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ORIGINAL RESEARCH

Outcomes of Patients Who Undergo Transfusion of Fresh Frozen Plasma: A Prospective, Observational, Multicentre Cohort Study in Hiroshima, Japan

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Purpose: Given the chronic shortage of blood for transfusion in Japan, promotion of appropriate use of fresh frozen plasma (FFP) urgently needs to be addressed by the national blood project in Japan. Whether FFP transfusions are administered appropriately in Japan is currently unclear. In this study, we aimed to investigate the outcomes of patients who undergo FFP transfusion and the appropriateness of use of FFP.

Patients and Methods: This multicentre, prospective, observational cohort study was conducted from September 2017 to April 2019 at the 15 medical institutions in Hiroshima Prefecture that are the top providers of FFP. All patients who underwent FFP transfusion during the study period were included, relevant data being extracted from the medical records. The indications for FFP transfusion were classified in accordance with the Guidelines of the Ministry of Health, Labour and Welfare of Japan. Factors associated with patient outcomes at day 28 after FFP transfusion were subjected to multivariable logistic regression analysis.

Results: In total, data of 1299 patients were eligible for analysis. At least 63.8% of indications for FFP were in accordance with the guideline for FFP transfusions. The mortality rate at day 28 after FFP transfusion was 16.2%. Older age (65–74 years: adjusted odds ratio [AOR]=4.3, ≥75 years: AOR=4.1), non-perioperative use (AOR=4.5), coagulopathy associated with liver damage (AOR=2.7), large volume of FFP transfused (AOR=2.5), and lack of improvement in blood coagulation following FFP transfusion were independently and significantly associated with death within 28 days after FFP transfusion.

Conclusion: Our findings do not support the simple conclusion that FFP transfusions contribute to prognosis. However, given that coagulopathy in patients with end-stage liver disease is infrequently improved by FFP transfusion, "inappropriate" use of FFP should be avoided. It is important to promote appropriate use of FFP so as not to waste blood resources.

Keywords: prognosis, coagulopathy, inappropriate use, compliance with guideline

Introduction

Though lower than in the USA and Germany, consumption of fresh frozen plasma (FFP) per 1000 people in Japan is still 1.4 times higher than in France and the UK.[1] Within Japan, the difference in FFP consumption per bed is up to four times greater in the prefecture with the highest consumption than in that with the lowest consumption. Consumption in Hiroshima Prefecture has been relatively high. However, the number of blood donations in Japan is continually decreasing because the birth rate is declining and the population is ageing.[2] Therefore, given the

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chronic shortage of blood for transfusion, promotion of appropriate use of FFP urgently needs to be addressed by the national blood project in Japan.

The Guideline for the Use of Blood Products formulated by the Ministry of Health, Labour and Welfare of Japan in 2005 states that a primary purpose of FFP transfusion is coagulant factor replacement in the absence of concentrated product.[3] It also states that, to prevent overuse, neither prophylactic use of FFP nor its use in patients with terminal illness is indicated, despite the fact that FFP has historically often been transfused for these purposes. After the guideline had been updated in 2017 (Table 1),[4] it came close to replicating international guidelines because it incorporated available evidence on blood transfusion.[5–8] The former guideline provides values for prothrombin time, activated partial thromboplastin time (APTT), and fibrinogen concentration that should trigger FFP transfusion,[3] whereas the revised guideline states that these values should not be used as triggers because they do not reliably predict a bleeding tendency. According to the Japanese guidelines, FFP transfusion is indicated to promote recovery from bleeding tendencies associated with coagulopathy or coagulation factor deficiency (eg, liver disease, disseminated intravascular coagulation, dilutional coagulopathy caused by massive red blood cell transfusion or fluid infusion), active bleeding alone not being a prerequisite for FFP transfusion. However, because many Japanese clinicians are not familiar with the revised guideline, some continue to transfuse FFP unnecessarily without determining the causes of the bleeding tendency.

