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Chest 2007;131:1308-1314; Prepublished online March 30, 2007;
DOI 10.1378/chest.06-3048

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Fresh-Frozen Plasma and Platelet Transfusions Are Associated With Development of Acute Lung Injury in Critically Ill Medical Patients*

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Background: Transfusion has long been identified as a risk factor for acute lung injury (ALI)/ARDS. No study has formally evaluated the transfusion of specific blood products as a risk factor for ALI/ARDS in critically ill medical patients.

Method: In this single-center retrospective cohort study, 841 consecutive critically ill patients were studied for the development of ALI/ARDS. Patients who received blood product transfusions were compared with those who did not, in univariate and multivariate propensity analyses.

Results: Two hundred ninety-eight patients (35%) received blood transfusions. Transfused patients were older (mean [\pm SD] age, 67 ± 17 years vs 62 ± 19 years; $p < 0.001$) and had higher acute physiologic and chronic health evaluation (APACHE) III scores (74 ± 32 vs 58 ± 23 ; $p < 0.001$) than those who had not received transfusions. ALI/ARDS developed more commonly (25% vs 18%; $p = 0.025$) in patients exposed to transfusion. Seventeen patients received massive RBC transfusions (*ie*, > 10 U of blood transfused within 24 h), of whom 13 also received fresh-frozen plasma (FFP) and 11 received platelet transfusions. When adjusted for the probability of transfusion and other ALI/ARDS risk factors, any transfusion was associated with the development of ALI/ARDS (odds ratio [OR], 2.14; 95% confidence interval [CI], 1.24 to 3.75). Among those patients receiving individual blood products, ALI/ARDS was more likely to develop in patients who received FFP transfusions (OR, 2.48; 95% CI, 1.29 to 4.74) and platelet transfusions (OR, 3.89; 95% CI, 1.36 to 11.52) than in those who received only RBC transfusions (OR, 1.39; 95% CI, 0.79 to 2.43).

Conclusion: Transfusion is associated with an increased risk of the development of ALI/ARDS in critically ill medical patients. The risk is higher with transfusions of plasma-rich blood products, FFP, and platelets, than with RBCs. (CHEST 2007; 131:1308–1314)

Key words: cohort study; fresh-frozen plasma; platelets; pulmonary edema; risk factor; transfusion-related acute lung injury

Abbreviations: ALI = acute lung injury; APACHE = acute physiologic and chronic health evaluation; CI = confidence interval; CPE = cardiogenic (hydrostatic) pulmonary edema; DIC = disseminated intravascular coagulation; FFP = fresh-frozen plasma; INR = international normalized ratio; MICU = medical ICU; OR = odds ratio; TRALI = transfusion-related acute lung injury

Massive transfusion, arbitrarily defined as > 10 to 15 U of blood transfused within 24 h,^{1,2} has long been identified as a risk factor for acute lung injury (ALI)/ARDS.^{1,3,4} While the underlying reasons for a transfusion, such as trauma or sepsis, may be important factors for the development of ALI/ARDS, blood product transfusion itself may be a causal or contributing factor. The following two distinct mechanisms have been implicated in the

development of transfusion-related ALI/ARDS: (1) passive transfer of antileukocyte antibodies from alloimmunized donors⁵; and (2) biological response modifiers accumulated during the storage of cellular blood products.⁶ The relationship between specific blood products and the development of ALI/ARDS has not been formally studied, and transfusion-related ALI (TRALI) was thought to be a rare occurrence.^{7,8} The interest in TRALI has surged

after US Food and Drug Administration reports suggested it to be the most common cause of transfusion-related mortality in the United States. Some studies in patients with trauma,^{9,10} in patients receiving mechanical ventilation,¹¹ and in a subsequent genomic study¹² found an association between submassive transfusion and ALI/ARDS. The specific aims of our study were as follows:

- To determine whether any transfusion is independently associated with the development of ALI/ARDS in critically ill medical patients; and
- To determine which specific blood products are most likely to be associated with ALI/ARDS.

