Effect of storage time of transfused plasma on early and late mortality after coronary artery bypass grafting

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Objectives: Because some concern has been raised about the storage time of red blood cells and outcomes after cardiac surgery, we investigated whether longer storage time of transfused plasma increases the risk for early or late mortality among patients who have undergone coronary artery bypass grafting.

Methods: We retrospectively analyzed the data of all 10,626 patients who underwent isolated coronary artery bypass grafting in Catharina Hospital, Eindhoven, The Netherlands, between January 1998 and December 2007. All patients who received at least 1 unit of plasma intraoperatively or during the first 5 postoperative days were studied. They were divided into 3 groups (only younger plasma, only older plasma, and any older plasma groups) according to the storage time of the plasma (cutoff point, 323 days).

Results: After we had excluded 122 patients who were unavailable for follow-up, we found that 375 of the remaining patients (n = 745) received only younger plasma 370 patients received any older plasma, and 200 patients received only older plasma (mean follow-up, 1565 ± 1137 days; median follow-up, 1629 days). The storage time of plasma, when entered as either a continuous variable or a dichotomous variable, was a risk factor for early but not late mortality. Log-rank testing revealed no statistical difference in long-term survival among the groups.

Conclusions: Longer storage time of plasma is a risk factor for early but not late mortality among patients who have undergone coronary artery bypass grafting. (J Thorac Cardiovasc Surg 2011;141:238-43)

Supplemental material is available online.

Critically ill patients, including those who have undergone cardiac surgery, often have more severe complications if they have received a blood transfusion during the perioperative period.[1,2] The storage time of red blood cells may influence the risk of such complications,[3-8] because these cells undergo structural and functional changes that can reduce their function and viability after transfusion.[8-10] Recently, some[11] but not all[12,13] authors have expressed concern about using older red blood cells for transfusion after cardiac surgery. In their reports, several end points regarding heterogeneous patient populations have been mentioned.

The transfusion of fresh-frozen plasma (FFP) from female donors can lead to transfusion-related acute lung injury.[14-19] To our knowledge, no data regarding the effect of the storage time of transfused FFP on early and late outcomes after coronary artery bypass grafting are available. We therefore studied whether the storage time of transfused FFP increases the risk for early or late mortality in a large group of patients who underwent coronary artery bypass grafting in a single center.

MATERIALS AND METHODS

Patients

This study included the data from all adult patients who underwent isolated coronary artery bypass grafting in Catharina Hospital, Eindhoven, The Netherlands, between January 1998 and December 2007. Data collection was initiated in January 1998, when clinical information (demographic data, risk factors, and complications) for the study subjects was prospectively collected in a database.

Study Design

Approval was obtained from the institution's research review board. Data on blood transfusions and the storage time of FFP were collected from the database of the hospital transfusion service. All patients who had received at least 1 unit of FFP between the day of operation and the 5th postoperative day were included in this study. Patients who had received more than 10 units of red blood cells were excluded from the analysis. The maximum time of storage of the transfused FFP per patient was

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Abbreviation and Acronym
FFP = fresh-frozen plasma

referred to as the maximum storage time. The patients were divided into 3 groups according to the storage time of FFP: patients who received only FFP that had been stored for less than 323 days (the younger FFP group), patients who received only FFP that had been stored for at least 323 days (the only older FFP group), and patients who received a least 1 unit of older FFP (the any older FFP group). We used a cutoff point of 323 days because that was the median maximum storage time of all FFP transfused in this study. Patients in the only older FFP group were also included in the any older FFP group.

Operative Technique

All patients received short-acting anesthetic drugs to facilitate early extubation. Normothermic extracorporeal circulation was performed with nonpulsatile flow. Either cold crystalloid cardioplegia (St. Thomas solution) or warm blood cardioplegia, according to the surgeon's preference, was used to induce and maintain cardioplegic arrest. All patients who underwent coronary artery bypass grafting with the use of extracorporeal circulation received low-dose aprotinin (2 million kallikrein inactivation units) during extracorporeal circulation that was administered in the prime solution of the heart–lung machine, as was the usual practice in our hospital. Patients who underwent off-pump surgery did not receive aprotinin.

