

# Early Fresh Frozen Plasma Transfusion: Can It Improve the Outcomes of Patients With Sepsis?

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## Research

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# Abstract

**Background:** So far, no study has investigated the effects of plasma transfusion in septic patients, especially in terms of prognosis. Therefore, our purpose is to explore the association of early fresh frozen plasma (FFP) transfusion with the outcomes of septic patients.

**Methods:** We performed a cohort study using data extracted from the Medical Information Mart for Intensive Care (MIMIC) database (v1.4). External validation was obtained from the First Affiliated Hospital of Wenzhou Medical University, China. We adopted the Sepsis-3 criteria to extract patients with sepsis and septic shock. The occurrence of infusion during the first 3 days of intensive care unit stay was regarded as early FFP transfusion. The primary outcome was 28-day mortality. We assessed the association of early FFP transfusion with patient outcomes using cox regression analysis. Furthermore, we performed sensitivity analysis, subset analysis and external validation to verify the true strength of the results.

**Results:** After adjusting for the covariates in 3 models respectively, the significantly higher risk of death in the FFP transfusion group at 28 days (e.g. Model 2: HR = 1.361, P = 0.018, 95% CI = 1.054–1.756) and 90 days (e.g. Model 2: HR = 1.368, P = 0.005, 95% CI = 1.099–1.704) remained distinctly. Contrarily, the mortality increased significantly with the increase of FFP transfusion volume. The outcomes of septic patients with low coagulation after early FFP transfusion were not significantly improved. Similar results can also be found in subset analysis of septic shock cohort. The results of external validation exhibited good consistency.

**Conclusions:** Our study provides new understanding of the rationale and effectiveness of FFP transfusion for septic patients. After recognizing the evidences of risk-benefit and cost-benefit, it is important to reduce the inappropriate use of FFP and avoid unnecessary adverse transfusion reactions.

## Background

Sepsis, a syndrome of pathophysiological abnormalities and severe organ dysfunction induced by infection, lead to high incidence and mortality rates worldwide [1,2,3,4]. Since 2002, the Surviving Sepsis Campaign has made a highly successful international effort to decrease sepsis mortality by the therapeutic strategies of bundle elements [5]. In its 2018 update, it is believed that early effective fluid therapies with intravenous injection are crucial for the stabilization of sepsis-induced tissue hypoperfusion [6]. The ideal fluid management in sepsis should improve euvoolemia without causing edema, potentially by rebuilding the damaged endothelial glycocalyx layer and repairing the injured endothelium [7]. Crystalloids are recommended as first-line therapy, however, the benefit following the administration of colloids compared with crystalloids in septic patients remains unclear [6,7,8].

Plasma, as a “super-colloid”, is rich of proteins, including albumin, coagulation factors, fibrin, immunoglobulins, antithrombin, Protein C and S [9]. The studies regarding the effects of plasma transfusion in critically ill patients are limited, and the conclusions have not reached an agreement. Much of what we know about plasma-based fluid management comes from studies performed in the setting of

trauma. Early plasma transfusion instead of other blood products has been associated with decreased mortality in trauma patients [10,11]. In traditional clinical practice, critically ill patients who have abnormal coagulation may benefit from plasma transfusion at intensive care unit (ICU) admission. However, Dara SI et al. considered that the risk-benefit ratio of FFP transfusion in critically ill patients with coagulopathy may not be favorable [12]. This contradiction may attribute to adverse effects accompanied by plasma transfusion in aspects of infections, immunomodulation, allergic reactions, circulatory overload and citrate toxicity [13].

As no previous studies for reference, the effects of plasma transfusion in septic patients remain unknown. Therefore, our purpose is to explore the potential relationship of early fresh frozen plasma (FFP) transfusion with the outcomes of septic patients at ICU admission. Furthermore, we hypothesize that early FFP transfusion does not benefit the short-term survival of most patients with sepsis.

## Methods

### Data source

We performed a retrospective cohort study using data extracted from the Medical Information Mart for Intensive Care (MIMIC) database (v1.4) which integrated deidentified and comprehensive clinical data of patients admitted to the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts [14]. MIMIC III database contains over 58000 hospital admissions data for adult patients and neonates admitted to various critical care units between 2001 and 2012. The Institutional Review Board of the BIDMC (Boston, MA, USA) and Massachusetts Institute of Technology (Cambridge, MA, USA) have approved the use of MIMIC III database for authorized users. Wei Zhou was allowed to download data from the database, having completed the “Data or Specimens Only Research” course (record identity: 25222342).

External validation was collected from the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China) after approval from that institution’s Ethical Committee.

Informed consents of all patients were not required because the present study neither contained any protected health information nor impacted clinical care.

