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Authors

Hsieh, SJ
Zhuo, H
Benowitz, NL
et al.

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Prevalence and Impact of Active and Passive Cigarette Smoking in Acute Respiratory Distress Syndrome

S. Jean Hsieh, MD[1]; Hanjing Zhuo, MD, MPH[2]; Neal L. Benowitz, MD[3,4]; B. Taylor Thompson, MD[5]; Kathleen D. Liu, MD, PhD, MAS[6,7]; Michael A. Matthay, MD[2,7,8]; Carolyn S. Calfee, MD, MAS[4,7,8]; and the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network

[1]Division of Critical Care Medicine, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

[2]Cardiovascular Research Institute, University of California, San Francisco, CA.

[3]Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, CA.

[4]Center for Tobacco Control Research and Education, University of California, San Francisco, CA.

[5]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

[6]Division of Nephrology, Department of Medicine, University of California, San Francisco, CA.

[7]Department of Anesthesia, University of California, San Francisco, CA.

[8]Division of Pulmonary and Critical Care, Department of Medicine, University of California, San Francisco, CA.

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The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome participants can be viewed in **Appendix 1**.

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For information regarding this article, E-mail: shsieh@montefiore.org

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Objectives: Cigarette smoke exposure has recently been found to be associated with increased susceptibility to trauma- and transfusion-associated acute respiratory distress syndrome. We sought to determine 1) the incidence of cigarette smoke exposure in a diverse multicenter sample of acute respiratory distress syndrome patients and 2) whether cigarette smoke exposure is associated with severity of lung injury and mortality in acute respiratory distress syndrome.

Design: Analysis of the Albuterol for the Treatment of Acute Lung Injury and Omega Acute Respiratory Distress Syndrome Network studies.

Setting: Acute Respiratory Distress Syndrome Network hospitals.

Patients: Three hundred eighty-one patients with acute respiratory distress syndrome.

Interventions: None.

Measurements and Main Results: 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol, a validated tobacco-specific marker, was measured in urine samples from subjects enrolled in two National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network randomized controlled trials. Urine

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol levels were consistent with active smoking in 36% of acute respiratory distress syndrome patients and with passive smoking in 41% of nonsmokers (vs 20% and 40% in general population, respectively). Patients with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol levels in the active smoking range were younger and had a higher incidence of alcohol misuse, fewer comorbidities, lower severity of illness, and less septic shock at enrollment compared with patients with undetectable 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol levels. Despite this lower severity of illness, the severity of lung injury did not significantly differ based on biomarker-determined smoking status. Cigarette smoke exposure was not significantly associated with death after adjusting for differences in age, alcohol use, comorbidities, and severity of illness.

Conclusions: In this first multicenter study of biomarker-determined cigarette smoke exposure in acute respiratory distress syndrome patients, we found that active cigarette smoke exposure was significantly more prevalent among acute respiratory distress syndrome patients compared to population averages. Despite their younger age, better overall health, and lower severity of illness, smokers by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol had similar severity of lung injury as patients with undetectable 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. These findings suggest that active cigarette smoking may increase susceptibility to acute respiratory distress syndrome in younger, healthier patients. (*Crit Care Med* 2014; 42:2058–2068)

Key Words: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; acute respiratory distress syndrome; cigarette smoking; lung injury; mortality

Acute respiratory distress syndrome (ARDS) (1) remains an important and common cause of acute respiratory failure that is associated with significant mortality and poor long-term outcomes. Despite a decline in the incidence of ARDS and mortality over the last 10 years, the in-hospital mortality rate is still unacceptably high at nearly 40% (2, 3), and survivors suffer from significant functional and neuropsychological impairments and decreased health-related quality of life (4, 5). Identifying modifiable environmental risk factors that are associated with susceptibility and/or outcomes in ARDS will guide the development of preventative interventions, improve risk stratification of affected patients, and deepen our understanding of the pathogenesis of ARDS.

