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Role of Diabetes in the Development of Acute Respiratory Distress Syndrome

Shun Yu, BS¹, David C. Christiani, MD, MPH^{2,3}, B. Taylor Thompson, MD², Ednan K. Bajwa, MD, MPH², and Michelle Ng Gong, MD, MS^{1,4}

¹Division of Critical Care Medicine, Department of Medicine, Jay B. Langner Critical Care Service, Montefiore Medical Center, Bronx, NY

²Pulmonary and Critical Care Unit, Department of Medicine, Massachusetts General Hospital, Boston, MA

³Environmental Health Department, Environmental and Occupational Medicine and Epidemiology Program, Harvard School of Public Health, Boston, MA

⁴Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY

Abstract

Objectives—Diabetes has been associated with decreased development of acute respiratory distress syndrome in some, but not all, previous studies. Therefore, we examined the relationship between diabetes and development of acute respiratory distress syndrome and whether this association was modified by type of diabetes, etiology of acute respiratory distress syndrome, diabetes medications, or other potential confounders.

Design—Observational prospective multicenter study.

Setting—Four adult ICUs at two tertiary academic medical centers.

Patients—Three thousand eight hundred sixty critically ill patients at risk for acute respiratory distress syndrome from sepsis, pneumonia, trauma, aspiration, or massive transfusion.

Interventions—None.

Measurements and Main Results—Diabetes history was present in 25.8% of patients. Diabetes was associated with lower rates of developing acute respiratory distress syndrome on univariate (odds ratio, 0.79; 95% CI, 0.66–0.94) and multivariate analysis (adjusted odds ratio, 0.76; 95% CI, 0.61–0.95). After including diabetes medications into the model, diabetes remained protective (adjusted odds ratio, 0.75; 95% CI, 0.59–0.94). Diabetes was associated with decreased development of acute respiratory distress syndrome both in the subgroup of patients with sepsis

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Address requests for reprints to: Michelle Ng Gong, MD, MS, Division of Critical Care Medicine, Department of Medicine, Jay B. Langner Critical Care Service, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467. mgong@montefiore.org.

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(adjusted odds ratio, 0.77; 95% CI, 0.61–0.97) and patients with noninfectious etiologies (adjusted odds ratio, 0.30; 95% CI, 0.10–0.90). The protective effect of diabetes on acute respiratory distress syndrome development is not clearly restricted to either type 1 (adjusted odds ratio, 0.50; 95% CI, 0.26–0.99; $p = 0.046$) or type 2 (adjusted odds ratio, 0.77; 95% CI, 0.60–1.00; $p = 0.050$) diabetes. Among patients in whom acute respiratory distress syndrome developed, diabetes was not associated with 60-day mortality on univariate (odds ratio, 1.11; 95% CI, 0.80–1.52) or multivariate analysis (adjusted odds ratio, 0.81; 95% CI, 0.56–1.18).

Conclusions—Diabetes is associated with a lower rate of acute respiratory distress syndrome development, and this relationship remained after adjusting for clinical differences between diabetics and nondiabetics, such as obesity, acute hyperglycemia, and diabetes-associated medications. In addition, this association was present for type 1 and 2 diabetics and in all subgroups of at-risk patients.

Keywords

acute lung injury; acute respiratory distress syndrome; diabetes mellitus; hyperglycemia; risk factors

Acute respiratory distress syndrome (ARDS) is a common life-threatening condition in the critically ill, with an estimated 150,000 cases per year in the United States and affecting up to 20% of all mechanically ventilated patients (1–3). ARDS develop in patients with a predisposing injury such as sepsis, pneumonia, trauma, or aspiration (4–6), but this risk is then altered by genetic predispositions (7) and presence of risk modifiers, including alcohol abuse (8), hypoalbuminemia (9, 10), transfusions (10), tachypnea (11), high tidal volumes (12), and obesity (13).

Diabetes mellitus has been identified as another risk modifier in some, but not all, previous studies. Consistent with the fact that ARDS may be a heterogeneous syndrome, some studies have found diabetes to be associated with lower development of ARDS among patients with at least one predisposing ARDS condition such as sepsis (10, 11, 13–17), whereas one study found diabetes to increase risk of ARDS in postsurgical patients (18). However, another study found that diabetes was not associated with development of ARDS in an unselected ICU population (19).

These differing findings have raised questions about whether the association between diabetes and ARDS may be confounded by baseline differences between diabetics and nondiabetics, such as obesity, hyperglycemia, or treatment with medications that may be independently beneficial against lung injury, including aspirin (20–22), statins (23–25), angiotensin-converting enzyme inhibitors (26, 27), insulin (28–30), peroxisome proliferator-activated receptor (PPAR)- γ agonists (31–33), and metformin (34). In addition, it is currently unclear whether the effect of diabetes on ARDS development is confined to a particular predisposing risk condition like sepsis or is specific to a particular type of diabetes (type 1 or type 2). In a large prospective cohort of critically ill patients at risk for ARDS, we investigated the association between diabetes and ARDS development and the impact of potential confounders on this relationship.

MATERIALS AND METHODS

All patients in this study were enrolled at Massachusetts General Hospital (MGH) and Beth Israel Deaconess Medical Center (BIDMC) as part of the Molecular Epidemiology of ARDS study as described previously (10, 13, 35). Briefly, consecutive admissions to the adult medical and surgical ICUs were screened for one or more study-defined risk factors for ARDS and enrolled if eligible (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCM/A700>). The Human Subjects Committees of the MGH, BIDMC, and Harvard School of Public Health approved the study, and informed written consent was obtained from all subjects or their appropriate surrogates.

Baseline demographic and clinical data were collected from patient medical records, including age, gender, ethnicity, alcohol abuse, tobacco history, and comorbidities such as chronic liver disease and end-stage renal disease requiring dialysis. Vital signs and laboratory values, including blood glucose, were collected within the first 24 hours of ICU admission. Acute hyperglycemia was defined as blood glucose greater than 180 mg/dL and hypoglycemia defined as blood glucose less than 70 mg/dL as per American Association of Clinical Endocrinologist consensus guidelines (36). Cardiovascular (systolic blood pressure < 90 mm Hg), renal (creatinine > 2 mg/dL), hepatic (total bilirubin > 2 mg/dL), and hematologic (platelets < 80,000/m³) organ failure were defined according to Brussels Organ Dysfunction Score (37). Body mass index (BMI) was calculated based on admission height and weight.

