Clinical predictors of and mortality in acute respiratory distress syndrome: Potential role of red cell transfusion*

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Objective: **Clinical predictors for acute respiratory distress syndrome (ARDS) have been studied in few prospective studies. Although transfusions are common in the intensive care unit, the role of submassive transfusion in non-trauma-related ARDS has not been studied. We describe here the clinical predictors of ARDS risk and mortality including the role of red cell transfusion.**

Design: **Observational prospective cohort.**

Setting: **Intensive care unit of Massachusetts General Hospital.**

Patients: **We studied 688 patients with sepsis, trauma, aspiration, and hypertransfusion.**

Interventions: **None.**

Measurements and Main Results: **Two hundred twenty-one (32%) subjects developed ARDS with a 60-day mortality rate of 46%. Significant predictors for ARDS on multivariate analyses included trauma (adjusted odds ratio [OR_{adj}] 0.22, 95% confidence interval [CI] 0.09–0.53), diabetes (OR_{adj} 0.58, 95% CI 0.36–0.92), direct pulmonary injury (OR_{adj} 3.78, 95% CI 2.45–5.81), hematologic failure (OR_{adj} 1.84, 95% CI 1.05–3.21), transfer from another hospital (OR_{adj} 2.08, 95% CI 1.33–3.25), respiratory rate >33 breaths/min (OR_{adj} 2.39, 95% CI 1.51–3.78), hematocrit >37.5% (OR_{adj} 1.77, 95% CI 1.14–2.77), arterial pH <7.33 (OR_{adj} 2.00, 95% CI 1.31–3.05), and albumin ≤2.3 g/dL (OR_{adj} 1.80, 95% CI 1.18–2.73). Packed red blood cell transfusion was associated with ARDS (OR_{adj} 1.52, 95% CI 1.00–2.31, $p = .05$). Significant predictors for mortality in ARDS included age (OR_{adj} 1.96, 95% CI 1.50–2.53), Acute Physiology and Chronic Health Evaluation III score (OR_{adj} 1.78, 95% CI 1.16–2.73), trauma (OR_{adj} 0.075, 95% CI 0.006–0.96), corticosteroids before ARDS (OR_{adj} 4.65, 95% CI 1.47–14.7), and arterial pH <7.22 (OR_{adj} 2.32, 95% CI 1.02–5.25). Packed red blood cell transfusions were associated with increased mortality in ARDS (OR_{adj} 1.10 per unit transfused; 95% CI 1.04–1.17) with a significant dose-dependent response ($p = .02$).**

Conclusions: **Important predictors for the development of and mortality in ARDS were identified. Packed red blood cell transfusion was associated with an increased development of and increased mortality in ARDS. (Crit Care Med 2005; 33:1191–1198)**

KEY WORDS: acute respiratory distress syndrome; transfusion; mortality; respiratory failure; acute lung injury

Acute respiratory distress syndrome (ARDS) is a common pulmonary disorder of critically ill patients that usually occurs after an injury such as sepsis, trauma, or aspiration. The incidence, cytokine profile, and mortality rate in ARDS differ by the type of injury that predisposed the individual to ARDS (1, 2), suggesting that the pathogenesis and outcome of ARDS may differ for different predisposing clinical risks. Yet few prospective studies have examined the risk and outcomes of ARDS with each of these common disorders (1, 3–5) and none have used the American European Consensus Conference definition of ARDS that is used widely today. Such epidemiologic standardization is necessary before we can assess the contribution of biomarkers to the development of ARDS.

There has been much recent debate about transfusion practices in critically ill patients. The Transfusion Requirement in Critical Care Study showed no benefit to a liberal transfusion strategy (6). Blood replacement has been associated with lung injury as a result of both transfusion-related lung injury (TRALI) and massive transfusions (1, 4, 7). Some have advocated transfusion of critically ill patients to improve oxygen delivery given its properties in volume expansion and oxygen delivery (8, 9). However, transfusion has been linked to increased complications and infections among critically ill patients and in patients after cardiac surgery (10–13). ARDS patients often have evidence of oxygen debt, but consequences of red cell transfusions in ARDS patients have not been studied.

We describe a large epidemiologic prospective study of critically ill patients at risk for ARDS as a result of sepsis, pneumonia, trauma, massive transfusions, and aspiration. We report on the clinical factors associated with the development of and mortality in ARDS including an association between transfusion of red cells and the development of and mortality in ARDS.

***See also p. 1420.**

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Supported, in part, by research grant RO1 HL60710 from the National Heart, Lung, and Blood Institute (Massachusetts General Hospital, Boston, MA); grant K23 HL67197 from the National Heart, Lung, and Blood Institute (MNG, Massachusetts General Hospital and Mount Sinai School of Medicine, New York); and grant T32 HL07874 (PDB), Massachusetts General Hospital.