### Study cohort

A flowchart of the inclusion and exclusion procedure for the MIMIC III was depicted in Figure 1. We adopted the third international consensus definitions (Sepsis-3, a diagnosis flowchart was presented in Figure S1) to extract patients with sepsis and septic shock from the database [1]. Based on the Sepsis-3 criteria, patients with suspected infection and evidence of organ dysfunction [Sequential Organ Failure Assessment (SOFA) score  $\geq 2$ ] were identified as septic patients [1]. Suspected infection was defined as the concomitant administration of antibiotics and sampling of body fluid cultures (blood, urine, sputum, etc) [1]. In other words, if the culture was obtained, the antibiotic was required to be administered within

72 hours, whereas if the antibiotic was first, the culture was required within 24 hours [1]. Moreover, we defined the period of suspected infection as ranging between 24 hours before and 24 hours after admission to an ICU. Patients in the CareVue and MetaVision information systems of MIMIC III were admitted before and after 2008, respectively. Only patient data stored in the MetaVision system were collected for analysis. Antibiotic prescription data were only available after 2002, thus, there was a fraction (1/7) of the CareVue patients who had missing data for the suspected infection definition. It was the simplest option for us to limit the cohort to the MetaVision system, because the resulting sample size was sufficient. Additionally, the exclusion criteria for the initial sepsis cohort were as follows: (1) repeat hospitalization at ICU, (2) aged 16 years or younger, and (3) current service relating to cardiac, vascular or thoracic surgery. We assumed that these sub-populations had physiological abnormalities yet caused by factors unrelated to sepsis. Furthermore, we excluded the patients who had incomplete covariate data for further multivariate analysis.

External validation data were collected between September 15, 2018 and December 31, 2020 according to the same inclusion and exclusion criteria. The main diagnosis of these patients clearly met the Sepsis-3 criteria within 24 hours of ICU admission. The clinical outcomes were followed up for 90 days after admission (13 patients were excluded due to loss to follow-up).

## Data extraction

The data were extracted from MIMIC III and our hospital system, including gender, age, laboratory data, vital statistics, comorbidities, ICU interventions, and hospital length of stay (LOS). Severity scores of illness including Simplified Acute Physiology Score 2 (SAPS 2), Acute Physiology and Chronic Health Evaluation 2 (APACHE 2) and SOFA were calculated on the basis of their predefined criteria [15,16,17]. The mean values of laboratory data and vital statistics during the first 24 hours of ICU stay were regarded as baseline data. The scores of Glasgow coma scale (GCS), SAPS 2, APACHE 2 and SOFA as well as the necessity to perform interventions with vasopressor and mechanical ventilation were evaluated during the first 24 hours of ICU stay. Additionally, SAPS 2 and APACHE 2 were used for MIMIC III and external validation data analysis, respectively.

## Predictor and outcome variables

We recorded the FFP transfusion status of each patient during the first 3 days of their ICU stays. To minimize the potential bias, the values of international normalized ratio (INR) and partial thromboplastin time (PTT) were obtained before FFP transfusion.

The primary end point was 28-day mortality. The secondary end points were 90-day and in-hospital mortality. Mortality information in the MIMIC III was calculated based on the dates of admission and death obtained from social security records.

## Statistical analysis

Kolmogorov-Smirnov normality test was used to check the normality assumption for numerical variables. Differences in the normally and non-normally distributed variables were compared using the unpaired Student's t-test and Wilcoxon rank-sum test, respectively. Comparisons for categorical variables were performed by Pearson  $\chi^2$  test and Fisher exact test. Normally distributed data were expressed as the means with standard deviations, and non-normally distributed data were expressed as the medians with inter-quartile ranges (IQRs). Categorical variables were expressed as frequencies with percentages.

We assessed the association of early FFP transfusion with survival in septic patients using logistic regression and Kaplan-Meier (K-M) analysis. The results were presented in form of odds ratios (ORs) with 95% confidence intervals (CIs) and survival curve, respectively.

For the cox regression analysis, 3 multivariate models were constructed as follows: Model 1, adjusting only for gender and age; Model 2, adjusting for gender, age, and scores of SAPS 2 (APACHE 2 for external validation) and SOFA; Model 3, adjusting for gender, age, laboratory data (white blood cell, platelet, hemoglobin, lactate and creatinine), vital statistics (heart rate, mean blood pressure, respiration rate, temperature, pulse oxygen saturation and glucose), scores of GCS, SOFA and SAPS 2 (APACHE 2 for external validation), ICU interventions (vasopressor, mechanical ventilation and renal replacement therapy), history of alcohol abuse, comorbidities, and hospital LOS. The hazard ratios (HRs) and 95% CIs were calculated for these models.

Sensitivity analysis was performed to further validate the effects of early FFP transfusion in septic patients with low coagulation and non-low coagulation status. Moreover, subset analysis was performed for patients with FFP transfusion ( $N = 288$ ) to evaluate the relationship between infusion volume of FFP and survival. Subsequently, we performed an additional subset analysis to establish whether similar results also existed in septic shock cohort ( $N = 625$ ). Finally, external validation was introduced to verify whether similar results can be observed in the East Asian population.

A two-sided P-value  $< 0.05$  was regarded as representing statistical significance. Statistical analyses were performed using SPSS software 20.0 (SPSS, Chicago, IL, USA) and MedCalc software 19.0.5 (MedCalc, Ostend, Belgium).