History of diabetes mellitus was determined based on review of the patient's past medical history. Medications used by patients prior to ICU admission were retrospectively collected from medical records for patients enrolled prior to March 2008, but prospectively collected afterward. Criteria for categorizing type of diabetes were selected a priori, based on prior studies (38–40), younger age of diagnosis in type 1 diabetics (41, 42), and differences in therapies between type 1 and type 2 diabetes (43). If medical records did not explicitly specify type 1 or type 2 diabetes, then patients were categorized as having type 1 diabetes if 1) the patient was on insulin and no oral hypoglycemic medication and either 2) had diabetes diagnosed before age 25 or 3) was started on insulin less than 2 years after diagnosis of diabetes. Patients were categorized as type 2 diabetics if 1) the patient was on any oral hypoglycemic medication such as metformin, sulfonylureas, meglitinides, or thiazolidinediones, 2) had diabetes diagnosed after age 25, or 3) was started on insulin more than 2 years after diagnosis of diabetes. Diabetic patients who could not be categorized as either type 1 or type 2 diabetes were classified as diabetes type-unknown.

Research staff screened all patients daily for the development of ARDS, as per American-European Consensus Committee (AECC) (44): 1) hypoxemic respiratory failure requiring intubation and Pao₂/Fio₂ less than or equal to 200 mm Hg; 2) bilateral infiltrates on chest radiograph; and 3) pulmonary arterial occlusion pressure less than or equal to 18 mm Hg or no suspicion of congestive heart failure. Two physicians reviewed the chest radiographs daily, with disagreements arbitrated by a third physician. All physicians underwent consensus training on the radiographic criteria for ARDS. The κ for radiologic agreement

was good (0.75; 95% CI, 0.60–0.90) (45). Patients in whom ARDS developed were followed for all-cause 60-day mortality.

Statistical Analysis

Univariate analysis was performed using Fisher exact test for dichotomous variables and Student *t* test or Wilcoxon rank sum test for normal and nonnormal continuous variables, respectively. Thirty-three patients (1%) were missing past medical history pertaining to diabetes and were excluded from this analysis. In addition, 466 patients (12%) had missing BMI, 487 patients (13%) had missing tobacco history, 109 patients (3%) had missing transfusion information, and 183 patients (5%) had missing medication data. All other variables were complete in more than 99% of subjects. Patients missing BMI data were imputed the median BMI for the cohort as suggested (46, 47) while all other missing data were treated as missing during multivariate analysis.

Multivariate logistic regression was performed to account for potential confounders. In addition, the model was stratified by hospital center and year of enrollment to account for site-specific differences and temporal changes over the course of the study, respectively. Variables related to diabetes and development of ARDS on univariate analysis ($p < 0.1$) were included into a backward elimination model and eliminated if p value was greater than 0.1. Eliminated variables were added back to the model if it produced a change in estimate of greater than 10%. In addition, clinically important variables were added, such as direct pulmonary injury (10), alcohol abuse within the past year (8), and hyperglycemia within 24 hours of ICU admission, for analyzing risk of developing ARDS, and history of metastatic cancer (35, 48) and sepsis (35, 48, 49), for mortality in ARDS. A p value of less than or equal to 0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Between September 9, 1999, and March 27, 2012, 3,860 subjects were enrolled in the Molecular Epidemiology of ARDS study. A total of 987 patients (26%) had a past medical history of diabetes (Fig. 1). Compared to nondiabetics, diabetic patients were older, sicker, more obese, and more likely to have history of chronic liver and end-stage renal disease (Table 1). Diabetics were more likely to be at risk for ARDS from septic shock but less likely to have trauma and multiple transfusions as the predisposing clinical risk factor.

Development of ARDS

A total of 954 patients (25%) developed ARDS a median of 1 day after ICU admission (25–75% quartile, 0–2 d). Prevalence of ARDS was significantly higher among patients with septic shock and those with direct cause of pulmonary injury (defined as pneumonia, aspiration, or pulmonary contusion) (Table 2). At baseline, ARDS developed in patients who were generally younger, had higher BMI, and were more likely to have comorbidities of liver disease, end-stage renal disease, alcohol abuse, and active tobacco use. ARDS developed in patients who had higher Acute Physiology and Chronic Health Evaluation

(APACHE) III scores and were more likely to have evidence of other organ failures within the first 24 hours of ICU admission.

On univariate analysis, progression to ARDS was lower among diabetics, occurring in 21% of diabetic patients compared to 26% of nondiabetic patients (odds ratio [OR], 0.79; 95% CI, 0.66–0.94) (Fig. 2). On multivariate analysis, after adjusting for age, BMI, APACHE III score, ICU admission hyperglycemia, renal failure, hematologic failure, comorbidities such as tobacco and alcohol use, and predisposing condition for ARDS, diabetes remained significantly associated with decreased development of ARDS (adjusted odds ratio [OR_{adj}], 0.76; 95% CI, 0.61–0.95) (Table 3). By contrast, ICU admission hyperglycemia was associated with increased risk of ARDS on univariate analysis (OR, 1.20; 95% CI, 1.04–1.39) but not after multivariate analysis (OR_{adj}, 1.04; 95% CI, 0.86–1.26).

A number of medications were associated with both diabetes and development of ARDS on univariate analysis, including angiotensin-converting enzyme inhibitors, statins, aspirin, clopidogrel, and warfarin (Tables 1 and 2). On multivariate analysis, only clopidogrel (OR_{adj}, 0.59; 95% CI, 0.34–1.00) and warfarin (OR_{adj}, 0.66; 95% CI, 0.48–0.90) remained significantly associated with ARDS development. Adding clopidogrel and warfarin to the multivariate model did not change the protective association between diabetes and ARDS development (OR_{adj}, 0.75; 95% CI, 0.59–0.94) (Table 3).

Exploratory Analysis

Type I Versus Type II Diabetes—We explored whether the protective association between diabetes and development of ARDS was specific to the type of diabetes. Among the 987 diabetic patients in our cohort, 70 patients (7%) and 688 patients (70%) were categorized as type 1 and type 2 diabetics, respectively. Of these, 96% (726 of 758) were categorized based on prior documentation of the diabetes type. The remaining 229 diabetics (23%) could not be clearly categorized as type 1 or type 2 diabetes based on available medical records and were designated as “diabetes type-unknown.” Overall, the type-unknown diabetics were more similar to type 2 than type 1 diabetics in baseline characteristics such as age and BMI (Supplemental Table 2, Supplemental Digital Content 1, <http://links.lww.com/CCM/A700>).

Compared to nondiabetics, all types of diabetics had lower development of ARDS on univariate analysis, although this was statistically significant only among type 2 diabetics (OR, 0.77; 95% CI, 0.63–0.94; $p = 0.01$), likely due to the fewer number of patients with type 1 diabetes (OR, 0.79; 95% CI, 0.44–1.40; $p = 0.42$) and type-unknown diabetes (OR, 0.87; 95% CI, 0.63–1.20; $p = 0.39$). However, after multivariate adjustment, both type 1 (OR_{adj}, 0.50; 95% CI, 0.26–0.99; $p = 0.046$) and type 2 diabetes (OR_{adj}, 0.77; 95% CI, 0.60–1.00; $p = 0.050$) were significantly associated with decreased development of ARDS. (Fig. 3). In a sensitivity analysis, when all patients with diabetes type-unknown were recategorized as type 2 diabetes, the association between type 2 diabetes and ARDS remained (OR_{adj}, 0.77; 95% CI, 0.61–0.98; $p = 0.04$).

