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Does Erythrocyte Blood Transfusion Prevent Acute Kidney Injury?

Propensity-matched Case Control Analysis

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ABSTRACT

Background: Acute kidney injury is a common occurrence in intensive care unit patients with a reported incidence of 11–67% and is associated with an increased risk of death. In other patient populations, erythrocyte transfusion has been associated with increased risk of adverse outcomes including sepsis, multisystem organ dysfunction, and death. The purpose of this study was to determine the effect of erythrocyte transfusion on the development of acute kidney injury.

Methods: This was a retrospective analysis of prospectively collected data that used propensity matched transfused and nontransfused patients. Propensity matching was done using semiparsimonious logistic regression. McNemar test for nonindependent data sets was used to compare groups.

Results: Four hundred two patients from a trial on fluid management in patients with acute lung injury were matched. 38% of transfused patients had a rise in creatinine the day after transfusion compared with 33% of their nontransfused matches ($P = 0.315$). By day 7, creatinine had increased in 51% of transfused patients compared with 52% in nontransfused patients ($P = 0.832$). The incidences of renal risk, injury, and failure were 39 (19%), 27 (13%), and 11 (5%) in the transfused group and 38 (19%), 24 (12%), and 11 (5%) in the nontransfused group, $P = 1.00$, 0.785, and 1.00, respectively.

Conclusions: Transfusion of erythrocytes to patients with acute lung injury had no effect on the development of acute kidney injury.

What We Already Know about This Topic

- Acute kidney injury (AKI) occurs commonly in critically ill patients and is associated with death
- Erythrocyte transfusion may worsen AKI after cardiopulmonary bypass

What This Article Tells Us That Is New

- In a retrospective, secondary analysis of 402 patients with acute lung injury, measures of AKI were not different in those who received erythrocyte transfusions from those who did not

ACUTE kidney injury (AKI) is a common occurrence in intensive care unit (ICU) patients with a reported incidence of 11–67% depending on the population studied and the definition employed.[1–5] When AKI develops, there is a progressive increase in mortality associated with the severity of the renal dysfunction.[1,3,6–11] Even minimal increase (less than 0.5 mg/dl) in serum creatinine is associated with increased risk of death.[12] Anemia is common in ICU patients, and studies in cardiac surgery patients have shown that anemia is an independent risk factor for postoperative AKI.[13,14] In ICU patients with dialysis-dependent AKI, anemia (hemoglobin less than 9 g/dl) is independently associated with death.[15]

The renal medulla exists in a relatively ischemic penumbra and is very sensitive to mismatches in oxygen delivery and demand and thus teeters on the edge of ischemic injury.[16] Experiments have shown that normovolemic anemia produces a proportional fall in renal oxygenation and consumption.[17,18] Since the days of Adam and Lundy, who promul-

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gated the "10/30 rule," physicians have transfused anemic patients to try to prevent organ ischemia,[19] yet little study has been done to determine the effect of transfusion as a treatment for anemia on the development of AKI. Transfusing blood has been shown to increase systemic oxygen delivery, but not have any effect on systemic oxygen consumption.[20–23] During storage, erythrocytes are exposed to and produce substances that impair their functions when returned to the circulation. This leads to reduced functional capillary density (a measure of microvascular perfusion that is the number of erythrocyte-perfused capillaries per unit volume of tissue),[24] decreased erythrocyte deformability, increased adhesion of erythrocytes to vascular endothelium and decreased microvascular flow.[24,25] In this situation, transfusion may, instead of improving oxygenation through increased oxygen-carrying capacity, worsen renal oxygen balance and promote AKI.

Few studies have evaluated the effect of erythrocyte transfusion on renal function. Habib *et al.* found that anemia during cardiopulmonary bypass was associated with postoperative AKI and that transfusion to treat anemia on bypass was associated with worsening of AKI.[26] This finding that transfusion during cardiopulmonary bypass is nephrotoxic was confirmed by Huybregts *et al.* who measured *N*-acetyl-β-D-glucosaminidase, a sensitive marker of renal injury, and found that it increased 25-fold from 1.8 units/g creatinine (95% confidence interval, 0.8–2.8) to 45.3 units/g creatinine (95% confidence interval, 30.3–60.4) in the transfused group compared with only a 6-fold rise in *N*-acetyl-β-D-glucosaminidase from 1.9 units/g creatinine (95% confidence interval, 1.2–2.6) to 12.2 units/g creatinine (95% confidence interval, 9.1–15.2), $P < 0.05$ in the nontransfused group.[27] However, these studies in patients undergoing cardiopulmonary bypass may not be applicable to critically ill patients in the ICU. The purpose of this study is to determine the effect of erythrocyte transfusion on AKI as measured by changes in creatinine levels in patients critically ill with acute lung injury.