## Results

### Baseline data of study cohort

A total of 3629 septic patients from the MIMIC-2 database were included in final sepsis cohort (Fig. 1). The Baseline characteristics of final sepsis cohort were summarized in Table 1. The median infusion volume in FFP transfusion group was 627 mL (IQR: 532–1169 mL). Additionally, baseline laboratory data and vital statistics for further multivariate analysis were showed in Table 2.

Table 1  
Baseline characteristics of study cohort

Characteristics	Total	FFP transfusion	Non-FFP transfusion
	(N = 3629)	(N = 288)	(N = 3341)
Gender (men/women)	2023/1606	182/106	1841/1500**
Age (years)	66.6 (53.8–79.7)	68.4 (54.4–80.6)	66.4 (53.8–79.6)
≤ 30, n (%)	175 (4.8)	10 (3.5)	165 (4.9)
> 30, ≤ 60, n (%)	1132 (31.2)	87 (30.2)	1045 (31.3)
> 60, n (%)	2322 (64.0)	191 (66.3)	2131 (63.8)
Alcohol abuse, n (%)	388 (10.7)	41 (14.2)	347 (10.4)*
Culture specimen types			
Blood, n (%)	1572 (43.3)	109 (37.8)	1463 (43.8)
Lung, n (%)	122 (3.4)	8 (2.8)	114 (3.4)
Urinary system, n (%)	610 (16.8)	49 (17.0)	561 (16.8)
Gastrointestinal system, n (%)	11 (0.3)	0 (0)	11 (0.3)
Others, n (%)	1314 (36.2)	122 (42.4)	1192 (35.7)*
Culture positive, n (%)	476 (13.1)	46 (16.0)	430 (12.9)
Vasopressor (first 24 hours), n (%)	1082 (29.8)	101 (35.1)	981 (29.4)*
Mechanical ventilation (first 24 hours), n (%)	1884 (51.9)	177 (61.5)	1707 (51.1)**
Renal replacement therapy, n (%)	173 (4.8)	27 (9.4)	146 (4.4)**
GCS score	15 (13–15)	15 (14–15)	15 (13–15)**
SOFA score	5 (3–6)	6 (4–7)	4 (3–6)**
SAPS  score	37.0 (30.0–46.0)	40.5 (34.0–50.0)	37.0 (29.0–46.0)**
Comorbidities			

\* P-value < 0.05; \*\* P-value < 0.01. Data were expressed as median (inter-quartile range) or frequency (percentage). FFP, fresh frozen plasma; GCS, Glasgow coma scale; LOS, length of stay; SAPS , Simplified Acute Physiology Score ; SOFA, Sequential Organ Failure Assessment.

Characteristics	Total	FFP transfusion	Non-FFP transfusion
	(N = 3629)	(N = 288)	(N = 3341)
Congestive heart failure, n (%)	850 (23.4)	72 (25.0)	778 (23.3)
Cardiac arrhythmias, n (%)	1089 (30.0)	135 (46.9)	954 (28.6)**
Hypertension, n (%)	2140 (59.0)	159 (55.2)	1981 (59.3)
Chronic pulmonary, n (%)	788 (21.7)	55 (19.1)	733 (21.9)
Renal failure, n (%)	634 (17.5)	55 (19.1)	579 (17.3)
Liver disease, n (%)	347 (9.6)	57 (19.8)	290 (8.7)**
Solid tumor, n (%)	231 (6.4)	23 (8.0)	208 (6.2)
Diabetes, n (%)	1043 (28.7)	78 (27.1)	965 (28.9)
Hospital LOS (days)	7.7 (4.9–12.7)	10.4 (6.2–16.5)	7.6 (4.8–12.4)**

, P-value < 0.05; \*\*, P-value < 0.01. Data were expressed as median (inter-quartile range) or frequency (percentage). FFP, fresh frozen plasma; GCS, Glasgow coma scale; LOS, length of stay; SAPS , Simplified Acute Physiology Score ; SOFA, Sequential Organ Failure Assessment.

Table 2  
Baseline laboratory data and vital statistics

Parameters	FFP transfusion	Non-FFP transfusion
	(N = 288)	(N = 3341)
<b>Laboratory data</b>		
WBC ( $10^9/L$ )	11.3 (7.9–15.2)	11.6 (8.4–15.6)
Platelet ( $10^9/L$ )	166.3 (108.8–240.0)	209.7 (153.0–277.7)**
Hemoglobin (g/dL)	10.1 (9.0–11.5)	10.9 (9.6–12.3)**
Lactate (mmol/L)	2.2 (1.6–3.2)	1.8 (1.3–2.5)**
Creatinine (mg/dL)	1.1 (0.8–1.6)	1.0 (0.8–1.5)*
PTT (s)	34.1 (28.6–43.1)	28.3 (25.0–33.4)**
INR	1.8 (1.4–2.8)	1.2 (1.1–1.4)**
<b>Vital statistics</b>		
Heart rate (bpm)	89.2 (75.1–100.4)	87.2 (76.0–98.8)
Mean blood pressure (mmHg)	74.7 (69.8–82.9)	75.7 (69.5–83.3)
Respiration rate (times/min)	18.7 (16.4–21.6)	19.0 (16.6–22.1)
Temperature (°C)	36.7 (36.3–37.2)	36.8 (36.5–37.3)**
SpO <sub>2</sub> (%)	97.8 (96.2–99.1)	97.3 (95.9–98.6)**
Glucose (mg/dL)	138.2 (112.8–166.4)	133.3 (112.3–163.1)