Diabetes and ARDS by Clinical Risk Factor for ARDS—Since ARDS is a heterogeneous syndrome, we examined whether the protective effect of diabetes was

confined to only certain predisposing conditions for ARDS (Fig. 4). We found that diabetes was associated with decreased development of ARDS both in the subgroup of patients with sepsis or septic shock (OR_{adj} , 0.77; 95% CI, 0.61–0.97; $p = 0.03$) and in the subgroup of patients with only noninfectious risks for ARDS (OR_{adj} , 0.30; 95% CI, 0.10–0.90; $p = 0.03$). However, for each noninfectious risk factor such as trauma (OR_{adj} , 0.59; 95% CI, 0.11–3.15), aspiration (OR_{adj} , 1.00; 95% CI, 0.43–2.30), and multiple transfusion (OR_{adj} , 0.53; 95% CI, 0.23–1.23), the association was not significant, likely due to smaller sample size within each subgroup.

Mortality in ARDS

Among the 954 patients with ARDS, all-cause 60-day mortality was 34%. On univariate analysis, diabetes was not associated with mortality among patients with ARDS (OR , 1.11; 95% CI, 0.80–1.52). Differences in baseline characteristics between survivors and nonsurvivors with ARDS are shown in Table 2. After adjusting for age, severity of illness, sepsis, chronic liver disease, and other clinical variables associated with diabetes and mortality on univariate analysis, diabetes was not significantly associated with 60-day mortality (OR_{adj} , 0.81; 95% CI, 0.56–1.18) (Table 4). On multivariate analysis, no medications were significantly associated with 60-day ARDS mortality ($p > 0.1$).

DISCUSSION

In a cohort of critically ill patients with predisposing ARDS risk factors, diabetes was found to be independently protective against development of ARDS even after adjusting for baseline clinical differences, risk factors for ARDS, obesity, acute hyperglycemia, and diabetic medications. This association was not specific to a diabetes subtype or any particular ARDS risk condition such as sepsis. Similar to previous studies, we found that diabetes did not influence mortality among patients in whom ARDS developed (14, 15).

This study has a number of strengths. This is a large, multicenter, prospective study of ICU patients with clearly characterized risks for ARDS. This cohort was specifically designed to investigate the development of ARDS and therefore patients were prospectively screened for presence of ARDS daily. Clinicians underwent consensus training to promote uniformity and minimize phenotype misclassification. Unlike many prior studies, potential confounders such as diabetes medication, acute hyperglycemia, obesity, and type of diabetes were measured and accounted for in the analysis. The larger size of the cohort allowed for subgroup analysis to determine whether the association between diabetes and ARDS varied with the predisposing condition for lung injury.

In our cohort, diabetes was associated with decreased development of ARDS. This is consistent with findings from the original study by Moss et al (14) and five subsequent observational studies which have found similar results both in patients with septic shock (11) and among patients with any predisposing ARDS risk condition (10, 13, 16, 17) (Table 5).

Conversely, another study found that diabetes was associated with increased development of ARDS in a postsurgical cohort (18). However, patients with preexisting ARDS risk

conditions were notably excluded from this cohort, in contrast to our study. The vast majority of ARDS develop only in patients with at least one ARDS risk condition such as sepsis, shock, pneumonia, aspiration, or trauma (5). Diabetics may be at higher risk for developing ARDS because they are more likely to acquire a major predisposing ARDS risk condition, such as pneumonia or sepsis through attenuation of the immune system (50, 51), aspiration through gastroparesis (52, 53), and hypotension through autonomic neuropathy (54). Therefore, the protective association between diabetes and development of ARDS may be present only among patients who have already developed a predisposing ARDS condition. Inclusion of patients without a clear predisposing injury for ARDS into a cohort could lend heterogeneity to the population and dilute any potential protective association between diabetes and development of ARDS. For example, a study by Koh et al (19) found no association between diabetes and development of ARDS in an unselected ICU population where the majority of patients did not have any predisposing ARDS conditions.

The mechanism by which diabetes impacts development of ARDS is still unclear. Since inflammation is central to the pathogenesis of ARDS (55), many have suggested that diabetes may reduce development of ARDS through attenuation of cytokine release and impairment of neutrophil function (56, 57). Other pathways are altered in diabetes mellitus, and recent studies have shown that some may also impact development of acute lung injury, including PPAR- γ (31–33), nuclear factor- κ B (58), insulin-like growth factor-1 (59, 60), leptin (61), and development of advanced glycation end products (62, 63).

This study demonstrated that the association between diabetes and ARDS is not restricted to either type 1 or type 2 diabetes. All previous clinical studies examined diabetes mellitus as a single group although the pathogenesis of type 1 and type 2 diabetes is different. Type 1 diabetes is characterized by an autoimmune attack on pancreatic β -cells (64), whereas type 2 diabetes is a consequence of insulin resistance and is often associated with obesity, hypertension, hyperlipidemia, and hyperuricemia (65, 66). Indeed, preclinical studies have found reduced inflammatory markers and development of lung injury in animal models of both type 1 and type 2 diabetes (67). By demonstrating a relationship between type 1 diabetes and ARDS, our findings suggest that the protective effect of diabetes is not solely driven by features present only in type 2 diabetics, such as the metabolic syndrome. Similarly, we found that this association was present among patients with and without sepsis, even though the clinical features of sepsis-related ARDS may be different from non-sepsis-related ARDS (35).

Our study found that the association between diabetes and development of ARDS cannot be attributed to potential confounders, such as obesity, acute ICU hyperglycemia, and medications used to treat complications of diabetes, even though a number of preclinical and clinical studies have found that medications such as aspirin (20–22), statins (23–25), angiotensin-converting enzyme inhibitors (26, 27), insulin (28–30), PPAR- γ agonists (31–33), and metformin (34) may be independently protective against development of lung injury. However, as the prevalent use of some of these medications was low and undocumented medication use would not be detected, the results of this study do not imply the lack of benefit from these medications in ARDS. Rather, in this study, these medications do not account for the protective association between diabetes and ARDS development.

Additionally, as this is an observational study, the potential for unmeasured confounders remained. For example, prehospitalization care, such as vaccinations, could influence susceptibility to respiratory failure and ARDS. Indeed, pneumococcal vaccinations that are recommended as part of diabetic management (68, 69) have been linked to decreased mortality and respiratory failure among patients in whom pneumonia developed (70, 71).

Interestingly, we found significant associations between development of ARDS and prehospitalization use of clopidogrel (Plavix) and warfarin (Coumadin), independent of diabetes status. Although no prior study, to our knowledge, has studied the relationship between warfarin and acute lung injury, one study found antiplatelet therapy to be associated with reduced prevalence of acute lung injury (22). There may be biological plausibility for these associations since the coagulation pathway is central to the pathogenesis of acute lung injury, either through platelet activation or up-regulation of tissue factor (21, 72–74), although further studies are warranted to confirm these findings.