Almost all of the many studies that have investigated the appropriate use of blood component products in Japan have reported only differences in, or annual changes in, the amounts used.[8–10] Therefore, whether FFP is transfused in accordance with the guidelines or in eligible patients only remains unclear. Moreover, few studies have provided evidence for the efficacy of FFP transfusion. Although the massive transfusion of FFP mentioned in some guidelines was recently reported to be effective,[11,12] the prognosis of patients who undergo FFP transfusion for other reasons is unknown.[13–15]

The Joint Committee for Blood Transfusion Therapy in Hiroshima Prefecture, which consists of representatives from the local government and major medical institutions, therefore conducted a multicentre, prospective, observational study on outcomes of patients who undergo FFP transfusion. Use of FFP in accordance with the Japanese guideline was also analysed as a secondary endpoint.

Patients and Methods

This multicentre, prospective, observational cohort study was conducted from September 2017 to April 2019 at the 15 medical institutions in Hiroshima Prefecture that are the top providers of FFP. All patients who received FFP transfusion in those institutions during the study period were included. They were registered at each institution, the goal being to enrol 1000 patients in total. In order to meet the purpose of this study and at the same time to minimize the on-site burden related to data collection, the following 11 items were extracted from the medical records: 1. age; 2. sex; 3. primary disease; 4. date and number of days of FFP transfusion; 5. whether FFP was used perioperatively (related to surgery) and, if so, the type of surgery performed; 6. the indications for it, and dose of FFP; 7. coagulation test results before and after FFP use (prothrombin time–international normalised ratio [PT-INR], APTT, and fibrinogen concentration); 8. adverse reactions after FFP use; 9. presence and amount of red blood cell (RBC) transfusion; 10. duration of hospitalisation or discharge date; and 11. survival outcome 28 days after the first day of FFP transfusion. The indications for FFP transfusion were classified into the following categories in accordance with the Guidelines for the Use of Blood Products (revised in 2017 by the Ministry of Health, Labour and Welfare of Japan) (Table 1):[4] coagulopathy associated with liver disease, coagulopathy associated with disseminated intravascular coagulation (DIC), dilutional coagulopathy as a result of massive transfusion and fluid infusion, coagulation factor replacement in the absence of concentrated product, acute correction of warfarin effects, and plasma exchange. Although the indications for FFP were determined by the clinicians in each institution, they were reviewed during analysis because some were obviously wrongly classified. If FFP had been used in the absence of any of the indications in the guideline, its use was defined as "inappropriate". Massive transfusion was defined as transfusion of ≥10 units of RBCs within 24 hours. Each recruiting institution sent their data to the central institution, Hiroshima University Hospital, after anonymisation. All data were compiled and analysed by the Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University. In the case of patients who had received multiple transfusions during the same episode, the data were merged and the FFP doses summed. When the same patient was

Table 1 Guidelines for FFP Transfusion Established by Ministry of Health, Labour and Welfare of Japan (2017)

Trigger values of coagulation tests (as reference)	<PT> <APTT>	(i) INR 2.0 or higher, or (ii) 30% or lower Above twice the upper limit of the standard value at each medical institution	
	<Fibrinogen>	150 mg/dL or less, or when there is a risk of further deterioration	
Indications for FFP	1) Coagulation factor supplementation		
		a) Complex coagulopathy	i. Liver disease with bleeding tendency ii. L-asparaginase administration related ii. Disseminated intravascular coagulation (DIC) iv. Dilutional coagulopathy caused by massive transfusion and fluid infusion
		b) Coagulation factor replacement in the absence of concentrated product (when bleeding or before invasive procedures)	
		c) Correction of warfarin effect	
	2) Plasma exchange (thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome)		
Inappropriate indications	1. Expansion of circulatory volume		
	2. For nutritional purposes		
	3. For promotion of wound healing		
	4. Administration to terminal patients		
	5. Prophylactic transfusion ✓ In case of surgery or trauma that does not require a large amount of blood transfusion ✓ Chronic liver disease ✓ Severe burns ✓ Acute pancreatitis		

Abbreviations: FFP, fresh frozen plasma; PT, prothrombin time; INR, international normalised ratio; APTT, activated partial thromboplastin time.

enrolled more than once, each patient was included in the analysis if the purpose of FFP transfusion was different. If the purpose was the same but the reason for hospitalisation was different, we included each instance. During the study period, there were 1499 FFP transfusion events at the 15 recruiting medical institutions. After merging repeated use of FFP during the same episodes, 1299 patients were eligible for analysis.

