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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



Association of RBC Transfusion With Mortality in Patients With Acute Lung Injury*

Giora Netzer, MD, MSCE, FCCP; Chirag V. Shah, MD;
Theodore J. Iwashyna, MD, PhD; Paul N. Lanken, MD, FCCP;
Barbara Finkel, MSN; Barry Fuchs, MD, FCCP; Wensheng Guo, PhD;
and Jason D. Christie, MD, MSCE

Background: RBC transfusion has been associated with increased morbidity and mortality in a variety of clinical settings. We assessed the effect of RBC transfusion on in-hospital mortality in patients with acute lung injury (ALI).

Methods: Cohort study of 248 consecutive patients with ALI. RBC transfusion was evaluated as both dichotomous and continuous variables, with outcome being in-hospital mortality adjusted for clinical confounders and length of total hospital stay.

Results: Overall in-hospital mortality rate was 39.5%. Of these patients, 207 of 248 patients (83.5%) received ≥ 1 U of packed RBCs. The transfusion of any packed RBCs was associated with an increased risk of death (adjusted odds ratio [OR], 3.12; 95% confidence interval [CI], 1.28 to 7.58; $p < 0.001$). The overall OR per unit was 1.06 (95% CI, 1.04 to 1.09; $p < 0.001$) in the complete multivariable model. Transfusion after ALI onset was associated with an adjusted OR of 1.13 (95% CI, 1.07 to 1.20; $p < 0.001$), while transfusion before ALI onset was not associated with higher risk. The adjusted OR per unit of nonleukoreduced RBC transfused was 1.14 (95% CI, 1.07 to 1.21; $p < 0.001$), while the adjusted OR for leukoreduced cells per unit transfused was 1.06 (95% CI, 1.03 to 1.09; $p < 0.001$).

Conclusions: Transfusion of RBCs in patients with ALI was associated with increased in-hospital mortality. This risk occurred with RBC transfusion after the onset of ALI, and was greater for nonleukoreduced than for leukoreduced RBCs. Aggressive transfusion strategies in patients with established ALI should be questioned, pending further study. (CHEST 2007; 132:1116–1123)

Key words: blood component transfusion; blood transfusion; mortality; respiratory distress syndrome, adult

Abbreviations: ALI = acute lung injury; APACHE = acute physiology and chronic health evaluation; ARMA = Acute Respiratory Distress Syndrome Network Low Tidal Volume; CI = confidence interval; OR = odds ratio; TRALI = transfusion-related lung injury

Acute lung injury (ALI) and its more severe presentation, the ARDS, are common and devastating syndromes of acute hypoxemic respiratory failure. Although the incidence of ALI/ARDS was previously thought to be approximately 1.5 to 8.3 per 100,000, more recent literature^{1–4} suggests that the incidence of ALI/ARDS is as high as 306 per 100,000 person-years in the oldest age group. Although the mortality rate has decreased in recent years, in part due to a protective lung ventilatory strategy, it remains high at 40%.⁵ Thus, ALI may account for 74,500 deaths and 3.6 million hospital days in the United States alone.⁴

Blood transfusion has been implicated in worsening lung injury, and thus may lead to higher mortality. More than 20 years ago, blood transfusion was described as a potential risk factor for the

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development of ALI/ARDS.^{6,7} Transfusion has also been associated with increased mortality after coronary artery bypass surgery, increased rate of ventilator-associated pneumonia and nosocomial infection, diminished organ function and increased mortality in

medical critically ill patients, and worsened outcome in burn injury and trauma.^{8–23} More recent literature^{24–26} shows the risk of ALI/ARDS is increased with transfusion in a medical-surgical population, as well as after trauma and cardiac surgery. In addition to increasing the risk for ALI/ARDS, transfusion may increase the risk of death from it.²⁷

The use of liberal transfusion strategies remains widespread despite multiple studies showing that transfusion does not improve outcome in patients receiving ventilation and that outcomes are at least equivalent and may be improved in critically ill patients given fewer transfusions as part of a more conservative strategy.^{28–30} In fact, the rate of transfusion and the clinical threshold for transfusion have not significantly changed in the past 10 years.³¹

We hypothesized that blood transfusion was associated with worsened outcome in patients with ALI/ARDS. The purpose of this cohort study was to evaluate the association between the transfusion of packed RBCs and mortality in patients with ALI/ARDS.