Storage of FFP

After withdrawal of the donor blood, the plasma was frozen and stored for at least 6 months at –30°C before it was released for transfusion. During those 6 months, the donor was tested for viral diseases. The maximum allowed storage time is 2 years.

Follow-up

Follow-up data on the mortality of the patients studied were gathered from the databases of Dutch health insurance companies. Initially, the data for 9% of the total patient group could not be retrieved from those databases. We then contacted the general practitioners of those subjects to obtain the required mortality data. If necessary, we also contacted the authorities of the city in which those patients lived at the time of surgery. Postoperative mortality was defined as early (≤30 days) or late (>30 days).

Indication for Transfusion of FFP

The main indication for plasma transfusion in our center is excessive postoperative bleeding caused by coagulation disorder. FFP was given if 1 or more of the following laboratory tests yielded abnormal results: activated partial thromboplastin time, prothrombin time, international normalized ratio, and fibrinogen level. The choice to transfuse old or young FFP was made randomly, without any previously agreed protocol.

Statistical Analyses

Discrete variables were compared with the χ^2 test and are presented as numbers and percentages of patients. Continuous variables were compared with the *t* test and analysis of variance and are presented as the mean ± SD. Univariate and multivariate logistic regression analyses were performed to investigate the impact of biomedical variables on early mortality. Multivariate analyses were used to test for the potentially confounding effects of biomedical and demographic factors on outcome. Cox proportional hazard regression analyses were performed for the same analyses of late mortality. If they were significant, confounders were included in multivariate logistic and Cox regression analyses.

Factors that were significant in the univariate analyses were entered into a multivariate model, together with the items of interest (the number of transfused FFP units and the maximum storage time per patient as a continuous variable and as a dichotomous variable). The following 3 factors were entered in 3 separate models, together with other variables: maximum storage time of FFP, only older FFP, and any older FFP. Long-term survival was described with the Kaplan–Meier method. A comparison of long-term survival was performed with log-rank statistics. The zero time point indicated the time of coronary artery bypass grafting. Odds ratios and hazard ratios with 95% confidence intervals are reported. All statistical analyses were performed with SPSS software (Statistical Product and Service Solutions, version 15.0; SSPS Inc, an IBM Company, Chicago, Ill).

RESULTS

During a 10-year period (January 1998–December 2007) 10,626 patients underwent coronary artery bypass grafting in our hospital. Excluded from the analysis were patients who were unavailable for follow-up (n = 122) and those who received more than 10 units of red blood cells (n = 80). Of the remaining patients, 375 received only younger FFP, 370 received any older FFP, and 200 patients received only older FFP. The mean follow-up was 1565 ± 1137 days (range, 0–3704 days), with follow-up considered 0 days in cases of operative death. The median follow-up was 1506 days, the mean storage time for FFP was 341 ± 94 days (range, 196–730 days), and the median storage time for FFP was 323 days. The distribution of FFP storage times is shown in Figure E1.

Baseline characteristics stratified by storage time are shown in Table 1. None of the differences among the patient groups in baseline characteristics was significant except for re-exploration, which occurred more often among patients who had received only younger FFP, and the numbers of transfused units of FFP and platelets, which were higher among patients who had received any older FFP. Only the number of units of transfused platelets was higher in the group of patients who had received only older FFP.

Early mortality occurred more often among patients who received older FFP (ie, in 7.0% of those who received any older FFP and in 9.0% of those who received only older FFP) than in patients who received younger FFP (3.2%), as shown in Table E1. Univariate logistic regression analyses (Table E2) revealed that the maximum storage time of FFP was a significant risk factor for early mortality, both as a continuous variable and as a dichotomous variable with a cutoff point of 323 days (only older FFP plasma and any older FFP versus younger FFP). Other risk factors for early mortality were age, chronic obstructive pulmonary disease, diabetes, low creatinine clearance, a left ventricular ejection fraction lower than 35%, a low preoperative hemoglobin level, previous cardiac surgery, emergency operation, perioperative myocardial infarction, and the numbers of units of transfused red blood cells, FFP, and platelets. Univariate Cox regression analyses did not reveal the maximum storage time of FFP as a risk factor for late mortality.