Materials and Methods

Patient Selection

This study was a secondary analysis of ARDSNet05 Fluid and Catheter Treatment Trial, a study sponsored by the National Institutes of Health (Bethesda, MD) to evaluate the effect of pulmonary artery *versus* central venous catheters and a liberal *versus* conservative fluid strategy on mortality in patients with acute lung injury.[28] The initial study was approved by the respective site institutional review boards, and all patients or their surrogates gave written informed consent. After this study was approved by the St. Vincent Mercy Medical Center Institutional Review Board, a data distribution agreement was signed for the release and analysis of deidentified data. Patient eligibility, inclusion criteria, and methods of the original study have been described previously. Briefly, adult patients who were receiving positive-pressure ventilation by endotracheal tube and had a ratio of the partial pressure of arterial oxygen (Pa_{O_2}) to the fraction of inspired oxygen (F_{IO_2}) less than 300 (adjusted if the altitude exceeded 1,000 m) and bilateral infiltrates on chest radiography consistent with the presence of pulmonary edema not caused by left atrial hypertension were eligible for the study.[28] Patients were excluded if acute lung injury was present for more than 48 h or if chronic conditions were present "that could independently influence survival, impair weaning, or compromise compliance with the protocol, such as dependence on dialysis or severe lung or neuromuscular disease; and irreversible conditions for which the estimated 6-month mortality rate exceeded 50%, such as advanced cancer."[28] Patients were enrolled between June 8, 2000, and October 3, 2005. Data collection included demographics, comorbidities, presumed etiologies of acute lung injury, acute physiology and chronic health evaluation system (APACHE) III scores, and baseline ventilatory settings, laboratory values, and hemodynamic data. In addition, hemodynamic data, laboratory values, fluid types (including erythrocyte transfusions) and amounts, and diuretic and vasopressor administration fluids for study days 1–6 were included. Ventilator settings and blood gas results were only collected for days 1–4. Per protocol, patients who were receiving dialysis were not eligible for the study and were excluded.[28]

To isolate the effect of transfusion on the development of AKI and the need for dialysis and because transfusion is not a random event but is physician-driven and based on factors such as hypotension and anemia that may predispose both to renal dysfunction and transfusion, transfused and nontransfused patients were matched using propensity scores. Propensity scores were determined by first converting continuous variables to categorical ones by binning them into deciles based on their rank order, as is done in goodness-of-fit tests.[29] Because missing data are not random, but may reflect differences in patient morbidity, missing data were assigned their own categorical bin.[30] This allowed all patients to be included in the analysis rather than excluding patients with missing data or imputing values for the missing data, which introduces potentially damaging biases.[31,32] Propensity scores (or the likelihood of being transfused), between 0 and 1, were calculated separately for each day of the study, thus producing six separate scores for each patient, using semiparsimonious binary logistic regression. Values selected for entry into the propensity score calculation were demographics, comorbidities, APACHE III scores, etiologies of acute respiratory distress syndrome, and daily laboratory values, ventilator settings, and hemodynamic data and were based on the univariable *P* value of the binned variables being less than 0.20, using the Fisher exact test or the chi-square test. (Because there must be fewer variables in the model than transfused patients, a semiparsimonious model using variables that were most likely to differ was chosen.) Because the original purpose of the study was to compare fluid management (liberal *vs.* conservative) and type of catheter (pulmonary artery *vs.* central venous), these four groups were forced into

