



## Original article

# Dose-dependent mortality risk of plasma transfusion in critically ill patients

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## ABSTRACT

**Objectives:** Plasma transfusion is commonly used in intensive care units, often for non-bleeding indications despite limited evidence. This study aimed to evaluate the association between plasma transfusions and in-hospital mortality among critically ill patients.

**Methods:** A retrospective cohort study was conducted using data from 282 adult intensive care unit patients who received transfusion therapy between January and December 2020. Patients were grouped by their exposure to plasma transfusion and further by the transfusion volume. First, multivariable Cox regression coupled with propensity score matching was used to control for baseline confounders and quantify the independent association of plasma transfusion with in-hospital mortality. Subsequently, Cox models and Kaplan-Meier survival curves were employed to elucidate the dose-response relationship between transfusion volume and mortality risk, with additional subgroup analyses.

**Results:** In the unadjusted analysis, plasma transfusion was significantly associated with increased in-hospital mortality (Hazard ratio = 4.199; 95% confidence interval: 2.53–6.97; p-value <0.001). This association persisted after propensity score matching adjusted for key confounders (Hazard ratio = 3.271; 95% confidence interval: 1.30–8.21; p-value = 0.012). Kaplan-Meier survival analysis demonstrated significantly lower survival probabilities in the transfusion group (log-rank p-value <0.05). Furthermore, a dose-dependent relationship was revealed: mortality risk increased at higher volumes, reaching statistical significance at >800 mL (Hazard ratio = 4.09; 95% confidence interval: 1.19–14.04; p-value = 0.025). Subgroup analysis indicated that the elevated risk was particularly pronounced among patients who concurrently received red blood cell transfusions.

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*Conclusion:* Plasma transfusion is independently and dose-dependently associated with increased mortality in critically ill patients, particularly when used without clear indications. These findings support a restrictive, evidence-based approach, emphasizing correction of underlying coagulopathy over prophylactic transfusion. Strict adherence to guidelines and an individualized risk-benefit assessment are essential to improve patient safety.

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## Q3 Introduction

In the field of critical care medicine, transfusion therapy is frequently employed as a supportive treatment to address anemia, replenish blood volume, and correct coagulopathy [1]. The use of frozen plasma (FP) in intensive care units (ICUs) remains prevalent. Epidemiologic data from a recent large international multicenter study indicate that roughly 10% of critically ill patients receive plasma transfusions during their hospital stay, of which up to 37% are given for non-hemorrhagic indications [2]. This aligns with earlier observations from studies conducted in the UK, Australia, and other countries [3–5].

Several international guidelines [6–10] outline limited indications for FP use, such as active bleeding with coagulation factor deficiencies, plasma exchange, specific coagulopathies requiring replacement therapy, and massive transfusion protocols. However, the evidence supporting prophylactic FP use in critically ill patients remains limited and controversial [11]. Studies have shown that early high-ratio plasma transfusion (plasma-to-red-cell ratio  $\geq 1:2$ ) in patients undergoing massive transfusion can reduce mortality rates [12–14]. Conversely, research conducted in Hiroshima indicated that the lack of improvement in coagulation following FFP transfusion was independently and significantly associated with death within 28 days [15]. Additionally, Qin et al. found that early FFP transfusion in sepsis patients was significantly correlated with an increased risk of mortality [16].

Despite this, plasma transfusion remains prevalent in current clinical practice, with its potential risks often underestimated. A retrospective audit at a tertiary hospital revealed that up to 51.8% of plasma transfusions were administered outside of guideline recommendations, including unnecessary prophylactic use [17]. Such inappropriate transfusions waste limited blood resources and expose patients to a range of transfusion-related adverse effects [18,19].

Employing a retrospective cohort analysis, this study investigates the relationship between plasma transfusion dosage and mortality risk among critically ill patients. It aims to evaluate clinical outcomes to establish evidence-based risk thresholds and provide decision support for optimizing transfusion practices.