MATERIALS AND METHODS

In this single-center retrospective cohort study, consecutive critically ill patients who had been admitted to the medical ICU (MICU) were followed up for the development of ALI/ARDS. Patients who had received a transfusion with any blood product were compared with those who had not undergone transfusion. The study was approved by the institutional review board of Mayo Clinic, and informed consent was waived in accordance with Code of Federal Regulations code 46.116 (d).

All patients who were admitted to the MICU of St. Mary's Hospital, Mayo Clinic, Rochester, MN, between March 19, 2004, and March 31, 2005, were screened for inclusion criteria (Fig 1). This MICU is a 24-bed general medical noncardiac ICU with approximately 2,000 admissions per year, approximately 15% of which are for low-risk monitoring. Patients who had pulmonary edema (hydrostatic or ALI/ARDS) on MICU admission and those who had been admitted to the MICU for < 24 h were excluded from the study. Also, patients who declined research authorization were excluded from the study.

The primary outcome variable was the development of ALI/ARDS, which was defined according to the standard American-European Consensus Conference on ARDS definition¹³ as follows:

- New or worsening hypoxemia with a PaO_2 /fraction of inspired oxygen ratio of < 300 mm Hg;
- New bilateral pulmonary infiltrates seen on a chest radiograph; and
- A pulmonary artery occlusion pressure of < 18 mm Hg and/or the absence of clinical signs of left atrial hypertension.

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DOI: 10.1378/chest.06-3048

Cardiogenic (hydrostatic) pulmonary edema (CPE) was defined by a combination of features (including hemodynamic monitoring when available), as was outlined in our previous work.¹⁴ An ejection fraction of < 45% signified systolic dysfunction. Diastolic dysfunction was reported semiquantitatively (on a scale of + to +++) by trained echocardiographers according to the transmitral Doppler flow velocity/tissue Doppler myocardial velocity ratio.

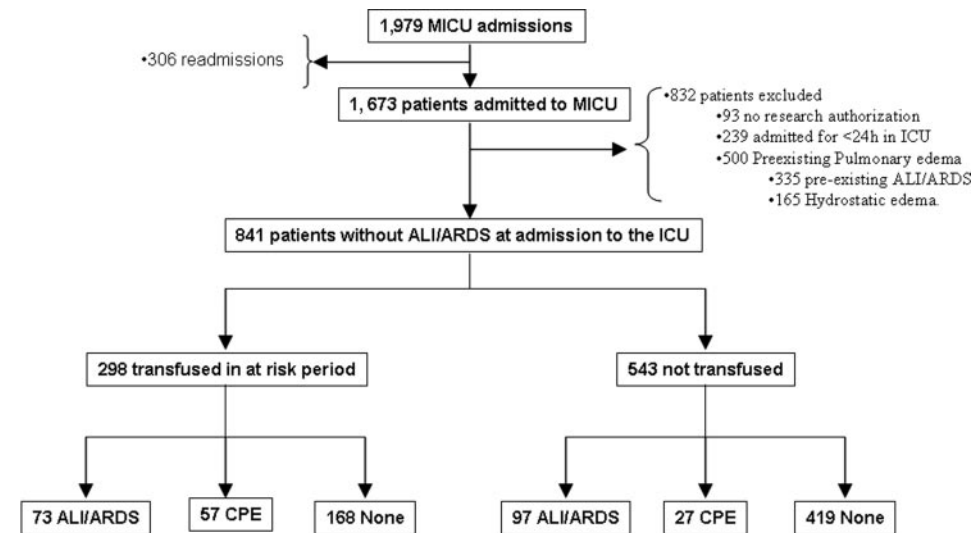
Daily portable chest radiographs were independently reviewed by study investigators (intensivists) who were blinded to the predictor variables. Any discordant readings were resolved by consensus after a detailed review of the chest radiograph and the radiologic report. At the time of the review of the chest radiographs, the investigators were not aware of the transfusion status of the patients.