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TABLE 1. Baseline characteristics stratified by storage age of fresh-frozen plasma transfused

	Younger FFP (N = 375)	Any older FFP (N = 370)	*P* value	Only older FFP (N = 200)	*P* value
Preoperative factors					
Age (y, mean ± SD)	65.0 ± 9.4	65.7 ± 9.9	.288	66.4 ± 9.3	.088
Male (no.)	305 (81.3%)	307 (83.0%)	.313	164 (82.0%)	.470
Diabetes (no.)	76 (20.3%)	69 (18.6%)	.321	37 (18.5%)	.348
Hypertension (no.)	146 (38.9%)	134 (36.2%)	.245	83 (41.5%)	.305
Chronic obstructive pulmonary disease (no.)	45 (12.0%)	50 (13.5%)	.305	29 (14.4%)	.234
Peripheral vascular disease (no.)	48 (12.8%)	44 (11.9%)	.396	28 (14.0%)	.388
Left ventricular ejection fraction <35% (no.)	12 (3.4%)	18 (5.3%)	.163	6 (3.2%)	.560
Creatinine clearance (mL/min, mean ± SD)	71.2 ± 23.9	70.5 ± 23.9	.690	70.1 ± 24.3	.606
Emergency (no.)	46 (12.3%)	49 (13.2%)	.386	29 (14.5%)	.263
Preoperative hemoglobin (g/dL, mean ± SD)	13.7 ± 1.5	13.8 ± 1.4	.414	13.6 ± 1.1	.494
Cardiac reoperation (no.)	55 (14.7%)	52 (14.1%)	.447	28 (14.0%)	.467
Perioperative and postoperative factors					
No of grafts (mean ± SD)	3.3 ± 1.2	3.4 ± 1.1	.471	3.3 ± 1.1	.708
Off pump (no.)	26 (6.9%)	26 (7.0%)	.537	18 (9.0%)	.233
Extracorporeal circulation time (min, mean ± SD)	66.2 ± 44.0	65.4 ± 42.9	.798	65.2 ± 45.6	.786
Intra-aortic balloon pump (no.)	32 (8.5%)	30 (8.1%)	.469	15 (7.5%)	.398
Re-exploration (no.)	134 (35.7%)	120 (32.4%)	.191	50 (25.0%)	.005
Perioperative myocardial infarction (no.)	32 (8.5%)	28 (7.6%)	.364	14 (7.0%)	.318
Red blood cells (units, mean ± SD)	3.7 ± 2.7	3.8 ± 2.8	.740	3.3 ± 2.5	.066
FFP (units, mean ± SD)	2.5 ± 1.1	2.8 ± 1.5	.001	2.4 ± 1.1	.409
Platelets (units, mean ± SD)	0.29 ± 0.56	0.46 ± 0.81	.001	0.42 ± 0.75	.016

FFP, Fresh-frozen plasma.

Factors that were significant for late mortality were age, chronic obstructive pulmonary disease, diabetes, low creatinine clearance, low preoperative hemoglobin level, previous cardiac surgery, peripheral vascular disease, hypertension, perioperative myocardial infarction, and the numbers of units of transfused red blood cells and FFP. All risk factors that were identified in univariate analyses were entered into the multivariate logistic regression and multivariate Cox regression models (Table 2).

Early Mortality

The maximum storage time of FFP, when entered as a continuous and as a dichotomous variable with a cutoff point of 323 days (only older FFP and any older FFP versus younger FFP), was identified as an independent risk factor for early mortality. Because the numbers of red blood cell, FFP and platelet units were entered into the multivariate model, this effect was independent of the number of transfusion of blood products. The number of transfused platelet units was not significant as a predictor of early mortality. Other independent risk factors for early mortality were as follows: diabetes, a left ventricular ejection fraction less than 35%, and perioperative myocardial infarction.

Late Mortality

The maximum storage time of FFP, when entered as either a continuous variable or a dichotomous variable with a cutoff point of 323 days (older versus younger FFP), was not identified as an independent risk factor for late mortality. Independent risk factors for late mortality were the number of transfused FFP units, age, chronic obstructive pulmonary disease, diabetes, low preoperative hemoglobin level, and perioperative myocardial infarction. The number of transfused platelet units was not significant in the univariate analysis for late mortality and therefore was not entered into the multivariate analysis.