## Material and methods

### Study design

This single-center retrospective cohort study was conducted at Hunan Provincial People's Hospital (The First Affiliated

Hospital of Hunan Normal University), a tertiary Grade A general hospital directly under the Hunan Provincial Health Commission. As a regional medical center, it holds major responsibilities in clinical care, teaching, research, and the management of critically ill patients. Its comprehensive ICU is equipped with standard monitoring and life-support devices, serving a diverse population of critically ill medical and surgical patients. This setting provided an adequate case source for the study. The admitted cases were patients hospitalized in the ICU who received blood transfusion therapy from January 2020 to December 2020. This study was approved by the hospital's Ethics Committee.

### Inclusion and exclusion criteria

The inclusion criteria were age  $\geq 18$  years and ICU stay  $\geq 24$  h. Required core data items were available and complete in all medical records. These data comprised: (1) baseline demographic characteristics (sex, age) and disease severity (Acute Physiology and Chronic Health Evaluation II [APACHE II] score); (2) key pre-transfusion laboratory parameters (hemoglobin [Hb], prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen, among others); (3) detailed records of plasma and other blood product transfusions; and (4) in-hospital survival outcomes.

The exclusion criteria were patients aged  $< 18$  years, ICU stay  $< 24$  h (to minimize the inclusion of patients dying rapidly from their primary disease), and patients receiving plasma exchange. For patients with multiple ICU admissions, data collection was restricted to the hospitalization during which they received their first plasma transfusion.

After applying these criteria, 282 critically ill patients were included in the final cohort.

### Data collection

Plasma transfusion involves the administration of various plasma preparations, including fresh frozen plasma (FFP), frozen plasma (FP), cryoprecipitate-reduced plasma, and cold supernatant. Indications for plasma transfusion are categorized as prophylactic or therapeutic. Prophylactic transfusions correct coagulation abnormalities in non-bleeding patients or reduce perioperative bleeding risks in those undergoing invasive procedures or surgery. Therapeutic transfusions are primarily used for hemostatic support in actively bleeding patients, antithrombin III (AT3) supplementation, and plasma exchange. The indications for plasma transfusion applied in this study were based on

88 contemporary international guidelines [6,9], which align with  
89 current clinical practice in China.

90 Plasma transfusion is indicated in a range of critical  
91 clinical scenarios, including severe bleeding due to single  
92 or multiple coagulation factor deficiencies; dilutional coagulation  
93 following massive blood loss or transfusion; cases requiring emergent reversal of warfarin anticoagulation; heparin resistance associated with AT3 deficiency; disseminated intravascular coagulation (DIC); thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS); as well as in the setting of major trauma, extensive burns, and large-volume autologous blood salvage (>1000 mL in adults). Plasma transfusion is also utilized during therapeutic plasma exchange procedures.

103 Patients were divided into two groups, plasma transfusion  
104 group and no plasma transfusion group, according to whether  
105 they received plasma transfusion during hospitalization in  
106 the ICU. The following data were collected: demographic  
107 data, ICU hospitalization time, APACHE II score, blood transfusion  
108 data, and pre-transfusion laboratory tests, including  
109 Hb, C-reactive protein, procalcitonin, PT, APTT, fibrinogen,  
110 AT3 activity, total bilirubin, alanine aminotransferase (ALT),  
111 creatinine and others.

### Statistical analysis

112  
113 All analyses were conducted in Statistical Package for Social  
114 Sciences (SPSS) 25.0. For continuous variables, normally distributed  
115 data are summarized as means  $\pm$  standard deviation and compared using Student's t-test. Non-normally distributed data are reported as medians and interquartile range and compared using the Wilcoxon test. For categorical variables, data are presented as numbers (percentages) and compared using the Chi-square ( $\chi^2$ ) test.