Table 1. Variables Used in the Propensity Score and Match

	Transfused (n = 201)		Nontransfused (n = 201)		
Baseline	Number	%	Number	%	*d* (%)
Male	99	49	110	55	11
White	129	64	129	64	4.5
Central venous catheter group	91	45	91	45	0
Liberal fluid group	113	56	114	57	1.3
	Mean	SD	Mean	SD	*d* (%)
APACHE III	101	31	96	31	8.9
Age, yr	50	17	51	15	7.9
Height, cm	170	10	169	12	8.7
Creatinine, mg/dl	1.2	0.8	1.2	0.8	3.2
	Median	IQ Range	Median	IQ Range	*d* (%)
Weight, kg	78	63–95	84	70–99	12.8
On Day of Transfusion	Number	%	Number	%	*d* (%)
Capillary refill normal	170	84	159	79	3.1
Mottled knees	5	2	8	4	5.1
Cold extremities	10	5	19	9	7.3
Anasarca present	57	28	45	22	9.0
Vasopressor use	60	30	65	32	4.3
Diuretics used	78	39	79	39	6.1
	Mean	SD	Mean	SD	*d* (%)
Hemoglobin, g/dl	9.3	1.4	9.4	1.4	4.2
Sodium, mM	140	6	140	6	7.7
Chloride, mM	108	7	107	7	6.9
Bicarbonate, meq/l	24	6	24	6	4.9
Total protein, g/dl	4.7	1.0	4.9	0.9	7.4
PAOP, mmHg	16	5	15	5	7.0
Plateau pressure, cm H_2O	26	7	25	6	8.3
Peak airway pressure, cm H_2O	32	9	31	9	5.1
Temperature, Celsius	37.2	0.9	37.4	1.0	8.0
	Median	IQ Range	Median	IQ Range	*d* (%)
Potassium, mM	3.9	3.5–4.3	3.9	3.5–4.3	6.5
Glucose, mg/dl	123	101–154	125	97–162	6.5
Creatinine, mg/dl	1.1	0.7–1.9	1.1	0.8–1.8	6.9
Blood urea nitrogen, mg/dl	24	14–42	23	14–37	6.5
Albumin, g/dl	1.9	1.5–2.4	2.0	1.6–2.4	5.9
Central venous pressure, mmHg	12	9–16	11	9–14	6.0
Cardiac index, l/min/m^2	4.2	3.3–5.5	3.9	3.2–4.7	8.1
Urine output, ml/kg/h	1.2	0.7–2.4	1.4	0.8–2.3	9.6
Ventilator rate, min^{-1}	25	20–32	25	20–31	4.9
Total respiratory rate, min^{-1}	28	24–35	28	22–35	5.3
Total minute ventilation, l	12	10–14	12	10–14	5.1
PEEP, cm H_2O	8	5–12	8	5–10	7.2
Mean airway pressure, cm H_2O	15	12–19	14	11–17	6.6
F_{IO_2}	0.5	0.4–0.7	0.5	0.4–0.6	8.7
Pa_{O_2}, mmHg	78	67–95	76	66–94	8.1
Pa_{CO_2}, mmHg	40	36–48	40	35–48	9.9
Arterial pH	7.36	7.32–7.43	7.38	7.31–7.43	7.8
Heart rate, min^{-1}	98	85–112	97	84–110	8.3
Systolic blood pressure, mmHg	112	100–129	114	99–128	9.4
Diastolic blood pressure, mmHg	56	50–66	60	51–68	5.9

(*continued*)

Table 1. Continued

	Median	IQ range	Median	IQ range	*d* (%)
Mean arterial pressure, mmHg	75	67–85	77	67–89	4.5
Weight gain, kg	3.1	−0.4–2.9	3.1	−0.3–2.9	3.1
Fluid in, l	4.2	2.8–5.8	3.9	2.5–5.3	6.0
Fluid out, ml	2.1	1.4–3.5	2.7	1.6–4.2	8.4

d values are calculated based by their binned frequencies, but continuous variables are unbinned and displayed as mean ± SD or median and interquartile range.

APACHE = Acute Physiology and Chronic Health Evaluation system; *d* = distance metric; F_{IO_2} = fraction of inspired oxygen; IQ range = interquartile range; P_{aCO_2} = partial pressure of arterial carbon dioxide; P_{aO_2} = partial pressure of arterial oxygen; PAOP = pulmonary artery occlusion pressure; PEEP = positive-end expiratory pressure.

the propensity model. Patients who were transfused were matched with patients who were never transfused on the basis of near-identical (within 0.01) propensity scores on the day of transfusion using a greedy algorithm. First-transfused and nontransfused subjects whose propensity scores differed by less than 0.00001 were matched; then those who differed by less than 0.0001, then less than 0.001, and finally less than 0.01 were matched (Visual Basic, Excel; Microsoft, Redmond, WA). Patients who were transfused on more than 1 day were only included once. The balance of the propensity model was confirmed by quantifying bias using the *d* statistic $d = 100\% \ (P_t - P_c)/([P_t(1 - P_t) + P_c(1 - P_c)]/2)$.[5] where P_t is the prevalence or proportion of that variable who received transfusion and P_c is the prevalence or proportion of that variable who did not receive transfusion.[33] Where there were more than two categories for a variable, *d* was calculated for each category and the mean *d* presented. Small absolute values of *d*, usually less than 10%, support the assumption of balance.[33]