\* , P-value < 0.05; \*\* , P-value < 0.01. Data were expressed as median (inter-quartile range). FFP, fresh frozen plasma; INR, international normalized ratio; PTT, partial thromboplastin time; SpO<sub>2</sub>, pulse oxygen saturation; WBC, white blood cell.

Comparison of baseline characteristics of initial sepsis cohort vs. final sepsis cohort was presented in Table S1. Similar baseline data were found between the two cohorts.

### Associations of early FFP transfusion with primary and secondary outcomes

The rates of 28-day, 90-day and in-hospital mortality of two groups were as follows: FFP transfusion group = 24.3%, 32.6%, 22.2%, respectively, and non-FFP transfusion group = 14.7%, 20.3%, 11.1%, respectively. For the univariate logistic regression analysis, the mortality of FFP transfusion group was significantly higher than non-FFP transfusion group in 28-day, 90-day and in-hospital (OR = 1.859, P <

0.001, 95% CI = 1.397–2.474; OR = 1.907, P < 0.001, 95% CI = 1.470–2.474; OR = 2.287, P < 0.001, 95% CI = 1.698–3.081, respectively).

Moreover, based on K-M survival analysis of 28-day and 90-day, patients of non-FFP transfusion conferred more favourable prognosis than those of FFP transfusion (P < 0.001, both) (Fig. 2a,b).

### Multivariate analysis, sensitivity analysis and subset analysis

In clinical practice, patients with FFP transfusion are often more serious and accompanied by coagulation abnormalities, thus, multivariate analysis, sensitivity analysis and subset analysis still need to be performed to verify the true intrinsic relationship on the premise of excluding potentially relevant bias.

The actual associations of FFP transfusion with 28-day and 90-day mortality were evaluated by cox regression models. As shown in Table 3, after adjusting for the covariates of Model 1, Model 2 and Model 3 respectively, the significantly higher risk of death in the FFP transfusion group at 28 days and 90 days remained distinctly. Additionally, for the in-hospital mortality, a similar result can be found using multivariate logistic regression analysis (Model 1: OR = 2.282, P < 0.001, 95% CI = 1.685–3.091; Model 2: OR = 1.887, P < 0.001, 95% CI = 1.366–2.606; Model 3: OR = 1.899, P < 0.001, 95% CI = 1.350–2.672).

Sensitivity analysis on the basis of 2 different coagulation indexes was performed in our study. INR and PTT, representing exogenous and endogenous coagulation function respectively, were divided to non-low coagulation and low coagulation status according to upper limit of their normal range [18,19]. As presented in Table 4, after correcting for the same covariates (Model 2), the outcomes of septic patients with low coagulation after early FFP transfusion were not significantly improved in cox regression models. Contrarily, for patients with PTT ≤ 40, there was a statistically significant increasing trend for septic patients of early FFP transfusion in the risk of death at 28 days and 90 days.

The distribution of infusion volume in FFP transfusion group (N = 288) during the first 3 days of ICU stay was as follows: the lowest tertile range from 220 to 567 mL; the medium tertile from 567 to 926 mL; the highest tertile from 926 to 8148 mL. There seemed to be an increasing trend from the lowest tertile to the highest tertile in the risk of death at both 28 days (HR = 1.783, P = 0.055, 95% CI = 0.987–3.219) and 90 days (HR = 1.710, P = 0.035, 95% CI = 1.039–2.813) after correcting for the covariates of Model 2. Meanwhile, survival curves of the 3 groups were presented in Figure 3a,b. The detailed distribution of FFP transfusion volume was showed in Figure S2.

The comparison of baseline characteristics of septic shock cohort vs. sepsis cohort was summarized in Table S2. There were significant differences between septic shock cohort (N = 625) and sepsis cohort (N = 3629) in severity of disease (P < 0.001 for SOFA and SAPS Ⅱ, both). For the subset analysis of septic shock cohort (Table S3), early FFP transfusion can also not improve 28-day and 90-day survival, even in the low coagulation group. Similarly, no significant dose-effect relationship was found between infusion volume and prognosis.

## External validation

Baseline characteristics of external validation cohort ( $N = 294$ ) were presented in Table S4 and Table S5. New data collected from our hospital also led to similar results (Table 5) as in the primary analysis, indicating that even in the low coagulation group, early FFP transfusion can not improve the outcomes of patients with sepsis, even was unfavorable. Additionally, in the subset analysis of septic shock cohort (Table S6), early FFP transfusion can also not improve 28-day and 90-day survival. Contrarily, the mortality of high infusion volume was higher than that of low infusion volume.