Information on patient demographics, MICU admission diagnosis, severity of illness, physiologic variables (*ie*, mean arterial pressure, heart rate, and respiratory rate), laboratory variables (*ie*, hematocrit; creatinine, glucose, and albumin levels; pH; base excess; and PaO_2 /fraction of inspired oxygen), and ICU and hospital outcomes were prospectively collected by the bedside nurse into the institutional acute physiologic and chronic health evaluation (APACHE) III database.¹⁵ The characteristics of the MICU and APACHE III databases have been previously described.¹⁶ The ALI/ARDS risk factors that were studied included any transfusion, transfusion of individual blood products, sepsis, aspiration, pneumonia, drug overdose, disseminated intravascular coagulation (DIC), pancreatitis, alcohol use, cigarette smoking, and demographics. Except for smoking and alcohol abuse, risk factors for ALI/ARDS (including transfusions) were implicated only if they were present up to 48 h prior to the development of ALI/ARDS.

A blood transfusion was defined as the infusion of any plasma-containing blood product, including RBCs, platelets, fresh-frozen plasma (FFP), or cryoprecipitates. A massive transfusion was defined in our study as the transfusion of > 10 U of a blood product over a 24-h period. Blood filters were routinely used, but warmers were used in some but not all transfusions. Leukoreduction was fully implemented during the second half of the study. The at-risk period of transfusion was defined as 48 h before the development of pulmonary edema for the study group (*ie*, the ALI/ARDS group), and 48 h before MICU admission to 24 h after for the control group. Sepsis was defined according to the standard criteria.¹⁷ Aspiration was defined as the witnessed or strongly suspected aspiration of gastric contents into the airway. Pneumonia was defined as a new infiltrate seen on a chest radiograph with compatible clinical features (*ie*, at least two symptoms of acute lower respiratory tract infection and auscultatory findings of altered breath sounds or localized rales).¹⁸ Alcohol abuse was defined as the known or suspected intake of more than three alcoholic beverages daily as noted in the patient or family information provided at the time of hospital admission. Tobacco abuse was defined as a known history of cigarette smoking based on the information provided in the standardized form on hospital admission. DIC was defined as thrombocytopenia with elevated d-dimer or fibrin split products in the absence of significant liver disease.¹⁹ Acute pancreatitis was defined by the presence of elevated levels of biomarkers (*ie*, lipase and amylase) in the presence of clinical features of abdominal pain and tenderness.²⁰

Statistical Analysis

Continuous and categorical variables were compared using the Wilcoxon rank sum, the Fisher exact test, or the χ^2 test, as appropriate. Demographics, baseline characteristics, ALI/ARDS risk factors, and transfusion factors were compared between



Patient enrollment from March 19, 2004 to March 31, 2005.

FIGURE 1. Flow diagram outlining the progress of patients in the cohort study.

patients who had been exposed and had not been exposed to blood product transfusion. The comparisons were also made between patients in whom ALI/ARDS developed and those in whom it did not develop, excluding patients in whom hydrostatic pulmonary edema developed. Risk factors for ALI/ARDS were considered for multivariable logistic regression models if they (1) were statistically significant in univariate analysis ($p < 0.05$), (2) had high odds ratios (ORs) [≥ 2]; or (3) were biologically plausible. Both factors associated with the probability of transfusion (*ie*, the propensity score) and ALI/ARDS were included in the multivariate analysis. Because of collinearity, each of the blood product types (*ie*, RBCs, FFP, or platelets) were also included into separate logistic models. In addition to nontransfusion risk factors, each model contained a probability of transfusion of specific blood products. A statistical software package (JMP, version 6.0; SAS Institute; Cary, NC) was used for all analyses.

RESULTS

One thousand nine hundred seventy-nine MICU admissions were reviewed, which included 1,673 patients, of which 306 were readmissions (Fig 1). Eight hundred forty-one patients were included in the study, of whom 298 were transfused during the at-risk period. ALI/ARDS developed in 170 patients (20%) in a median time of 7.4 h (interquartile range, 2.8 to 27) after MICU admission. Of these patients, only 18 patients had ALI, while 152 had ARDS.