We acknowledge several limitations to our study. More refined characterization of diabetes and the metabolic syndrome was not possible. However, the prevalence of diabetes in our cohort is comparable to other studies of critically ill patients (14, 16, 75). In addition, the proportion of type 1 diabetes in our cohort (7% of all diabetics) is consistent with previous estimates of 5% (64, 76). We did not collect inflammatory biomarkers or data on genetic polymorphisms, which could provide a deeper understanding of the molecular pathways involved. Finally, while glucose levels within the first 24 hours were analyzed, data on chronic glucose control such as hemoglobin A1c were not available so we could not investigate whether long-term glucose control was associated with ARDS development.

CONCLUSIONS

Diabetes is associated with decreased development of ARDS but not with mortality among patients with ARDS. This study expands our understanding of the role of diabetes in the development of ARDS by showing that this association is present in both types of diabetes and among both infectious and noninfectious causes of ARDS. Furthermore, we demonstrated that the protective association found in this study is not confounded by diabetic medications, acute hyperglycemia, obesity, or other factors associated with diabetes. Future studies with additional information on genetic polymorphisms, inflammatory biomarkers, and prehospitalization data may further our knowledge in this topic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005; 353:1685–1693. [PubMed: 16236739]
2. Zaccardelli DS, Pattishall EN. Clinical diagnostic criteria of the adult respiratory distress syndrome in the intensive care unit. *Crit Care Med*. 1996; 24:247–251. [PubMed: 8605796]
3. National Heart and Lung Institute. Task Force Report on Problems, Research Approaches, Needs. Washington, DC: U.S. Government Printing Office; 1972. p. 167-180.
4. Pepe PE, Potkin RT, Reus DH, et al. Clinical predictors of the adult respiratory distress syndrome. *Am J Surg*. 1982; 144:124–130. [PubMed: 7091520]
5. Hudson LD, Milberg JA, Anardi D, et al. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995; 151(2 Part 1):293–301. [PubMed: 7842182]
6. Ferguson ND, Frutos-Vivar F, Esteban A, et al. Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: A prospective observational study. *Crit Care*. 2007; 11:R96. [PubMed: 17784960]
7. Gong MN. Genetic epidemiology of acute respiratory distress syndrome: Implications for future prevention and treatment. *Clin Chest Med*. 2006; 27:705–724. abstract x. [PubMed: 17085257]
8. Moss M, Bucher B, Moore FA, et al. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA*. 1996; 275:50–54. [PubMed: 8531287]
9. Mangialardi RJ, Martin GS, Bernard GR, et al. Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis. Ibuprofen in Sepsis Study Group. *Crit Care Med*. 2000; 28:3137–3145. [PubMed: 11008971]
10. Gong MN, Thompson BT, Williams P, et al. Clinical predictors of and mortality in acute respiratory distress syndrome: Potential role of red cell transfusion. *Crit Care Med*. 2005; 33:1191–1198. [PubMed: 15942330]
11. Iscimen R, Cartin-Ceba R, Yilmaz M, et al. Risk factors for the development of acute lung injury in patients with septic shock: An observational cohort study. *Crit Care Med*. 2008; 36:1518–1522. [PubMed: 18434908]
12. Gajic O, Frutos-Vivar F, Esteban A, et al. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive Care Med*. 2005; 31:922–926. [PubMed: 15856172]
13. Gong MN, Bajwa EK, Thompson BT, et al. Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax*. 2010; 65:44–50. [PubMed: 19770169]
14. Moss M, Guidot DM, Steinberg KP, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. *Crit Care Med*. 2000; 28:2187–2192. [PubMed: 10921539]
15. Esper AM, Moss M, Martin GS. The effect of diabetes mellitus on organ dysfunction with sepsis: An epidemiological study. *Crit Care*. 2009; 13:R18. [PubMed: 19216780]
16. Trillo-Alvarez C, Cartin-Ceba R, Kor DJ, et al. Acute lung injury prediction score: Derivation and validation in a population-based sample. *Eur Respir J*. 2011; 37:604–609. [PubMed: 20562130]
17. Gajic O, Dabbagh O, Park PK, et al. U.S. Critical Illness and Injury Trials Group. Lung Injury Prevention Study Investigators (USCIITGLIPS): Early identification of patients at risk of acute lung injury: Evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med*. 2011; 183:462–470. [PubMed: 20802164]
18. Kor DJ, Warner DO, Alsara A, et al. Derivation and diagnostic accuracy of the surgical lung injury prediction model. *Anesthesiology*. 2011; 115:117–128. [PubMed: 21694510]
19. Koh GC, Vlaar AP, Hofstra JJ, et al. In the critically ill patient, diabetes predicts mortality independent of statin therapy but is not associated with acute lung injury: A cohort study. *Crit Care Med*. 2012; 40:1835–1843. [PubMed: 22488007]

