Effect of Intra- and Postoperative Fluid and Blood Volume on Postoperative Pulmonary Edema in Patients With Intraoperative Massive Bleeding: Multi-Center Cohort Study Using Time Varying Analysis

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Abstract

Background

In patients with massive bleeding during surgery, the effect of intra- and postoperative fluid and blood volume on postoperative pulmonary edema is uncertain. The aim of this study is evaluating the occurrence risk relationship through time-varying analysis between postoperative pulmonary edema and intra- and postoperatively administered volume of fluid and blood in patients with intraoperative massive bleeding.

Methods

This study is a retrospective cohort study and data was obtained from the clinical data warehouse at Hallym University Medical Center, a multi-institutional data registry of 5 hospitals of Hallym University. Patients with intraoperative massive bleeding ($\geq 40\%$ of average blood volume) and who underwent a non-cardiac surgery at 5 hospitals between January 1, 2010, and December 31, 2019 were enrolled the study. The primary outcome was postoperative pulmonary edema occurrence within 72 hours after surgery. Secondary outcomes were postoperative pulmonary edema with hypoxemia.

Results

In total, 2090 patients were included in the postoperative pulmonary edema analysis, and 300 patients developed pulmonary edema within 72 hours after surgery. The postoperative pulmonary edema hypoxemia analysis with hypoxia included 1660 patients; pulmonary edema with hypoxemia occurred in 161 patients. The increase in the amount of red blood cells/average blood volume/hour after surgery increased the risk of developing pulmonary edema after surgery (hazard ratio: 1.03, 95% confidence interval [1.01–1.05], $P = 0.013$) and the risk of developing pulmonary edema with hypoxemia (hazard ratio: 1.04, 95% confidence interval [1.01–1.07], $P = 0.024$).

Conclusion

In this study, an increase in the transfusion of red blood cells per hour after surgery increased the risk of developing pulmonary edema after surgery. This increase can be considered a risk factor for the incidence of pulmonary edema.

Background

Massive bleeding during surgery is a life-threatening event in the operating room and increases postoperative mortality.[1] When massive bleeding occurs during surgery, When massive bleeding occurs during surgery, a relatively large volume of fluid and blood is administered to compensate for the loss thereof, which could result in fluid overload. Fluid overload with high hydrostatic pressures resulting in left ventricular dysfunction would be the most common consequence of postoperative pulmonary edema. [2] Massive transfusion after massive bleeding may cause coagulopathy,[3] acid-base abnormalities,[4]

hypothermia,[5] and transfusion-related acute lung injury.[6] These complications of massive transfusions may also be related to pulmonary edema.[7-10]

Intraoperative fluid therapy is complex because it generally includes replacement of the maintenance requirement, existing fluid deficits, and surgical wound losses including blood loss. Moreover, it is challenging to evaluate accurately the bleeding volume during surgery[11] and to perform transfusion safely.[12] After surgery, more fluid and blood may be needed due to postoperative bleeding, or complications due to intraoperative massive transfusion. Therefore, administration of fluid and transfusion therapy are more difficult after surgery. Moreover, currently, there is no clinical approach to safely administer fluid and blood. Surgeons and anesthesiologists perform fluid and transfusion therapy based on a combination of various clinical approximations. Perioperative fluid and transfusion management in massive bleeding during surgery continues to be a daily challenge to surgeons and anesthesiologists.

In this study, we aimed to determine the intra- and postoperative fluid and transfusion volume, which can be measured accurately. We also investigated the effect of the volume of fluid and blood administered during and after surgery on the development of postoperative pulmonary edema in patients with intraoperative massive bleeding using a time-varying hazards analysis.

Materials And Methods

Data collection

This retrospective cohort study was approved by the Clinical Research Ethics Committee of Chuncheon Sacred Heart Hospital, Hallym University. All data were obtained from the clinical data warehouse of 5 hospitals at Hallym University Medical Center, between January 1, 2010, and December 31, 2019. The clinical data warehouse is a database of medical records, prescriptions, and test results; the data can be searched in multiple ways to identify patients, i.e., by prescription, examination type, and diagnosis. The time and results of patient tests can be extracted, in addition to their drug administration status, transfusion status, and overall medical records, in an unstructured text format.

Patients

Bleeding is divided into four classes according to the American College of Surgeons' Advanced Trauma Life Support classification.[13] Class 4 corresponds to a loss of > 40% of the circulating blood volume. In this study, estimated blood loss > 40% of average blood volume (males: body weight [kg] × 75 ml; female: body weight [kg] × 65 ml)[11] during surgery was defined as massive bleeding; patients with massive bleeding during surgery were included. Patients meeting specific criteria were excluded, which include:

- Patients < 18 years of age;
- Patients undergoing cardiac surgery;
- Patients who underwent a previous surgery within 7 days before the present surgery.

- Patients with pulmonary edema or hypoxemia ($\text{PaO}_2/\text{FiO}_2 \leq 300$) before surgery

Although no arterial blood gas (ABG) analysis was found, patients who did not receive oxygen therapy due to no respiratory symptoms after surgery and did not have pulmonary edema findings on chest X-ray were considered to have absence of hypoxemia.

Primary and Secondary Outcomes

The primary outcome was the presence of pulmonary edema on postoperative chest X-ray. chest X-rays were used for consistency in the diagnosis of pulmonary edema, and all chest X-rays were evaluated by radiologists. The secondary outcome was pulmonary edema with hypoxemia after surgery. $\text{PaO}_2/\text{FiO}_2 \leq 300$ was defined as hypoxemia. The results with the least time interval between chest X-ray and ABG analysis were used. Patients who had no pulmonary edema on chest X-ray and did not receive oxygen therapy due to no respiratory symptoms were considered to have absence of pulmonary edema. Since postoperative pulmonary edema could occur up to 3 days after the operation, [12] it was confirmed whether postoperative pulmonary edema occurred until 72 hours after surgery.