Patient demographics and the baseline characteristics of the cohort, segregated by which patients had been transfused and had not been transfused, are shown in Table 1. Patients who were transfused were older and more severely ill, as indicated by higher

APACHE III scores, lower hematocrit, lower platelet counts, and higher international normalized ratio (INR) values. Both ALI/ARDS (25% vs 18%, respectively; $p = 0.025$) and hydrostatic pulmonary edema (19% vs 5%, respectively; $p < 0.001$) developed more commonly in patients who had been exposed to transfusion. Pulmonary artery catheterization was performed in 65 patients (8%), of whom 33 had ALI/ARDS, 14 had CPE, and 18 had other conditions. The hospital mortality rate (17% vs 11%, respectively; $p = 0.022$) and ICU length of stay (mean length of stay, 3.8 vs 3.3 days, respectively; $p = 0.007$) were significantly higher in the transfused group. Among the transfused patients, 88% received RBCs, 41% received FFP, and 14% received platelets. Only 10 patients received a cryoprecipitate transfusion. Among the 17 patients who received a massive RBC transfusion (*ie*, > 10 U of a blood product transfused over a 24-h period), 13 (76%) also received FFP and 11 (65%) received platelets. The reasons for the RBC transfusion were active bleeding in 58% of patients, anemia in 37% of patients, and other conditions in 5% of patients. The reasons for FFP transfusion were active bleeding in 52% of patients, prior to invasive procedure in 31% of patients, and other conditions in 17% of patients. The reasons for platelet transfusion were active bleeding in 35% of patients, prior to invasive procedure in 52% of patients, and other conditions in 13% of patients.

Table 2 outlines the comparison of severity of illness, transfusion, and other ALI/ARDS risk factors between MICU patients in whom ALI/ARDS did and did not develop, excluding those patients in

Table 1—Baseline Characteristics of MICU Patients Segregated by Transfusion

Characteristics	Transfused Group (n = 298)	Nontransfused Group (n = 543)	p Value
Age, yr	67 ± 17	62 ± 19	< 0.001
Female gender	130 (44)	246 (45)	0.639
APACHE III scores	74 ± 32	58 ± 23	< 0.001
Hematocrit	26.3 ± 5.2	34.6 ± 5.4	< 0.001
INR	1.6 (1.1–2.8)	1.1 (1.0–1.2)	< 0.001
Platelet count	133 (77–195)	175 (125–246)	< 0.001
Smoking	217 (73)	382 (70)	0.474
Alcohol abuse	88 (33)	141 (30)	0.458
Liver failure	26 (9)	12 (2)	< 0.001
Diabetes	63 (21)	104 (19)	0.527
Sepsis	100 (34)	134 (25)	0.008
Aspiration	31 (10)	44 (8)	0.312
Pneumonia	46 (15)	132 (24)	0.003
DIC	16 (5)	8 (1)	0.002
Pancreatitis	8 (3)	21 (4)	0.433
Drug overdose	1 (0.3)	57 (11)	< 0.001

*Values are given as the mean ± SD, No. (%), or median (interquartile range), unless otherwise indicated.

whom CPE developed. The probability of transfusion was predicted by higher APACHE III scores, older age, lower hematocrit, lower platelet count, and higher INR level (Table 3)

In a multivariate analysis, when adjusted for the probability of transfusion and other ALI risk factors,

any transfusion was found to be an independent risk factor for the development of ALI/ARDS (Table 4). Among the individual blood products, the development of ALI/ARDS was more likely in recipients of FFP and platelet transfusions than in patients who received only transfusions of RBCs (Table 5). The dose response was noted for each of the blood product transfusions (Fig 2)

In an adjusted analysis, the period after leukoreduction was not associated with a significantly reduced incidence of ALI/ARDS (OR, 0.85; 95% confidence interval [CI], 0.55 to 1.32). Compared to patients in whom no pulmonary edema developed, patients with ALI/ARDS who had a higher hospital mortality rate (33% vs 8%, respectively; $p < 0.001$), and ICU length of stay (mean length of stay, 6.2 vs 2.6 days, respectively; $p < 0.001$). When adjusted for APACHE III score predicted mortality, the development of ALI/ARDS was associated with an increased risk of hospital mortality (OR, 2.69; 95% CI, 1.60 to 4.49).