20. Sigurdsson GH, Vallgren S, Christenson JT. Influence of aspirin and steroids on acute lung injury after i.v. Injection of a sclerosing agent. *Acta Chir Scand.* 1989; 155:163–170. [PubMed: 2741624]
21. Looney MR, Nguyen JX, Hu Y, et al. Platelet depletion and aspirin treatment protect mice in a two-event model of transfusion-related acute lung injury. *J Clin Invest.* 2009; 119:3450–3461. [PubMed: 19809160]
22. Erlich JM, Talmor DS, Cartin-Ceba R, et al. Prehospitalization anti-platelet therapy is associated with a reduced incidence of acute lung injury: A population-based cohort study. *Chest.* 2011; 139:289–295. [PubMed: 20688925]
23. O'Neal HR Jr, Koyama T, Koehler EA, et al. Prehospital statin and aspirin use and the prevalence of severe sepsis and acute lung injury/acute respiratory distress syndrome. *Crit Care Med.* 2011; 39:1343–1350. [PubMed: 21336116]
24. Yao HW, Mao LG, Zhu JP. Protective effects of pravastatin in murine lipopolysaccharide-induced acute lung injury. *Clin Exp Pharmacol Physiol.* 2006; 33:793–797. [PubMed: 16922808]
25. Jacobson JR, Barnard JW, Grigoryev DN, et al. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. *Am J Physiol Lung Cell Mol Physiol.* 2005; 288:L1026–L1032. [PubMed: 15665042]
26. He X, Han B, Mura M, et al. Angiotensin-converting enzyme inhibitor captopril prevents oleic acid-induced severe acute lung injury in rats. *Shock.* 2007; 28:106–111. [PubMed: 17510605]
27. Liu H, Zhao J. An experimental study of therapeutic effect of ACEI on chemical-induced ARDS in rats. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2002; 36:93–96. [PubMed: 12410960]
28. Chen HI, Yeh DY, Liou HL, et al. Insulin attenuates endotoxin-induced acute lung injury in conscious rats. *Crit Care Med.* 2006; 34:758–764. [PubMed: 16505662]
29. Donnelly M, Condrón C, Murray P, et al. Modulation of the glycemic response using insulin attenuates the pulmonary response in an animal trauma model. *J Trauma.* 2007; 63:351–357. [PubMed: 17693835]
30. Hagiwara S, Iwasaka H, Hasegawa A, et al. Effects of hyperglycemia and insulin therapy on high mobility group box 1 in endotoxin-induced acute lung injury in a rat model. *Crit Care Med.* 2008; 36:2407–2413. [PubMed: 18596634]
31. Standiford TJ, Keshamouni VG, Reddy RC. Peroxisome proliferator-activated receptor- γ as a regulator of lung inflammation and repair. *Proc Am Thorac Soc.* 2005; 2:226–231. [PubMed: 16222042]
32. Liu D, Zeng BX, Zhang SH, et al. Rosiglitazone, an agonist of peroxisome proliferator-activated receptor γ , reduces pulmonary inflammatory response in a rat model of endotoxemia. *Inflamm Res.* 2005; 54:464–470. [PubMed: 16307220]
33. Genovese T, Mazzon E, Di Paola R, et al. Role of endogenous and exogenous ligands for the peroxisome proliferator-activated receptor α in the development of bleomycin-induced lung injury. *Shock.* 2005; 24:547–555. [PubMed: 16317386]
34. Zmijewski JW, Lorne E, Zhao X, et al. Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. *Am J Respir Crit Care Med.* 2008; 178:168–179. [PubMed: 18436790]
35. Sheu CC, Gong MN, Zhai R, et al. Clinical characteristics and outcomes of sepsis-related vs non-sepsis-related ARDS. *Chest.* 2010; 138:559–567. [PubMed: 20507948]
36. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists; American Diabetes Association: American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care.* 2009; 32:1119–1131. [PubMed: 19429873]
37. Bernard GR, Doig G, Hudson L. Quantification of organ failure for clinical trials and clinical practice. *Am J Respir Crit Care Med.* 1995; 151:A323.
38. Perez-Bravo F, Carrasco E, Gutierrez-Lopez MD, et al. Genetic pre-disposition and environmental factors leading to the development of insulin-dependent diabetes mellitus in Chilean children. *J Mol Med (Berl).* 1996; 74:105–109. [PubMed: 8820406]
39. Karvonen M, Viik-Kajander M, Moltchanova E, et al. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. *Diabetes Care.* 2000; 23:1516–1526. [PubMed: 11023146]

40. Home PD, Lindholm A, Riis A. European Insulin Aspart Study Group. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: A randomized controlled trial. *Diabet Med*. 2000; 17:762–770. [PubMed: 11131100]
41. Liese AD, D'Agostino RB Jr, Hamman RF, et al. The burden of diabetes mellitus among US youth: Prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics*. 2006; 118:1510–1518. [PubMed: 17015542]
42. Lipton RB, Drum M, Burnet D, et al. Obesity at the onset of diabetes in an ethnically diverse population of children: What does it mean for epidemiologists and clinicians? *Pediatrics*. 2005; 115:e553–e560. [PubMed: 15867020]
43. American Diabetes Association. Standards of medical care in diabetes— 2011. *Diabetes Care*. 2011; 34 (Suppl 1):S11–S61. [PubMed: 21193625]
44. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994; 149(3 Part 1):818–824. [PubMed: 7509706]
45. Meade MO, Cook RJ, Guyatt GH, et al. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2000; 161:85–90. [PubMed: 10619802]
46. Little, RJA.; Rubin, DB. *Statistical Analysis With Missing Data*. 2. Hoboken, NJ: Wiley; 2002.
47. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*. 1999; 18:681–694. [PubMed: 10204197]
48. Zilberberg MD, Epstein SK. Acute lung injury in the medical ICU: Comorbid conditions, age, etiology, and hospital outcome. *Am J Respir Crit Care Med*. 1998; 157(4 Part 1):1159–1164. [PubMed: 9563734]
49. Doyle RL, Szaflarski N, Modin GW, et al. Identification of patients with acute lung injury. Predictors of mortality. *Am J Respir Crit Care Med*. 1995; 152(6 Part 1):1818–1824. [PubMed: 8520742]
50. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. *Diabetologia*. 2007; 50:549–554. [PubMed: 17187246]
51. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care*. 2003; 26:510–513. [PubMed: 12547890]
52. Goyal RK, Spiro HM. Gastrointestinal manifestations of diabetes mellitus. *Med Clin North Am*. 1971; 55:1031–1044. [PubMed: 4946755]
53. Mulhall BP, O'Fearghail M. Diabetic gastroparesis. Case report and review of the literature. *Anaesthesia*. 1984; 39:468–469. [PubMed: 6731776]
54. Burgos LG, Ebert TJ, Asiddao C, et al. Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. *Anesthesiology*. 1989; 70:591–597. [PubMed: 2929996]
55. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000; 342:1334–1349. [PubMed: 10793167]
56. Delamaire M, Maugeudre D, Moreno M, et al. Impaired leucocyte functions in diabetic patients. *Diabet Med*. 1997; 14:29–34. [PubMed: 9017350]
57. Alba-Loureiro TC, Munhoz CD, Martins JO, et al. Neutrophil function and metabolism in individuals with diabetes mellitus. *Braz J Med Biol Res*. 2007; 40:1037–1044. [PubMed: 17665039]
58. Filgueiras LR Jr, Martins JO, Serezani CH, et al. Sepsis-induced acute lung injury (ALI) is milder in diabetic rats and correlates with impaired NFkB activation. *PLoS One*. 2012; 7:e44987. [PubMed: 23024779]
59. Krein PM, Sabatini PJ, Tinmouth W, et al. Localization of insulin-like growth factor-I in lung tissues of patients with fibroproliferative acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2003; 167:83–90. [PubMed: 12502480]
60. Schnapp LM, Donohoe S, Chen J, et al. Mining the acute respiratory distress syndrome proteome: Identification of the insulin-like growth factor (IGF)/IGF-binding protein-3 pathway in acute lung injury. *Am J Pathol*. 2006; 169:86–95. [PubMed: 16816363]
61. Bellmeyer A, Martino JM, Chandel NS, et al. Leptin resistance protects mice from hyperoxia-induced acute lung injury. *Am J Respir Crit Care Med*. 2007; 175:587–594. [PubMed: 17185651]