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DOI: 10.1097/01.CCM.0000165566.82925.14

MATERIALS AND METHODS

Study Population. As part of a molecular epidemiology study of ARDS, admissions to the neurologic, cardiac, medical and surgical intensive care units (ICUs) of the Massachusetts General Hospital (MGH, Boston, MA) were screened daily for risk factors for ARDS (Table 1). Exclusion criteria included age <18 yrs, diffuse alveolar hemorrhage or chronic lung disease, which may mimic ARDS, and directive to withhold intubation. Because inflammatory cytokines are examined in the parent study, patients with neutropenia not secondary to sepsis and immunosuppression secondary to medication or diseases such as HIV infection were excluded. Treatment with granulocyte colony-stimulating factor or inhibitors of tumor necrosis factor was excluded. After November 2000, immunosuppression secondary to corticosteroid was removed as an exclusion criterion due to the increasing use of steroids in sepsis. Patients enrolled after this change were more likely to be female ($p = .01$), Caucasian ($p = .03$), with a history of steroid use ($p < .001$) and diabetes ($p = .02$), and were more likely to have been transfused with blood ($p = .007$). There was no difference in the rate of or mortality in ARDS, clinical risk factor, age, severity of illness, and baseline comorbid condition. Adjusting for whether the patient was enrolled before or after the change in exclusion criteria changed the estimates in the final models for ARDS and mortality in ARDS 0–7% with no change in statistical significance. The change in estimate for transfusion and the development of ARDS or mortality in ARDS was <1%.

Patients admitted to the ICU with at least one defined risk factor for ARDS (Table 1) and no exclusion criteria were eligible for the study. The Human Subjects Committees of the MGH and Harvard School of Public Health approved the study, and informed written consent was obtained from all subjects or their appropriate surrogates.

Baseline clinical data and demographics such as age, past history of ARDS, diabetes or liver disease, alcohol abuse, or tobacco use were collected. Organ failure was defined according to the Brussels Organ Dysfunction Score (14), whereby cardiovascular failure is defined as systolic blood pressure <90 mm Hg or need for vasopressor, renal failure is defined as creatinine <2.0 mg/L, hepatic failure is defined by total bilirubin >2.0 mg/dL, and hematologic failure is defined as platelets <80,000/m^3. Vital signs and laboratory values in the first 24 hrs of ICU admission were collected. Recollection and re-entry of the clinical data from 89 (13%) subjects selected at random revealed a data-entry error rate of 1% and a data collection error rate of 2.8%. All data were collected onto clinical data forms and entered into an ACCESS database at the Harvard School of Public Health.

As part of quality control for genotyping in the parent study, the transfusion history in the 8 days before enrollment into the study was recorded (15). Ninety percent of the subjects were enrolled within 7 days of ICU admission, with ARDS developing a median of 1 day after ICU admission (25–75% quartile 0–3 days). In 66 (30%) of ARDS patients, at least one transfusion during the period of observation occurred after development of ARDS. Thus, the analysis was repeated after excluding transfusion received after development of ARDS. As a result, the period of observation for ARDS patients was shorter (median 7 days, 25–75% quartile 6–7 days) than for non-ARDS patients. Data on type, date, and number of transfusions were collected from the blood bank's computerized clinical database. Decision to transfuse was left to the treating physicians, and no predetermined transfusion protocol was enforced. Research coordinators were blinded to the possibility that transfusion may be related to ARDS.

For each patient, research coordinators collected daily information on respiratory failure, arterial blood gas, presence of bilateral infiltrates on chest radiographs, and pulmonary arterial occlusion pressure if right heart catheter was present or notation of congestive heart failure on progress notes. For each day of the study, enrolled patients were screened for ARDS as defined by respiratory failure requiring intubation and fulfillment of American European Consensus Conference criteria for ARDS as follows (16): a) presence of hypoxemia as evidenced by $Pao_2/Fio_2 \leq 200$ mm Hg; b) presence of bilateral infiltrates on chest radiographs; and c) absence of left atrial hypertension as evidenced by pulmonary arterial occlusion pressure ≤18 mm Hg or lack of notation for congestive heart failure as a problem in the progress note.