Major variables

The major variables to be evaluated in this study were divided into intra- and postoperative variables. Intraoperative variables include the total amount of fluid administered during surgery, the amount of fluid administered per hour, the total amount of red blood cells administered, the amount of red blood cells administered per hour, the total amount of frozen fresh plasma (FFP) administered and the amount of FFP administered per hour.

Postoperative variables include the total amount of fluid administered after surgery, the amount of fluid administered per hour, the total amount of red blood cells administered, the amount of red blood cells administered per hour, the total amount of FFP administered and the amount of FFP administered per hour. All postoperative major variables were used as time-varying variables. The amount of fluid and blood administered after surgery were measured based on the ABG analysis test time or the chest X-ray test time. In the analysis of pulmonary edema with hypoxemia, when both ABG analysis and chest X-ray were tested, the dose was measured based on the ABG analysis test time, and when there were no respiratory symptoms and only the chest X-ray test was performed, the amount was measured based on the chest X-ray test time. The administered fluid and blood volume were expressed as a percentage of the patient's average blood volume. Each patient had 1–3 time-varying variables and observation periods depending upon the number of measurements according to the test frequency. The first observation period was from the end of anesthesia to the time of the first test; the second observation period was from the time of the first test to the second test, and the third observation period was from the second test to the third test.

Other variables

Many other covariates were used to adjust for any residual confounding or indication bias. Demographic variables included old age (≥ 70 years), male sex, and obesity (body mass index ≥ 30). Preoperative variables included emergency, American Society of Anesthesiologists physical status >2 , smoking, brain trauma, multiple fractures, hyponatremia (<135 mmol/L), hypoalbuminemia (<3.5 g/dL) and glomerular filtration rate. Intraoperative variables included general anesthesia, anesthesia time, kinds of surgery (acute abdomen, aorta, brain, spine, thoracic), massive transfusion (packed red blood cells more than 4 pint/hour), [14] urine output < 0.5 ml/kg/hour, continuous inotropes use and estimated blood loss. Postoperative variables included patient-controlled analgesia and whether or not creatinine increased by 0.3 compared to that before surgery. [15]

Statistical Analysis

Continuous variables were expressed as median and interquartile ranges due to skewness. Categorical variables were summarized as frequency and percentages. Continuous data were analyzed using the Mann-Whitney test, to compare patients with postoperative pulmonary edema and patients without postoperative pulmonary edema. Categorical data were analyzed using the chi-square test. Cox's time-varying hazards model was used to analyze the hazard ratio of the major variables for the occurrence of postoperative pulmonary edema within 72 hours after surgery. Time-varying covariance occurs when the covariate changes over time during the tracking period. These variables can be analyzed with a time-varying Cox regression model to estimate their effect on event occurrence time. [16] All reported P-values were two-sided; a P-value < 0.05 was considered to indicate statistical significance. SPSS (version 24.0; IBM Corp., Armonk, NY, USA) was used for all statistical analyses except for time-varying Cox regression analysis. Anaconda (Python version 3.7, <https://www.anaconda.com>; Anaconda Inc., Austin, TX) and Lifelines (version 0.24.15; <https://github.com/CamDavidsonPilon/lifelines/blob/master/docs/index.rst>) were used for time-varying Cox regression analysis.

Results

Study population

Between January 1, 2010, and December 31, 2019, there were a total of 2161 patients who had a bleeding amount $>40\%$ of average blood volume during surgery, and hence these patients were included. Seventy-one patients were excluded because of missing data, and 2090 patients without missing data were included in the primary outcome analysis. There was one follow-up period in 638 patients, two follow-up periods in 407 patients, and three follow-up periods in 1045 patients. Furthermore, 300 patients had pulmonary edema findings on chest X-ray; the time-fixed variables and time-varying variables are summarized in Table 1. In the analysis of pulmonary edema with hypoxemia, 430 patients without data of PO_2 or FiO_2 were excluded, and 1630 patients were included. Moreover, 161 patients had postoperative pulmonary edema with hypoxemia; the time-fixed variables and time-varying variables are summarized in Table 2. There was one follow-up period in 848 patients, two follow-up periods in 499 patients, and three follow-up periods in 313 patients.

Follow-up period

The observation period was divided into 6 types according to the start time and the end time of follow-up observation, and variables and observation results were expressed in each observation period (Tables 1 [page 19] and 2 [page 23]). There was one observation result during the follow-up period, and depending on the

number of observations, patients were included in several periods. The number of patients included in each period and the number of patients with outcomes are listed in Tables 1 (page 19) and 2, respectively. The median of the time interval between the chest X-ray and ABG analysis was 2.4 (interquartile range, 1.1–5.6) hours.