MATERIALS AND METHODS

A single-center, prospective, cohort study was performed including 248 patients with ALI/ARDS admitted between 1999 and 2002 and followed up until death or hospital discharge. The data were collected as part of a prior National Institutes of Health, National Heart, Lung, and Blood Institute Specialized Centers of Research study in ALI/ARDS. Complete blood bank transfusion records were abstracted subsequently without knowledge of ALI/ARDS outcome. All patients >13 years old admitted to the medical or surgical ICUs of the Hospital of the University of Pennsylvania were screened for ALI/ARDS. Those who met American European Consensus Conference criteria³² were enrolled into the study within 48 h of onset of ALI/ARDS. Patients were excluded if they had current or prior congestive heart failure, respiratory disease, or conditions that mimicked ALI/ARDS, including vasculitis with diffuse alveolar hemorrhage; were burned >30% of total body area; or were lung or bone marrow recipients. The institutional review board for the University of Pennsylvania reviewed and approved this study with waiver of informed consent.

*From the Division of Pulmonary and Critical Care (Dr. Netzer), University of Maryland School of Medicine, Baltimore, MD; Division of Pulmonary, Allergy and Critical Care (Drs. Shah, Iwashyna, Lanke, Finkel, Fuchs, and Christie), Hospital of the University of Pennsylvania, Philadelphia, PA; and Center for Clinical Epidemiology and Biostatistics (Dr. Guo), University of Pennsylvania School of Medicine, Philadelphia, PA. This research was supported in part by National Institutes of Health National Heart, Lung, and Blood Institute grant P01-HL79063. The authors have no conflicts of interest to disclose. Manuscript received January 23, 2007; revision accepted April 15, 2007.

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Correspondence to: Giora Netzer, MD, MSCE, FCCP, Division of Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, MSTF Bldg, Room 800, 685 W Baltimore St, Baltimore, MD 21201; e-mail: gnetzer@medicine.umaryland.edu
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The primary exposure variable, packed RBCs, was evaluated both as a dichotomous variable (any transfusion) and linear variable (total number of packed RBCs transfused). To correct for immortal time bias, the total number of packed RBCs was adjusted for length of stay in all analyses.^{33,34} The primary outcome was in-hospital mortality because mortality as a dichotomous outcome is the standard outcome in studying critical illness.³⁵

During the time period of the cohort study, several changes in practice occurred. Most notably, the blood bank at our institution had begun administering leukoreduced blood products, and the results of the National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Clinical Trial Network study³⁶ of lower vs traditionally sized tidal volume ventilatory strategies was published (May 4, 2000). To address the effects of time, we tested our models for calendar date, using linear time adjustment, 365-day epochs, spline, marginal spline, functional cubic form for time, and quadratic time. Nearly all patients in this study who received transfusion of multiple units of packed RBCs received a combination of leukoreduced and nonleukoreduced RBCs. The percentage of leukoreduced products relative to nonleukoreduced also increased over time during the cohort. To assess the impact of leukoreduced and nonleukoreduced products, both were evaluated separately as risk factors, and both variables were included simultaneously in the same logistic regression model.

Furthermore, we sought to investigate whether transfusion of blood products occurring before ALI/ARDS onset had a different effect than transfusion occurring after ALI/ARDS onset. In comparing the association of mortality with RBCs transfused before and after the onset of ALI/ARDS, each was evaluated separately and included simultaneously in logistic regression models. Additionally, the effect of massive transfusion as an etiology of ALI/ARDS was evaluated as a potential confounder of this relationship.

Clinical confounding variables are presented in Table 1. We chose potential confounders based on review of relevant studies of ALI mortality,^{37–39} as well as hypotheses regarding effects on transfusion requirement. The effect of these variables on the relationship of RBC transfusion took place in two stages. First, each variable was evaluated individually for effect on the association of RBC transfusion with mortality in logistic regression models. Second, those variables that altered the odds ratio (OR) of RBC transfusion by $\geq 15\%$ were included in a final multivariable explanatory regression model.⁴⁰ All statistical analysis was conducted using statistical software (STATA v.9; StataCorp LP; College Station, TX).

RESULTS

Between 1999 and 2002, 262 consecutive patients met eligibility criteria and were enrolled in the study.