Infiltrates on chest radiographs were defined as opacities that cannot be explained completely by pleural effusions, mass, body habitus, or collapse. Upper zone redistribution and pulmonary vascular congestion were not considered infiltrates. Daily chest radiographs were interpreted by two pulmonary and critical care physicians (MNG, PDB, BTT, or DCC). Any disagreement went to a third intensivist for arbitration. All physicians underwent a consensus training session on the radiologic criteria for ARDS. All were blinded to the clinical status of the patients and the presence of other criteria for ARDS. The kappa score for agreement between radiologic interpretation of bilateral infiltrates was 0.75 (95% confidence interval [CI] 0.62–0.89), which is comparable to other reports after consensus training (17). Patients with ARDS were followed for all-cause 60-day mortality.

Statistical Analysis. Serum albumin, bilirubin, and arterial pH were missing for 90 (13%), 87 (13%), and 50 (7%) subjects, respectively. All other variables were complete in ≥95% of the patients. Like the Acute Physiology and Chronic Health Evaluation (APACHE) III study, missing values tended to occur in patients with stable vital signs or laboratory values ($p \leq .03$). Similar to the APACHE III study, normal values closest to the median value for the cohort were assigned to missing values here (18). Nonphysiology data such as history of diabetes or tobacco use were coded as missing.

Univariate analyses were performed using Fisher's exact test for dichotomous variables and Wilcoxon rank sum for continuous variable as the data did not have a normal distribution. Continuous variables were modeled assuming a linear or step function after categorizing by quartiles. When no model appeared to be the best, a linear relationship was assumed. Clinical risks and predictors from the univariate analyses with $p \leq .06$ were studied in a multiple logistic regression model using a backward elimination algorithm and eliminated if they did not meet $p \leq 0.1$. Final

Table 1. Study required risk factors for acute respiratory distress on admission to intensive care unit

Sepsis: As defined by SCCM (53) to be a known or suspected source of systemic infection and at least two of the following: a) temperature >38°C or <36°C; b) heart rate >90 beats/min; c) respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg; d) WBC >12,000/mm^3, <4000/mm^3, or >10% bands.

Septic shock: Fulfill requirements for sepsis and one of the following: a) SBP <90 mm Hg or reduction of ≥40 mm Hg from baseline for ≥30 mins unresponsive to 500 mL of fluid resuscitation; b) need for vasopressors to maintain SBP 90 mm Hg or within 40 mm Hg of baseline.

Pneumonia: Fulfill two or more of the following: a) new infiltrate on CXR; b) temperature >38.3°C or <36.0°C or WBC >12,000 or <4000 or >10% bandemia; c) positive microbiologic culture.

Trauma: Defined as multiple fractures and/or pulmonary contusions. Multiple fractures are defined as a fracture of two long bones, an unstable pelvic fracture, or one long bone and a pelvic fracture. Pulmonary contusion is defined as infiltrates on CXR within 8 hrs of admission to the emergency room and evidence of blunt trauma to the chest such as fractured ribs or ecchymosis overlying the infiltrate.

Multiple transfusions: Defined as receiving ≥8 units of PRBCs within 24 hrs.

Aspiration: Defined as witnessed or documented aspiration event or the retrieval of gastric contents from the oropharynx, endotracheal tube, or bronchial tree

SCCM, Society of Critical Care Medicine; WBC, white blood cell count; SBP, systolic blood pressure; CXR, chest radiograph; PRBC, packed red blood cells.

models included predictors from backward elimination as well as clinically relevant factors such as age and APACHE III scores for the development of ARDS and alcohol abuse, chronic liver disease, and septic shock for mortality in ARDS. The C-statistic was 0.80 for the final model for development of ARDS and 0.83 for the final model on mortality in ARDS. Interactions between transfusion and other clinical risks factors for ARDS in the model were tested with the addition of an interaction term, but no significant interaction was found in the final models for development of ARDS and mortality in ARDS ($p > .2$). In the final model, $p \leq .05$ was considered statistically significant. All analyses were conducted using SAS version 8 (SAS Institute, Cary, NC).

RESULTS

Between September 9, 1999, and August 7, 2002, 1,072 admissions were eligible for the study. In 58 subjects, the treating physician declined the study, whereas 51 subjects died before consent. No appropriate surrogate was available for 83 patients, and 151 patients or their surrogates declined the study. Three admissions before November 2000 were excluded after enrollment because corticosteroid was initiated. Thirty-eight individuals qualified for the study on more than one ICU admission, but only the first admission was included in this study. Thus, 688 individuals were available for analyses.

Clinical information was available in 299 (87%) eligible nonparticipants for whom consent was not obtained. Nonparticipants were significantly more likely to be non-Caucasian and less likely to have aspiration or sepsis without hypotension on admission to the ICU. Otherwise, participants and nonparticipants did not differ significantly in age, gender, severity of illness, comorbid diseases, and frequency of alcohol or tobacco abuse ($p > .06$).