Endpoint Evaluation

The study evaluated four endpoints of AKI as determined by the Risk, Injury, Failure, Loss, End-stage renal disease system (RIFLE): RIFLE-Risk (an increase in creatinine by 50%), RIFLE-Injury (a doubling of creatinine), RIFLE-Failure (a tripling of creatinine), and any rise in creatinine.[12,34] Because of lack of data on 6- or 12-h urine volumes, only serum creatinine criteria were used to determine the RIFLE category. Previous study has shown that creatinine criteria are more accurate than urine criteria in predicting mortality.[2] To control for the fact that transfusion given after AKI occurs cannot be the cause of the renal dysfunction, patients who received blood only after AKI occurred were censored at the time of dysfunction and were treated for analysis as being nontransfused. To determine the effect of transfusion on renal function, we evaluated the change in creatinine levels between day of transfusion (or day of no-transfusion in the matched patients) and day 7, the end of the study. For the most sensitive criteria—any rise in creatinine—we also analyzed the effect of transfusion on the daily change in serum creatinine, calculated as creatinine on day n + 1 minus creatinine on day n, using the matched patients.

Statistical Analysis

McNemar test for nonindependent datasets was used to compare groups. $P < 0.05$ denotes statistical significance. Based on a power analysis with 80% power and $\alpha = 0.05$, 400 patients were needed to find a rise to 60% or a fall to 40% in the incidence of AKI (assuming the incidence in nontransfused patients of the most sensitive indicator—any rise in creatinine—is 50%). For the RIFLE-Risk category, assuming a 20% incidence in nontransfused patients, these 400 patients would have an 80% power and $\alpha = 0.05$ to find an increase to 29% or a decrease to 12.5% in the incidence associated with transfusion. SPSS 16.0 and 17.0 (SPSS, Inc., Chicago, IL) and EXCEL 2003 (Microsoft, Inc.) were used for analysis. Continuous data are presented as mean ± SD or median with interquartile range as determined by the Shapiro-Wilk statistic and categorical data as number and percentage. All *P* values are two-tailed.

Results

In the initial ARDSNet study, 327 of the 1,000 participants received erythrocyte transfusions on days 1–6. Two hundred and one (61.5%) of the 327 transfused patients were matched with a nontransfused patient, producing 402 subjects. There were 99 pairs from day 1, 19 from day 2, 35 from day 3, 22 from day 4, 10 from day 5, and 16 from day 6. The paired patients were well balanced, with mean distance, $d = 6.7 \pm 2.4$ and only 2 of 47 variables, weight and sex, having $d \geq 10.0\%$ (table 1). Similarly, near-identical median propensity scores for each day and their ranges indicated good balance, and the *c* statistic appropriately showed an inability to discriminate between the two well-matched groups (table 2).

Pneumonia and sepsis were the most common causes of acute lung injury (table 3). Patients were predominantly male (52%), white (64%), and middle-aged (51 ± 16 yr). Vasopressors were being administered to 31% and diuretics to 39%. On the day of the transfusion decision, serum creatinine was 1.2 ± 0.8 mg/dl, and hemoglobin was 9.3 ± 1.4 g/dl. More than one-third (38%) of patients had any rise in creatinine the day after transfusion compared with 33% of their nontransfused matches ($P = 0.315$) The occurrences of RIFLE-Risk, Injury, and Failure were similar in both groups (table 4). By 90 days, 42 (21%) of the transfused patients received dialysis compared to with (15%) of the nontrans-

Table 2. Daily Propensity Scores of Transfused and Matched Nontransfused Patients on the Day of the Match

	Transfused		Nontransfused					
Day	Median	Range	Median	Range	*P* Value*	*c* Statistic	SE	*P* Value†
1	0.81090	0.36366–0.98869	0.80956	0.36682–0.98871	0.989	0.501	0.041	0.986
2	0.50544	0.04419–1.00000	0.50940	0.05193–1.00000	0.965	0.496	0.095	0.965
3	0.79740	0.34631–0.98966	0.79867	0.35002–0.98961	0.997	0.501	0.070	0.986
4	0.91192	0.71354–0.99320	0.91192	0.71354–0.99320	1.000	0.500	0.088	1.000
5	0.80143	0.42277–0.97085	0.80146	0.42109–0.97064	1.000	0.505	0.133	0.970
6	0.83239	0.61401–0.99154	0.83288	0.61404–0.99154	0.997	0.508	0.104	0.940