Hazard ratio of postoperative pulmonary edema with and without hypoxemia postoperatively within 72 hours

The unadjusted and adjusted hazard ratio for major variables and kidney-related variables (preoperative glomerular filtration rate, intraoperative urine output ≤ 0.5 ml/kg/hour, postoperative creatinine increasing) of pulmonary edema with and without hypoxemia postoperatively within 72 hours are shown in Figure 1 and Figure 2, respectively. Postoperatively administered total fluid (adjusted hazard ratio, 1.00; 95% confidence interval, 1.00–1.00; $P < 0.001$) and postoperative red blood cells per hour (adjusted hazard ratio, 1.03; 95% confidence interval, 1.01–1.05; $P = 0.013$) showed significant difference in hazard ratio in the unadjusted and adjusted analyses of postoperative pulmonary edema. Postoperative administered total fluid (adjusted hazard ratio, 1.00; 95% confidence interval, 1.00–1.00; $P = 0.005$) and postoperative red blood cells per hour (adjusted hazard ratio, 1.04; 95% confidence interval, 1.01–1.07; $P = 0.024$) showed significant differences in hazard ratio in the unadjusted and adjusted analyses of postoperative pulmonary edema with hypoxemia. Intraoperative FFP per hour had a significant difference in hazard ratios only in postoperative pulmonary edema (adjusted hazard ratio, 1.03; 95% confidence interval, 1.00–1.06; $P < 0.042$). The other major variables did not show significant results. The data of adjusted hazard ratio of variables that are not shown in Figures 1 and 2 are shown in Table 3 (page 27) and 4 (page 28).

Discussion

Through time-varying Cox regression, it was shown that the total amount of fluid administered after surgery and the amount of red blood cells administered per hour were associated with an increased risk of postoperative pulmonary edema with hypoxemia as well as postoperative pulmonary edema. However, the hazard ratio for the occurrence of postoperative pulmonary edema in the total amount of fluid administered after surgery was so small that the clinical significance was not significant.

Our findings show that in patients with massive intraoperative bleeding, the amount of red blood cells administered per hour after surgery increases the risk of developing postoperative pulmonary edema. Exacerbation of pre-existing anemia, bleeding during surgery and repeated laboratory blood test are

common causes of postoperative anemia.[17-19] If the anemia is severe or difficult to correct, more red blood cell transfusions may be required. Anemia and pulmonary edema are interrelated.[20-22] Existing severe anemia can often be associated with salt and water retention,[23-25] and hormonal and metabolic changes due to low hemoglobin levels can also cause direct myocardial toxicity, myocardial hypertrophy, and increase salt and water retention.[20, 26] Heart failure can lead to anemia through a variety of mechanisms such as iron deficiency, inflammation, low erythropoietin level, medication, hemodilution, and medullar dysfunction .[27]

The essential principle of fluid balance in the body is that the amount of water lost should be equal to the amount of fluid received.[28] However, increased weight is common in patients undergoing surgery; this is typically a result of a positive fluid balance.[29, 30] Cooperman et al. reported 2.1 ± 0.4 L of bleeding and 3.7 ± 0.6 L of replacement in postoperative pulmonary edema patients; fluid overload was exhibited by half of their patients.[31] Arieff et al. reported that if fluid retention exceeded 67 ml/kg/day, postoperative pulmonary edema could occur.[32] Holte et al. reported that administration of 40 ml/kg infusion of lactated Ringer's solution for 3 hours caused a reduction in pulmonary function.[33] Massive bleeding also causes fluid imbalance, and massive volumes of fluid and blood should be administered rapidly in such cases. Massive administration of blood products may cause transfusion-associated circulatory overload,[14] and fluid overload can in turn cause postoperative pulmonary edema.[2, 31, 32, 34]

In this study, there were no variables related to both the occurrence risk of postoperative pulmonary edema and postoperative pulmonary edema with hypoxemia in the amounts of fluid and blood administered during surgery. Perioperative fluids and blood transfusions can cause hypothermia,[35-37] which can lead to impaired coagulation and acidosis,[38, 39] as well as pulmonary edema.[9] Administered fluid and blood following bleeding can occur due to dilutional coagulopathy, platelet dysfunction, fibrinolysis, or hypofibrinogenemia. And they are prone to occur when massive bleeding and large amounts of fluids and blood are administered as compensation for bleeding.[3, 40, 41] Coagulation disorders such as the above are present in many patients after surgery and make the patient's bleeding worse.[42, 43] Exacerbation of bleeding and resulting anemia increases the need for blood transfusions after surgery.[44] Increased exposure to blood transfusions may pose a risk of developing transfusion-related acute lung injury and transfusion-associated circulatory overload.[45, 46] Acidosis and hypocalcemia caused by increased blood transfusions can be predisposing conditions that affect heart contractility and cause pulmonary edema.[47-49] However, correctable abnormalities may not last long, because during surgery, close monitoring is performed to check for abnormalities such as anemia,[50] volume status,[51] body temperature, electrolyte and coagulation abnormalities that may affect the occurrence of postoperative pulmonary edema, and immediate correction is attempted.[35-39, 52] Because pulmonary edema is not visible on chest X-ray until the amount of lung fluid increases by 30% relative to normal volume,[53] if there is no sudden increase of lung fluid due to close monitoring during surgery, postoperative pulmonary edema may not be visible. However, in patients with massive bleeding, if sufficient resuscitation is not achieved during surgery, organ failure may occur after surgery,[54] which may affect the development of pulmonary edema after surgery.[55-57] Even after surgery, it is recommended to frequently monitor the patient's volume condition using readily available clinical

parameters such as vital signs, urine output, lung auscultation, weight change, and net fluid retention calculations[58, 59] but even doctors do not seem to monitor closely until lung edema is diagnosed.[32]

In this study, an increase in FFP/hour during surgery increased the risk of postoperative pulmonary edema. While FFP is used in cases of clotting factor deficiency to prevent clotting disorders, the use of FFP puts the patients at risk for transfusion-related acute lung injury[6] and can cause circulatory overload in patients with kidney or cardiopulmonary failure.[60] The fact that an increase in FFP/hour during surgery is not associated with an increased risk of postoperative pulmonary edema with hypoxemia is a matter for further study.