Development of ARDS. A total of 221 (32%) subjects developed ARDS a median of 1 day after ICU admission (25–75% quartile 0–3 days). Table 2 shows the proportions of patients who developed ARDS with each precipitating condition. Sepsis and septic shock patients with pneumonia were more likely to develop ARDS than those with extrapulmonary sources of infections (odds ratio [OR] 3.41, 95% CI 1.79–6.48 in sepsis and OR 2.84, 95% CI 1.77–4.57 in septic shock). Septic shock increased the risk of ARDS in patients with pneumonia (OR 1.55, 95% CI 1.00–2.42).

The baseline characteristics between ARDS patients and at-risk non-ARDS patients are shown in Table 3. On univariate analysis of the physiology variables, patients who developed ARDS also had higher heart rates ($p < .001$), respiratory rates ($p < .001$), and hematocrit ($p = .01$), and lower albumin ($p < .001$) and arterial pH ($p < .001$) than did non-ARDS subjects in the first 24 hrs of ICU admission. The median hematocrit for patients with ARDS was 34.4% (25–75% quartile 31.1–39.5) compared with 33.6% in those without ARDS (25–75% quartile 30.3–36.8, $p = .01$). Subjects with ARDS were enrolled a median of 2 days after ICU admission (25–75% quartile, 1–4 days) compared with a median of 1 day for non-ARDS patients (25–75% quartile 1–2 days, $p < .001$). Race, age, alcohol or tobacco abuse, corticosteroid treatment, kidney or liver failure, mean arterial pressure, temperature, urine output, white blood cell count, serum sodium, potassium, blood urea nitrogen, glucose, and bicarbonate were not significantly associated with ARDS ($p > 01$).

Table 4 shows the clinical predictors for development of ARDS in the final multivariate model after adjusting for days between enrollment and admission. Trauma as a risk factor for ARDS and diabetes was associated with a decreased risk of ARDS, whereas direct pulmonary injury, hematologic failure defined as platelets ≤80,000/mm, transfer from outside hospital, respiratory rate >33 breaths/min, hematocrit >37.5%, arterial pH <7.33, serum albumin ≤2.3 g/dL, and transfusion of packed red blood cells (PRBCs) were associated with increased development of ARDS.

ARDS patients were transfused more frequently (61%) than non-ARDS patients (49%, $p = .004$), with ARDS patients receiving a median of 1 unit of PRBCs (25–75% quartile 0–3) compared with a median of 0 units (25–75% quartile 0–3) among non-ARDS patients ($p = .04$). On multivariate analysis (Table 4), transfusion of any number of units of

Table 2. Etiology of acute respiratory distress syndrome (ARDS) in cohort

	Development of ARDS				60-Day Mortality in ARDS			
Risk for ARDS	Non-ARDS (n = 467), No. (%)	ARDS (n = 221), No. (%)	Rate of ARDS, %[a]	*p* Value	Survivors (n = 119), No. (%)	Nonsurvivors (n = 102), No. (%)	Mortality Rate, %[b]	*p* Value
Sepsis syndrome	174 (37)	71 (32)	29	NS	48 (40)	23 (23)	32	.006
Pneumonia source	91 (19)	56 (25)	38	<.001	36 (30)	20 (20)	36	NS
Extrapulmonary source	83 (18)	15 (7)	15		12 (10)	3 (3)	20	
Septic shock	205 (44)	121 (55)	37	.009	54 (45)	67 (66)	55	.003
Pneumonia source	91 (19[e])	84 (38)	48	<.001	37 (31)	47 (47)	56	NS
Extrapulmonary source	114 (24[e])	37 (17)	25		17 (14)	20 (19)	54	
Trauma	46 (10)	10 (5)	18	0.02	9 (8)	1 (1)	10	0.02
Multiple transfusions	57 (12)	23 (10)	29	NS	10 (8)	13 (13)	57	NS
Aspiration	38 (8)	23 (10)	38	NS	11 (9)	12 (12)	52	NS
>1 risk for ARDS	54 (12)	27 (12)	33	NS	13 (11)	14 (14)	52	NS
Direct pulmonary injury[c]	226 (48)	155 (70)	41	<.001	85 (71)	70 (69)	45	NS
Indirect pulmonary injury[d]	241 (52)	66 (30)	22		34 (29)	32 (31)	48	

NS, not statistically significant ($p > .05$). Numbers of patients with each risk add up to more than 688 patients because of multiple risks in 58 patients.
[a]Number of subjects with risk with ARDS/total number of subjects with risk in cohort; [b]number of ARDS nonsurvivors with risk/TOTAL number of ARDS subjects with risk; [c]pneumonia, aspiration, or pulmonary contusions were categorized as direct pulmonary injury; [d]sepsis from an extrapulmonary source, trauma without pulmonary contusions, and multiple transfusions were categorized as indirect pulmonary injury: patients with both direct and indirect pulmonary injuries were considered to have direct pulmonary injury; [e]does not sum up to expected percentage because of rounding.