Prior studies have demonstrated that active smoking induces pathological changes to the pulmonary endothelium and epithelium similar to what is observed in ARDS (6–10) and that the effects of passive smoke exposure on endothelial function and inflammation are nearly equivalent to those of active smoking (11). We recently reported that active and passive cigarette smoking are associated with an increased risk of developing ARDS after severe blunt trauma (12). Similarly, cigarette smoking was recently found to be independently associated with an increased risk of developing transfusion-related ARDS (13) and with an increased risk of primary graft dysfunction and increased mortality after lung transplantation (14, 15). However, the effect of cigarette smoke exposure on severity of disease and clinical outcomes in a broad sample of patients with ARDS has not been studied.

Studies on the role of cigarette smoke exposure in critical illness have been limited by barriers to obtaining accurate smoking histories in a critically ill population (16, 17). Furthermore, accurate quantification of passive cigarette smoke exposure is difficult to obtain even with self-report (18). Lack of accurate assessment can lead to misclassification and bias study results. Tobacco-specific biomarkers, such as NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), quantify the biologically active dose of toxins to which patients are exposed, are highly sensitive and specific to cigarette smoke exposure, correlate better with cigarette smoke exposure than self-report (which substantially underestimates exposure), can accurately discriminate between active and passive smoking, and have been used to establish causal relationships between both active and passive smoke exposure and disease (18–22). Measurement of biomarkers of cigarette smoke exposure in critically ill patients, including NNAL, identifies a higher incidence of cigarette smoke exposure than smoking history obtained through surrogate report and medical records (23). Furthermore, because urine NNAL has a long half-life (10–18 d) (24), it is particularly useful in a critically ill population where there may be some delay between exposure and biomarker measurement. To date, no studies have investigated the impact of biomarker-determined active and passive smoke exposure on the clinical outcomes of patients with ARDS. The goals of this study were to determine 1) the incidence of cigarette smoke exposure and 2) whether active and/or passive smoke exposure, as measured by urine NNAL, are associated with severity of disease and 60-day mortality in a diverse cohort of patients enrolled in two National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (NHLBI ARDS) Network randomized controlled trials.

METHODS

Patients

Subjects who were enrolled in the ARDS Network Albuterol for the Treatment of Acute Lung Injury (ALTA) study or the ARDS Network Omega study and who had available urine samples were included. Details of the original trials have previously been published and are available in the **online supplement** (Supplemental Digital Content 1, http://links.lww.com/CCM/A977) (25, 26). Both studies were stopped early for futility, after the enrollment of 272 and 282 patients, respectively (37 co-enrolled). This secondary analysis was determined to be exempt from review by the Institutional Review Board of the University of California at San Francisco.

Measurement of Cigarette Smoke Exposure

Urine was collected at the time of patient randomization and frozen at –80°C. Concentrations of NNAL were determined by liquid chromatography-tandem mass spectrometry using 0.5–2 mL of urine (27). The limit of quantification (LOQ) of

urine NNAL was 1 pg/mL for 0.5 mL. A prior study found that a urine NNAL cutoff of 47.3 pg/mL accurately distinguishes active from passive smokers (sensitivity: 87.4% and specificity: 96.5%; area under the curve, 0.965) (19). Subjects were classified as active smokers (urine NNAL ≥ 47.3 pg/mL), passive smokers (urine NNAL < 47.3 pg/mL and > LOQ), and unexposed nonsmokers (urine NNAL < LOQ). Analyses were repeated using a NNAL cutoff corrected for urine creatinine to adjust for differences in urine concentration (online supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/A977). Smoking history was obtained from surrogates using a standardized questionnaire and from medical records if surrogates were unavailable. Smokers were defined as patients who had smoked more than 100 cigarettes in a lifetime and were divided into current and former smokers by history. Alcohol use history was obtained from surrogates using a validated survey instrument (the Alcohol Use Disorders Identification Test [AUDIT]) (28). Alcohol use was defined using validated gender-specific cutoffs in AUDIT scores (29) (**Supplement Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A977).