Kidney function may also be closely related to the development of pulmonary edema.[57, 61, 62] Our study evaluated renal function with preoperative glomerular filtration rate, intraoperative oliguria, and increased postoperative creatinine, and it was found that increased postoperative creatinine increased the risk of postoperative pulmonary edema. The kidneys play an important role in many homeostasis mechanisms in the body and communicate with the lungs by regulating acid-base balance, increasing oxygen-carrying capacity through red blood cell production, and regulating blood pressure through the renin-angiotensin-aldosterone axis. However, as the acute kidney injury (AKI) progresses, these processes can become impaired.[57] If there is anemia, shock, or hemodilution during surgery, the risk of developing AKI increases after the surgery,[63, 64] but these are more likely to occur in patients with massive bleeding during surgery.[65-67] During anesthesia, because the blood vessels expand, fluid retention may occur,[68] and since the operation time is shorter than the follow-up period after surgery, it may be difficult to see kidney damage due to oliguria during surgery.[69]

In this study, time-varying Cox regression was used to evaluate the hazard ratio. Time-varying covariance occurs when a given covariate changes over time during the follow-up period, a phenomenon commonly seen in clinical studies.[16, 70] In patients with massive bleeding during surgery, the patient's condition after surgery may change in various ways, and according to the change in condition, several tests are performed and the results are measured. In addition, the fluid and transfusion volume will be modified accordingly. In such cases where there are many changes after surgery, a time-varying model may be appropriate.

Limitations

A strength of this study was that a large number of patients with massive bleeding during surgery were included. However, because it is difficult to perform a randomized controlled trial of massive bleeding patients, this study used a retrospective design, which is subject to bias. pulmonary edema is either cardiogenic or non-cardiogenic, but we could not stratify patients based on pulmonary edema type. Although the different types of pulmonary edema have different causes, it is difficult to distinguish them due to their similar clinical features. In addition, the causes can be complex in critically ill patients[55] and both types of postoperative pulmonary edema can occur in patients with massive bleeding during surgery.[34, 45, 46] The gold standard for determining the cause of acute pulmonary edema is the insertion of a pulmonary artery catheter but, this is not routinely performed.[71] Instead, in this study, we

assessed pulmonary edema using a much less invasive method, the chest X-ray, and considered certain radiographic features that may help determine the cause of the edema.[55, 72] In addition, hypoxemia was considered and analyzed to evaluate the objectivity and severity of pulmonary edema symptoms. Finally, this study did not include data on the output of body fluids after surgery. Except for some serious patients admitted to the intensive care unit, no data on postoperative fluid output were available for the follow-up period. Instead, we evaluated the assessment of kidney function related to urinary excretion with changes in creatinine levels.

Conclusions

This study provides information that the incidence of postoperative pulmonary edema is high in patients with massive bleeding during surgery, and an increase in the amount of transfusion of red blood cells after surgery present in the perioperative fluid and blood may be a risk factor for the incidence of pulmonary edema and thus expands the results of previous studies. In patients with massive bleeding during surgery, close monitoring and rapid correction of factors that cause postoperative anemia and bleeding may be more important. Further prospective population-based studies are needed to explain the mechanism underlying the association between postoperative red blood cells transfusion and the risk of developing postoperative pulmonary edema in patients with intraoperative massive bleeding.

Abbreviations

ABG arterial blood gas

FFP fresh frozen plasma

AKI acute kidney injury

Declarations

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of Chuncheon Sacred Heart Hospital, Hallym University. (IRB No. 2019-01-012)

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Young suk Kwon contributed to this work as first authors.

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Tables

Table 1. Demographic characteristics and clinical data in analysis of postoperative pulmonary edema

Variable	No Postoperative pulmonary edema (n = 1790)	Postoperative pulmonary edema (n = 300)	P
Demographics			
Old Age, No. (%)	496 (27.7)	108 (36.0)	0.003
Men, No. (%)	904 (50.5)	148 (49.3)	0.71
Obesity, No. (%)	68 (3.8)	11 (3.7)	0.91
Preoperative Clinical features			
Emergency, No. (%)	647 (36.1)	148 (49.3)	<0.001
American Society of Anesthesiologists physical status > 2, No. (%)	862 (48.2)	186 (62.0)	<0.001
Tobacco use, No. (%)	415 (23.2)	62 (20.7)	0.346
Brain trauma, No. (%)	230 (12.8)	42 (14.0)	0.58
Multiple fracture, No. (%)	127 (7.1)	33 (11.0)	0.02
Hyponatremia, No. (%)	240 (13.4)	34 (11.3)	0.33
Hypoalbuminemia, No. (%)	542 (30.3)	117 (39.0)	0.003
Glomerular filtration rate, median (interquartile range), mL/min/1.73m ²	93.4 (72.7,93.4)	84.4 (68.3,84.4)	<0.001
Intraoperative Clinical features			
General anesthesia, No. (%)	1730 (96.6)	299 (99.7)	0.004
Anesthesia time, median (interquartile range), hour	5.0 (3.5,5.0)	5.1 (2.9,5.1)	0.54
Acute abdomen surgery, No. (%)	119 (6.6)	34 (11.3)	0.004
Aorta surgery, No. (%)	30 (1.7)	7 (2.3)	0.42
Brain surgery, No. (%)	391 (21.8)	59 (19.7)	0.40
Spine surgery, No. (%)	270 (15.1)	58 (19.3)	0.06
Thoracic surgery, No. (%)	53 (3.0)	13 (4.3)	0.21
Massive transfusion, No. (%)	57 (3.2)	33 (11.0)	<0.001
Urine output ≤ 0.5ml/kg/hour, No. (%)	202 (11.3)	39 (13.0)	0.39
Continuous inotropes use, No. (%)	375 (20.9)	96 (32.0)	<0.001
Red blood cells, median (interquartile	24.3 (12.1,24.3)	32.9	<0.001