Statistical Analysis

Coagulation test values of patients before and after FFP transfusion were compared using a paired *t*-test. Outcomes with and without massive transfusion of FFP (≥2400 mL) were compared by the χ^2 test. After exclusion of cases of plasma exchange, factors associated with mortality 28 days after the first FFP transfusion were analysed using the χ^2 test and logistic regression for univariate and multivariable analysis. In the multivariable analysis, sex, age, and amount of transfused FFP were forced entry predictors, the other 11 variables being selected using the stepwise method ($p<0.25$). Statistical analysis was performed with JMP 14.2.0 (SAS Institute, Cary, NC, USA), and the significance level was set at 0.05.

Ethics

There were no burdens or anticipated risks to patients as a result of the medical record review. In addition, decisions to transfuse FFP were made by the attending physician. The data were anonymised at each hospital before being sent to the central institution, and the created database was stored in a password-protected computer with no external connection. Careful consideration was given to the handling of personal information. An opt-out procedure was used for informed consent. The study was approved by the Ethics Committee of Hiroshima University (Approval No. E-976).

Results

The most common recipient age was within the seventh decade of life, accounting for 30.5% of the total sample (Figure 1) and 62.0% of the patients were men. The total

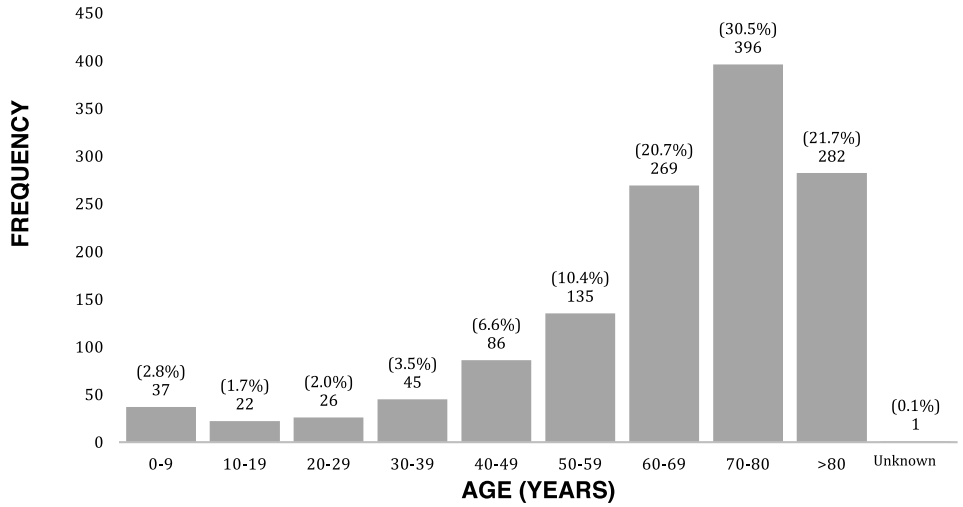


Figure 1 Age distribution of patients who underwent FFP transfusion.