DISCUSSION

Our study indicates that any transfusion, and in particular a transfusion of plasma-rich blood products (*ie*, platelets and FFP), is associated with the development of ALI/ARDS in critically ill medical patients. Massive RBC transfusions were a rare

Table 2—Baseline Characteristics of Patients in Whom ALI/ARDS Did and Did Not Develop*

Characteristics	ALI/ARDS Group (n = 170)	No Edema Group (n = 587)	p Value
Age, yr	63 ± 18	64 ± 18	0.291
APACHE III score	82 ± 31	58 ± 23	< 0.001
Female gender	78 (46)	252 (43)	0.495
Alcohol use	51 (35)	158 (30)	0.315
Smoking	132 (78)	406 (69)	0.035
Hematocrit	29 (25–34)	31 (26–37)	0.016
INR	1.4 (1.1–2.4)	1.1 (1.0–1.4)	< 0.001
Platelet count	136 (69–214)	172 (123–238)	< 0.001
Liver failure	11 (6)	20 (3)	0.082
Diabetes	232 (19)	115 (20)	0.912
Sepsis	96 (56)	115 (20)	< 0.001
Aspiration	38 (22)	32 (5)	< 0.001
Pneumonia	85 (50)	78 (13)	< 0.001
Drug overdose	4 (2)	54 (9)	0.002
DIC	7 (4)	12 (2)	0.160
Pancreatitis	9 (5)	16 (2)	0.139
Massive transfusion (> 10 U)	14 (8)	17 (3)	0.004
RBCs in at-risk period, U	1.4 ± 3.7	0.9 ± 2.1	0.217
FFP in at-risk period, U	1.2 ± 2.7	0.5 ± 2.2	< 0.001
Platelets in at-risk period, U	0.2 ± 0.7	0.0 ± 0.2	< 0.001
RBCs in ICU, U	1.8 ± 3.5	1.1 ± 2.7	< 0.001
FFPs in ICU, U	3.4 ± 12.1	0.6 ± 2.6	< 0.001
Platelets in ICU, U	0.4 ± 1.5	0.1 ± 0.6	< 0.001

*Values are given as the mean ± SD, No. (%), or median (interquartile range), unless otherwise indicated.

Table 3—Predictors of Transfusion in 757 Medical Critically Ill Patients in Whom Either ALI Developed or There Was No Edema*

Risk Factors	OR	95% CI	p Value
Hematocrit	0.74	0.70–0.77	< 0.001
INR	1.72	1.43–2.10	< 0.001
Platelet count	1.00	0.99–1.00	0.124
Age	1.01	0.99–1.02	0.025
APACHE III score	1.01	1.00–1.02	0.025

*Values were calculated per 1-U increase (area under the curve, 0.90).

occurrence and were almost always accompanied by FFP and platelet transfusions. ALI/ARDS was more likely to develop in patients with sepsis, pneumonia, and aspiration.

Massive RBC transfusion has long been implicated as a risk factor for ALI/ARDS.^{1,21} The association between massive transfusion and ALI/ARDS was generally considered to be a marker for severe illness and not a cause-effect relationship. In the present series, the majority of patients who had received a massive RBC transfusion also received FFP and platelets, a finding that has not been reported in previous ALI/ARDS risk factor studies. In a prospective observational study focused on the genetic predisposition for ALI/ARDS, Gong et al¹² reported significantly higher odds of the development of ALI/ARDS in patients receiving a transfusion (OR, 2.19; 95% CI, 1.42 to 3.36). In a retrospective observational study of 332 critically ill, mechanically ventilated patients for ≥ 48 h, Gajic et al²² showed that the OR of the development of ALI/ARDS in any transfusion was 2.97 (95% CI, 1.56 to 5.90). In 2005, Croce et al,⁹ in a retrospective review of 5,260 trauma patients, showed a much higher risk of ALI/ARDS in those patients who had received any transfusion (OR, 3.42; 95% CI, 4.02 to 34.12). In a study by Silverboard et al,¹⁰ a significantly higher number of blunt trauma patients receiving > 5 U of RBCs developed ARDS when compared to those

Table 4—Predictors of ALI/ARDS*

Risk Factors	OR	95% CI	p Value
Any transfusion	2.14	1.24–3.75	0.008
Probability of transfusion	1.00	0.43–2.31	0.992
Pneumonia	6.89	4.37–10.95	< 0.001
Aspiration	2.07	1.11–3.88	0.023
Sepsis	4.95	3.28–7.53	< 0.001
Pancreatitis	2.70	0.92–7.30	0.058

*Multivariate analysis was accomplished by a propensity score using any transfusion vs none during the at-risk period (area under the curve, 0.82).