	range), %		(20.9,32.9)	
	Red blood cells /hour, median (interquartile range), %/hour	4.6 (2.0,4.6)	6.3 (3.7,6.3)	<0.001
	FFP, median (interquartile range), %	1.5 (0.0,1.5)	9.5 (0.0,9.5)	<0.001
	FFP/hour, median (interquartile range), %/hour	0.1 (0.0,0.1)	1.7 (0.0,1.7)	<0.001
	Total fluid, median (interquartile range), %	113.7 (87.9,113.7)	119.7 (89.7,119.7)	0.04
	Total fluid/hour, median (interquartile range), %	22.6 (17.2,22.6)	24.3 (17.8,24.3)	0.01
	Estimated blood loss, median (interquartile range), %	54.4 (45.5,54.4)	63.0 (48.6,63.0)	<0.001
Postoperative clinical features				
	Patient controlled analgesia, No. (%)	1139 (63.6)	181 (60.3)	0.27
Time-varying postoperative clinical features				
Period 1 (No Postoperative pulmonary edema, n = 1866; Postoperative pulmonary edema, n = 192)	Start time, median (interquartile range), hour	0.0 (0.0,0.0)	0.0 (0.0,0.0)	1.000
	End time, median (interquartile range), hour	10.4 (5.6,16.1)	0.8 (0.3,6.2)	<0.001
	Total Fluid, median (interquartile range), %	29.0 (10.2,58.2)	2.4 (0.0,24.5)	<0.001
	Total Fluid/hour, median (interquartile range), %/hour	2.8 (1.3,4.7)	1.5 (0.0,4.4)	<0.001
	Red blood cells, median (interquartile range), %	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.79
	FFP, median (interquartile range), %	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.76
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.34
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.88
	Increasing creatinine, No. (%)	190 (10.2)	20 (10.4)	0.92

Period 2 (No Postoperative pulmonary edema, n = 20; Postoperative pulmonary edema, n = 1)	Start time, median (interquartile range), hour	0.0 (0.0,0.0)	0.0 (0.0,0.0)	1.000
	End time, median (interquartile range), hour	33.8 (29.2,37.2)	43.4 (43.4,43.4)	0.48
	Total Fluid, median (interquartile range), %	69.9 (42.7,119.4)	25.6 (25.6,25.6)	0.38
	Total Fluid/hour, median (interquartile range), %/hour	2.5 (1.5,3.4)	0.6 (0.6,0.6)	0.29
	Red blood cells, median (interquartile range), %	0.0 (0.0,12.8)	5.0 (5.0,5.0)	0.86
	FFP, median (interquartile range), %	0.0 (0.0,4.5)	0.0 (0.0,0.0)	0.67
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0,0.4)	0.1 (0.1,0.1)	0.86
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0,0.1)	0.0 (0.0,0.0)	0.67
Period 3 (No Postoperative pulmonary edema, n = 11; Postoperative pulmonary edema, n =0)	Increasing creatinine, No. (%)	2 (10.0))	1 (100.0)	0.14
	Start time, median (interquartile range), hour	0.0 (0.0,0.0)		
	End time, median (interquartile range), hour	59.2 (58.3,64.1)		
	Total Fluid, median (interquartile range), %	74.8 (22.0,140.3)		
	Total Fluid/hour, median (interquartile range), %/hour	1.2 (0.4,2.3)		
	Red blood cells, median (interquartile range), %	0.0 (0.0,0.0)		
	FFP, median (interquartile range), %	0.0 (0.0,0.0)		

	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0,0.0)		
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0,0.0)		
	Increasing creatinine, No. (%)	2 (18.2)		
Period 4 (No Postoperative pulmonary edema, n = 1301; Postoperative pulmonary edema, n = 63)	Start time, median (IQR), hour	11.4 (7.0,17.1)	11.0 (8.8,16.0)	0.73
	Start time, median (interquartile range), hour	35.6 (31.1,41.2)	34.2 (30.9,37.5)	0.08
	End time, median (interquartile range), hour	106.1 (68.3,163.5)	111.1 (77.9,158.9)	0.29
	Total Fluid, median (interquartile range), %	4.6 (2.8,7.2)	5.0 (3.7,7.7)	0.09
	Total Fluid/hour, median (interquartile range), %/hour	0.0 (0.0,10.3)	9.5 (0.0,25.9)	<0.001
	Red blood cells, median (interquartile range), %	0.0 (0.0,7.0)	4.0 (0.0,17.9)	<0.001
	FFP, median (interquartile range), %	0.0 (0.0,0.4)	0.4 (0.0,1.5)	<0.001
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0,0.3)	0.2 (0.0,0.8)	<0.001
	FFP/hour, median (interquartile range), %/hour	198 (15.2)	16 (25.4)	0.03
Period 5 (No Postoperative pulmonary edema, n = 81; Postoperative pulmonary edema, n= 2)	Start time, median (interquartile range), hour	10.3 (5.1,15.7)	9.6 (9.2,10.0)	0.78
	End time, median (interquartile range), hour	58.5 (53.8,64.6)	55.9 (54.8,57.0)	0.49
	Total Fluid, median (interquartile range), %	89.2 (60.9,160.2)	124.3 (111.2,137.5)	0.53
	Total Fluid/hour,	2.0 (1.4,3.2)	2.7 (2.4,2.9)	0.43