Table 3. Baseline characteristics in the cohort

	Development of ARDS			Mortality in ARDS		
	Non-ARDS (n = 467)	ARDS (n = 221)	*p* Value	Survivors (n = 119)	Nonsurvivors (n = 102)	*p* Value
Females, n (%)	183 (39)	102 (46)	NS	50 (42)	52 (51)	NS
White, n (%)	433 (93)	199 (90)	NS	105 (88)	94 (92)	NS
Age, median (range)	67 (18–94)	65 (18–97)	NS	55 (18–89)	73 (22–97)	<.001
APACHE III, median (range)[a]	63 (10–137)	68 (8–136)	.03	70 (8–128)	89 (40–150)	<.001
Diabetes, n (%)[b]	123 (26)	41 (19)	.03	25 (21)	16 (16)	NS
History of alcohol abuse, n (%)	49 (10)	28 (13)	NS	12 (10)	16 (16)	NS
Tobacco abuse, n (%)[c]	223 (60)	104 (63)	NS	56 (67)	48 (64)	NS
Chronic liver disease, n (%)[b]	22 (5)	11 (5)	NS	4 (3)	7 (7)	NS
End-stage renal disease, n (%)	25 (5)	6 (3)	NS	2 (2)	4 (4)	NS
History of steroid use, n (%)	39 (8)	24 (11)	NS	9 (8)	15 (15)	NS
Transfer from another hospital, n (%)	82 (16)	78 (35)	<.001	40 (34)	37 (36)	NS
Transfusion of PRBCs, n (%)	228 (49)	134 (61)	.001	65 (55)	69 (68)	.05
Number of PRBCs transfused, median (range)	0 (0–74)	1 (0–63)	.04	1 (0–31)	2 (0–63)	.02
Systolic BP <90 mm Hg, n (%)	319 (68)	169 (76)	.03	86 (72)	83 (81)	NS
Creatinine > 2.0 mg/L, n (%)	159 (34)	68 (31)	NS	29 (24)	39 (38)	.03
Bilirubin >2.0 mg/dL, n (%)	55 (12)	34 (15)	NS	14 (12)	20 (20)	NS
Hematologic failure (platelets ≤80,000/mm), n (%)	59 (13)	40 (18)	.06	16 (13)	24 (24)	.05

ARDS, acute respiratory distress syndrome; NS, not statistically important for final model ($p \geq .1$); APACHE, Acute Physiology and Chronic Health Evaluation; PRBCs, packed red blood cells; BP, blood pressure.

[a]For development of ARDS, APACHE III scores for patients and controls were calculated without the Pao_2/Fio_2 component: For mortality in ARDS, the APACHE III score was calculated with all components; [b]chronic health information was missing on one patient and two controls; [c]tobacco history was missing in 56 (26%) patients and 97 (22%) controls.

PRBCs was associated with increased odds of developing ARDS (OR_{adj} 2.19, 95% CI 1.42–3.36, $p < .001$). After categorizing by quartile, there was a trend toward increasing rate of ARDS with increased transfusion ($p = .05$, Fig. 1). Although the rate of ARDS appears to decline in those patients transfused with >3 units of PRBCs compared with those transfused with ≤3 units, this is due to a higher proportion of trauma patients (18% vs. 5%, $p < .001$), who had the lowest rate of ARDS, and a lower percentage of patients with septic shock (35% vs. 51%, $p < .001$) and direct pulmonary injury (27% vs. 63%, $p < .001$), who had the highest rates of ARDS. There was no difference between patients transferred to the study hospital and nontransfers in the frequency of transfusions (49% of transfers vs. 54% of nontransfers, $p > .3$) or in the number of PRBCs transfused (median of 0 units, 25–75% quartile 0–2 units for transfers compared with median of 1 unit, 25–75% quartile 0–3 units among nontransfers, $p > .08$).