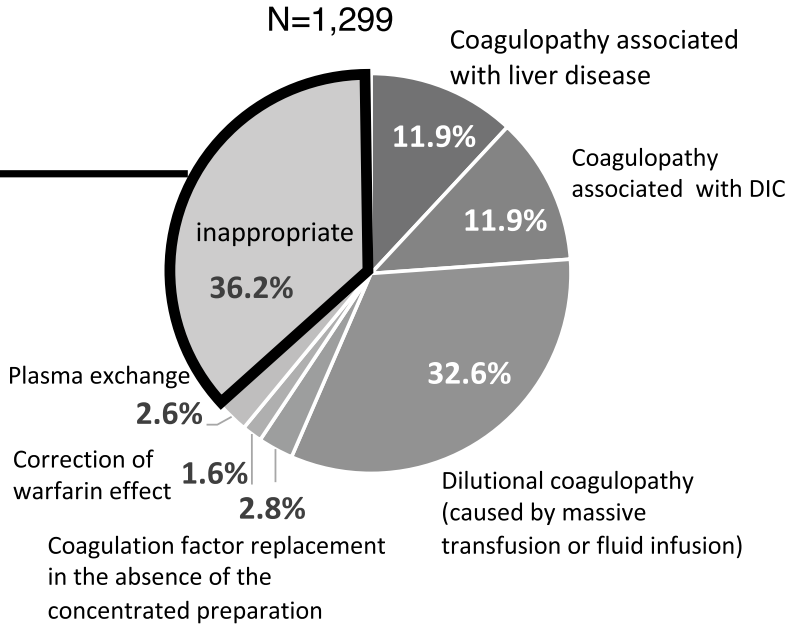
dose of FFP was 16,700 units (one unit is equivalent to 120 mL in Japan; thus, 16,700 units = 2,004,000 mL). The median (min−max) FFP transfusion volume per patient was six (1–428) units. FFP was transfused perioperatively in 63.0% of cases, cardiovascular surgery being the most common form of surgery at 32.5%.

The rates of performing coagulation tests before FFP transfusion were 90.3% for PT-INR, 85.4% for APTT, and 65.9% for fibrinogen. The post-transfusion test rates were 86.0% for PT-INR, 79.2% for APTT, and 61.7% for fibrinogen. Trigger values stated in the former Japanese guideline were met for all three coagulation tests before FFP transfusion in 39.4% (512/1299) of cases, the values being confirmed to have improved after FFP transfusion in 18.2% (236/1299).

The indications for FFP transfusion are shown in Figure 2. "Inappropriate" was the most frequent, accounting for 473 cases (36.2%), followed by dilutional coagulopathy (424 cases, 32.6%), coagulopathy associated with DIC (155 cases, 11.9%), and coagulopathy associated with liver disease (155 cases, 11.9%). The main underlying diseases in the 473 patients who received FFP inappropriately were aortic dissection (100/473, 21.3%), ischaemic heart disease (39/473, 8.3%), and valvular disease (34/473, 7.2%).

Outcomes 28 days after transfusion were 75.2% alive, 16.2% dead, and 8.5% unknown. There were no severe adverse effects related to FFP transfusion, such as transfusion-related acute lung injury or transfusion-associated circulatory overload. The results of coagulation tests before and after FFP transfusion by patient outcome 28 days after transfusion are shown in Table 2. There were significant improvements in all coagulation test values in the surviving patients ($p<0.0001$ for all), but no significant improvement in the patients who had died (PT-INR, $p=0.1954$; APTT, $p=0.1891$; fibrinogen, $p=0.6863$). The total number of days of FFP transfusion was also compared. Overall, FFP was transfused on significantly more days in the deceased group than in the surviving patients ($p<0.0001$). Twenty or more units (≥2400 mL) of FFP were transfused in 15.2% (197/1299) of all patients. The main reasons for using such large amounts of FFP were dilutional coagulopathy (38.1%), coagulopathy associated with DIC (17.8%), and plasma exchange (17.3%). The mortality rate was significantly higher among patients who underwent FFP transfusion of ≥20 than <20 units (32.0% vs 13.4%, respectively; $p<0.0001$, χ^2 test).

Excluding the 34 patients who received FFP for plasma exchange, factors associated with death 28 days after FFP transfusion were analysed using multivariable logistic regression. Older age (65–74 years: adjusted odds ratio [AOR], 3.5; 95% confidence interval [95% CI], 1.0–11.9; $p=0.0463$ and ≥75 years: AOR, 3.4; 95% CI, 1.0–11.0; $p=0.0452$), non-perioperative use of FFP (AOR, 4.6; 95% CI, 2.6–8.2; $p<0.0001$), coagulopathy associated with liver damage (AOR, 2.7; 95% CI, 1.6–6.2; $p=0.0190$), transfusion of seven or more units of FFP (AOR, 2.4; 95% CI, 1.1–4.9; $p=0.0175$), post-transfusion PT-INR of ≥2.0 (AOR, 12.8; 95% CI, 4.8–34.1; $p<0.0001$), and post-transfusion APTT of ≥75 seconds (AOR, 9.5; 95% CI, 3.1–29.0; $p<0.0001$) were independently and significantly associated factors (Table 3).