Statistical Analysis

Statistical significance was defined as p value less than or equal to 0.05, using two-tailed tests of hypotheses. Categorical data were analyzed by chi-square test or Fisher exact test. Normally distributed continuous variables were analyzed by t test or analysis of variance. Nonparametric continuous variables were analyzed using Wilcoxon rank-sum test or Kruskal-Wallis test. Because NNAL is not normally distributed, NNAL levels were log-transformed or analyzed in categories as described above for regression analysis. Multivariable logistic regression with manual stepwise backward selection was performed to determine the independent association between NNAL levels and 60-day mortality. First, we adjusted for variables that were likely to influence mortality, selected a priori based on prior studies (i.e., age [3], race [30], gender [30], etiology of ARDS [31], alcohol use [32], Acute Physiology and Chronic Health Evaluation (APACHE) III score [33], and septic shock [31]). Second, we adjusted for variables that differed by NNAL-determined smoking status in our sample ($p \leq 0.10$) and were likely to influence 60-day mortality (i.e., immune suppression, prior myocardial infarction, hepatic failure, diabetes, congestive heart failure, stroke, dementia, and chronic obstructive pulmonary disease). Covariates were then serially eliminated from the backward selection model on the basis of the highest p value (threshold $p < 0.10$). Less than 10% change in the odds ratio (OR) for active smokers by NNAL was observed for each covariate removed. No interaction was found between smoking and treatment allocation, and thus, analyses were not stratified by treatment group. The multivariable logistic regression model was assessed with the Hosmer-Lemeshow test. Statistical analysis was performed with STATA/MP 12 (Statacorp, College Station, TX).

RESULTS

Incidence of Cigarette Smoke Exposure

Of the 517 patients enrolled in the ALTA and Omega studies, 381 had available urine samples to measure urine NNAL. Excluded patients ($n = 136$) had similar incidence of smokers by history and similar 60-day mortality (**Supplement Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A977). Overall, the excluded patients were older, were more dependent on chronic dialysis, and had more comorbidities. Of the included patients, urine NNAL levels were consistent with active smoking in 36% (95% CI, 31–41); this was significantly higher than the national population incidence of 20% ($p < 0.01$) (34). In addition, 41% (95% CI, 36–46) of subjects with NNAL levels in the nonsmoking range had evidence of passive smoke exposure, which is similar to the nationwide incidence of 40% (35). NNAL levels were consistent with active smoking in 22% ($n = 16$) of former smokers by history and 9% ($n = 13$) of nonsmokers by history (**Table 1**; **Supplement Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A977). Of patients with unknown smoking history ($n = 41$), 44% ($n = 18$) had NNAL levels consistent with active smoking and 22% ($n = 9$) had NNAL levels consistent with passive smoking.

Baseline Characteristics of Study Participants

Table 1 describes baseline characteristics of study subjects ($n = 381$) stratified by cigarette smoke exposure, as defined by NNAL levels. Overall, the primary etiology of lung injury did not differ between levels of cigarette smoke exposure. Patients with NNAL levels in the active range were younger than patients with undetectable NNAL. Active smokers by NNAL had a higher incidence of mild to severe alcohol misuse and unknown alcohol history and had fewer comorbidities than nonsmokers by NNAL. Specifically, the incidence of immune suppression, diabetes, prior myocardial infarction, hypertension, congestive heart failure, prior stroke with sequelae, and dementia was lower in patients with NNAL in the active smoking range compared with patients with NNAL in the undetectable range ($p < 0.05$). In addition to these pronounced differences in the incidence of chronic illness, acute severity of illness differed between active smokers and nonsmokers by NNAL: subjects with NNAL levels consistent with active smoking had lower APACHE III scores and were less likely to require vasopressors and to be in septic shock at enrollment compared with subjects with undetectable NNAL.

Table 2 describes similar demographic and clinical data stratified by mortality before hospital discharge (to hospital day 60). Overall 60-day mortality was 22%. Patients who died by 60 days were older, had higher APACHE III scores, and had a higher incidence of AIDS, malignancy, and immune suppression. They also had greater vasopressor use during the 24 hours prior to randomization and more septic shock. Active smokers by history had a lower 60-day mortality rate. Of note, the primary etiology of lung injury and the Lung Injury Score, including all four of its components (Pa_{O_2}/F_{IO_2}, positive