Figure E1 shows the normal distribution of maximum storage time of FFP per patient. The predicted probability for early mortality increased with storage time for all patients, as well as for patients who received 1 or 2 units of FFP, as shown in Figures 1 and 2.

The survival curves of patients who received a transfusion only of younger FFP and those who received any older FFP are shown in Figure E2. The survival curves of those patients who received a transfusion of younger FFP and of those who received only older FFP are shown in Figure 3. The differences between the curves did not reach statistical significance. It is clear, however, that there is a distinct difference in the early postoperative period.

DISCUSSION

This retrospective study shows that the transfusion of older FFP is an independent risk factor for early but not late mortality. The study population consisted of patients

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TABLE 2. Multivariate logistic regression analyses for early mortality and Cox regression analyses for late mortality

	Early mortality			Late mortality		
Risk factor	**OR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
FFP maximum storage time*	1.004	1.001–1.008	.023	1.001	0.998–1.003	.622
Any older FFP	2.29	1.00–5.22	.048	0.93	0.62–1.51	.104
Only older FFP	3.43	1.32–8.92	.011	0.78	0.42–1.43	.159
Red blood cell units transfused*	1.067	0.902–1.261	.451	0.931	0.852–1.016	.110
FFP units transfused*	1.025	0.785–1.338	.856	1.347	1.165–1.558	< .0001
Platelet units transfused*	1.406	0.847–2.332	.188			
Age*	1.022	0.972–1.075	.401	1.048	1.016–1.081	.003
Chronic obstructive pulmonary disease	1.83	0.72–1.07	.201	2.68	1.67–4.31	< .0001
Diabetes	3.34	1.46–7.62	.004	1.75	1.10–2.79	.018
Creatinine clearance*	0.995	0.974–1.016	.640	0.986	0.972–1.001	.064
Left ventricular ejection fraction <35%	3.65	1.08–12.29	.036			
Preoperative hemoglobin*	0.837	0.649–1.079	.170	0.860	0.744–0.995	.043
Cardiac reoperation	1.74	0.68–4.47	.244	1.57	0.95–2.61	.078
Peripheral vascular disease				1.40	0.81–2.42	.216
Emergency	2.22	0.68–7.18	.183			
Perioperative myocardial infarction	4.11	1.54–10.95	.005	3.62	2.00–6.56	< .0001

HR, Hazard ratio; *CI,* confidence interval; *OR,* odds ratio; *FFP,* fresh-frozen plasma. *Entered as a continuous variable.

who received at least 1 unit of FFP and as many as 10 units of red blood cells intraoperatively or within the first 5 postoperative days after coronary artery bypass grafting. Patients who received more than 10 units of red blood cells were excluded from this study. The reason is that most of these patients had massive blood loss as a result of surgical calamities that caused various complications, including death. Thus the outcome in such cases was mainly influenced by the major surgical insult. The decision to transfuse younger or older FFP was random, according to the availability of the FFP. The cutoff point for younger and older FFP of 323 days (the median storage time) was arbitrary. In the multivariate logistic regression analyses, the maximum storage time used both as a continuous variable and as a dichotomous variable was revealed as an independent risk factor. The year of operation did not prove to be an independent risk factor for early mortality, and the storage protocol did not change with time. This indicates a real effect of storage age on early mortality. The predicted probability for early mortality increased with longer per patient maximum storage time. The same was found for patients who received 1 or 2 units of FFP. This confirms the results of the multivariate regression analyses, which showed the storage time to be an independent risk factor.

Although the late mortalities were less in the any older FFP group and the only older FFP group, multivariate analyses revealed that late mortality was not influenced by the storage time of FFP. Surprisingly, the numbers of units of transfused red blood cells, FFP, and platelets did not prove to be a risk factor for early mortality. This can be probably explained by the fact that in this subgroup of patients who received FFP, the mean number of transfused red blood cell units was already high (mean 3.6 ± 2.6 units). The transfusion of additional red blood cells in those patients did not increase the risk for mortality or morbidity any further.

In previous reports, transfusion-related acute lung injury has been described,[14-19] The authors of those reports suggested that leukocyte antibodies and FFP from female donors might be important risk factors for the development of transfusion-related acute lung injury in critically ill patients. A recent report,[20] however, did not support this finding.