121 First, multivariable Cox proportional hazards regression was performed on the overall cohort to identify risk factors for mortality and to estimate the unadjusted association between plasma transfusion and patient outcomes, reporting results as hazard ratios (HR) with 95% confidence intervals (95% CI). To better isolate the effect of plasma transfusion by minimizing baseline confounding and enhancing intergroup comparability, 1:1 propensity score matching (PSM) was subsequently performed. In the matched cohort, a Cox proportional hazards model (PSM model) was applied to re-evaluate the association between plasma transfusion and mortality risk. This model was further adjusted for key covariates (age, patient type, PT) to assess robustness. Survival probabilities were visualized using Kaplan-Meier curves, and the log-rank

**Table 1 – Baseline characteristics after propensity score matching.**

Variable	All (n = 110)	Plasma (n = 55)	Non-plasma (n = 55)	Z/ $\chi^2$	p-value
Sex				0.00 <sup>[3]</sup>	1.000
Male	68(61.8%)	34(61.8%)	34(61.8%)		
Female	42(38.2%)	21(38.2%)	21(38.2%)		
Age (years)	58.8 $\pm$ 16.1	57.4 $\pm$ 15.9	60.1 $\pm$ 16.3	0.89 <sup>[1]</sup>	0.373
Length of ICU stay (days)	12.3 $\pm$ 13.7	12.1 $\pm$ 12.7	12.5 $\pm$ 14.7	0.49 <sup>[2]</sup>	0.625
APACHE II score	23.6 $\pm$ 7.7	23.4 $\pm$ 7.1	23.8 $\pm$ 8.3	0.32 <sup>[1]</sup>	0.750
Patient category				0.93 <sup>[3]</sup>	0.335
Surgical care	63(57.3%)	34(61.8%)	29(52.7%)		
Medical care	47(42.7%)	21(38.2%)	26(47.3%)		
Sepsis				0.69 <sup>[3]</sup>	0.405
Yes	15(13.6%)	9(16.4%)	6(10.9%)		
No	95(86.4%)	46(83.6%)	49(89.1%)		
Hemoglobin (g/L)	77.2 $\pm$ 26.2	78.5 $\pm$ 27.5	75.8 $\pm$ 25.0	0.14 <sup>[2]</sup>	0.891
C-reactive protein (g/L)	113.0 $\pm$ 93.9	116.8 $\pm$ 91.4	109.1 $\pm$ 97.0	0.65 <sup>[2]</sup>	0.515
Procalcitonin (g/L)	17.9 $\pm$ 29.6	19.7 $\pm$ 30.9	16.0 $\pm$ 28.5	0.67 <sup>[2]</sup>	0.505
Prothrombin time (s)	14.5 $\pm$ 4.3	14.7 $\pm$ 5.0	14.2 $\pm$ 3.6	0.66 <sup>[2]</sup>	0.511
APTT (s)	36.5 $\pm$ 16.9	37.0 $\pm$ 13.2	36.0 $\pm$ 20.1	1.81 <sup>[2]</sup>	0.071
Fibrinogen (g/L)	3.9 $\pm$ 2.1	4.0 $\pm$ 2.1	3.8 $\pm$ 2.1	0.61 <sup>[2]</sup>	0.544
AT3 (%)	65.8 $\pm$ 20.7	66.3 $\pm$ 20.9	65.3 $\pm$ 20.7	0.14 <sup>[2]</sup>	0.888
Total bilirubin ( $\mu$ mol/L)	41.2 $\pm$ 54.6	39.7 $\pm$ 48.3	42.6 $\pm$ 60.6	0.04 <sup>[2]</sup>	0.971
ALT (U/L)	220.4 $\pm$ 763.9	177.2 $\pm$ 491.3	263.6 $\pm$ 965.8	0.93 <sup>[2]</sup>	0.351
Creatinine ( $\mu$ mol/L)	159.6 $\pm$ 162.5	171.0 $\pm$ 173.1	148.1 $\pm$ 152.0	0.13 <sup>[2]</sup>	0.893
RBC transfusion				1.23 <sup>[3]</sup>	0.268
Yes	83(75.5%)	39(70.9%)	44(80.0%)		
No	27(24.5%)	16(29.1%)	11(20.0%)		
Platelet transfusion				0.05 <sup>[3]</sup>	0.829
Yes	29(26.4%)	14(25.5%)	15(27.3%)		
No	81(73.6%)	41(74.5%)	40(72.7%)		
Cryo transfusion				0.79 <sup>[3]</sup>	0.376
Yes	13(11.8%)	5(9.1%)	8(14.5%)		
No	97(88.2%)	50(90.9%)	47(85.5%)		

ICU: Intensive care unit; APTT: activated partial thromboplastin time; ALT: Alanine aminotransferase; AT3: antithrombin III; Cryo: Cryoprecipitate.