TABLE 1. Baseline Characteristics by Smoking Exposure

Baseline Characteristic	Smoking Status by Urine 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol			
	Nonsmoker	Passive Smoker	Active Smoker	
	0 pg/mL	> 0, < 47.3 pg/mL	≥ 47.3 pg/mL	
	n = 143	*n* = 101	*n* = 137	*p*
Age (yr), mean ± SD	59 ± 18	47 ± 16[a]	48 ± 13[b]	< 0.001
Male gender, *n* (%)	70 (49)	59 (58)	84 (61)	0.1
Race, *n* (%)				0.004
White	112 (78)	65 (64)	113 (82)	
African American	17 (12)	27 (27)	19 (14)	
Asian	6 (4)	2 (2)	0 (0)	
Other	8 (6)	7 (7)	5 (4)	
Hispanic ethnicity, *n* (%)	12 (8)	14 (14)	14 (10)	0.39
Primary etiology of lung injury, *n* (%)				0.18
Trauma	6 (4)	9 (9)	11 (8)	
Sepsis	44 (31)	24 (24)	23 (17)	
Multiple transfusion	3 (2)	4 (4)	1 (1)	
Aspiration	21 (15)	16 (16)	30 (22)	
Pneumonia	62 (43)	42 (42)	63 (46)	
Other	7 (5)	6 (6)	9 (7)	
Alcohol use, *n* (%)[c]				< 0.001
Abstinence	89 (62)	46 (46)	38 (28)	
Low risk	36 (25)	27 (27)	28 (20)	
Mild to moderate alcohol misuse	2 (1)	7 (7)	12 (9)	
Severe alcohol misuse	2 (1)	11 (11)	31 (23)	
Unknown history	14 (10)	10 (10)	28 (20)	
Smoking history				< 0.001
Nonsmoker	94 (65)	45 (45)	13 (9)	
Former smoker	35 (24)	24 (24)	16 (12)	
Active smoker	1 (1)	23 (23)	90 (66)	
Unknown history	14 (10)	9 (9)	18 (13)	
Pack-years, median (IQR)	0 (0, 5)	0 (0, 17)	30 (9, 45)[b]	0.0001
Time in hospital prior to urine collection (d), median (IQR)	1 (0, 3)	2 (0, 4)	1 (0, 3)	0.10

(*Continued*)

TABLE 1. (*Continued*). Baseline Characteristics by Smoking Exposure

Baseline Characteristic	Smoking Status by Urine 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol			
	Nonsmoker	Passive Smoker	Active Smoker	
	0 pg/mL	> 0, < 47.3 pg/mL	≥ 47.3 pg/mL	
	n = 143	*n* = 101	*n* = 137	*p*
Comorbidities, *n* (%)				
Immune suppression	20 (14)	8 (8)	3 (2)[b]	0.001
Diabetes	49 (34)	28 (28)	26 (19)[b]	0.02
Prior myocardial infarction	15 (10)	5 (5)	4 (3)[b]	0.03
Hypertension	79 (55)	43 (43)[a]	33 (24)[b]	< 0.001
Congestive heart failure	11 (8)	8 (8)	2 (1)[b]	0.02
Chronic pulmonary disease	13 (9)	2 (2)[e]	14 (10)	0.03
Prior stroke with sequelae	10 (7)	3 (3)	0 (0)[b]	0.002
Dementia	9 (6)	2 (2)	2 (1)	0.09
AIDS	2 (1)	3 (3)	2 (2)	0.62
Hepatic failure	0 (0)	2 (2)	0 (0)	0.07
Malignancy	3 (2)	1 (1)	0 (0)	0.23
Acute Physiology and Chronic Health Evaluation III score, mean ± SD	97 ± 29	91 ± 28	85 ± 26[b]	0.001
Vasopressor use at baseline, *n* (%)	84 (59)	50 (50)	56 (41)[b]	0.01
Septic shock at enrollment, *n* (%)	72 (50)	36 (36)[a]	42 (31)[b]	0.002

IQR = interquartile range.

[a]Passive versus nonsmoker, $p \leq 0.05$.

[b]Active smoker versus nonsmoker, $p \leq 0.05$.

[c]As defined by Alcohol Use Disorders Identification Test scores (Supplement Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/A977).

end-expiratory pressure, compliance, and chest radiograph quadrants with opacities), did not differ significantly between those alive and dead at 60 days.