Because the period of observation overlapped with the development of ARDS in some ARDS patients, the analysis was repeated after excluding transfusions received after the development of ARDS. In one patient without ARDS and in 16 patients with ARDS, the number of units transfused or the timing of transfusions relative to the development of ARDS could not be determined accurately as these patients had received transfusions at another institution before transfer to MGH. These patients were also excluded, leaving 205 patients with ARDS and 466 patients without ARDS for the restricted analysis. Although the period of observation for transfusion was shorter for ARDS patients (median 7 days, 25–75% quartile 6–8) compared with the 8 days of observation for non-ARDS patients ($p < .001$), the association between transfusion and the development of ARDS in the restricted analysis remained significant (OR_{adj} 1.52, 95% CI 1.00–2.31, $p = .05$). Transfusions were given a median of 1 day before development of ARDS (25–75% quartile, 4 days before to day of development of ARDS). Although prior reports of transfusion and ARDS pertained mostly to massive transfusions of ≥10 units of blood (1, 2, 4), only 12% of patient in this study were massively transfused (Table 2) and the majority of patients in this study received submassive amounts of PRBCs (median 3 units, 25–75% quartile 2–8).

Mortality in ARDS. The 60-day mortality rate for the 221 patients with ARDS was 46%. The etiology for ARDS and baseline characteristics between survi-

Table 4. Multivariate analysis for the development of acute respiratory distress syndrome (ARDS)

	Odds Ratio (95% Confidence Interval)	*p* Value
Trauma	0.22 (0.09–0.53)	<.001
Diabetes	0.58 (0.36–0.92)	.02
Direct pulmonary injury	3.78 (2.45–5.81)	<.001
Transfer from another hospital	2.08 (1.33–3.25)	.001
Hematologic failure (platelets <80,000/mm^3)	1.84 (1.05–3.21)	.03
HR >99 beats/min	1.58 (0.96–2.61)	NS
RR >33 breaths/min	2.39 (1.51–3.78)	<.001
Hematocrit >37.5%	1.77 (1.14–2.77)	.01
Arterial pH <7.33	2.00 (1.31–3.05)	.001
Albumin ≤2.3 g/dL	1.80 (1.18–2.73)	.006
APACHE III, per point increase	1.00 (0.99–1.01)	NS
Age, per year of age	1.00 (0.99–1.01)	NS
Transfusion of PRBCs	2.19 (1.42–3.36)	<.001

HR, heart rate; NS, not statistically significant, $p > .05$; RR, respiratory rate; APACHE, Acute Physiology and Chronic Health Evaluation; PRBCs, packed red blood cells. APACHE III score was calculated without the arterial-alveolar oxygen gradient score as it is a part of the criteria for ARDS.

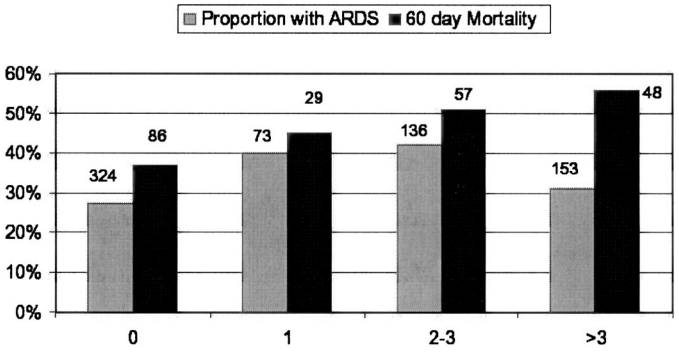

Figure 1. Development of acute respiratory distress syndrome (*ARDS*) and 60-day mortality rate in ARDS by number of packed red cells transfused in the 8 days before enrollment. Number of patients analyzed is specified within each bar. The *p* value for chi-square trend test was .05 for ARDS and .02 for mortality in ARDS. Two patients were not included because of missing data on total number of units transfused.

vors and nonsurvivors with ARDS are shown in Tables 2 and 3, respectively. ARDS secondary to sepsis without hypotension and trauma had the lowest mortality rates (32% and 10%, respectively). All other risk factors were associated with similar mortality rate in ARDS. Direct pulmonary injury was associated with a greater risk of ARDS ($p < .001$) but no difference in mortality rate ($p = .7$).

On univariate examination of physiologic variables in the first 24 hrs of ICU admission, nonsurvivors were more likely to have lower temperatures ($p = .02$), mean arterial blood pressures ($p < .001$), urine output ($p = .002$), and arterial pH ($p = .008$) and higher blood urea nitrogen ($p = .004$). There were no statistically significant differences between the survivors and nonsurvivors for gender, race, time between ICU admission and study enrollment, history of diabetes, liver or kidney failure or disease, tobacco or alcohol use, frequency of shock on admission, lung injury score, and tidal volume/kg of ideal body weight on first day of ARDS (median 9.7 mL/kg 25–75% quartile 8.2–11.5 for the cohort, $p > .8$).