Underlying disease	N	%
Aortic aneurysm / aortic dissection	100	21.3%
Ischemic heart disease	39	8.3%
Valvular heart disease	34	7.2%
Gastrointestinal perforation / gastrointestinal bleeding	33	7.0%
Colorectal cancer	17	3.6%
Acute subdural hematoma	12	2.6%
Femur fracture	11	2.3%
Other underlying diseases of 10 or less patients	227	48.0%
Total	473	100%

Figure 2 Distribution of indications for FFP transfusion, and underlying disease in which the reason for FFP use was "inappropriate".

Discussion

A major strength of this study is that all cases at 15 major medical institutions were registered prospectively for 1.5 years and that 1299 patients were analysed. In this study, the mortality rate 28 days after FFP transfusion was 16.2%. We also found that a significant proportion of FFP use (36.2%) was outside the indications in the Japanese guidelines (Table 1). The rate of inappropriate use of FFP has varied from 21% to 78% in surveys conducted in other regions.[16–23] In comparison, the rate in this study was not very high. Conversely, 63.8% of transfused FFP was used appropriately according to the guideline. Considering the reported 70% compliance rate with the guideline in general medical practice,[24,25] the use of FFP in Hiroshima appears to be largely in compliance with it.[4]

Table 2 Coagulation Test Values Before and After FFP Transfusion by Patients' Outcomes at Day 28

		N	Before FFP Transfusion	After FFP Transfusion	P*
PT-INR	Total	1051	1.3 (0.1–14.6)	1.2 (0.2–23.9)	<0.0001
	Alive	826	1.3 (0.1–14.1)	1.2 (0.2–23.9)	<0.0001
	Dead	151	1.6 (0.9–14.6)	1.5 (0.9–5.6)	0.1954
APTT	Total	947	36.1 (7.8–321)	34.7 (1.2–378)	<0.0001
	Alive	746	34.9 (7.8–200)	33.5 (1.2–378)	<0.0001
	Dead	132	51.2 (24.5–321)	44.2 (9.9–250)	0.1891
Fib	Total	654	206.6 (1–965)	236.9 (1.2–1023)	<0.0001
	Alive	541	213.7 (1–965)	246 (1.2–901)	<0.0001
	Dead	94	173.4 (25–796)	184.9 (41–1023)	0.6863

Notes: Data are shown as median (min-max). *Paired *t*-test between before and after FFP transfusion.
Abbreviations: FFP, fresh frozen plasma; SD, standard deviation; PT-INR, prothrombin time–international normalised ratio; APTT, activated partial thromboplastin time; Fib, fibrinogen.

Table 3 Univariate and Multivariate Analysis on Factors Associated with the Outcome at Day 28 After FFP Transfusion