Association Between Cigarette Smoke Exposure and Lung Injury Severity

The severity of lung injury classified using the Berlin Definition (1) and as measured by the Murray Lung Injury Score (36) and its components did not differ based on NNAL levels (**Table 3**) or smoking history (data not shown). Likewise, there were no significant differences in Pao_2/Fio_2 and oxygenation index (37) on study days 1–7 between the three groups (**Supplement Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A977).

Association Between Cigarette Smoke Exposure and Clinical Outcomes

In unadjusted analysis, subjects with NNAL levels in the active smoking range had better clinical outcomes than subjects with undetectable NNAL (**Table 4**). Specifically, subjects with NNAL levels consistent with active smoking had significantly lower 60-day mortality before hospital discharge (active smoking vs nonsmoking unadjusted OR, 0.44; 95% CI, 0.24–0.78; $p = 0.006$), more ventilator-free days, and more organ failure–free days compared with nonsmokers by NNAL ($p \leq 0.05$ for all). Passive smokers by NNAL had similar 60-day mortality, ventilator-free days, and organ failure–free days compared with nonsmokers by NNAL.

However, after adjusting for baseline differences in both acute severity of illness and comorbidities, including age, primary risk factor for lung injury, hazardous drinking, APACHE III, and septic shock within 24 hours prior to randomization, there was no significant association between cigarette smoke exposure and death at 60 days (**Table 5**) (active smoking vs nonsmoking OR, 0.58; 95% CI, 0.28–1.22; $p = 0.15$; passive smoking vs nonsmoking OR, 1.00; 95% CI, 0.49–2.02; $p > 0.99$). In the full initial model, before backward selection (**Supplement Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A977), these ORs were 0.56 and 0.94, respectively. Analysis was also performed treating log-transformed urine NNAL as a continuous variable and yielded similar results (data not shown). Likewise, all analyses were repeated using urine NNAL corrected for urine creatinine to adjust for differences in urine concentration, and results were

TABLE 2. Baseline Characteristics by 60-Day Mortality Before Hospital Discharge

Characteristic	Alive at Day 60 (*n* = 297)	Dead at Day 60[a] (*n* = 84)	*p*
Age (yr), mean ± SD	50 ± 16	61 ± 15	< 0.001
Male gender, *n* (%)	162 (55)	51 (61)	0.32
Race, *n* (%)			0.37
White	221 (74)	69 (82)	
African American	51 (17)	12 (14)	
Asian	8 (3)	0 (0)	
Other	17 (6)	3 (4)	
Hispanic ethnicity, *n* (%)	31 (10)	9 (11)	0.94
Primary etiology of lung injury, *n* (%)			0.16
Trauma	20 (7)	6 (7)	
Sepsis	68 (23)	23 (27)	
Multiple transfusion	5 (2)	3 (4)	
Aspiration	56 (19)	11 (13)	
Pneumonia	127 (43)	40 (48)	
Other	21 (7)	1 (1)	
Smoking history by surrogate or chart report, *n* (%)			0.006
Nonsmoker	122 (41)	30 (36)	
Former smoker	53 (18)	21 (25)	
Active smoker	97 (33)	17 (20)	
Unknown history	25 (8)	16 (19)	
Pack-year, median (IQR)	2 (0, 30)	5 (0, 33)	0.64
Alcohol use[b], *n* (%)			0.12
Abstinence	134 (45)	39 (46)	
Low risk	75 (25)	16 (19)	
Mild to moderate alcohol misuse	19 (6)	2 (2)	
Severe alcohol misuse	35 (12)	18 (21)	
Unknown history	34 (11)	18 (21)	
Comorbidities, *n* (%)			
Immune suppression[c]	19 (6)	12 (14)	0.02
Diabetes	76 (26)	27 (32)	0.23
Hypertension	115 (39)	40 (48)	0.15
Prior myocardial infarction	15 (5)	9 (11)	0.06
Congestive heart failure	13 (4)	8 (10)	0.07
Chronic pulmonary disease	23 (8)	6 (7)	0.85
Prior stroke with sequelae	12 (4)	1 (1)	0.20
Dementia	8 (3)	5 (6)	0.15
AIDS	3 (1)	4 (5)	0.05
Hepatic failure	1 (0)	1 (1)	0.34
Malignancy	0 (0)	4 (5)	0.002