The results for the multivariate analysis for mortality in ARDS are shown in Table 5. Trauma as a risk factor for ARDS was associated with decreased mortality in ARDS. Significant predictors for increased mortality in ARDS include age, APACHE III score on admission, corticosteroid treatment ≥15 mg/day prednisone or ≥300 mg of prednisone in the 21 days before development of ARDS, arterial pH < 7.22, and transfusion of PRBCs.

Among those with ARDS, 65 (55%) survivors and 69 (68%) nonsurvivors were transfused (OR 1.79, 95% CI 1.03–3.11, Table 3). Survivors received a median of 1 unit of PRBCs (25–75% quartile 0–2) compared with 2 units (25–75% quartile 0–4) in nonsurvivors ($p = .02$). On multivariate analysis, transfusion of PRBCs was associated with increased risk of mortality in ARDS (OR_{adj} 1.10 per unit transfused, 95% CI 1.04–1.17). All transfusions in the 8 days before enrollment into the study both before and after development of ARDS were used in this analysis. After we categorized the number of units of blood transfused according to quartiles, there was a significant trend to increasing mortality rate with increased transfusions ($p = .02$, Fig. 1).

DISCUSSION

We identified several clinically important factors in the development and outcome of ARDS in a large prospective cohort of at-risk individuals including an association between transfusion and the development of and mortality in ARDS. This is consistent with findings from the Transfusion Requirement in Critical Care Study, in which patients randomized to the liberal transfusion strategy had a nonstatistically significant greater risk of developing ARDS (11.4% vs. 7.7%, $p = .06$) and a greater mortality rate (23.3% vs. 18.7%, $p = .11$) than the patients in the restrictive group (6).

This study has the benefit of being a prospective cohort at risk for ARDS, which reduces several potential problems such as recall or coding biases associated with retrospective studies. In addition, the clear characterization of clinical risks for ARDS in this study is advocated by some in decreasing the clinical heterogeneity in studies of ARDS given that the incidence, natural history, cytokine profiles, and outcomes of ARDS differ significantly by etiology of ARDS (19–21). Finally, the focus of this study on critically ill patients who have the opportunity to develop the outcome is more clinically relevant to the critical care physician.

The associations found between ARDS and the clinical risk factors, low arterial pH, hematologic failure, hypoalbuminemia, and absence of diabetes, are consistent with previous reports (1, 5, 22–25). Unlike previous studies (5, 26), we did not find an association between alcohol abuse or chronic liver disease and ARDS, likely a result of insufficient power since only 5% patients had evidence of chronic liver disease and only 1% of patients had a history of alcohol abuse in this cohort. The association between mortality in ARDS and age and severity of illness is consistent with other reports (26–30).

We report several novel observations. In this study, direct pulmonary injury

Table 5. Multivariable analysis for predictors of mortality in acute respiratory distress syndrome (ARDS)

	Odds Ratio (95% Confidence Interval)	*p* Value
Trauma	0.075 (0.006–0.96)	<.05
Age, per decade of age	1.96 (1.50–2.53)	<.001
APACHE III, per 25-point increase[a]	1.78 (1.16–2.73)	.008
History of corticosteroid treatment before ARDS	4.65 (1.47–14.7)	.009
History of alcohol abuse	2.68 (0.93–7.74)	NS
Chronic liver disease	3.07 (0.65–14.5)	NS
Septic shock	1.24 (0.58–2.62)	NS
Arterial pH <7.22	2.32 (1.02–5.25)	.04
Pack red blood cells, per unit transfused	1.10 (1.04–1.17)	.001

APACHE, Acute Physiology and Chronic Health Evaluation.
[a]Calculated with all components of the APACHE III.

progressed to ARDS significantly more frequently than indirect pulmonary injury. However, when pneumonia is complicated by a systemic insult such as septic shock, the risk of ARDS increases significantly. This suggests an additive role of direct alveolar injury from pneumonia and endothelial injury from systemic inflammatory response associated with pneumonia-induced severe sepsis. However, although direct pulmonary injury was significantly associated with the development of ARDS, there was no effect on the outcome in ARDS. This finding is consistent with some, but not all, prior studies (27, 31).

An association between a high hematocrit and an increased risk for developing ARDS has not been reported previously. This finding may represent hemoconcentration from increased systemic and pulmonary capillary leak in those patients who progress to ARDS. The association between steroid treatment before admission and mortality in ARDS has not been described. Immunosuppression or relative adrenal insufficiency may increase mortality in ARDS. Alternatively, steroid treatment may be a marker of comorbid disease. The importance of these two findings is unclear and will need to be confirmed.