Table 1—Baseline Characteristics of the ALI Cohort*

Characteristics	Alive (n = 150)	Dead (n = 98)	p Value
Age, yr	45.2 ± 19.0	53.9 ± 17.1	<0.001
Male gender	92 (61)	64 (65)	0.527
Trauma	51 (34)	16 (16)	0.002
APACHE III score	59.5 ± 20.7	80.5 ± 28.0	<0.001
Total length of ICU stay, d	20.3 ± 17.3	12.6 ± 12.9	<0.001
Total length of stay, d	35.6 ± 25.8	17.2 ± 17.5	<0.001
Long-term alcohol use	17 (11)	25 (26)	0.004
Diabetes	16 (11)	21 (22)	0.020

*Data are presented as mean ± SD or No. (%).

In-hospital outcome was not documented in seven patients, complete transfusion records were not available for six patients, and one patient was lacking both outcome and transfusion records. This provided 248 patients in the cohort for analysis.

Baseline characteristics of the study cohort are shown in Table 1. Overall mortality rate was 39.5%. Patients who died were older (53.9 years vs 45.2 years, $p < 0.001$), had worse APACHE (acute physiology and chronic health evaluation) III scores (80.5 vs 59.5, $p < 0.001$), were more likely to have a history of chronic alcohol use (26% vs 11%, $p = 0.004$) or diabetes (22% vs 11%, $p = 0.020$), and were less likely to have trauma as the inciting etiology for their ALI (16% vs 34%, $p = 0.002$). Patients who died were also more likely to have received a packed RBC transfusion (92% vs 78%, $p = 0.004$) and platelets (56% vs 41%, $p = 0.017$).

Diabetes, trauma as etiology, and history of long-term alcohol use were found to change the point estimate of the OR for RBC transfusion and death and were therefore included in the multivariable explanatory model. History of hypertension and tobacco use did not impact the model. The lung injury score and a $\text{PaO}_2/\text{fraction of inspired oxygen ratio} < 200$ also were not statistically significant as confounders because neither changed the OR by $\geq 15\%$. Additionally, other chronic health conditions were evaluated, including malignancy, cirrhosis, and renal insufficiency, and the effect of these in the complete multivariable model was an OR similar to that of the APACHE III score (Table 2). Due to concerns about collinearity, only the APACHE III score was included in the final multivariable model.

RBC transfusion was evaluated as a risk factor using several methods, all of which revealed an association with mortality. As a dichotomous variable, the transfusion of any RBCs (≥ 1 U) was associated with an unadjusted OR for mortality of 2.90 (95% confidence interval [CI], 1.32 to 6.35; $p = 0.008$) compared to those never receiving RBCs. This increased OR remained significant (3.12; 95% CI, 1.28 to 7.58; $p = 0.012$) when adjusted for age, gender, APACHE III score, and precipitating event in a logistic regression model.

The amount of RBC transfusion was adjusted for duration of hospitalization by adjusting RBC transfusion per unit by total length of stay. In both bivariable and multivariable models, there was an association of RBC transfusion with mortality. The risk of mortality per unit of packed RBCs transfused adjusted for length of stay was 1.05 (95% CI, 1.02 to 1.07; $p < 0.001$) in the bivariable model, rising to 1.06 (95% CI, 1.04 to 1.09; $p < 0.001$) in the full explanatory multivariable model (Table 3). In addition, the OR for the administration of packed RBCs

Table 2—OR for In-Hospital Mortality Per Unit of Packed RBCs Transfused for Selected Comorbidities

Logistic Regression Model	OR (95% CI)	p Value
Adjusted for total length of stay, age, gender, leukemia (acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple myeloma), trauma, alcohol use, diabetes	1.06 (1.04–1.09)	<0.001
Adjusted for total length of stay, age, gender, non-Hodgkin lymphoma, trauma, alcohol use, diabetes	1.06 (1.04–1.09)	<0.001
Adjusted for total length of stay, age, gender, solid tumor with metastasis, trauma, alcohol use, diabetes	1.06 (1.04–1.09)	<0.001
Adjusted for total length of stay, age, gender, cirrhosis, trauma, alcohol use, diabetes	1.07 (1.04–1.10)	<0.001
Adjusted for total length of stay, age, gender, chronic dialysis, trauma, alcohol use, diabetes	1.06 (1.04–1.09)	<0.001
Adjusted for total length of stay, age, gender, all malignancy, cirrhosis, dialysis, trauma, alcohol use, diabetes	1.06 (1.03–1.09)	<0.001
Adjusted for total length of stay, age, gender, APACHE III score, trauma, alcohol use, diabetes	1.06 (1.04–1.09)	<0.001

per unit transfused remained consistent after adjustment for time using date of admission, linear time adjustment, 365-day epochs based on the Acute Respiratory Distress Syndrome Network Low Tidal Volume (ARMA) publication date, spline, marginal spline, and functional cubic form for time and quadratic time to account for any possible change in clinical practice from the ARMA study (*ie*, increasing