	Outcome at 28 Days		Univariable Analysis*		Multivariable Analysis#	
	Dead N (%)	Alive N (%)	OR [95% CI]	p-value	AOR [95% CI]	p-value
Age (years)						
≤39	12(10.2)	106(89.8)	1		1	
40–64	48(17.1)	233(82.9)	1.8[0.9–3.6]	0.2337	1.7 [0.5–5.7]	0.4151
65–74	50(15.8)	266(84.2)	1.7[0.9–3.2]	0.4029	3.5 [1.0–11.9]	0.0463
Over 75	89(20.3)	349(79.7)	2.3[1.2–4.3]	0.0333	3.4 [1.0–11.0]	0.0452
Sex						
Female	66(15.2)	368(84.8)	0.8[0.6–1.1]	0.1520	1.2 [0.7–2.0]	0.5223
Male	133(18.5)	586(81.5)	1		1	
Perioperative use of FFP						
No	128(31.9)	273(68.1)	4.8[3.4–6.6]	<0.0001	4.6 [2.6–8.2]	<0.0001
Yes	66(9.0)	671(91.0)	1		1	
Indication for FFP						
Coagulopathy caused by liver disease	50(33.6)	99(66.4)	6.5[3.9–10.7]	<0.0001	2.7[1.2–6.2]	0.0190
Coagulopathy associated with DIC	48(33.1)	97(66.9)	6.4[3.8–10.5]	<0.0001	2.1[0.9–5.2]	0.0922
Dilutional coagulopathy	59(15.7)	316(84.3)	2.4[1.5–3.8]	<0.0001	1.4[0.6–2.9]	0.4094
Coagulation factor replacement	6(17.1)	29(82.9)	2.7[1.0–6.9]	0.0368	1.3[0.2–7.2]	0.7691
Warfarin effects correction	6(30.0)	14(70.0)	5.5[2.0–15.4]	0.0003	5.8[1.0–32.3]	0.0613
Inappropriate use	31(7.2)	399(92.8)	1		1	
Pre-dose PT-INR						
≥2	59(35.1)	109(64.9)	3.2[2.2–4.6]	<0.0001	-	
<2	130(14.6)	761(85.4)	1			
Pre-dose APTT(seconds)						
≥75	49(48.0)	53(52.0)	5.6[3.7–8.7]	<0.0001	1.5[0.7–3.2]	0.2760
<75	127(14.1)	775(85.9)	1		1	
Pre-dose Fibrinogen (mg/dl)						
≤150	61(26.8)	167(72.3)	2.2[1.5–3.2]	<0.0001		
>150	78(14.3)	468(85.7)	1			
Amount of transfused FFP (Units)						
≥7	127(22.8)	431(77.2)	2.1[1.5–2.9]	<0.0001	2.4[1.1–4.9]	0.0175
<7	73(12.3)	523(87.8)	1		1	
Amount of transfused RBC (Units)						
≥7	92(20.7)	352(79.3)	1.5[1.1–2.1]	0.0090	1.4[0.7–2.9]	0.3116
<7	102(14.7)	590(85.3)	1		1	
Ratio FFP/RBC						
>1.5	59(23.5)	192(76.5)	1.8[1.2–2.6]	0.0017	1.2[0.6–2.3]	0.6373
≤1.5	99(14.8)	572(85.3)	1		1	
Post-dose PT-INR						
≥2	44(58.5)	30(40.5)	11.7[7.0–19.4]	<0.0001	12.8[4.8–34.1]	<0.0001
<2	104(11.2)	829(88.9)	1		1	
Post-dose APTT (seconds)						
≥75	27(57.5)	20(42.3)	9.6[5.2–17.7]	<0.0001	9.5[3.1–29.0]	<0.0001
<75	109(12.3)	776(87.7)	1		1	

(*Continued*)

Table 3 (Continued).

	Outcome at 28 Days		Univariable Analysis*		Multivariable Analysis#	
	Dead N (%)	Alive N (%)	OR [95% CI]	p-value	AOR [95% CI]	p-value
Post-dose Fibrinogen (mg/dl)						
≤150	41(36.0)	73(64.0)	4.3[2.7–6.8]	<0.0001		
>150	74(11.6)	566(88.4)	1			
Total number of days of FFP administration (days)						
≥3	52(29.9)	122(70.1)	2.4[1.7–3.5]	<0.0001		
<2	147(15.1)	828(84.9)	1			

Notes: Excluding the cases of plasma exchange (N=34), factors associated with the mortality outcome at 28 days after FFP transfusion were analysed. *Chi-square test with post-hoc multiple comparisons by Bonferroni correction were used to compare groups. #Logistic regression analysis with the stepwise method: sex, age, and the amount of transfused FFP were forced entry predictors, and the other 11 variables were selected using the stepwise method ($p<0.25$). $R^2 = 0.3084$, model p-value < 0.0001, n = 1265.
Abbreviations: OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; FFP, fresh frozen plasma; DIC, disseminated intravascular coagulation; APTT, activated partial thromboplastin time; PT-INR, prothrombin time and international normalized ratio; RBC, red blood cells.