62. Zhang H, Tasaka S, Shiraishi Y, et al. Role of soluble receptor for advanced glycation end products on endotoxin-induced lung injury. *Am J Respir Crit Care Med*. 2008; 178:356–362. [PubMed: 18535257]
63. Calfee CS, Ware LB, Eisner MD, et al. NHLBI ARDS Network: Plasma receptor for advanced glycation end products and clinical outcomes in acute lung injury. *Thorax*. 2008; 63:1083–1089. [PubMed: 18566109]
64. Daneman D. Type 1 diabetes. *Lancet*. 2006; 367:847–858. [PubMed: 16530579]
65. Polonsky KS, Sturis J, Bell GI. Seminars in Medicine of the Beth Israel Hospital, Boston. Non-insulin-dependent diabetes mellitus—A genetically programmed failure of the beta cell to compensate for insulin resistance. *N Engl J Med*. 1996; 334:777–783. [PubMed: 8592553]
66. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: Principles of pathogenesis and therapy. *Lancet*. 2005; 365:1333–1346. [PubMed: 15823385]
67. Honiden S, Gong MN. Diabetes, insulin, and development of acute lung injury. *Crit Care Med*. 2009; 37:2455–2464. [PubMed: 19531947]
68. National Center for Immunization and Respiratory Diseases. General recommendations on immunization—Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011; 60:1–64.
69. Prevention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1997; 46:1–24.
70. Fisman DN, Abrutyn E, Spaude KA, et al. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. *Clin Infect Dis*. 2006; 42:1093–1101. [PubMed: 16575726]
71. Johnstone J, Marrie TJ, Eurich DT, et al. Effect of pneumococcal vaccination in hospitalized adults with community-acquired pneumonia. *Arch Intern Med*. 2007; 167:1938–1943. [PubMed: 17923592]
72. Ware LB, Camerer E, Welty-Wolf K, et al. Bench to bedside: Targeting coagulation and fibrinolysis in acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2006; 291:L307–L311. [PubMed: 16648240]
73. Schultz MJ, Haitsma JJ, Zhang H, et al. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia—A review. *Crit Care Med*. 2006; 34:871–877. [PubMed: 16521285]
74. Frank AJ, Thompson BT. Pharmacological treatments for acute respiratory distress syndrome. *Curr Opin Crit Care*. 2010; 16:62–68. [PubMed: 19952736]
75. Stegenga ME, Vincent JL, Vail GM, et al. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. *Crit Care Med*. 2010; 38:539–545. [PubMed: 19851093]
76. Johnson JA, Pohar SL, Majumdar SR. Health care use and costs in the decade after identification of type 1 and type 2 diabetes: A population-based study. *Diabetes Care*. 2006; 29:2403–2408. [PubMed: 17065675]

Figure 1.

Patient recruitment and prevalence of diabetes mellitus and acute respiratory distress syndrome (ARDS) in the Molecular Epidemiology of ARDS cohort.

Figure 2.

Odds ratio of diabetes in univariate model, multivariate model without medications, and multivariate model with clopidogrel and warfarin. ARDS = acute respiratory distress syndrome. *Filled diamond* = point representing the magnitude of the odds ratio.

Figure 3.

Adjusted odds ratio for development of acute respiratory distress syndrome (ARDS) by type of diabetes. The reference group is patients with no diabetes. *Filled diamond* = point representing the magnitude of the odds ratio.

Figure 4.

Adjusted odds ratio between diabetes and development of acute respiratory distress syndrome (ARDS) by ARDS risk groups.

Sample size of subgroups does not add up to total number of patients in the cohort because a patient may be in multiple subgroups. ^aIncluded patients with only noninfectious etiologies. Patients with both infectious and noninfectious risk factors for ARDS were excluded from this subgroup. ^bIncluded patients with both infectious and noninfectious risk factors for ARDS.

Pulm Inj = pulmonary injury. *Filled diamond* = point representing the magnitude of the odds ratio.

Table 1

Patient Characteristics Between Diabetics and Nondiabetics

Characteristics	Nondiabetics (n = 2,840)	Diabetics (n = 987)	p
Clinical risk for ARDS, n (%)			
Sepsis syndrome	832 (29)	273 (28)	0.3
Pneumonia source	496 (60)	159 (58)	0.7
Septic shock	1,392 (49)	547 (55)	0.001
Pneumonia source	847 (61)	293 (54)	0.004
Trauma	281 (10)	41 (4)	< 0.001
Multiple transfusion ^a	316 (11)	70 (7)	< 0.001
Aspiration	192 (7)	67 (7)	1.0
Direct pulmonary injury ^b	1,651 (58)	559 (57)	0.4
Baseline characteristics			
Age, mean (sd)	58 (19)	65 (13)	< 0.001
Acute Physiology and Chronic Health Evaluation III, mean (sd) ^c	56 (22)	64 (20)	< 0.001
Body mass index, median (IQR)	27 (23–29)	28 (25–33)	< 0.001
Females, n (%)	1,095 (39)	379 (38)	0.9
Caucasian, n (%)	2,551 (90)	863 (87)	0.04
Hyperglycemia (glucose > 180 mg/dL), n (%)	957 (34)	703 (71)	< 0.001
Hypoglycemia (glucose < 70 mg/dL), n (%)	111 (4)	53 (5)	0.07
Creatinine > 2.0 mg/L, n (%)	614 (22)	392 (40)	< 0.001
Bilirubin > 2.0 mg/dL, n (%)	428 (15)	125 (13)	0.07
Systolic blood pressure < 90 mm Hg, n (%)	2,012 (71)	741 (75)	0.01
Platelets < 80,000/mm ³ , n (%)	367 (13)	90 (9)	0.001
Respiratory rate > 30, n (%)	928 (33)	307 (31)	0.4
Postoperative elective surgery, n (%)	185 (7)	40 (4)	0.005
Comorbid conditions, n (%)			
Chronic liver disease ^d	145 (5)	73 (7)	0.01
Alcohol abuse in past year ^e	420 (15)	82 (8)	< 0.001
Former smoker (quit > 1 yr)	742 (30)	348 (39)	< 0.001
Active smoker in past year	744 (30)	213 (24)	< 0.001
End-stage renal disease ^f	141 (5)	112 (12)	< 0.001
Metastatic cancer	75 (3)	16 (2)	0.09
Hematologic malignancy	15 (1)	7 (1)	0.5
Autoimmune disease	293 (10)	112 (11)	0.4
Medications, n (%)			
Oral hypoglycemic agents	0 (0)	358 (38)	< 0.001
Thiazolidinediones	0 (0)	44 (5)	< 0.001
Sulfonylureas/meglitinides	0 (0)	193 (21)	< 0.001
Metformin	0 (0)	195 (21)	< 0.001

Characteristics	Nondiabetics (<i>n</i> = 2,840)	Diabetics (<i>n</i> = 987)	<i>p</i>
Angiotensin-converting enzyme inhibitors	460 (17)	328 (35)	< 0.001
Angiotensin receptor blockers	95 (3)	86 (9)	< 0.001
Cyclooxygenase 2 inhibitors	54 (2)	18 (2)	1.0
Aspirin	679 (25)	436 (47)	< 0.001
Clopidogrel	71 (3)	72 (8)	< 0.001
Warfarin	281 (10)	163 (18)	< 0.001
Statins	557 (20)	455 (49)	< 0.001
Insulin	154 (6)	535 (59)	< 0.001
Outcomes			
ARDS, <i>n</i> (%)	730 (26)	212 (21)	0.008
Days from ICU admission to fulfillment of ARDS criteria, median (IQR) ^g	1 (0–2)	1 (0–3)	0.3
Mortality in ARDS, <i>n</i> (%) ^g	250 (35)	77 (37)	0.6

ARDS = acute respiratory distress syndrome, IQR = interquartile range.