## Discussion

The present study revealed that regardless of whether patients were in low coagulation or non-low coagulation, early FFP transfusion can not improve survival of 28-day, 90-day and in-hospital for patients with sepsis, even was unfavorable. Contrarily, both 28-day and 90-day mortality increased significantly with the increase of FFP transfusion volume. Additionally, for the subset analysis of septic shock, early FFP transfusion can also not improve 28-day and 90-day survival, even in the low coagulation group. Similarly, the results of external validation exhibited good consistency, which suggests the conclusions of our study have a certain generalization value.

Sepsis, a syndrome of immense clinical importance, accounts for high incidence, high mortality and high ICU admission rate in recent years [3,20,21]. The latest Sepsis-3 definition, replacing previous definitions of sepsis gradually, is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1,22]. Johnson AEW et al. performed a comparative analysis of sepsis identification methods in the MIMIC 3 database (v1.4), indicating that Sepsis-3 criteria had several advantages over previous methods as follows: (1) less susceptibility to coding practices changes, (2) provision of temporal context because of extracting sepsis cohort by suspected of infection with associated organ failure at a time point not by ICD-9 codes, and (3) more conform to the contemporary understanding of the pathophysiology of sepsis [23]. Therefore, it is appropriate to extract septic patients from the MIMIC 3 database via Sepsis-3 criteria.

Early effective fluid management is a mainstay in initial treatment of sepsis. The controversy for the effects of fluid therapies with colloids vs. crystalloids on mortality in septic patients has always attracted much attention. As lack of any clear benefit following the administration of colloids compared with crystalloids in septic patients, crystalloids are still recommended as first-line therapy [6]. However, a systematic review suggested that patients with severe sepsis might benefit from fluid therapies with albumin [24]. The relevant study on sepsis concerning plasma involved in fluid therapies has, to the best of our knowledge, not been previously reported.

Plasma, a biological product containing the acellular portion of blood after centrifugation or by plasmapheresis, has important clinical effects including volume expansion, correction of abnormal coagulation tests, and transfusion-associated immunomodulation [13]. The studies regarding the effects of plasma transfusion in critically ill patients are limited, and the conclusions have not reached an

agreement. Much of what we know about the effects of plasma transfusion comes from studies performed in the setting of trauma. With the deep understanding of trauma-induced coagulopathy, many studies advocated that early FFP transfusion of high ratio was associated with improved survival in severe traumatic patients [10,11,25,26]. However, as to systemic meningococcal disease, Busund R et al's study revealed that the use of FFP may negatively influence the outcomes [27]. Similarly, in critically ill children, plasma transfusion seemed to be independently associated with an increased occurrence of new or progressive multiple organ dysfunction syndrome, nosocomial infections, prolonged length of stay and risk of mortality [28,29]. Moreover, with regard to rat and foal models of sepsis, several studies discovered that plasma transfusion was beneficial for the survival of septic animals [30,31].

For the traditional clinical experience, critically ill patients with coagulation disorder may benefit from early FFP transfusion, thus, it is worthy to verify this hypothesis by the setting of sensitivity analysis with different coagulation indexes. Obviously, early FFP transfusion can not improve survival for septic patients with low coagulation in our study. Similarly, Dara SI et al's study also showed that the outcomes of FFP transfusion group in critically ill patients with coagulopathy had no statistically significant improvement [12]. Additionally, as failing to induce a more procoagulant state, Müller MC et al. didn't advocate FFP transfusion in non-bleeding critically ill patients with coagulopathy [32]. The prophylactic use of FFP before invasive procedures to correct abnormal INR or PTT has never been shown to reduce bleeding, because there is no correlation between coagulation tests and risk of bleeding [33,34]. These previous studies support our findings in a sense.

As to the septic shock, Nanna R et al's study showed that ICU mortality, 30-day mortality, 90-day mortality and 365-day mortality were comparable between FFP transfused and non-transfused patients [35], which was consistent with our results of subset analysis. Due to lack of sufficient references and guidelines, the role of FFP in fluid therapy of septic shock remains to be further studied.