Note:<sup>[1]</sup> = student t-test; <sup>[2]</sup> = Wilcoxon test; <sup>[3]</sup>.

135 test was used to compare survival between transfusion  
136 groups. A two-sided p-value <0.05 was considered statisti-  
137 cally significant.

## 138 Results

### 139 Baseline characteristics

140 A total of 282 critically ill patients met the inclusion criteria,  
141 of which 192 survived, accounting for 68.09% of the total num-  
142 ber. Baseline characteristics, including gender, age, duration  
143 of ICU stay, APACHE II score, and patient category, were simi-  
144 lar between the two groups. However, patients in the plasma  
145 transfusion group exhibited worse coagulation function (pro-  
146 longed PT and APTT; lower fibrinogen and AT3 levels), poorer  
147 liver function (elevated total bilirubin), and received more pla-  
148 telets and cryoprecipitate. They also had milder anemia  
149 (higher Hb levels), received fewer red blood cell (RBC) transfu-  
150 sions, and had a higher in-hospital mortality rate. PSM (1:1)  
151 yielded a final cohort of 110 patients for analysis. Comparison  
152 of the matched groups demonstrated no statistically signifi-  
153 cant differences in any baseline characteristics (all p-value  
154 >0.05) (Table 1).

### 155 Risk factors for mortality

156 The multivariable Cox regression results are presented in  
157 Table 2. Significant independent predictors of mortality were  
158 age (HR = 1.04 per year increase; p-value = 0.029), plasma  
159 transfusion (HR = 3.34; p-value = 0.017), and RBC transfusion

**Table 2 – Predictors of mortality by Cox regression analysis.**

Variable	Hazard Ratio	95% CI	p-value
Sex	1.03	0.68–1.56	0.948
Age (years)	1.04	1.03–1.06	0.029*
Patient category	0.13	0.07–0.23	0.002*
Length of ICU stay (days)	0.94	0.92–0.97	0.043*
APACHE II score	1.06	1.03–1.09	0.096
Sepsis	2.52	1.32–4.79	0.231
Hemoglobin (g/L)	1.00	0.98–1.01	0.883
C-reactive protein (g/L)	1.00	1.00–1.00	0.797
Procalcitonin (g/L)	1.01	1.00–1.02	0.408
Prothrombin time (s)	1.10	1.04–1.16	0.130
APTT (s)	1.01	1.00–1.02	0.364
Fibrinogen (g/L)	0.99	0.85–1.15	0.944
AT3 (%)	1.02	1.01–1.03	0.166
Total bilirubin ( $\mu$ mol/L)	1.00	1.00–1.01	0.480
ALT (U/L)	1.00	1.00–1.00	0.464
Creatinine ( $\mu$ mol/L)	1.00	1.00–1.00	0.323
Plasma transfusion	3.34	2.19–5.09	0.017*
RBC transfusion	10.74	4.21–27.39	0.034*
Platelet transfusion	2.16	1.29–3.63	0.214
Cryo transfusion	0.47	0.21–1.05	0.433

95%: CI: 95% Confidence interval; ICU: Intensive care unit; APTT: activated partial thromboplastin time; ALT: Alanine aminotransferase; AT3: antithrombin III; Cryo: Cryoprecipitate.

Cox proportional hazards regression was performed on the propensity score-matched cohort, adjusting for all available covariates.

**Table 3 – Association of plasma transfusion with in-hospital mortality.**

Model	Hazard Ratio	95% Confidence interval	p-value
Model 1	4.199	2.53–6.97	<0.001*
PSM	3.271	1.30–8.21	0.012*

95%: CI: 95% Confidence interval; PSM: Propensity score-matched. Model 1 is the univariate Cox regression. The PSM Model is derived from a propensity score-matched analysis, incorporating adjustments for the following covariates: age, patient category, red blood cell transfusion status, and intensive care unit length of stay.

(HR = 10.74; p-value = 0.034). Notably, a longer ICU stay was associated with a lower mortality risk (HR = 0.94 per additional day; p-value = 0.043), a result potentially confounded by survivor bias. Furthermore, surgical patient status was a strong protective factor compared to medical patient status (HR = 0.13; p-value = 0.002).