	median (interquartile range), %/hour			
	Red blood cells, median (interquartile range), %	0.0 (0.0,10.7)	2.6 (1.3,4.0)	0.81
	FFP, median (interquartile range), %	0.0 (0.0,0.0)	1.8 (0.9,2.7)	0.53
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0,0.2)	0.1 (0.0,0.1)	0.81
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0,0.0)	0.0 (0.0,0.1)	0.53
	Increasing creatinine, No. (%)	1 (1.2)	0 (0.0)	>0.999
Period 6 (No Postoperative pulmonary edema, n = 1008; Postoperative pulmonary edema, n = 42)	Start time, median (interquartile range), hour	35.3 (30.9,40.9)	35.4 (30.9,41.5)	0.96
	End time, median (interquartile range), hour	59.0 (54.9,64.9)	58.2 (52.4,63.1)	0.21
	Total Fluid, median (interquartile range), %	178.7 (109.1,268.1)	166.5 (108.0,237.0)	0.46
	Total Fluid/hour, median (interquartile range), %/hour	7.7 (4.6,11.5)	6.9 (4.9,11.1)	0.79
	Red blood cells, median (interquartile range), %	0.0 (0.0,13.9)	11.6 (0.0,25.2)	0.001
	FFP, median (interquartile range), %	0.0 (0.0,8.3)	0.0 (0.0,14.4)	0.19
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0,0.6)	0.4 (0.0,1.2)	0.001
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0,0.4)	0.0 (0.0,0.6)	0.17
	Increasing creatinine, No. (%)	153 (15.2)	13 (31.0)	0.01

*Period 1: From end of anesthesia to 24 hours after anesthesia; Period 2: From end of anesthesia to 48 hours post anesthesia; Period 3: From end of anesthesia to 72 hours after anesthesia; Period 4: 24 hours after anesthesia to 48 hours after anesthesia; Period 5: 24 hours after anesthesia to 72 hours after anesthesia; Period 6: 48 hours after anesthesia to 72 hours after anesthesia

*Red blood cells, FFP, total fluid and estimated blood loss are expressed as ratio for average blood volume.

*FFP: fresh frozen plasma

Table 2. Demographic characteristics and clinical data in analysis of postoperative pulmonary edema with hypoxemia

Variable	No Postoperative pulmonary edema with hypoxemia (n = 1499)	Postoperative pulmonary edema with hypoxemia (n = 161)	P
Demographics			
Old Age, No. (%)	384 (25.6)	63 (39.1)	<0.001
Men, No. (%)	730 (48.7)	88 (54.7)	0.15
Obesity, No. (%)	46 (3.1)	6 (3.7)	0.65
Preoperative Clinical features			
Emergency, No. (%)	516 (34.4)	89 (55.3)	<0.001
American Society of Anesthesiologists physical status > 2, No. (%)	698 (46.6)	117 (72.7)	<0.001
Tobacco use, No. (%)	332 (22.1)	36 (22.4)	0.95
Brain trauma, No. (%)	183 (12.2)	24 (14.9)	0.33
Multiple fracture, No. (%)	106 (7.1)	19 (11.8)	0.03
Hyponatremia, No. (%)	195 (13.0)	21 (13.0)	0.99
Hypoalbuminemia, No. (%)	443 (29.6)	69 (42.9)	0.001
Glomerular filtration rate, median (interquartile range), mL/min/1.73m ²	94.1 (72.8-122.9)	83.7 (65.4-108.6)	<0.001
Intraoperative Clinical features			
General anesthesia, No. (%)	1445 (96.4)	160 (99.4)	0.05
Anesthesia time, median (interquartile range), hour	5.0 (3.5-6.9)	4.7 (2.8-7.2)	0.58
Acute abdomen surgery, No. (%)	97 (6.5)	26 (16.1)	<0.001
Aorta surgery, No. (%)	12 (0.8)	5 (3.1)	0.01
Brain surgery, No. (%)	319 (21.3)	35 (21.7)	0.89
Spine surgery, No. (%)	235 (15.7)	25 (15.5)	0.96
Thoracic surgery, No. (%)	41 (2.7)	6 (3.7)	0.47
Massive transfusion, No. (%)	35 (2.3)	25 (15.5)	<0.001
Urine output ≤ 0.5ml/kg/hour, No. (%)	154 (10.3)	21 (13.0)	0.28

Continuous inotropes use, No. (%)		279 (18.6)	62 (38.5)	<0.001
Red blood cells, median (interquartile range), %		23.7 (11.8-37.2)	34.6 (21.1-61.0)	<0.001
Red blood cells /hour, median (interquartile range), %/hour		4.6 (1.9-8.0)	6.9 (3.8-16.7)	<0.001
FFP, median (interquartile range), %		0.0 (0.0-10.1)	9.7 (0.0-18.6)	<0.001
FFP/hour, median (interquartile range), %/hour		0.0 (0.0-2.1)	1.9 (0.0-5.4)	<0.001
Total fluid, median (interquartile range), %		113.6 (87.8-146.9)	126.9 (91.9-178.0)	0.02
Total fluid/hour, median (interquartile range), %		22.8 (17.3-31.6)	26.5 (18.0-40.1)	0.02
Estimated blood loss, median (interquartile range), %		54.3 (45.5-72.6)	66.7 (51.0-104.2)	<0.001
Postoperative clinical features				
Patient controlled analgesia, No. (%)		979 (65.3)	83 (51.6)	0.001
Time-varying postoperative clinical features				
Period 1 (No Postoperative pulmonary edema with hypoxemia, n = 1275; Postoperative pulmonary edema with hypoxemia, n = 72)	Start time, median (interquartile range), hour	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	>0.999
	End time, median (interquartile range), hour	9.9 (3.3, 15.3)	1.3 (0.8, 7.1)	<0.001
	Total Fluid, median (interquartile range), %	27.1 (5.4, 54.5)	0.9 (0.0, 22.4)	<0.001
	Total Fluid/hour, median (interquartile range), %/hour	2.7 (1.1, 4.5)	0.3 (0.0, 2.8)	<0.001
	Red blood cells, median (interquartile range), %	0.0 (0.0, 0.0)	0.0 (0.0, 7.1)	0.001
	FFP, median (interquartile range), %	0.0 (0.0, 0.0)	0.0 (0.0, 5.3)	0.004
	Red blood	0.0 (0.0, 0.0)	0.0 (0.0, 1.7)	<0.001

