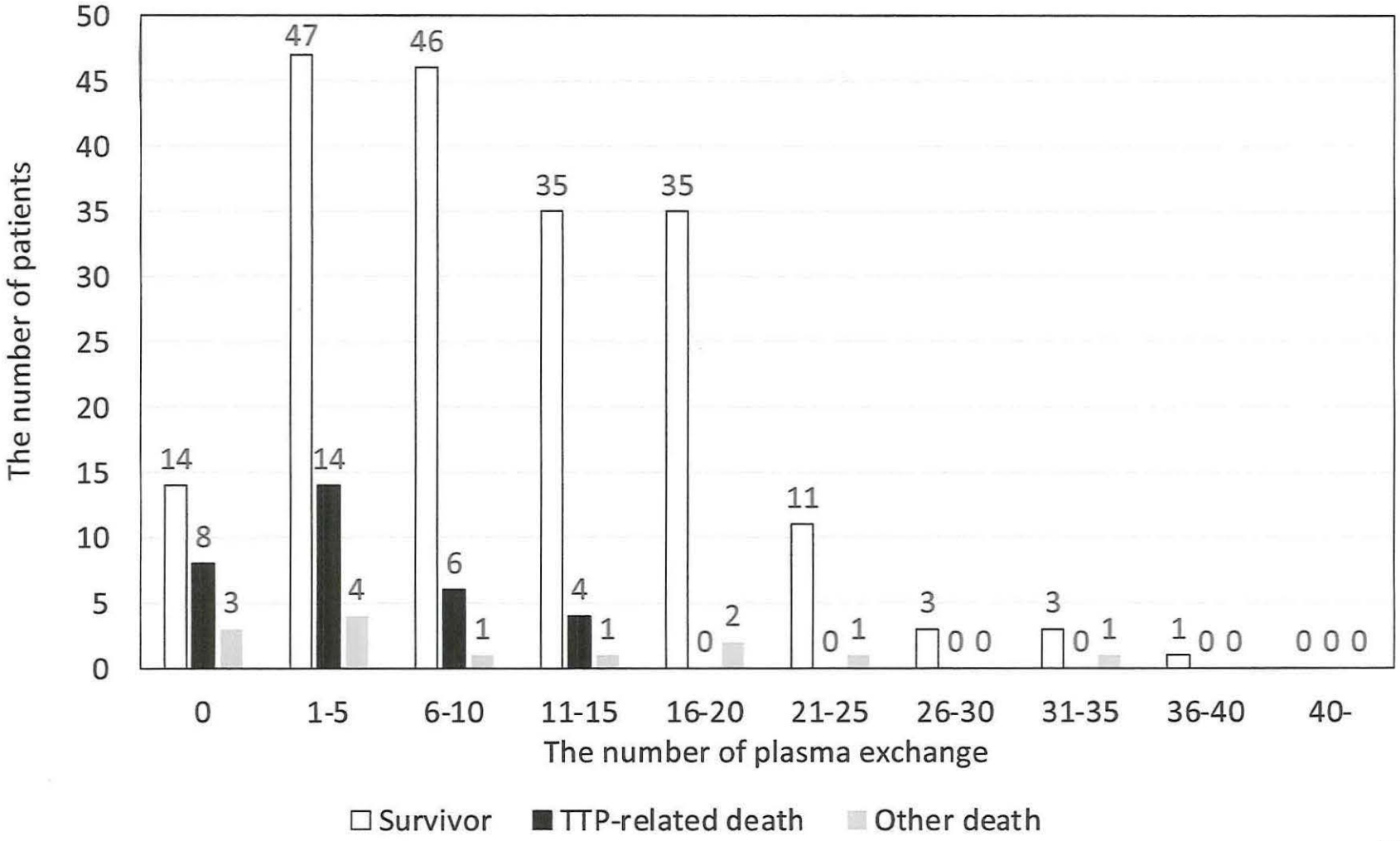
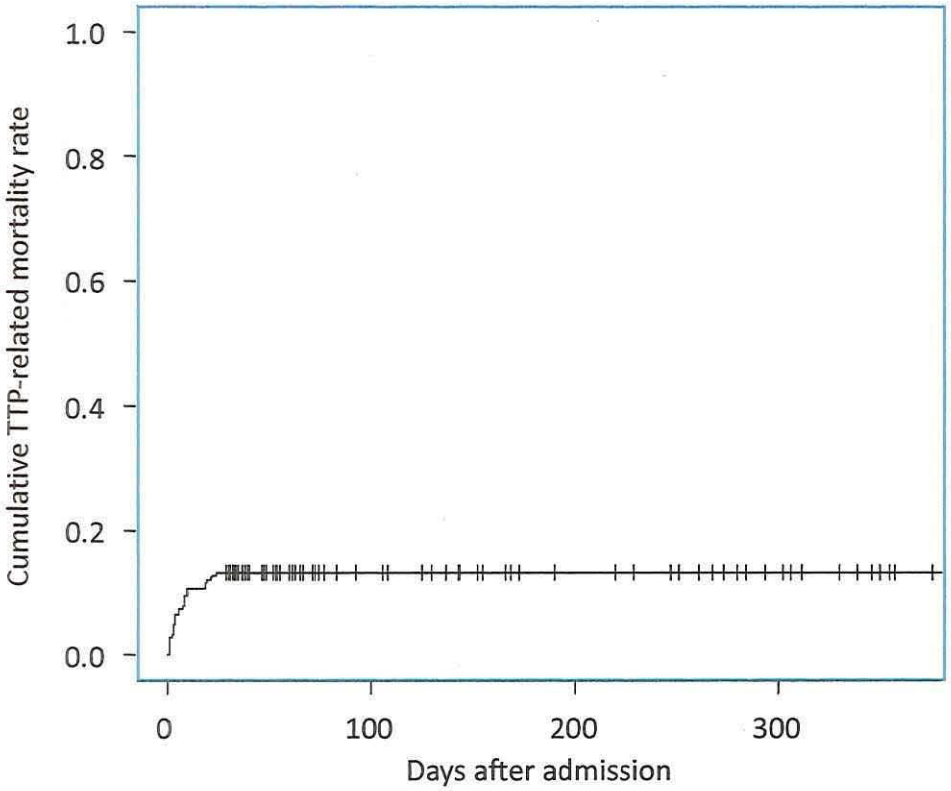