To our knowledge, no data are available regarding the effect of the storage time of FFP on short-term and long-term outcomes after coronary artery bypass grafting. We found a clear relationship between the storage time of FFP and

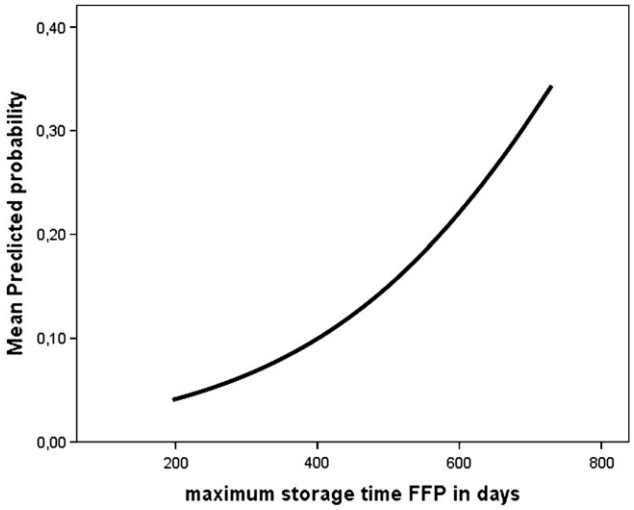

FIGURE 1. Predicted probability for early mortality for all patients. *FFP,* Fresh-frozen plasma.

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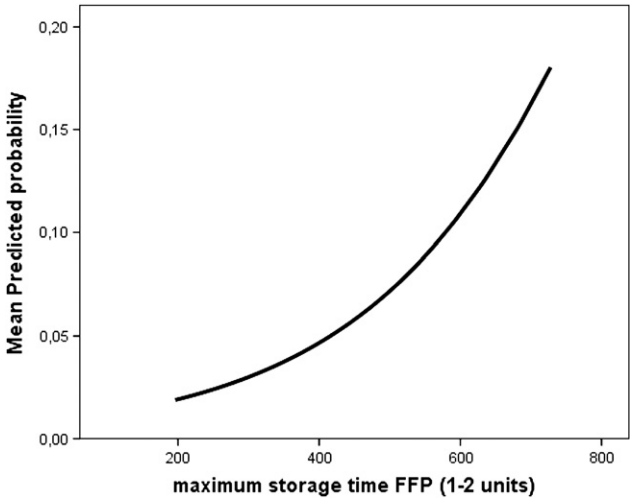

FIGURE 2. Predicted probability for early mortality for patients with 1 to 2 units of fresh-frozen plasma *(FFP).*

early mortality. Baseline characteristics were similar between patients who received younger FFP and those who received older FFP. To further eliminate the effect of confounders, multivariate analyses were performed. The results of those analyses led to the conclusion that the transfusion of older FFP resulted in a poorer early outcome but that there was no relationship between the storage time of FFP and late outcome. The predicted probability for early mortality increased with longer per patient maximum FFP storage time. The same was found for patients who received 1 or 2 units of FFP. This confirms the results of the multivariate regression analyses, which showed that the FFP storage time was an independent risk factor.

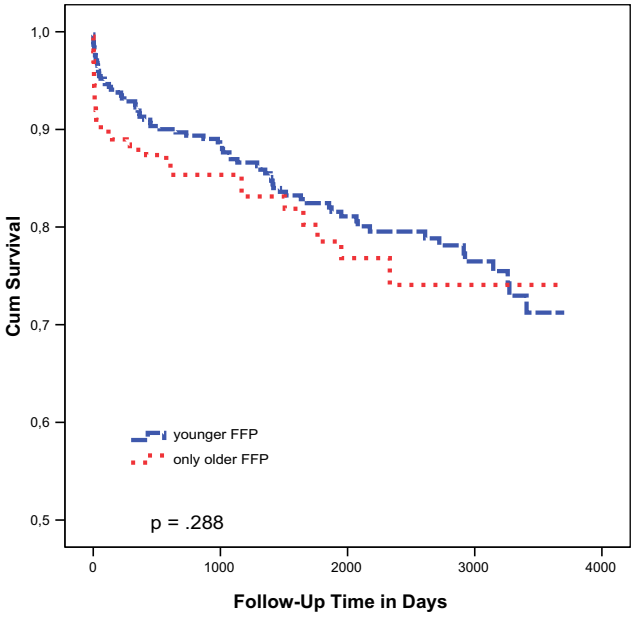

FIGURE 3. Kaplan–Meier curves for patients receiving younger or only older fresh-frozen plasma *(FFP). Cum,* Cumulative.