^a Multiple transfusion defined as 8 units of packed RBCs within 24 hr.

^b Direct pulmonary injury defined as presence of pneumonia, aspiration, or pulmonary contusion.

^c Acute Physiology and Chronic Health Evaluation III scores calculated without Pao₂/Fio₂ component.

^d Defined as chronic liver disease including cirrhosis and hepatic failure with encephalopathy.

^e Defined as hospitalization or treatment for alcohol dependence, or alcohol-related condition such as withdrawal or delirium tremens.

^f Defined as end-stage renal disease requiring dialysis.

^g Only calculated for patients with ARDS in each category.

Table 2
Characteristics of Cohort for Development of Acute Respiratory Distress Syndrome (ARDS) and 60-Day Mortality Among Patients in Whom ARDS Developed

Characteristics	Development of ARDS		60-Day Mortality in ARDS	
	No ARDS (n = 2,906)	ARDS (n = 954)	Survivors (n = 605)	Nonsurvivors (n = 329)
Characteristics				<i>p</i>
Clinical risk for ARDS, <i>n</i> (%)				
Sepsis syndrome	922 (32)	194 (20)	127 (21)	64 (19)
Pneumonia source	504 (55)	158 (81)	101 (80)	54 (84)
Septic shock	1,320 (45)	631 (66)	382 (63)	235 (71)
Pneumonia source	655 (50)	494 (78)	303 (79)	178 (76)
Trauma	268 (9)	66 (7)	61 (10)	5 (2)
Multiple transfusion	308 (11)	81 (8)	52 (9)	29 (9)
Aspiration	171 (6)	92 (10)	53 (9)	35 (11)
Direct pulmonary injury	1,493 (51)	738 (77)	473 (78)	246 (75)
Baseline characteristics				
Age, mean (sd)	61 (18)	57 (18)	53 (18)	65 (16)
Acute Physiology and Chronic Health Evaluation III, mean (sd)	56 (21)	64 (23)	58 (20)	77 (23)
Body mass index, median (interquartile range)	27 (24–30)	27 (24–32)	28 (24–33)	27 (23–32)
Females, <i>n</i> (%)	1,134 (39)	353 (37)	220 (36)	122 (37)
Hyperglycemia (glucose >180 mg/dL), <i>n</i> (%)	1232 (43)	446 (47)	266 (44)	175 (54)
Hypoglycemia (glucose <70 mg/dL), <i>n</i> (%)	112 (4)	52 (6)	20 (3)	31 (10)
Caucasian, <i>n</i> (%)	2,587 (89)	852 (89)	536 (89)	301 (91)
Creatinine > 2.0 mg/L, <i>n</i> (%)	714 (25)	295 (31)	158 (26)	134 (41)
Bilirubin > 2.0 mg/dL, <i>n</i> (%)	373 (13)	185 (19)	82 (14)	97 (29)
Systolic blood pressure < 90 mm Hg, <i>n</i> (%)	2,006 (69)	767 (80)	481 (80)	272 (83)
Platelets < 80,000/mm ³ , <i>n</i> (%)	306 (11)	155 (16)	76 (13)	79 (24)
Respiratory rate > 30, <i>n</i> (%)	826 (28)	422 (45)	246 (41)	166 (51)
Postoperative elective surgery, <i>n</i> (%)	183 (6)	44 (5)	27 (4)	17 (5)
Comorbid conditions, <i>n</i> (%)				

Characteristics	Development of ARDS		60-D Mortality in ARDS	
	No ARDS	ARDS	Survivors	Nonsurvivors
	(n = 2,906)	(n = 954)	(n = 605)	(n = 329)
Diabetes mellitus	775 (27)	212 (23)	131 (22)	77 (24)
Chronic liver disease	141 (5)	77 (8)	28 (5)	46 (14)
Alcohol abuse in past year	341 (12)	168 (18)	105 (17)	56 (17)
Former smoker (quit > 1 yr)	845 (33)	245 (30)	131 (26)	109 (38)
Active smoker in past year	684 (27)	282 (35)	198 (39)	76 (26)
End-stage renal disease	178 (6)	75 (8)	41 (7)	34 (10)
Metastatic cancer	72 (2)	19 (2)	8 (1)	10 (3)
Hematologic malignancy	19 (1)	3 (0)	1 (0)	2 (0)
Autoimmune disease	311 (11)	94 (10)	53 (9)	38 (12)
Medications, n (%)				
Oral hypoglycemic agents	277 (10)	81 (9)	58 (10)	22 (7)
Thiazolidinediones	36 (1)	8 (1)	6 (1)	2 (1)
Sulfonylureas/meglitinides	146 (5)	47 (5)	31 (5)	15 (5)
Metformin	148 (5)	47 (5)	34 (6)	13 (4)
Angiotensin-converting enzyme inhibitors	628 (23)	160 (18)	105 (19)	51 (17)
Angiotensin receptor blockers	137 (5)	44 (5)	26 (5)	16 (5)
Cyclooxygenase 2 inhibitors	52 (2)	20 (2)	12 (2)	8 (3)
Aspirin	888 (32)	227 (25)	128 (23)	94 (30)
Clopidogrel	121 (4)	22 (2)	12 (2)	10 (3)
Warfarin	370 (13)	74 (8)	41 (7)	33 (11)
Statins	813 (29)	199 (22)	126 (22)	69 (22)
Insulin	539 (20)	151 (17)	86 (15)	61 (20)

ARDS = acute respiratory distress syndrome.

^aMultiple transfusion defined as ≥ 8 units of packed RBCs within 24 hr.

^bDirect pulmonary injury defined as presence of pneumonia, aspiration, or pulmonary contusion.

^cAcute Physiology and Chronic Health Evaluation III scores calculated without Pao₂/Fio₂ component.

^dDefined as chronic liver disease including cirrhosis and hepatic failure with encephalopathy.

^e Defined as hospitalization or treatment for alcohol dependence, or alcohol-related condition such as withdrawal or delirium tremens.

^f Defined as end-stage renal disease requiring dialysis.

^g Only calculated for patients with ARDS in each category.