Table 3—OR of In-Hospital Mortality Per Unit of Packed RBCs Transfused

Logistic Regression Model	OR (95% CI)	p Value
Base model adjusted for total length of stay	1.05 (1.02–1.07)	<0.001
Adjusted for total length of stay, age	1.05 (1.03–1.08)	<0.001
Adjusted for total length of stay, age, gender	1.05 (1.03–1.08)	<0.001
Adjusted for total length of stay, age, gender, APACHE III score	1.05 (1.03–1.08)	<0.001
Adjusted for total length of stay, age, gender, APACHE III score, trauma	1.06 (1.03, 1.09)	<0.001
Adjusted for total length of stay, age, gender, APACHE III score, trauma, alcohol use, diabetes	1.06 (1.04–1.09)	<0.001

Table 4—OR of In-Hospital Mortality Per Unit of Packed RBCs

Logistic Regression Model	OR (95% CI)	p Value
Before onset of ALI		
Base model adjusted for total length of stay	1.02 (0.98–1.06)	0.430
Adjusted for total length of stay, RBCs administered after onset of ALI	1.00 (0.96–1.04)	0.899
Adjusted for total length of stay, RBCs administered after onset of ALI, gender, APACHE III score, trauma, alcohol use, diabetes	1.01 (0.97–1.06)	0.615
After onset of ALI		
Base model adjusted for total length of stay	1.10 (1.05–1.16)	<0.001
Adjusted for total length of stay, RBCs administered before onset of ALI	1.11 (1.05–1.16)	<0.001
Adjusted for total length of stay, RBCs administered before onset of ALI, gender, APACHE III score, trauma, alcohol use, diabetes	1.13 (1.07–1.20)	<0.001

use of low tidal volumes) or the increasing use of leukoreduced blood over the length of the study.

The association with mortality for RBCs administered before and after the onset of ALI was evaluated in both a base model adjusted only for total length of stay, and complete multivariable logistic models with all confounders. In the multivariable model, the transfusion of blood after the onset of ALI was associated with an OR for mortality of 1.13 (95% CI, 1.07 to 1.29; $p < 0.001$) per unit transfused, while the administration of blood prior to ALI was not a risk factor for mortality (Table 4). The increased risk of mortality associated with post-ALI blood administration and the lack of association for blood before ALI also remained statistically significant when unadjusted for total length of stay.

In our study, 21 patients were identified with multiple transfusions as their primary risk factor for ALI/ARDS, while an additional 45 patients were identified as having massive transfusion as a secondary risk factor. This risk factor did not change the OR of RBC transfusion and death by >15%; therefore, there was no confounding. Additionally, when included in a logistic regression with total RBCs transfused, neither massive transfusion as a primary or secondary risk factor had a statistically significant effect on the OR for mortality.

The OR for nonleukoreduced packed RBCs per unit transfused was higher than that for leukoreduced RBCs per unit transfused. The OR in the base model adjusted for total length of stay and leukoreduced RBC transfusion was 1.10 (95% CI, 1.05 to

Table 5—OR of In-Hospital Mortality Per Unit of Packed RBCs

Logistic Regression Model	OR (95% CI)	p Value
Nonleukoreduced		
Adjusted for total length of stay	1.09 (1.04–1.14)	0.001
Adjusted for total length of stay and leukoreduced RBCs administered	1.10 (1.05–1.16)	<0.001
Adjusted for total length of stay, leukoreduced RBCs administered, age, gender, APACHE III score, trauma, alcohol use, diabetes	1.14 (1.07–1.21)	<0.001
Leukoreduced		
Adjusted for total length of stay	1.03 (1.00–1.05)	0.039
Adjusted for total length of stay and nonleukoreduced RBCs administered	1.04 (1.01–1.07)	0.007
Adjusted for total length of stay, nonleukoreduced RBCs administered, age, gender, APACHE III score, trauma, alcohol use, diabetes	1.06 (1.03–1.09)	<0.001