	cells/hour, median (interquartile range), %/hour			
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0, 0.0)	0.0 (0.0, 0.6)	0.002
	Increasing creatinine, No. (%)	99 (7.8)	11 (15.3)	0.02
Period 2 (No Postoperative pulmonary edema with hypoxemia, n = 148; Postoperative pulmonary edema with hypoxemia, n = 42)	Start time, median (interquartile range), hour	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	>0.999
	End time, median (interquartile range), hour	37.2 (31.3, 41.6)	35.3 (30.0, 39.6)	0.12
	Total Fluid, median (interquartile range), %	102.3 (70.7, 150.7)	102.9 (54.0, 145.5)	0.76
	Total Fluid/hour, median (interquartile range), %/hour	2.9 (1.9, 4.1)	2.8 (1.6, 4.4)	0.93
	Red blood cells, median (interquartile range), %	0.0 (0.0, 7.4)	0.0 (0.0, 21.2)	0.05
	FFP, median (interquartile range), %	0.0 (0.0, 0.0)	7.9 (0.0, 21.6)	<0.001
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0, 0.2)	0.0 (0.0, 0.6)	0.04
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0, 0.0)	0.3 (0.0, 0.6)	<0.001
	Increasing creatinine, No. (%)	17 (11.5)	19 (45.2)	<0.001
Period 3 (No Postoperative pulmonary edema with hypoxemia, n =	Start time, median (interquartile range), hour	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	>0.999

86; Postoperative pulmonary edema with hypoxemia n = 21)	End time, median (interquartile range), hour	59.1 (55.3, 64.8)	57.2 (54.5, 61.2)	0.20
	Total Fluid, median (interquartile range), %	132.7 (75.9, 222.2)	198.8 (118.1, 279.2)	0.05
	Total Fluid/h, median (interquartile range), %/hour	4.3 (0.0, 21.7)	38.5 (10.0, 82.3)	0.04
	Red blood cells, median (interquartile range), %	2.2 (1.3, 3.8)	3.4 (2.1, 5.0)	0.01
	FFP, median (interquartile range), %	0.1 (0.0, 0.3)	0.6 (0.2, 1.4)	0.01
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0, 14.0)	11.0 (0.0, 44.0)	0.01
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0, 8.5)	8.3 (0.0, 40.0)	0.01
	Increasing creatinine, No. (%)	9 (10.5)	7 (33.3)	0.01
Period 4 (No Postoperative pulmonary edema with hypoxemia, n = 583; Postoperative pulmonary edema with hypoxemia, n = 0)	Start time, median (interquartile range), hour	11.4 (5.6, 16.0)		
	End time, median (interquartile range), hour	36.9 (31.9, 40.8)		
	Total Fluid, median (interquartile range), %	116.0 (78.3, 178.2)		
	Total Fluid/hour, median (interquartile range), %/hour	0.0 (0.0, 20.7)		
	Red blood cells, median	4.6 (3.0, 7.4)		

	(interquartile range), %			
	FFP, median (interquartile range), %	0.0 (0.0, 0.8)		
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0, 10.2)		
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0, 7.9)		
	Increasing creatinine, No. (%)	71 (12.2)		
Period 5 (No Postoperative pulmonary edema with hypoxemia, n = 148; Postoperative pulmonary edema with hypoxemia, n= 12)	Start time, median (interquartile range), hour	10.5 (5.5, 15.5)	9.4 (7.1, 16.9)	0.66
	End time, median (interquartile range), hour	60.0 (55.6, 64.3)	59.5 (55.1, 63.2)	0.77
	Total Fluid, median (interquartile range), %	137.2 (79.0, 211.5)	227.4 (186.0, 284.8)	0.003
	Total Fluid/hour, median (interquartile range), %/hour	0.0 (0.0, 16.9)	22.3 (0.0, 41.4)	0.003
	Red blood cells, median (interquartile range), %	2.8 (1.7, 4.4)	5.0 (3.5, 5.9)	0.39
	FFP, median (interquartile range), %	0.0 (0.0, 0.4)	0.5 (0.0, 0.9)	0.03
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0, 13.9)	5.9 (0.0, 14.0)	0.32
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0, 5.2)	6.8 (0.0, 24.2)	0.03