The number of patients
50
45
40
35
30
25
20
15
10
5
0
14
8
3
47
14
4
46
6
1
35
4
1
35
0
2
11
0
1
3
0 0
3
0
1
1
0 0
0 0 0
0
1-5
6-10
11-15
16-20
21-25
26-30
31-35
36-40
40-
The number of plasma exchange
Survivor
TTP-related death
Other death

Figure 3


Cumulative TTP-related mortality rate
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
Days after admission
Number at risk
240
170
156
148

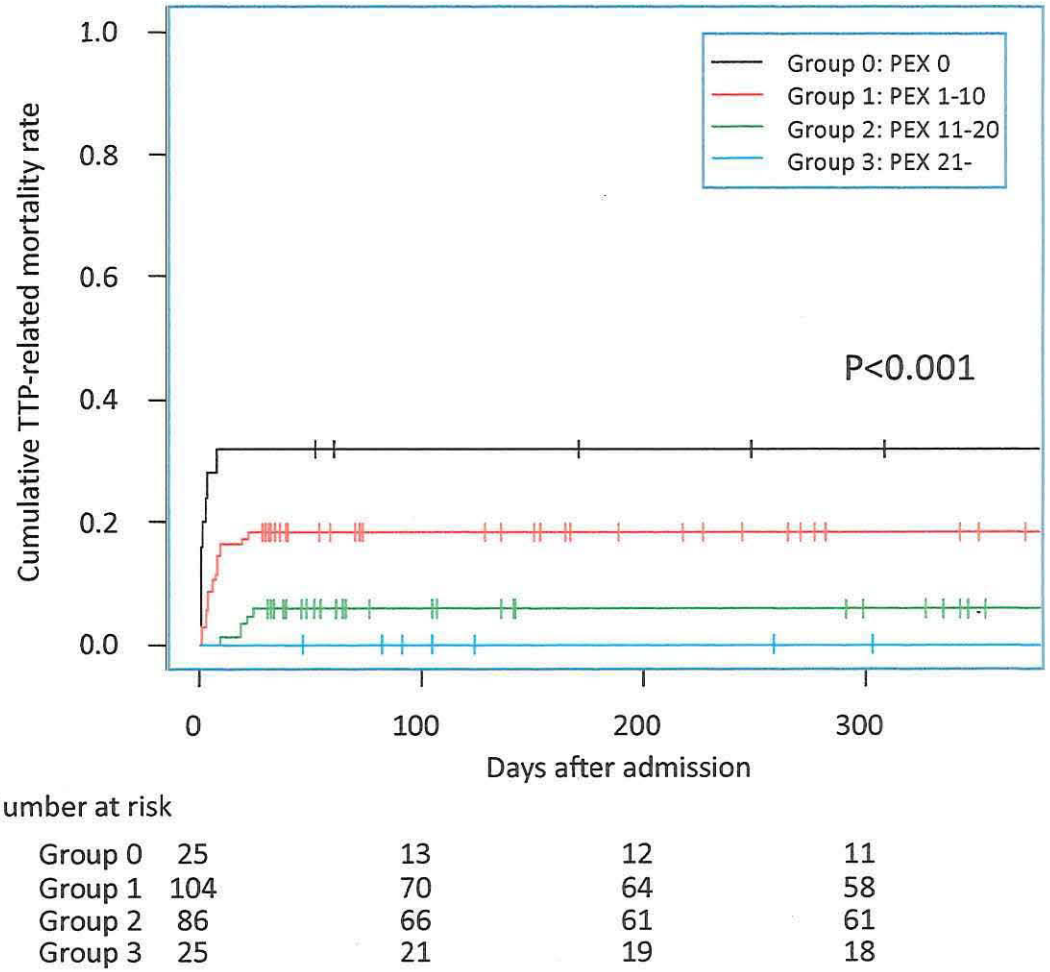

Cumulative TTP-related mortality rate
1.0
0.8
0.6
0.4
0.2
0.0
Group 0: PEX 0
Group 1: PEX 1-10
Group 2: PEX 11-20
Group 3: PEX 21-
P<0.001
0
100
200
300
Days after admission
Number at risk
Group 0 25 13 12 11
Group 1 104 70 64 58
Group 2 86 66 61 61
Group 3 25 21 19 18

Figure 4