1.16; $p < 0.001$) and was 1.14 (95% CI, 1.07 to 1.21; $p < 0.001$) in the complete multivariable model. The OR for leukoreduced cells per unit transfused adjusted for total length of stay and nonleukoreduced RBC transfusion was 1.04 (95% CI, 1.01 to 1.07; $p = 0.007$) and in the complete multivariable model was 1.06 (95% CI, 1.03 to 1.09; $p < 0.001$) [Table 5]. A test of heterogeneity showed that this difference was statistically significant.

The effect of platelet transfusion was also analyzed for association with mortality in ALI, both independently and adjusted for RBC transfusion. Although the administration of platelets was associated with a higher risk of mortality in unadjusted analysis, this was not statistically significant after adjustment for RBC transfusion (Table 6).

Table 6—OR of In-Hospital Mortality Per Unit of Platelets Transfused

Logistic Regression Model	OR (95% CI)	p Value
Adjusted for total length of stay	1.10 (1.04–1.16)	0.001
Adjusted for total length of stay, age, gender	1.10 (1.04–1.16)	0.002
Adjusted for total length of stay, age, gender, APACHE III score	1.06 (1.00–1.13)	0.037
Adjusted for total length of stay, age, gender, APACHE III score, trauma, alcohol use, diabetes	1.07 (1.01–1.14)	0.022
Adjusted for total length of stay, age, gender, APACHE III score, trauma, alcohol use, diabetes, total units of RBCs transfused	1.01 (0.95–1.07)	0.782

DISCUSSION

In this cohort study of patients with ALI/ARDS, any RBC transfusion increased the risk of mortality, and this risk increased with the number of units transfused. This association with increased risk of mortality occurred predominantly with transfusion after the onset of ALI/ARDS. Administration of leukoreduced RBCs was associated with an increased risk of mortality relative to receiving no RBCs at all, but with a lower OR than nonleukoreduced RBCs. Transfusion of platelets was not independently associated with mortality.

Our findings of the relationship between RBC transfusion and mortality are consistent with previous studies,^{8,11,12,21,22,27} in critically ill patients. It should be considered that our finding of an OR of 1.06 is per unit transfused; thus, a patient receiving 4 U of packed RBCs would have an OR increased 24% above those who did not receive transfusion. Our results confirm the findings of a study of patients with ALI/ARDS by Gong and colleagues,²⁷ and adds to their study by adjusting for the immortal time bias and by revealing that this risk occurs after the onset of ALI/ARDS. Additionally, our study compared the risk of leukoreduced vs nonleukoreduced RBCs in ALI/ARDS and is the first to do so.

The administration of allogeneic blood may increase mortality in ALI/ARDS by two mechanisms: immunomodulation and amplification of lung injury. The immunosuppressive effect of blood transfusion was noted decades ago⁴¹ and is likely exerted by several mechanisms, including microchimerism, changes in cytokine secretion, impairment of natural killer cell function, and decreases in CD4 percentage and tumor necrosis factor- α , interleukin-2, and interferon- γ .⁴²⁻⁴⁹ RBC transfusion may amplify lung injury by increasing pulmonary microvascular permeability by decreasing prostaglandin E₁ and by lipids in the transfusion causing direct lung injury.⁵⁰⁻⁵³ Additionally, packed RBCs, being less deformable, may sludge in the microvasculature, worsening end-organ ischemia.⁵⁴⁻⁵⁶

In our cohort study, most patients received a combination of leukoreduced and nonleukoreduced products. The OR for mortality was higher for nonleukoreduced products, consistent with previous studies⁵⁷⁻⁶⁰ that suggested a benefit of leukoreduction. A major concern in interpreting this finding is that the proportion of leukoreduced RBCs increased over time in this study, and this increase largely occurred after the publication of the ARMA study.³⁶ We adjusted for this potential confounder of reduced mortality using multiple methods, all of which resulted in a consistent OR for mortality.