In trauma patients, plasma can decrease edema-mediated and inflammatory-mediated complications which are detrimental processes that contribute to organ failure and increased mortality [36]. Several studies hypothesized that plasma also had the similar effects on sepsis, because sepsis produced trauma-like changes on the endothelial glycocalyx layer which was a matrix of membrane-bound glycoproteins and proteoglycans projecting from the luminal surface of endothelial cells [7]. However, as no definitive data that plasma mitigates endothelial injury in sepsis, it's too early to draw this conclusion. Contrarily, there may be factors in the donor plasma that are deleterious to the host. The passive transfusion of antileukocyte antibodies from alloimmunized donors and biological response modifiers accumulated during the storage of cellular blood products lead to the development of transfusion-related acute lung injury (TRALI) [37]. Several previous studies suggested that FFP transfusion for critically ill patients was associated with an increased risk of the development of TRALI, which was regarded as the most serious transfusion complication [37,38]. Moreover, FFP transfusion was associated with an increased risk of infection and systemic inflammatory response syndrome [39,40], thus, the double strike for septic patients may not conducive to the recovery of inflammatory response. In addition to TRALI and infection, there are other adverse reactions with FFP transfusion as follows: allergic reactions, febrile

reactions, citrate toxicity, circulatory overload, graft versus host disease and inhibitors against deficient proteins [41,42,43]. As we can imagine, FFP transfusion may not conducive to survival on septic patients when the effects of adverse reactions play a dominant role. As lack of relevant studies, the exact mechanisms remain to be elucidated.

Our study also has several limitations. First, there may existing potential bias caused by factors in FFP transfusion patients who tend to more serious. However, we adjusted severity scores of illness in Model 2 to eliminate the influence of confounding factors and make the research variables comparable. Second, our main study from MIMIC 2, due to its retrospective design, was vulnerable to selection bias as a result of the inclusion of only a single-center sample and the exclusion of patients with missing data. Moreover, this is a preliminary exploratory study, thus, further prospective studies are warranted to validate our findings via randomized controlled trial with different intervention groups.

## Conclusion

Through data analyses of dual centers and dual populations, the present study uncovered for the first time that even for septic patients with coagulopathy, early FFP transfusion can not improve the outcomes, even was unfavorable. Contrarily, the mortality increased significantly with the increase of FFP transfusion volume. Similar results can also be found in the subset analysis of septic shock cohort.

Significantly, our study provides new understanding of the rationale and effectiveness of FFP transfusion for septic patients in a different perspective. In the clinical practice, there may existing two misunderstandings that septic patients can benefit from early FFP transfusion as follows: (1) FFP can be used as a volume replacement, and (2) FFP should be used to correct abnormal INR or PTT even in non-bleeding patients who have no planned invasive procedures. After recognizing the evidences of risk-benefit and cost-benefit, it is important to reduce the inappropriate use of FFP and avoid unnecessary adverse transfusion reactions. However, it is too early to deny the role of plasma completely, further studies are warranted to explore guidelines for optimizing the rational use of FFP in septic patients.

## Abbreviations

APACHE 2, Acute Physiology and Chronic Health Evaluation 2; BIDMC, Beth Israel Deaconess Medical Center; CIs, confidence intervals; FFP, fresh frozen plasma; GCS, Glasgow coma scale; HRs, hazard ratios; ICU, intensive care unit; INR, international normalized ratio; IQRs, interquartile ranges; K-M, Kaplan-Meier; LOS, length of stay; MIMIC 2, Medical Information Mart for Intensive Care 2; ORs, odds ratios; PTT, partial thromboplastin time; SAPS 2, Simplified Acute Physiology Score 2; SOFA, Sequential Organ Failure Assessment; TRALI, transfusion-related acute lung injury.

## Declarations

### Ethics approval and consent to participate

The Institutional Review Board of the Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology have approved the use of the MIMIC III database. The study of external validation was approved by the Ethical Committee of the First Affiliated Hospital of Wenzhou Medical University. Requirement for individual patient consent was waived because all the studies did not impact clinical care and all protected health information was deidentified.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets used and analysed 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**

XYQ and WZ conceived and designed this study; WZ, XDZ and XH helped with the collection and assembly of data. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Not applicable.