* Compares transfused and nontransfused matched patients. † Compares the calculated *c* statistic with 0.500 (no association). *c* statistic = area under the receiver operator characteristic curve.

fused patients ($P = 0.202$) and 68 and 66 patients, respectively, had died ($P = 0.904$).

Discussion

We found that transfusion had no effect on AKI, as measured by increases in serum creatinine; it was neither beneficial nor harmful. Our results differ from one study in cardiac surgery patients, where transfusion had an additive effect to anemia on postoperative AKI.[26] However, our results of no effect is similar to another study in cardiac surgery patients.[14] In several studies of cardiac or aortic surgery patients, an association between AKI and transfusion has been claimed.[35–37] However, they failed to control for the relative timing of transfusion and AKI and cannot say whether transfusion preceded (and possibly caused) AKI or AKI preceded transfusion and hence transfusion could not cause AKI. Karkouti *et al.* found an association between AKI and transfusion given on the day of or the day after cardiac surgery.[38] But, even here, the timing of AKI was not given, and if it were simultaneous with surgery, AKI may have preceded transfusion. Boyle *et al.* found no association between AKI requiring dialysis and intraoperative transfusion in patients undergoing cardiac transplantation.[39]

Several studies have found that transfusion is associated with multiple organ system dysfunction as a composite outcome in critically ill patients; however, they did not report the incidences of AKI as an individual outcome.[40,41] Our study differs from those by evaluating only AKI. The effects of transfusion may vary by organ because different tissues have different tolerances for anemia.[17] Similarly, the effects may also vary by patient illness. For example, transfusion is associated with increased mortality after coronary artery bypass surgery and coronary artery combined with valve surgery, but not after isolated valve surgery.[42,43] Our lack of an effect by transfusion may only be applicable in patients with acute lung injury, and studies will need to be done in ICU patients suffering from other illnesses.

Anemia, even mild or moderate, is associated with the development of AKI,[44] and given the relatively hypoxic milieu, it is surprising why an increase in oxygen content from transfused erythrocytes failed to mitigate AKI. There are several possible reasons for this. The functionally impaired transfused erythrocytes may physically obstruct capillary flow thus worsening cellular and tissue oxygen balance.[22,24,25] Second, the alterations that erythrocytes undergo during storage that lead to increased neutrophil counts and macrophage inflammatory protein-2 and chemokine concentrations along with loss of the erythrocyte ability to scavenge inflammatory cytokines may lead to renal damage that negates the beneficial effects of increased oxygen delivery.[45] Transfusion-related acute lung injury is an increasingly commonly recognized complication that may affect as many as 8% of the population and is felt to be related to donor antibodies binding with recipient antigens leading to pulmonary epithelium damage.[46] Pulmonary and renal tissues may have similar responses to inflammation or antibodies. They

Table 3. Causes of Acute Lung Injury

	Transfused (n = 201)						Nontransfused (n = 201)						
	Primary		Secondary		Not a Factor		Primary		Secondary		Not a Factor		
Cause	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P* Value
Trauma	20	10	5	2.5	176	88	16	8	1	0.5	184	82	0.193
Sepsis	57	28	35	17	109	54	52	26	32	16	114	57	0.843
Aspiration	20	10	10	5	171	85	27	13	14	7	160	80	0.354
Pneumonia	87	43	26	13	88	44	92	36	37	18	72	36	0.160
Other	17	8.5	14	7	170	85	14	7	6	3	181	90	0.147

Shows the number of patients for each factor felt to be the primary cause (Primary) or a secondary cause (Secondary) or felt not be a factor (Not a Factor) of acute lung injury.