It has been demonstrated that prothrombin time and activated partial thromboplastin time are influenced by freezing and storage. This effect is more pronounced at –20°C than at –70°C.[21] Factor VIII levels are influenced by the storage temperature after thawing[22,23] or after storage without freezing.[24] It has also been shown that slow freezing causes a more pronounced decrease in the level of factor VIII than does more rapid freezing.[25] In The Netherlands, blood products are stored at –30°C. At that temperature, the degeneration of clotting factors and other proteins cannot be excluded. Degeneration may lead to less effective clotting factors, and the degenerated proteins may produce unknown adverse effects. This possible progressive degeneration of proteins might be the reason that our subjects who received older FFP had relatively worse outcomes. Further studies are needed to investigate the possible progressive degeneration of proteins. Because most transfused FFP is older than 300 days, it might be advantageous to use younger FFP for transfusion whenever possible until that issue has been further clarified.

Study Limitations

In this retrospective study, factors not included in the list of demographic characteristics may explain the differences between the patient groups. A prospective, randomized trial should resolve that shortcoming. The primary end point of the study was all-cause mortality. Unfortunately, we were not able to retrieve the causes of death for these patients, data that are equally important. Moreover, the effects of storage time of FFP on postoperative complications such as sepsis or pulmonary complications remain unknown. Correlation between the storage time of FFP and postoperative bleeding and re-exploration was also not determined. This is another important shortcoming.

This investigation was a single-center study performed in The Netherlands. Whether our results can be applied to coronary artery bypass grafting performed in other countries in which different protocols for blood withdrawal, processing, and storage are practiced remains to be determined.

CONCLUSIONS

In a study of the 745 of 10,626 patients undergoing coronary artery bypass grafting who received FFP intraoperatively or within the first 5 postoperative days after coronary artery bypass grafting, we found that the longer storage time of FFP was an independent risk factor for early but not late mortality.

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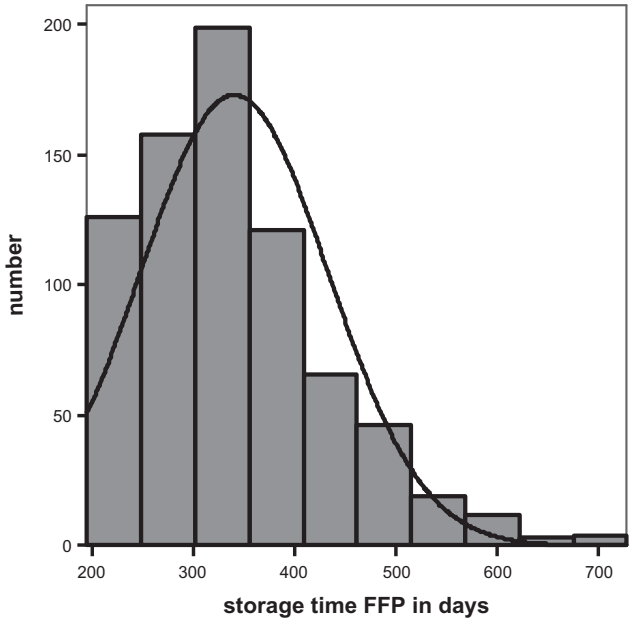

FIGURE E1. Distribution of maximum (per patient) storage time of fresh-frozen plasma *(FFP)*.