### Association between plasma transfusion and mortality

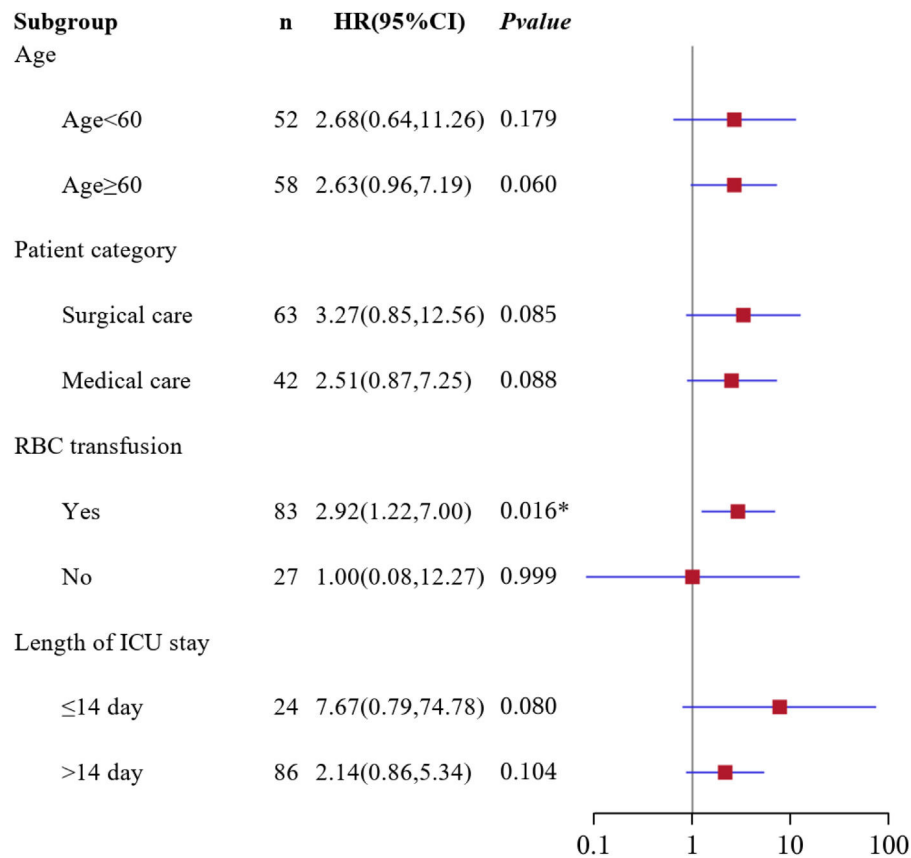
As shown in Table 3, plasma transfusion was significantly associated with increased in-hospital mortality. In the unadjusted model (Model 1), the HR was 4.199 (95% CI: 2.53–6.97; p-value <0.001). After adjusting for key covariates (age, patient category, RBC transfusion, and ICU length of stay) via PSM, the association remained significant, albeit attenuated, with an HR of 3.271 (95% CI: 1.30–8.21; p-value = 0.012).

### Subgroup analysis

Subgroup analyses were performed using the PSM cohort to assess the association between plasma transfusion and mortality risk across strata of age, patient category, RBC transfusion status, and ICU length of stay (Figure 1). After covariate adjustment, a statistically significant association was observed only for the subgroup of patients who had received RBC transfusions (HR = 2.92; 95% CI: 1.22–7.00; p-value = 0.016). For the subgroups stratified by age (<60 or  $\geq$ 60 years), patient category (surgical or medical), and ICU stay ( $\leq$ 14 or >14 days) the association between plasma transfusion and mortality risk was not statistically significant (all p-value >0.05).

### Dose-response relationship

Following PSM adjustment, a dose-response relationship was observed between plasma transfusion volume and in-hospital mortality (Table 4). Mortality risk increased progressively with higher volumes, reaching statistical significance only at the highest dose. Compared to no transfusion, the risk was elevated but not significant with  $\leq$ 400 mL (HR = 2.27; 95% CI: 0.86–6.01; p-value = 0.100) and 401–800 mL (HR = 2.52; 95% CI: 0.78–8.10; p-value = 0.121). A significantly higher risk was observed with volumes >800 mL, representing a 4.09-fold increase in mortality (HR = 4.09; 95% CI: 1.19–14.04; p-value = 0.025).