(*Continued*)

TABLE 2. (*Continued*). Baseline Characteristics by 60-Day Mortality Before Hospital Discharge

Characteristic	Alive at Day 60 ($n = 297$)	Dead at Day 60[a] ($n = 84$)	p
Acute Physiology and Chronic Health Evaluation III score, mean ± SD	87 ± 27	108 ± 28	< 0.001
Vasopressor use at enrollment, *n* (%)	135 (45)	55 (65)	0.001
Septic shock at enrollment, *n* (%)	103 (35)	47 (56)	< 0.001
Severity of lung injury at enrollment			
Lung Injury Score, mean ± SD	2.7 ± 0.5	2.8 ± 0.6	0.70
Pao_2/Fio_2 (mm Hg), mean ± SD	124 ± 66	125 ± 64	0.92
Positive end-expiratory pressure (cm H_2O), mean ± SD	9 ± 4	9 ± 4	0.64
Compliance (mL/cm H_2O), mean ± SD	34 ± 16	33 ± 15	0.53
Chest radiograph quadrants with opacities, median (IQR)	4 (3, 4)	4 (3, 4)	0.64

IQR = interquartile range.
[a]Sixty-day mortality is defined as death prior to discharge from a healthcare facility to home within 60 d from study entry.
[b]As defined by Alcohol Use Disorders Identification Test scores (Supplement Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/A977).
[c]Does not include AIDS.

TABLE 3. Baseline Severity of Lung Injury by Urine NNAL Level

	Smoking Status by Urine NNAL			
	Nonsmoker	Passive Smoker	Active Smoker	
	0 pg/mL	> 0, < 47.3 pg/mL	≥ 47.3 pg/mL	
Baseline Severity of Lung Injury	$n = 143$	$n = 101$	$n = 137$	p
Lung Injury Score, mean ± SD	2.7 ± 0.6	2.8 ± 0.6	2.8 ± 0.5	0.40
Pao_2/Fio_2 (mm Hg), mean ± SD	121 ± 53	123 ± 60	130 ± 79	0.48
Positive end-expiratory pressure (cm H_2O), mean ± SD	8.8 ± 3.6	8.8 ± 3.6	9.3 ± 3.3	0.41
Compliance (mL/cm H_2O), mean ± SD	35 ± 16	33 ± 19	33 ± 14	0.45
Chest radiograph quadrants with opacities, median (IQR)	4 (3, 4)	4 (3, 4)	4 (3, 4)	0.44
Oxygenation index, median (IQR)	10 (6, 16)	13 (7, 21)	11 (8, 18)	0.20
Berlin Definition of ARDS, *n* (%)				0.37
Mild ARDS ($n = 42$)	11 (8)	14 (14)	17 (13)	
Moderate ARDS ($n = 178$)	73 (53)	41 (41)	64 (48)	
Severe ARDS ($n = 152$)	55 (40)	44 (44)	53 (40)	

NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, IQR = interquartile range, ARDS = acute respiratory distress syndrome.

similar (**Supplement Tables S5 and S6**, Supplemental Digital Content 1, http://links.lww.com/CCM/A977).

DISCUSSION

To our knowledge, this analysis is the first to investigate the incidence of biomarker-determined cigarette smoke exposure and associated clinical outcomes in a multicenter cohort of critically ill ARDS patients. Using a highly sensitive and specific cigarette smoke biomarker, we found that the proportion of ARDS patients with NNAL levels in the active smoking range was markedly higher than the national population incidence of active smoking and that despite being younger and having fewer comorbidities and lower severity of acute illness, these patients had similar severity of lung injury compared with patients with undetectable NNAL levels. These findings suggest that smokers may be more susceptible to developing ARDS at a younger age and with fewer predisposing risk factors compared with nonsmokers.