Table 3

Multivariate Analysis for Predictors of Acute Respiratory Distress Syndrome Development

Variable	Multivariate Model		Multivariate Model With Clopidogrel and Warfarin	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Diabetes mellitus	0.76 (0.61–0.95)	0.015	0.75 (0.59–0.94)	0.013
Septic shock	2.54 (2.08–3.09)	< 0.0001	2.46 (2.01–3.02)	< 0.0001
Direct pulmonary injury	4.21 (3.41–5.22)	< 0.0001	4.22 (3.40–5.25)	< 0.0001
Multiple transfusion	1.73 (1.18–2.53)	0.005	1.72 (1.17–2.54)	0.006
Age	0.98 (0.97–0.99)	< 0.0001	0.98 (0.98–0.99)	< 0.0001
Body mass index	1.03 (1.02–1.04)	< 0.0001	1.04 (1.02–1.05)	< 0.0001
Acute Physiology and Chronic Health Evaluation III score	1.02 (1.01–1.02)	< 0.0001	1.02 (1.01–1.02)	< 0.0001
Active smoker in past year	1.19 (0.97–1.45)	0.10	1.21 (0.99–1.49)	0.07
Alcohol abuse in past year	1.29 (1.00–1.68)	0.05	1.23 (0.94–1.61)	0.13
Creatinine > 2.0 mg/L	0.81 (0.65–1.02)	0.08	0.85 (0.67–1.07)	0.17
Platelets < 80,000/mm	1.55 (1.16–2.07)	0.003	1.57 (1.17–2.11)	0.003
Acute hyperglycemia (glucose > 180 mg/dL)	1.04 (0.86–1.26)	0.7	1.04 (0.85–1.27)	0.7
Clopidogrel	N/A	N/A	0.59 (0.34–1.00)	0.05
Warfarin	N/A	N/A	0.66 (0.48–0.90)	0.008

OR = odds ratio, N/A = not applicable.

There were 3,333 patients in the multivariate model without medications and 3,183 patients in the multivariate model with clopidogrel and warfarin. See legend of Table 1 for footnotes.

Table 4

Multivariate Analysis for 60-Day Mortality Among Patients With Acute Respiratory Distress Syndrome

Variable	OR (95% CI)	<i>p</i>
Diabetes mellitus	0.81 (0.56–1.18)	0.27
Trauma	0.27 (0.10–0.78)	0.02
Transfusion of RBCs	1.50 (1.07–2.10)	0.02
Sepsis or septic shock	1.73 (0.98–3.06)	0.06
Age	1.04 (1.03–1.05)	< 0.0001
Acute Physiology and Chronic Health Evaluation III score	1.02 (1.01–1.03)	< 0.0001
Platelets < 80,000/mm	1.76 (1.13–2.74)	0.01
Chronic liver disease	2.75 (1.53–4.95)	0.001
Steroid use prior to ICU	2.55 (1.42–4.61)	0.002
Acute hypoglycemia (glucose < 70 mg/dL)	2.09 (1.07–4.10)	0.03
Metastatic cancer	1.36 (0.46–4.03)	0.6

OR = odds ratio.

See legend of Table 1 for footnotes.

Table 5

Previous Studies Which Examined the Relationship Between Diabetes and Development of Acute Respiratory Distress Syndrome

Authors (Reference)	Sample Size	Study Type	Population	Diabetes OR (95% CI) on Multivariate Analysis	Other Variables in Multivariate Model
Moss et al (14)	113 patients in 4 centers	Prospective	ICU patients with septic shock	0.33 (0.12–0.90), $p = 0.03$	Age, cirrhosis, source of infection
Ischimien et al (11)	160 patients in 1 center	Prospective	ICU patients with septic shock	0.44 (0.17–1.07), $p = 0.08$	Predisposing ARDS conditions: Aspiration Other: Alcohol abuse, chemotherapy, delayed goal-directed resuscitation, delayed antibiotics, tachypnea, transfusion of packed RBCs
Esper et al (15)	930 million patients in the United States	Retrospective, epidemiologic	Hospitalized patients with sepsis	Univariate: Among patients with sepsis, 9% of diabetics developed acute respiratory failure compared to 14% of nondiabetics	None
Gong et al (13)	1,795 patients in 2 centers	Prospective	ICU patients with > 1 predisposing ARDS condition ^a	0.62 (0.46–0.83), $p = 0.001$	Predisposing ARDS conditions: Direct pulmonary injury, septic shock Other: Age, Acute Physiology and Chronic Health Evaluation III, gender, hematologic failure, obesity, peak plasma glucose, transfusion of packed RBCs
Trillo-Alvarez et al (16)	409 patients in 1 center	Retrospective	ICU patients with > 1 predisposing ARDS condition ^b	0.16 (0.03–0.77), $p = 0.03$	Predisposing ARDS conditions: Aspiration, high-risk surgery, high-risk trauma, pancreatitis, pneumonia, sepsis, shock Other: Alcohol abuse, chemotherapy, hypoalbuminemia, oxygen supplementation, tachypnea, tobacco use
Gajic et al (17)	5,584 patients in 22 centers	Prospective	Hospitalized patients with > 1 predisposing ARDS condition ^b	0.55 (0.25–1.16), $p = 0.14^c$	Predisposing ARDS conditions: Aspiration, high-risk surgery, high-risk trauma, pancreatitis, pneumonia, sepsis, shock Other: Acidosis, alcohol abuse, chemotherapy, emergency surgery, hypoalbuminemia, obesity, oxygen supplementation, tachypnea, tobacco use
Kor et al (18)	4,366 patients in 1 center	Retrospective	Patients mechanically ventilated during elective surgery ^d ; Patients with any predisposing ARDS conditions ^e were excluded	1.80 (1.13–2.80), $p = 0.01$	Age, alcohol abuse, chemotherapy, chronic obstructive pulmonary disease, gastroesophageal reflux disease, medications, procedure type, restrictive lung disease, tobacco use
Koh et al (19)	2,013 patients in 1 center	Retrospective	Unselected ICU patients	0.76 (0.43–1.33)	Age, gender, myocardial infarction, medications, obesity

OR = odds ratio, ARDS = acute respiratory distress syndrome.

^aPredisposing ARDS conditions including sepsis, septic shock, aspiration, pneumonia, trauma, and multiple transfusions (8 units) were evaluated at the time of ICU admission.

^b Predisposing ARDS conditions including sepsis, shock, aspiration, pneumonia, trauma, high-risk surgery (all cardiac and aortic vascular surgeries, noncardiac thoracic surgeries, spine surgeries, and major abdominal surgeries), and pancreatitis were evaluated at the time of hospital admission.

^c Found diabetes was associated with lower development of ARDS only in patients with sepsis.

^d Includes all cardiac and aortic vascular surgeries, noncardiac thoracic surgeries, spine surgeries, major abdominal surgeries, hip and knee surgeries, cystectomies, neurosurgical procedures, and head and neck surgeries.

^e Includes sepsis, shock, aspiration, and trauma.