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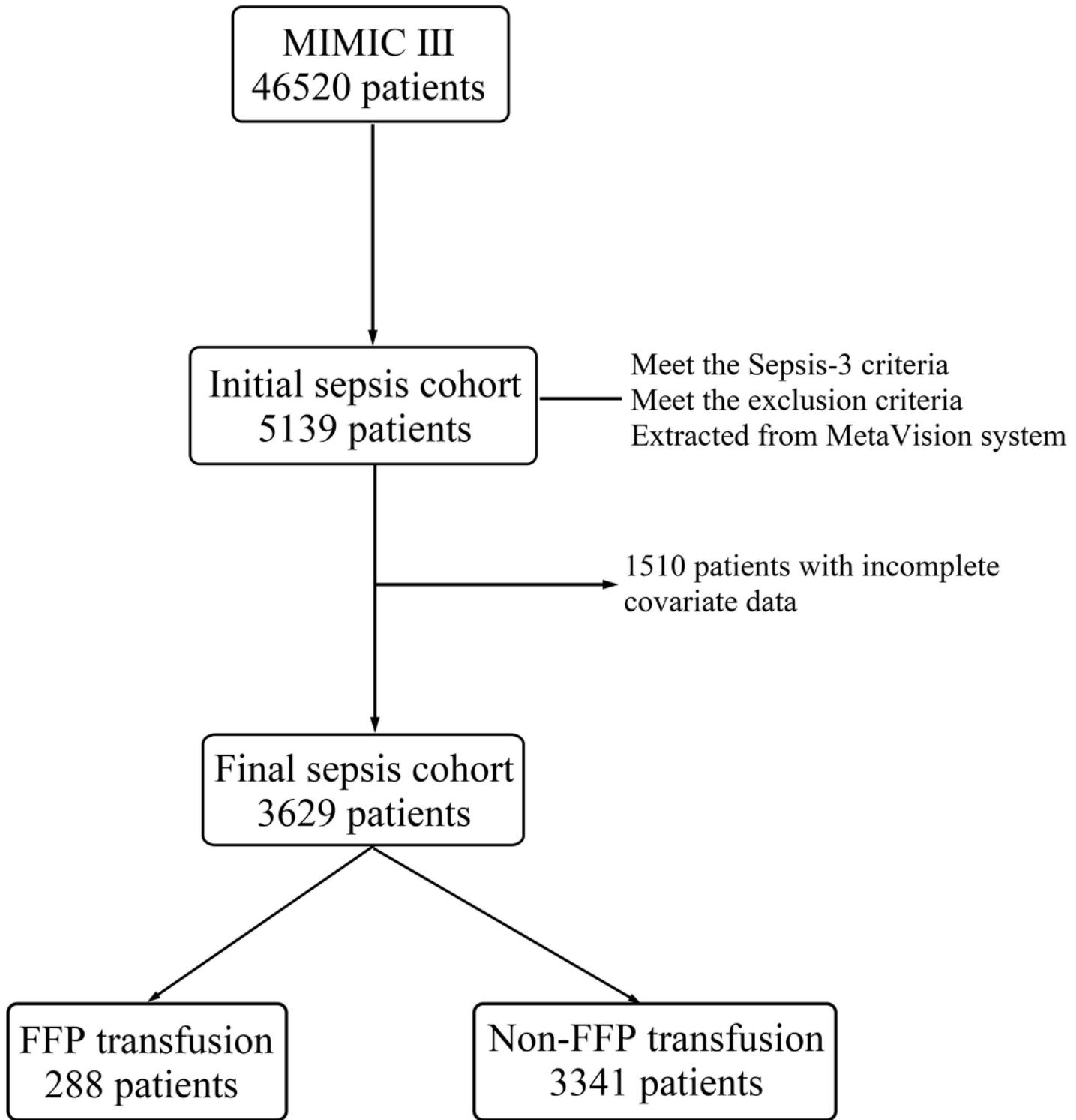
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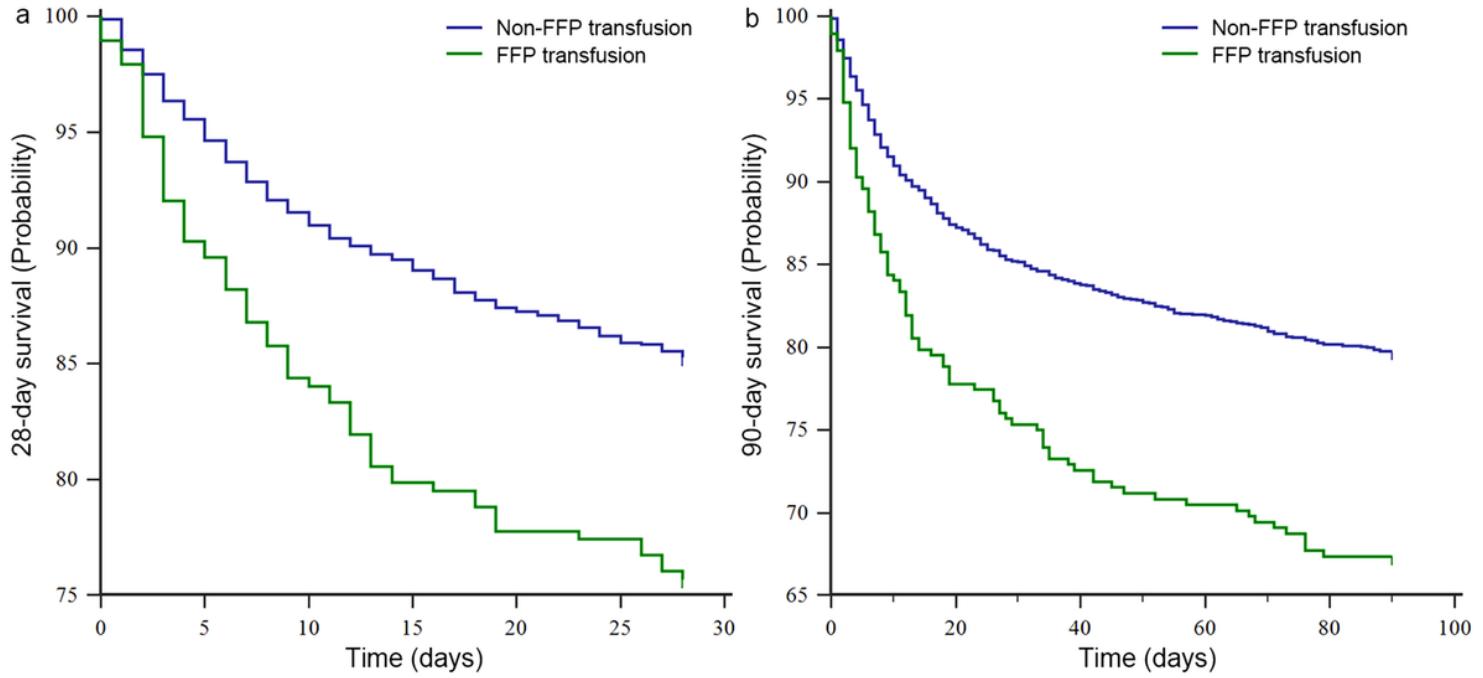
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## Figures