In this national cohort of ARDS patients, the marked differences in age, overall health, and severity of illness between smokers and nonsmokers by NNAL are consistent with the "healthy smoker effect" (38), in which patients who developed health problems may have quit smoking earlier in their lives

TABLE 4. Clinical Outcomes by NNAL Level

Clinical Outcome	Smoking Status Stratified by Urine NNAL: Nonsmoker 0 pg/mL *n* = 143	Passive Smoker > 0, < 47.3 pg/mL *n* = 101	Active Smoker ≥ 47.3 pg/mL *n* = 137	*p*
60-Day mortality, *n* (%)	42 (29)	21 (21)	21 (15)[a]	0.02
Ventilator-free days, median (IQR)[b]	18 (0, 25)	21 (0, 24)	21 (13, 25)[a]	0.10
Organ failure–free days, median (IQR)[b]	5 (0, 21)	6 (0, 19)	13 (0, 23)[a]	0.03
Cardiovascular failure–free days, median (IQR)	23 (12, 27)	25 (16, 27)	25 (18, 27)	0.27
Coagulation failure–free days, median (IQR)	28 (20, 28)	28 (22, 28)	28 (26, 28)[a]	0.01
Renal failure–free days, median (IQR)	28 (9, 28)	28 (13, 28)	28 (21, 28)[a]	0.05
Hepatic failure–free days, median (IQR)	28 (18, 28)	28 (19, 28)	28 (27, 28)[a]	0.03

NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, IQR = interquartile range.

[a]Active smoker versus nonsmoker, $p < 0.05$.

[b]Ventilator-free and organ failure–free days are from time of randomization to day 28 of enrollment.

TABLE 5. Multivariate Analysis for 60-Day Mortality

Predictor	OR for Death at 60 Days[a]	95% CI	*p*
Smoking status by urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol			
Nonsmoker	(reference)		
Passive smoker	1.00	0.49–2.02	1.0
Active smoker	0.58	0.28–1.22	0.15
Age, yr	1.04	1.02–1.06	< 0.001
Alcohol use[b]			
Low risk	(reference)		
Abstinence	0.89	0.43–1.82	0.75
Mild to moderate alcohol misuse	0.67	0.13–3.47	0.63
Severe alcohol misuse	1.57	0.55–4.50	0.40
Unknown	2.93	1.21–7.09	0.02
Acute Physiology and Chronic Health Evaluation III	1.02	1.01–1.03	< 0.001

OR = odds ratio.

[a]Multivariate logistic regression with backward selection was performed; covariates with $p < 0.10$ were retained in final model. Original model, which also contained comorbidities, primary risk factor of lung injury, and septic shock, is shown in Supplement Table S4 (Supplemental Digital Content 1, http://links.lww.com/CCM/A977).

[b]As defined by Alcohol Use Disorders Identification Test scores (Supplement Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/A977).

or refrained from smoking, leaving primarily patients with fewer health problems in the active smoking pool. This enrichment likely biased the relationship between smoking and 60-day mortality and made smoking appear to be associated with a lower risk of mortality at 60 days in univariate analyses. Indeed, in multivariate analysis controlling for the marked differences in age, comorbidities, and acute severity of illness, the association between smoking and decreased 60-day mortality was no longer significant. Another possible explanation is that smoking leads to a higher incidence of ARDS at a younger age in spite of fewer other predisposing risk factors. A similar relationship has been reported in acute myocardial infarction, in which smokers were younger and had fewer other cardiovascular risk factors compared with nonsmokers (39).

The high incidence of subjects with urine NNAL in the active smoking range in this multicenter cohort of ARDS patients is similar to previous single-center studies in critically ill patients with biochemically measured cigarette smoke exposure (36% vs 44% and 57%, respectively) (12, 23). Because the ALTA and Omega clinical trials excluded patients with comorbidities that

frequently occur with smoking, such as severe chronic lung or liver disease, the incidence in an unselected cohort of ARDS patients may be higher still.

The proportion of nonsmokers who had levels consistent with passive smoking was similar to national incidence levels (41% vs 40%) (18). It is possible that these data may underestimate the incidence of passive smoking in the cohort due to decay in NNAL levels with time and lower assay sensitivity (LOQ of 1 pg/mL vs 0.25 pg/mL in prior studies). This lowered sensitivity would not affect the accuracy of measured NNAL levels but would decrease the detection of lower levels of cigarette smoke exposure in a small fraction of passive smokers (less than 10% in a prior study) (19).