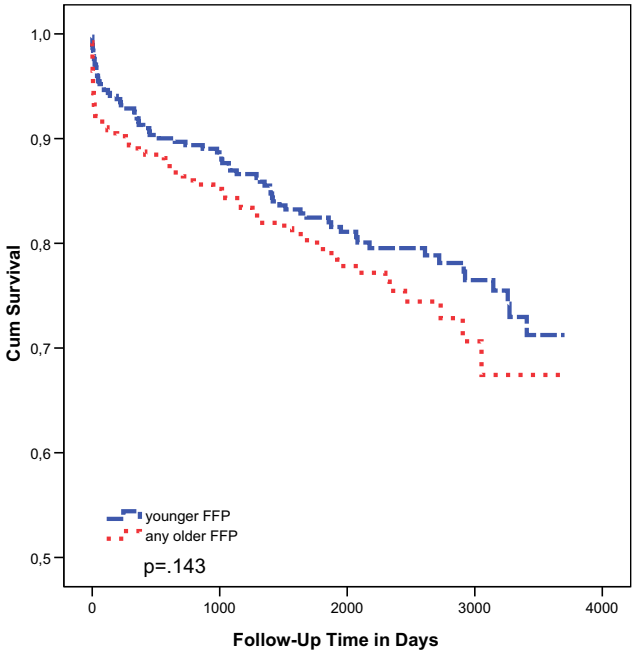

FIGURE E2. Kaplan –Meier curves for patients receiving only younger or any older fresh-frozen plasma *(FFP)*.

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TABLE E1. Early and late mortalities among patients receiving younger and older fresh-frozen plasma

	Younger FFP	Any older FFP	*P* value*	Only older FFP	*P* value*
Early mortality (no.)	12 (3.2%)	29 (7.8%)	.004	18 (9.0%)	.003
Late mortality (no.)	58 (15.5%)	43 (11.6%)	.077	17 (8.5%)	.011

FFP, Fresh-frozen plasma. *Versus younger fresh-frozen plasma.

TABLE E2. Univariate logistic regression analyses of risk factors for early mortality and Cox regression analyses for late mortality

	Early mortality			Late mortality		
Risk factor	**OR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Preoperative factors						
Age*	1.043	1.005–1.082	.027	1.077	1.051–1.104	< .0001
Male sex	0.65	0.31–1.37	.264	0.72	0.45–1.14	.169
Chronic obstructive pulmonary disease	2.34	1.11–4.96	.026	2.43	1.53–3.84	< .0001
Diabetes	2.54	1.31–4.94	.006	1.97	1.28–3.04	.002
Creatinine clearance*	0.977	0.961–0.992	.003	0.969	0.958–9.979	< .0001
Left ventricular ejection fraction <35%	4.20	1.50–11.73	.014	2.03	0.88–4.65	.093
Preoperative hemoglobin*	0.702	0.577–0.855	< .0001	0.767	0.671–0.877	< .0001
Cardiac reoperation	3.40	1.72–6.73	.001	1.78	1.11–2.86	.017
Peripheral vascular disease	1.78	0.80–4.00	.120	2.21	1.35–3.61	.001
Emergency	3.52	1.75–7.07	.001	1.54	0.89–2.66	.122
Hypertension	1.18	0.62–2.25	.355	1.50	1.01–2.23	.045
Perioperative and postoperative factors						
No. of grafts*	0.825	0.634–1.074	.152	1.003	0.857–1.175	.970
Perioperative myocardial infarction	3.04	1.33–6.91	.013	3.03	1.80–5.12	< .0001
Re-exploration	0.79	0.39–1.57	.313	0.93	0.62–1.40	.745
Off pump	1.47	0.50–4.31	.476	0.77	0.28–2.10	.616
Year of operation	0.972	0.975–1.080	.596	0.961	0.879–1.052	.390
FFP maximum storage time*	1/004	1.001–1.007	.005	1.001	0.999–1.003	.294
Any older FFP	2.57	1.29–5.12	.007	0.98	0.66–1.47	.943
Only older FFP	2.99	1.41–6.34	.004	0.80	0.46–1.39	.439
FFP units transfused	1.264	1.074–1.487	.005	1.239	1.096–1.400	.001
Platelet units transfused	1.698	1.228–2.347	.001	1.183	0.893–1.566	.242
Red blood cell units transfused	1.220	1.091–1.364	< .0001	1.089	1.016–1.168	.016

OR, Odds ratio; *CI,* confidence interval; *HR,* hazard ratio; *FFP,* fresh-frozen plasma. *Entered as a continuous variable.

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