Seventy-one (5.5%) patients received FFP for ≥3 days, and 28 (2.2%) for ≥10 days. Some of these patients may have had end-stage liver disease with coagulopathy because of impaired production of blood coagulation factors. Coagulopathy in patients with end-stage liver disease is difficult to eliminate, even with several FFP transfusions. This accounts for the tendency of clinicians to continue FFP transfusion over a long period, resulting in transfusion of large total volumes of FFP. In our study, patients who were still alive at 28 days had received FFP for significantly fewer days than those who had died. The mortality rate was also significantly higher in patients who had received ≥20 units of FFP than in those who had received <20 units. We cannot simply conclude that a longer duration or a large amount of FFP transfusion leads to a poor prognosis. However, these findings do indicate that FFP is still given to patients with terminal conditions and poor prognoses, and that such use of FFP is inefficient.

The second edition of the Japanese guideline states that blood coagulation tests are not necessary before FFP transfusion;[4] this differs from the recommendation in the first edition. However, in this study we found that, in most institutions, coagulation tests were performed to assess the patients' haemostatic status, assist decisions on whether to administer FFP, and determine the likely efficacy of FFP transfusion. Admittedly, the trigger values for the coagulation tests are only reference values. However, FFP may have been administered "inappropriately" to patients in whom one or more coagulation test results did not reach the trigger values. There were no significant differences in any coagulation test values between before and after FFP transfusion in the patients who subsequently died. This lack of improvement may indicate that patients whose conditions are very serious and who are at higher risk of dying have chronic rather than acute defects in coagulation.

The original purpose of FFP transfusion was not to improve patients' prognoses but to improve coagulation ability, stop bleeding, and reduce RBC transfusion volumes. However, because FFP should be administered only to eligible patients to prevent wasting of resources, determining survival rates after FFP transfusion is still important in Japan. Although 36.2% of FFP use was outside the indications and considered "inappropriate", this relatively low rate suggests that all "inappropriate" use of FFP was not fruitless. Some of these FFP transfusions may have improved coagulation ability and contributed to restoring good haemostasis, leading to a good prognosis. Even though the mortality rate in this study was 16.2%, it cannot be concluded that FFP transfusion contributed to patients' prognoses.

We used multivariable logistic regression to analyse factors associated with death at day 28 after FFP transfusion. The factors independently and significantly associated with death at day 28 after FFP transfusion were older age, non-perioperative use of FFP, coagulopathy associated with liver damage, FFP transfusion of seven or more units, post-transfusion PT-INR of ≥2, and post-transfusion APTT of ≥75 seconds. Patients with end-stage liver disease often have chronic coagulopathy that does not improve with FFP transfusion.

This study had several limitations. First, although bleeding volume is a mortality-related factor, it could not be included in the multivariable analysis. In addition, we did not include the patients' underlying diseases in the multivariable analysis because they were too diverse. As to specific causes of death, we confirmed that no deaths were due to bleeding. However, we did not further investigate the causes of death.

This is the first study to comprehensively determine the actual circumstances and outcomes of FFP transfusion in major medical institutions in Hiroshima Prefecture. Surveys need to be performed in other prefectures and nationwide and the results compared with those of this study. Our findings indicate that it is necessary to continue to promote appropriate FFP use to minimise wasting of blood resources.

Conclusion

In this multicentre prospective cohort study, which was performed to determine the actual circumstances and outcomes of FFP transfusion in Hiroshima Prefecture, we found that FFP was transfused appropriately in at least 63.8% of cases. The mortality rate 28 days after transfusion was 16.2%. The factors independently and significantly associated with mortality were older age, non-perioperative use of FFP, coagulopathy associated with liver damage, FFP transfusion of seven or more units, post-transfusion PT-INR of ≥2, and post-transfusion APTT of ≥75 seconds.

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. Especially, Aya Sugiyama and Junko Tanaka had a great contribution to analysing the data. Aya Sugiyama and Teruhisa Fujii mainly wrote the manuscripts, and the rest of all authors critically reviewed it. All authors gave final approval of the manuscript version to be published and agreed to be accountable for every aspect of the work.

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Disclosure

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