	Increasing creatinine, No. (%)	14 (9.5)	5 (41.7)	0.001
Period 6 (No Postoperative pulmonary edema with hypoxemia, n = 384; Postoperative pulmonary edema with hypoxemia, n = 14)	Start time, median (interquartile range), hour	37.3 (32.2, 41.3)	36.6 (32.9, 38.6)	0.63
	End time, median (interquartile range), hour	60.9 (55.6, 65.6)	60.1 (57.3, 63.2)	0.61
	Total Fluid, median (interquartile range), %	204.7 (125.8, 297.4)	172.5 (135.9, 218.7)	0.58
	Total Fluid/hour, median (interquartile range), %/hour	7.5 (0.0, 29.0)	30.1 (15.6, 68.9)	0.56
	Red blood cells, median (interquartile range), %	8.6 (5.3, 12.8)	7.1 (5.5, 9.0)	>0.999
	FFP, median (interquartile range), %	0.3 (0.0, 1.3)	1.4 (0.5, 2.8)	0.27
	Red blood cells/hour, median (interquartile range), %/hour	0.0 (0.0, 14.0)	18.4 (14.7, 37.0)	>0.999
	FFP/hour, median (interquartile range), %/hour	0.0 (0.0, 13.3)	2.6 (0.0, 22.9)	0.30
	Increasing creatinine, No. (%)	47 (12.2)	4 (28.6)	0.07

*Period 1: From end of anesthesia to 24 hours after anesthesia; Period 2: From end of anesthesia to 48 hours post anesthesia; Period 3: From end of anesthesia to 72 hours after anesthesia; Period 4: 24 hours after anesthesia to 48 hours after anesthesia; Period 5: 24 hours after anesthesia to 72 hours after anesthesia; Period 6: 48 hours after anesthesia to 72 hours after anesthesia

*Red blood cells, FFP, total fluid and estimated blood loss are expressed as ratio for average blood volume.

*FFP: fresh frozen plasma

Table 3. Adjusted hazard ratio of all variables for postoperative pulmonary edema occurrence

	Hazard ratio	Lower 95% confidence interval	upper 95% confidence interval	p
Old age	1.13	0.96	1.32	0.13
Male	1.04	0.90	1.21	0.56
Obesity	0.95	0.65	1.37	0.78
Emergency	1.09	0.93	1.27	0.30
American Society of Anesthesiologists physical status > 2	1.09	0.94	1.27	0.24
Anesthesia time	1.00	0.98	1.03	0.77
Anesthesia	1.43	0.91	2.24	0.12
Patient controlled analgesia	1.01	0.87	1.19	0.85
Tabaco use	0.96	0.81	1.14	0.65
Brain Trauma	0.96	0.77	1.19	0.73
Multiple fracture	1.09	0.84	1.41	0.52
Acute abdomen surgery	1.01	0.77	1.31	0.96
Aorta surgery	0.85	0.52	1.38	0.50
Brain surgery	0.93	0.77	1.12	0.42
Spine surgery	1.23	1.00	1.52	0.05
Thoracic surgery	1.05	0.72	1.52	0.80
Massive transfusion	1.24	0.87	1.77	0.24
Estimated blood loss	1.00	1.00	1.00	0.99
Intraoperative inotropes	1.04	0.88	1.24	0.62
Preoperative hyponatremia	0.94	0.76	1.16	0.57
Preoperative. hypoalbuminemia	1.10	0.94	1.28	0.25

FFP: fresh frozen plasma

Table 4. Adjusted hazard ratio of all variables for postoperative pulmonary edema with hypoxemia occurrence

	Hazard ratio	Lower 95% confidence interval	upper 95% confidence interval	p
Old age	1.27	1.03	1.58	0.03
Male	1.02	0.84	1.23	0.86
Obesity	1.10	0.62	1.93	0.74
Emergency	1.14	0.93	1.40	0.21
American Society of Anesthesiologists physical status > 2	1.24	1.02	1.50	0.03
Anesthesia time	1.01	0.97	1.04	0.73
Anesthesia	1.37	0.78	2.43	0.27
Patient controlled analgesia	0.92	0.75	1.13	0.41
Tabaco use	1.01	0.80	1.26	0.96
Brain Trauma	0.96	0.73	1.26	0.75
Multiple fracture	1.08	0.76	1.53	0.67
Acute abdomen surgery	1.10	0.78	1.55	0.58
Aorta surgery	1.49	0.66	3.41	0.34
Brain surgery	0.95	0.75	1.20	0.67
Spine surgery	1.12	0.85	1.48	0.42
Thoracic surgery	1.01	0.58	1.74	0.98
Massive transfusion	1.59	0.97	2.62	0.07
Estimated blood loss	1.00	1.00	1.00	0.95
Intraoperative inotropes	1.12	0.89	1.41	0.35
Preoperative hyponatremia	1.04	0.79	1.38	0.77
Preoperative. hypoalbuminemia	1.17	0.95	1.43	0.13

FFP: fresh frozen plasma

Figures

Hazard ratio (95% confidence interval)

Figure 1

Unadjusted and adjusted hazard ratio for postoperative pulmonary edema occurrence FFP: fresh frozen plasma

Hazard ratio (95% confidence interval)

Figure 1

Unadjusted and adjusted hazard ratio for postoperative pulmonary edema occurrence FFP: fresh frozen plasma

Hazard ratio (95% confidence interval)

Figure 1

Unadjusted and adjusted hazard ratio for postoperative pulmonary edema occurrence FFP: fresh frozen plasma

Hazard ratio (95% confidence interval)

Figure 2

Unadjusted and adjusted hazard ratio for occurrence of postoperative pulmonary edema with hypoxemia
FFP: fresh frozen plasma

Hazard ratio (95% confidence interval)

Figure 2

Unadjusted and adjusted hazard ratio for occurrence of postoperative pulmonary edema with hypoxemia
FFP: fresh frozen plasma

Hazard ratio (95% confidence interval)

Figure 2

Unadjusted and adjusted hazard ratio for occurrence of postoperative pulmonary edema with hypoxemia
FFP: fresh frozen plasma