**Fig. 1 – Subgroup analysis of the association between plasma transfusion and in-hospital mortality. The model was fit on the propensity score-matched (PSM) cohort, with adjustment for age, patient category, red blood cell (RBC) transfusion status, and intensive care unit (ICU) length of stay.**

## 199 Survival analysis

200 Survival analysis demonstrated that patients receiving  
 201 plasma transfusion had significantly lower survival probabili-  
 202 ties than non-transfused patients. In the unadjusted analysis,  
 203 the transfusion group exhibited a 4.17-fold higher mortality  
 204 risk (Figure 2a). In the PSM cohort, plasma transfusion  
 205 remained significantly associated with increased mortality,  
 206 with an adjusted hazard ratio of 2.60 (Figure 2b). The differen-  
 207 ces in survival curves were statistically significant in both  
 208 analyses (log-rank p-value <0.05).

**Table 4 – Association between plasma transfusion volume and in-hospital mortality.**

Variable	Hazard Ratio	95% CI	p-value
<400	2.27	0.86–6.01	0.100
401–800	2.52	0.78–8.10	0.121
≥801	4.09	1.19–14.04	0.025*

95% CI: 95% Confidence interval.

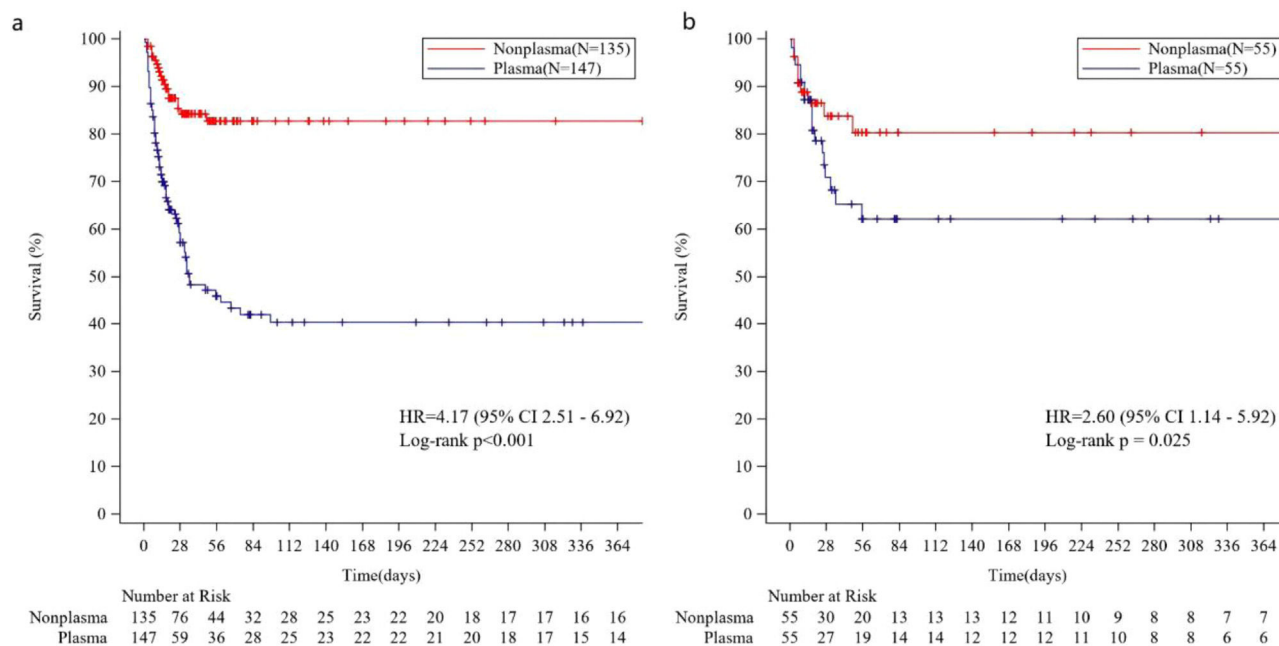
The model was fit on the propensity score-matched cohort, adjusted for age, patient category, red blood cell transfusion status, and intensive care unit length of stay. Patients who received no plasma transfusion (0 mL) served as the reference group.