Although massive transfusion of ≥10 units of blood over 12–48 hrs has been associated with ARDS, especially in trauma patients (1, 3, 4, 11, 32), it is not clear whether submassive transfusion of PRBCs may lead to increased development of and increased mortality in ARDS. We found in this cohort an association between transfusion of PRBCs and the development of and mortality in ARDS. The majority of these patients received modest transfusions (median 3 units, 25–75% quartile 2–8 units). Among ARDS patients, the transfusion of even one unit of PRBCs was associated with increased mortality in ARDS.

However, this study was not expressly designed to examine the role of transfusion in ARDS. Thus, other potentially important factors that may clarify the nature of the association between transfusion and ARDS, such as the age of stored blood products, transfusion of other blood products, the percentage of leukocyte-filtered blood given, and the transfusion history for the entire ICU course of the patients, cannot be assessed. Although clinically suspected pulmonary edema from volume overload must be excluded for the diagnosis of ARDS, transfusions resulting in unsuspected pulmonary edema cannot be excluded as a pulmonary artery catheter was not required for ARDS. Last, although age and severity of illness were adjusted for in the final analyses, it is difficult to exclude confounding by indication in an uncontrolled study. Indeed, the odds ratio for the development of ARDS was reduced from 2.19 to 1.53 after excluding transfusions given after development of ARDS. This could be secondary to the shorter period of observation for transfusion in ARDS patients compared with non-ARDS patients, which would bias the result toward the null. However, although the association between transfusion and ARDS remained significant after exclusion of transfusion given after ARDS, we cannot exclude the possibility that transfusion is a marker of clinical suspicion for ARDS or poor outcome not captured by the data collected. Thus, these findings will need to be confirmed, preferably in randomized controlled study.

TRALI is generally thought to be rare with an incidence of 1 in 5,000 transfusions (34, 35), and none of the ARDS patients in this study was considered to have TRALI. A possible association between transfusion and ARDS in this study raises the question of the true incidence of TRALI, especially in ICU patients, where other risk factors for lung injury are common. Although granulocyte and human leukocyte antigen antibodies have been implicated in TRALI (35, 36), the exact mechanism of lung injury in TRALI is unclear. A "two-hit" model of TRALI has been theorized whereby some predisposing comorbid condition such as infection results in sequestration of neutrophils in the lung (37, 38). Then, a second hit consisting of exposure to lysophosphotidylcholine accumulated in stored PRBCs results in lung injury. Such a model has important clinical implications with regard to transfusion of critically ill patients.

No study, to our knowledge, has examined the relationship between transfusion and outcomes specifically in ARDS. Our finding that transfusion of PRBCs was associated with increased mortality rate in ARDS in a dose-dependent manner is consistent with prior reports of transfusion in other critically ill patients (12, 39–42). This association has been attributed to aged, stored blood (40, 45) and the immunosuppressive effects of allogenic blood (44), with a resultant increased risk of nosocomial infections and ventilator-associated pneumonia (47). Indeed, transfusions have been associated with increased immunosuppression and down-regulation of inflammatory cytokine response in septic rats and after surgery (46–51). The risk of infection is particularly relevant here, as most patients with ARDS die of sepsis (52).

We acknowledge a few limitations to our study. MGH is a tertiary academic hospital and frequently accepts transfers of patients with ARDS, so the results here may not be generalizable to community hospital setting. However, transfers are unlikely to explain the finding between transfusions and ARDS because they were adjusted for in the analyses and there was no association between transfer from another hospital and the frequency and volume of transfusion received. In addition, because of the study design, the results may not be generalizable to minorities, to immunocompromised hosts, or to patients without risk factors for ARDS or with different clinical risk factors for ARDS. Nevertheless, the population stud-

Packed red blood cell transfusion was associated with an increased development of and increased mortality in acute respiratory distress syndrome.

ied is relevant to a large proportion of critically ill patients.

CONCLUSION

This study describes differences in the development and outcome of ARDS with different clinical risk conditions and identifies several novel clinical predictors for the development of ARDS such as a high hematocrit and chronic corticosteroid treatment. Although massive transfusions have been associated with ARDS, we report here a possible association between submassive transfusion of PRBCs and development of and mortality in ARDS. A randomized control trial is needed to definitively determine whether transfusions can increase the risk of lung injury and mortality in ARDS and whether a simple change in transfusion practice can decrease the incidence of ARDS and improve mortality rates in at-risk patients.

ACKNOWLEDGMENTS

We thank Wei-Ling Zhang, Kelly McCoy, Thomas McCabe, and Barbara Bean for patient recruitment; Andrea Solomon, Andrea Shafer, and Lia Shimada for research support; Janna Frelich, Marcia Chertok, Sal Mucci, and Richard Rivera for data management; Paige Williams, PhD, for statistical assistance; and David Miller, ScD, for his epidemiologic advice.

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