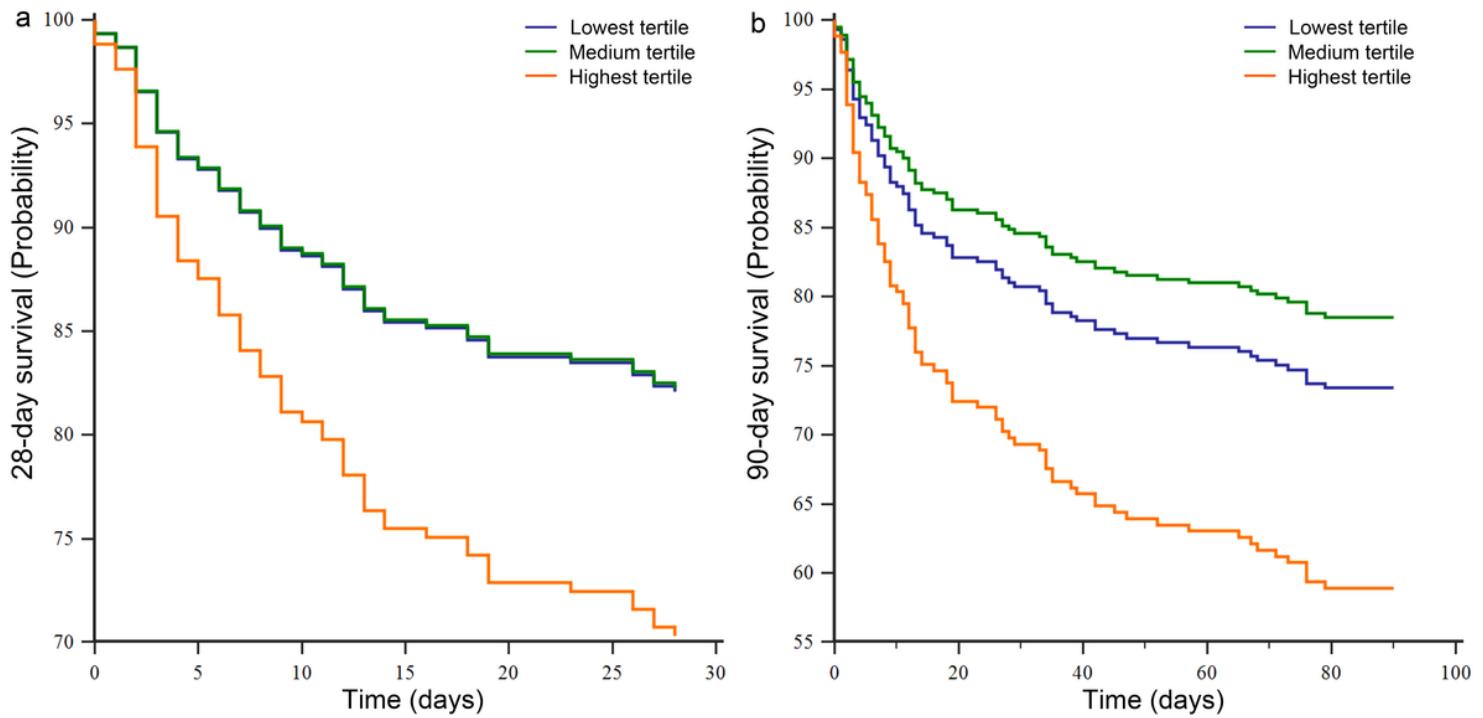
**Figure 1**

The flowchart of the inclusion and exclusion procedure for the MIMIC III database. FFP, fresh frozen plasma; MIMIC Ⅲ, Medical Information Mart for Intensive Care Ⅲ.



**Figure 2**

Kaplan-Meier survival analysis of sepsis cohort in the MIMIC III database. (a) 28-day survival curve and (b) 90-day survival curve. FFP, fresh frozen plasma; MIMIC, Medical Information Mart for Intensive Care.



**Figure 3**

Survival curves of cox regression analysis for subset analysis in the MIMIC III database. (a) 28-day survival curve and (b) 90-day survival curve. MIMIC, Medical Information Mart for Intensive Care.

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