Table 5—Risk for the Development of ALI/ARDS With the Transfusion of Individual Blood Products

Blood Products	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Any RBCs	1.28 (0.88–1.84)	1.39 (0.79–2.43)
Any FFP	3.25 (2.09–5.03)	2.48 (1.29–4.74)
Any platelet	5.99 (2.48–15.38)	3.89 (1.36–11.52)

*In addition to sepsis, aspiration, pancreatitis, and pneumonia, the propensity for transfusion with particular blood products was added to the multivariate regression model. Area under the curve: RBCs (hematocrit, APACHE III score, age and INR), 0.90; FFP (INR, platelet count, liver cirrhosis, hematocrit, APACHE III score), 0.91; platelets (thrombocytopenia, hematocrit, APACHE III score, and cirrhosis), 0.82.

patients who had received ≤ 5 U of RBCs (70% vs 27%, respectively; $p = 0.001$).

Perhaps the most significant relationship between transfusion and the subsequent development of ALI/ARDS has come from two randomized trials. In a landmark study of the Canadian Critical Care Trial Group,²³ 838 critically ill patients who were admitted to ICUs for > 24 h were randomized to either a liberal transfusion strategy (hemoglobin threshold for transfusion, 10 g/dL) or a restrictive transfusion strategy (hemoglobin threshold for transfusion, 7 g/dL). Liberal transfusion was associated with the development of ALI/ARDS (OR, 1.5; 95% CI, 0.97 to 2.49). Similarly, both the transfusion requirements and the incidence of ALI/ARDS was significantly lower in blunt trauma patients who had been randomized to receive recombinant factor VII (4% vs 16%, respectively; $p = 0.03$).²⁴

In our study, the risk of ALI/ARDS was higher in patients who had received platelets and FFP than in those who received only RBCs. This is in line with the following two leading hypotheses for the pathogenesis of TRALI²⁵: passive transfer of antileukocyte antibodies in plasma-rich blood products^{5,7,26}; and the accumulation of inflammatory mediators in stored platelets.⁶

In the original description of TRALI by Popovsky and Moore,⁷ RBCs were implicated in only 10 of the 36 confirmed cases of transfusion-related ALI/ARDS. In a nested case-control study with retrospective demographic and clinical laboratory data collection and a prospective evaluation of biological response modifiers, Silliman et al⁶ found that platelets were implicated in 74 of 90 TRALI cases. In a retrospective review of TRALI-related deaths reported to the US Food and Drug Administration over a 5-year period, Holness et al²⁷ found that FFP was the implicated unit in 50% of cases. FFP was also the most commonly implicated product in transfusion-related ALI/ARDS in a retrospective study of

mechanically ventilated patients.^{11,28} In a recent retrospective study by Sadis et al,²⁹ patients in whom ARDS developed after transfusion were more likely to have received a transfusion of FFP.

The studies by both Croce et al⁹ and Silverboard et al¹⁰ showed a dose-response relationship between the number of units of blood transfused and the development of ARDS, with the risk sharply rising after 5 U. Specifically, the use of FFP and platelets in transfusions was unfortunately not reported. Another interesting dose-response relationship was shown recently in a prospective observational cohort study by Taylor et al,³⁰ in which the number of units of RBCs transfused was independently associated with a risk of nosocomial infection (OR, 1.097; 95% CI, 1.028 to 1.171; $p = 0.005$).

In our study, the hospital mortality rate was found to be significantly higher in the transfused group (17% vs 11%, respectively; $p = 0.022$). In a multicenter, prospective observational study, Vincent et al,³¹ in a matched patient-propensity analysis, found a significantly higher 28-day mortality rate in those patients who were transfused compared to those who were not (22.7% vs 17.1%, respectively; $p = 0.02$). Corwin et al,³² in a prospective multicenter observational cohort study showed a dose-response relationship between the number of units of RBCs transfused and the 30-day mortality rate. With no transfusion being the reference point, the risk of 30-day mortality was highest with > 4 U of RBCs transfused (OR, 4.01; 95% CI, 2.74 to 5.87; $p < 0.0001$).