## 209 Discussion

210 This retrospective study of 282 critically ill ICU patients aimed  
 211 to investigate the impact of plasma transfusion and its dos-  
 212 age on mortality, clarifying the risks and benefits associated  
 213 with plasma use in critical care. After adjusting for baseline  
 214 confounders employing PSM, the mortality risk in the plasma  
 215 transfusion group remained significantly elevated, with a  
 216 hazard ratio of 3.271 (95% CI: 1.30–8.21; p-value = 0.012). More-  
 217 over, a dose-dependent relationship was evident, as the risk  
 218 increased to 4.09-fold (95% CI: 1.19–14.04; p-value = 0.025)  
 219 when the transfusion volume exceeded 800 mL.

220 Patients receiving plasma transfusions presented with  
 221 poorer baseline clinical characteristics, including more  
 222 severe coagulopathies, a higher incidence of sepsis, and  
 223 worse liver function. This suggests that transfusion deci-  
 224 sions largely followed clinical indications, targeting sicker  
 225 patients. However, after balancing 19 baseline variables  
 226 using PSM (Table 1), plasma transfusion remained inde-  
 227 pendently associated with increased mortality. This indi-  
 228 cates that, beyond reflecting illness severity, plasma  
 229 transfusion itself may confer additional risk.

230 The increased mortality risk associated with plasma trans-  
 231 fusion may be linked to several factors. First, immune-



**Fig. 2 – Kaplan-Meier survival estimates. (a) Estimates derived from the original (unmatched) cohort. (b) Estimates derived from the propensity score-matched (PSM) cohort.**

232 inflammatory storms [20,21], where plasma contains various  
 233 bioactive substances (complement, cytokines) that can activate  
 234 systemic inflammatory responses, leading to febrile  
 235 non-hemolytic transfusion reactions, allergic reactions,  
 236 transfusion-related acute lung injury (TRALI) [22], and even  
 237 hemolysis [23], potentially causing direct patient mortality or  
 238 complicating their condition. TRALI and transfusion-associated  
 239 circulatory overload (TACO) are leading causes of transfusion-  
 240 related deaths, identified as independent risk factors  
 241 for ICU mortality [24,25]. For instance, the UK SHOT report  
 242 attributed 52.54% of transfusion-related deaths to TACO  
 243 among a total of 59 cases [26]. Second, although volume over-  
 244 load is effective for volume replacement and coagulation cor-  
 245 rection [27], critically ill patients often have impaired  
 246 physiological functions and limited compensatory capacities,  
 247 making them less tolerant to large-volume plasma transfu-  
 248 sions, thus increasing the risk of acute left heart failure, pul-  
 249 monary edema [28], citrate toxicity-induced hypocalcemia  
 250 and myocardial depression. Third, plasma administration  
 251 can exacerbate coagulation imbalance [29]. Because  
 252 plasma is rich in procoagulant factors such as thrombin  
 253 and fibrinogen, it may alter blood flow dynamics and dis-  
 254 rupt the homeostatic balance, thereby increasing the risk  
 255 of thrombosis. This can trigger secondary inflammation,  
 256 tissue edema, or necrosis, ultimately worsening clinical  
 257 outcomes [30]. A study on FFP transfusion efficacy in ICU  
 258 patients with decompensated cirrhosis and coagulopathy  
 259 found no benefit in terms of mortality but increased hospi-  
 260 tal stays and multi-organ failure risk [31].