Table 4. Incidence of Acute Kidney Injury

	Next Day					By Day 7				
	Transfused n = 201		Not Transfused n = 201			Transfused n = 201		Not Transfused n = 201		
Incidence	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Any rise in creatinine	76	38	67	33	.315	102	51	105	52	0.832
RIFLE-Risk						39	19	38	19	1.00
RIFLE-Injury						27	13	24	12	0.785
RIFLE-Failure						11	5	11	5	1.00

The number of patients who had a rise in creatinine the day after a transfusion (next day) or anytime between transfusion and day 7 (by day 7) was given (transfused) or not given (not transfused) in the patients matched for propensity to be transfused on that day.
RIFLE = Risk, Injury, Failure, Loss, End-stage renal disease system; RIFLE-Risk = an increase in creatinine by 50%; RIFLE-Injury = a doubling of creatinine; RIFLE-Failure = a tripling of creatinine; and any rise in creatinine.[12,34]

both are the primary organs affected in antibody-mediated pulmonary-renal syndromes such as Goodpasture disease and necrotizing granulomatous vasculitis (formerly Wegener granulomatosis).[47,48] We can speculate that a third reason for the failure of transfused erythrocytes to protect renal function and ameliorate AKI is that erythrocyte transfusion may elicit a renal injury similar to its lung injury, and this injury may offset any benefit provided by increased oxygen content.

We used propensity scores to match transfused cases with nontransfused controls; however, there are limitations to its use. There may be unmeasured variables that affect the decision to transfuse, and their exclusion from the propensity score may bias the results.[49] Another limitation, as described by Nuttall and Houle, is that propensity scores are usually calculated on baseline data, thus introducing a bias created by the time dependence of transfusion[49]; that is, transfusions are not given on the day baseline data are collected, but are given several days later. To minimize these two limitations, we censored data at the time of transfusion; we used hemodynamic, laboratory, and ventilatory data present on the day of transfusion to compute the propensity score (daily values may have a greater effect on the decision to transfuse than do baseline values) and required nontransfused matched-controls to still be alive and in the ICU on the day of the propensity match.

Another limitation of this study is that patients were transfused at relatively high hemoglobin levels (9.3 ± 1.4 g/dl). Whereas one randomized study[50] found that a lower hemoglobin threshold, 7 g/dl, produced mortality outcomes that were at least equal to a higher hemoglobin threshold, 10 g/dl, and may have lowered the hemoglobin level at which some patients are transfused, other studies continue to show hemoglobin transfusion triggers, particularly in patients receiving mechanical ventilation, similar to the 9.3 ± 1.4 g/dl found in our study.[51–56] We also cannot exclude that transfusion may be renally protective or harmful at some other hemoglobin level. However, future studies will need to find this hemoglobin level.

A third limitation is that this is a retrospective analysis of data prospectively collected as part of a randomized trial evaluating fluid management in acute lung injury. As such, the results found here may not imply or exclude causality and randomized studies are recommended.

A fourth limitation is that creatinine values were only available through the seventh day of the study. We cannot exclude transfusion having either a delayed beneficial or harmful effect that did not occur until after the seventh day. Against this is that the dialysis rate was similar in both groups: 42 (21%) of the transfused patients received dialysis compared with 30 (15%) of the nontransfused patients ($P = 0.202$).

There are several strengths of this study. First, this is a multisite study, so the practice patterns and results may be more generalizable than a single-site study. Second, we chose to use four different rises (any, RIFLE-Risk, RIFLE-Injury, and RIFLE-Failure) in creatinine and two different times (next day and by seventh day) to assess the different severities and time courses of acute kidney injury. The results of no effect of transfusion on creatinine elevations were consistent across all creatinine levels and times. Even small rises in creatinine are associated with increased mortality, and the risk of death is proportional to the elevation in creatinine.[26,51,57]

Another strength is our use of propensity matching to balance the transfused and nontransfused groups. Both groups had similar demographics, vasopressor and diuretic use, and hemodynamic, ventilatory, and laboratory parameters with a mean distance, $d = 6.7 \pm 2.4$, and 98% were less than 10%. In particular, hemoglobin and creatinine values were the same. This allowed us to better separate the effects of transfusion from other causes of AKI.

We used a clinically relevant marker of AKI—change in creatinine—that has been shown to be linked with increased risk of dying, rather than more sensitive markers of AKI, such as *N*-acetyl-β-D-glucosaminidase, whose clinical relevance remains to be determined.[58] If these novel biomarkers prove clinically relevant, studies evaluating the effect of transfusion on AKI should include these biomarkers.

In summary, we found that erythrocyte transfusions in patients with acute lung injury had no effect on the develop-

ment of AKI. Future studies should evaluate the effects at lower levels of hemoglobin than found in this study.

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