We found that transfusions after the onset of ALI/ARDS were associated with an increased OR for

mortality. This may be due to a direct impact on lung injury or, alternately, because the cause of most deaths in patients with ALI/ARDS is not due to progressive hypoxemia^{61,62}; the immunomodulatory effect may be deleterious in this vulnerable population. Rivers et al⁶³ advocate an aggressive transfusion strategy in early sepsis, a strategy that has gained the endorsement in national guidelines for the treatment of sepsis.⁶⁴ Sepsis is both a leading precipitating factor for ALI/ARDS, as well as a leading cause of mortality in patients with established ALI/ARDS.⁴⁶ Our study illustrates that the administration of packed RBCs is a risk factor for mortality in patients with ALI/ARDS after the onset, but not before. It is reasonable therefore to conclude that a conservative transfusion strategy (*ie*, transfusing to keep hemoglobin >7 g/dL), which has been shown effective in the critical care population,²⁹ should be studied in patients with established ALI/ARDS.

Although a previous study⁶⁵ showed an association between platelet transfusion and mortality in ALI/ARDS, our findings indicate that platelet transfusion is likely just a marker for RBC transfusion in our study population because we found no statistically significant effect once adjusted for RBC transfusion. This is surprising, given that units of platelets contain leukocytes and likely cause immunomodulatory effects similar to packed RBCs.⁶⁶ It is possible that the effect is smaller and, since platelets are often administered with packed RBCs, that with adjustment for RBCs we were unable to detect this effect in our cohort.

Several limitations should be considered. In a cohort study such as ours, a major concern is that of confounding by indication; that patients with greater severity of illness require greater amounts of transfusion; and it is this severity of illness that is associated with mortality and not the blood products. This can be partially accounted for by including markers of severity of illness as well as clinical variables known to impact mortality into the multivariable explanatory model. As such, the findings of association with mortality were robust to adjustment for APACHE III score,²⁴ age and gender,²⁴ long-term alcohol use,⁶⁷ and diabetes.⁶⁸ Of note, consistent with these prior studies, we found an association of many of these variables with risk of mortality in simple unadjusted analyses, although this was not the purpose of this study. Our study is limited by the retrospective collection of transfusion data as well as the retrospective analysis of previously collected data. Furthermore, as this is a single-center study, its results may not be generalizable to other settings.

Of note, a further limitation of our study design may also explain why we did not find an association between transfusion before the onset of ALI/ARDS

and mortality. This study enrolled patients with established ALI/ARDS. It is possible that patients at risk for ALI/ARDS received transfusion and died before the onset of ALI/ARDS, reflecting an informed censoring of our patient population. Thus, this study was not designed to answer whether RBC transfusion is a risk factor for mortality in those at risk for ALI/ARDS, but addressed the risk in those who already have ALI/ARDS. Also, as a cohort study, our findings reflect an association of RBC transfusion and mortality but cannot prove causation.

This study was also unable to distinguish between ALI/ARDS and transfusion-related lung injury (TRALI). This noncardiogenic pulmonary edema syndrome resembles ALI/ARDS clinically and radiographically.⁶⁹ Survival in patients with TRALI is higher than in patients with ALI/ARDS,⁷⁰ and it is possible that the lack of association of RBCs administered before ALI/ARDS and death is due to misclassification of patients with TRALI. In our analysis, massive transfusion was not statistically significant as a primary or secondary risk factor, suggesting potential misclassification of TRALI as ALI/ARDS did not affect the validity of our results. While this still remains of concern, the most recent epidemiologic study⁵³ of TRALI suggests an incidence of 1 in 4,410 U of packed RBCs transfused; given the number of units transfused in our cohort (3,041), misclassification of TRALI as ALI/ARDS most likely has minimal statistical effect.

Our study showed that RBC transfusion was associated with increased risk of mortality in ALI/ARDS and that this deleterious effect was exerted predominantly by transfusions after the onset of ALI/ARDS. Given these findings, and in the absence of evidence suggesting otherwise, clinicians should not use a liberal transfusion strategy in patients with established ALI/ARDS. Given our findings, as well as previous literature cited, including the multicenter, prospective Transfusion Requirements in Critical Care study,²⁹ which showed that a conservative transfusion strategy was associated with a lower incidence of the development of ARDS as well as equivalent or better outcomes in morbidity and mortality, physicians should strongly consider using a transfusion threshold of a hemoglobin of 7 g/dL in their patients with established ALI/ARDS and no other indication for transfusion. Further study, including randomized control trials of transfusion strategies in patients with and at risk for ALI/ARDS is a logical next step.

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