261 Subgroup analysis provided further insights, revealing a  
 262 statistically significant increase in mortality specifically  
 263 among patients who received RBC transfusions (HR = 2.92;  
 264 95% CI: 1.22–7.00; p-value = 0.016). In contrast, this

265 association was not significant in subgroups stratified by age,  
 266 patient category, or ICU length of stay. This suggests that  
 267 patients requiring concomitant RBC and plasma transfusion  
 268 represent a particularly vulnerable population. In these criti-  
 269 cally ill patients that are often facing anemia, active bleeding,  
 270 or hemodynamic instability, plasma may compound risks  
 271 through volume overload, inflammatory activation, or coagul-  
 272 opathy. Thus, in multi-component transfusion settings, the  
 273 risks of plasma transfusion appear amplified, necessitating  
 274 cautious reassessment even when coagulation parameters  
 275 seem to justify its use. Clinical practice should adhere strictly  
 276 to evidence-based guidelines, prioritize treating underlying  
 277 conditions, and exercise heightened vigilance when consider-  
 278 ing plasma alongside other blood products.

279 This study has several limitations. First, as a retrospective  
 280 observational analysis, it may be subject to residual con-  
 281 founding despite adjustment for known factors via PSM. Sec-  
 282 ond, the exact time interval between plasma transfusion and  
 283 death was not consistently recorded in the medical records,  
 284 limiting our ability to establish a clear temporal relationship  
 285 or infer causality. To partially address this, we excluded  
 286 patients with an ICU stay of <24 h, thereby reducing the likeli-  
 287 hood of including deaths unrelated to transfusion or driven  
 288 solely by the underlying disease. Nevertheless, future studies  
 289 should aim to collect time-to-event data more systematically  
 290 to enable time-varying exposure analyses. Third, we were  
 291 unable to directly quantify specific adverse reactions such as  
 292 TRALI or TACO, limiting our ability to confirm the proposed  
 293 mechanisms. Fourth, the sample size was relatively modest,  
 294 particularly in subgroup and dose-response analyses, which  
 295 may have reduced statistical power and limited the generaliz-  
 296 ability of our findings. Therefore, these results should be

297 considered exploratory and warrant validation in larger, mul-  
298 ticenter prospective studies.

## 299 Conclusions

300 This study demonstrates that plasma transfusion is indepen-  
301 dently associated with significantly increased in-hospital  
302 mortality in critically ill patients, with a strong dose-depen-  
303 dent effect. The association remained significant after adjust-  
304 ing for confounding factors in PSM. Plasma use, particularly  
305 in the absence of active bleeding or clear indications, may  
306 cause more harm than benefit, likely due to complications  
307 like TRALI, TACO, and thrombosis.

308 Current clinical practices frequently diverge from estab-  
309 lished guidelines, potentially exposing patients to avoidable  
310 risks. Consequently, a more restrictive and evidence-based  
311 strategy for plasma transfusion is strongly warranted. Clini-  
312 cians are encouraged to avoid prophylactic use, particularly  
313 in hemodynamically stable patients, and should instead  
314 focus on addressing the underlying causes of coagulopathies.  
315 These findings underscore the need for stricter adherence to  
316 transfusion guidelines and highlight the importance of future  
317 prospective studies to enhance clinical decision-making in  
318 critical care settings.

319 Plasma transfusion should be regarded as a high-interven-  
320 tion therapy that carries substantial risks and requires metic-  
321 ulous patient-specific evaluation before administration.  
322 Future research efforts should aim to refine existing guide-  
323 lines through well-designed prospective studies and large-  
324 scale randomized controlled trials, with the goal of establish-  
325 ing precise, individualized dosing strategies. Ultimately, the  
326 objective is to improve patient outcomes by maximizing the  
327 therapeutic benefits of plasma transfusion while minimizing  
328 unnecessary exposure to risk.

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## 332 Author contributions

333 All listed authors have contributed to the manuscript sub-  
334 stantially and have agreed to the final submitted version. MZ  
335 contributed to the concept of the article, wrote the draft, and  
336 modified it. CSL and FY supported in data treatment and anal-  
337 ysis and reviewed the article. ZH, SF and FFC helped in data  
338 collection and modified the article. XSH reviewed and modi-  
339 fied the article. HJG did the data analysis, modified thoroughly  
340 the whole article, including the tables and the figures. PL  
341 helped in funding and reviewed the article.

## 342 Data availability

343 The data that support the findings of this study are available  
344 from the corresponding author upon reasonable request.

## Conflicts of interest

The authors declare that they have no conflict of interest.

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