Significant limitations of our study arise from its observational design. Though we have carefully considered indications for transfusion and most of the known risk factors of ALI/ARDS, and through multivariate analysis determined which risk factors had independent

associations, it is likely that some unknown risk factors have been missed and were actually responsible for the observed differences. To determine whether there was a history of alcohol abuse and smoking, we relied on the information provided by patient or family at the time of hospital admission, and we did not use standardized assessment tools. Unmeasured factors such as immunologic status, and hence inflammatory response, could partially account for the differences in the risk of the development of ALI/ARDS. While we analyzed INR, platelet count, hematocrit, and DIC, and demonstrated that these reasons for transfusion of blood products were not significantly associated with ALI/ARDS, other indications for blood product transfusion such as tissue ischemia or rapid blood loss were only indirectly assessed. We paid exquisite attention to accurately determine the onset of ALI/ARDS, but the ordering of the necessary diagnostic tests (*ie*, arterial blood gas measurements and chest radiographs) was done by individual providers. Given the relatively short median time to the development of pulmonary edema after MICU admission, it is conceivable that some of the patients in the study group in whom ALI/ARDS developed were in the process of having it develop due to the underlying condition that required ICU admission, regardless of coincidental transfusion. The reliability of the American-European Consensus Conference on ARDS definition,¹³ and in particular the distinction between ALI/ARDS and cardiogenic (hydrostatic) pulmonary edema, is far from perfect and may overlap in critically ill medical patients with multiple comorbidities.^{14,33-35} This was a single-center study and therefore depicts transfusion practices at this particular center. Since our MICU (respiratory) does have a high incidence of ALI/ARDS (in both transfused and nontransfused patients), the presence of other “hits” (*eg*, aspiration or sepsis) could have contributed to the observed effect of transfusion factors.

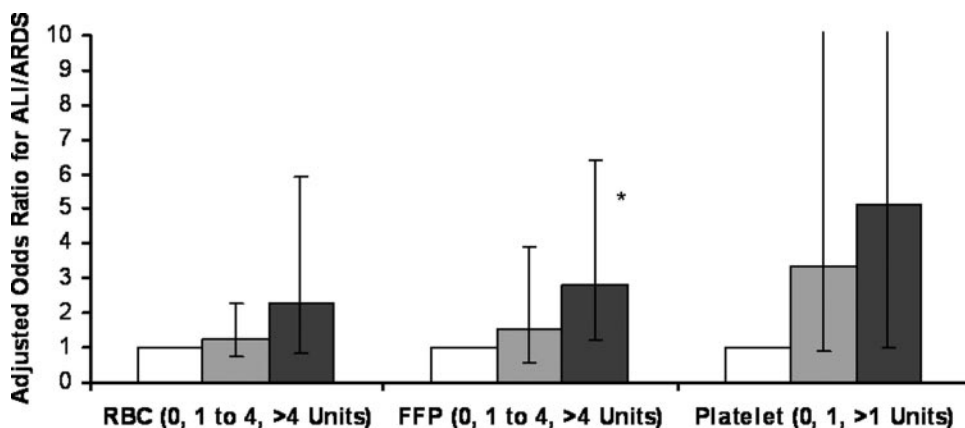


FIGURE 2. Adjusted ORs for the development of ALI/ARDS as a function of the number of individual blood product transfusions. * = $p < 0.05$.

In summary, our study demonstrates that transfusion is independently associated with the risk of ALI/ARDS in critically ill medical patients. The risk is higher with the transfusion of plasma-rich blood products (FFP and platelets) than with the transfusion of RBCs. It is not known whether the preventive strategies targeted for the transfusion of blood products could help to reduce the risk of ALI/ARDS in critically ill patients.

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Chest 2007;131;1308-1314; Prepublished online March 30, 2007;
DOI 10.1378/chest.06-3048

This information is current as of August 3, 2007

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