We have previously reported that cigarette smoke biomarkers detected a higher incidence of exposure in critically ill patients compared with smoking history obtained mostly through medical records (23). In this study, smoking history was mostly obtained through surrogate report, which has been shown to be more accurate about smoking status compared with medical records (40, 41). Even so, NNAL levels were consistent with active smoking in 9% of reported nonsmokers and 44% of patients with unknown history. These results indicate that urine NNAL provides significantly more detailed and objective information on cigarette smoke exposure compared with smoking history by surrogate report.

To our knowledge, this study provides the first comparison of the severity of lung injury among ARDS patients with different levels of cigarette smoke exposure. Given that subjects with NNAL levels in the active smoking range had markedly fewer risk factors for lung injury compared with subjects with undetectable NNAL (e.g., younger age [3], lower severity of illness [42], and less septic shock [43]), it is remarkable that the severity of lung injury at the time of enrollment and over the first 7 days of the study did not differ based on cigarette smoke exposure. This finding suggests that among patients with similar comorbidities and severity of illness, active smokers may be more susceptible to lung injury compared with nonsmokers, as has been suggested by prior studies in trauma-related ARDS, transfusion-related ARDS, and lung transplant cohorts (12–14). Future prospective studies of broader groups of patients at risk for ARDS will be needed to further test these associations.

It is well established that smokers have a higher incidence of alcohol use. While laboratory-based studies have demonstrated important effects of alcohol on lung epithelial barrier function (44, 45) and alcohol misuse has been implicated as a risk factor for poor outcomes in ARDS patients, prior clinical studies have controlled for smoking status as determined by clinical history rather than through biochemical assessment (32). We found no association between severe alcohol misuse and 60-day mortality after controlling for smoking status by NNAL levels. This lack of association may be explained by the use of biomarkers to classify smoking exposure, the inclusion of patients with unknown alcohol use history (which may be a marker of higher risk alcohol use or socioeconomic isolation), the relatively small number of subjects with severe alcohol misuse in the study which may reflect underreporting by surrogates, and/or the use of different outcome measures in prior studies (e.g., combined outcome of mortality and persistent hospitalization). Therefore, it is possible that alcohol misuse and smoking may have additive and/or synergistic effects on poor outcomes. Future studies are needed to identify a highly sensitive and specific biomarker for alcohol use to augment surrogate alcohol history, analogous to NNAL for smoking history, and to further investigate the joint contribution of these preventable risk factors.

A major strength of this study is that it used quantitative assessment of active and passive cigarette smoke exposure in a well-defined, diverse, multicenter cohort of ARDS patients. In addition, there are some limitations to this study. First, although we adjusted for several potential confounders, there may have been additional latent confounding by unmeasured characteristics. Second, the effect of acute kidney injury on NNAL excretion is unknown. However, sensitivity analysis showed that classification of exposure did not differ when using urine NNAL levels that were corrected for urine creatinine (Supplement Tables S5 and S6, Supplemental Digital Content 1, http://links.lww.com/CCM/A977) (46). Third, urine NNAL can be elevated due to either cigarette smoke exposure or use of other tobacco products. Nationally, the use of other tobacco products (e.g., smokeless tobacco) is dwarfed by the use of cigarettes (47). Notably, the use of nicotine replacement therapy does not affect NNAL levels. Fourth, decline in urine NNAL levels between cessation of use and sample collection may have led to underestimation of both active and passive exposure. This type of misclassification could have biased our findings. Arguing against this concern, sensitivity analysis restricted to patients with urine specimens obtained less than 3 days from hospital admission showed no difference in exposure category and clinical outcomes. Fifth, we do not have biological measures of the duration of past smoking or quantification of past use in former smokers. Although these factors may affect 60-day mortality, we found no association between total pack-years reported and 60-day mortality. Finally, the generalizability of our findings may be limited due to biases inherent to large randomized clinical trials, such as differences in age, surrogate availability, and exclusion of moribund patients (48, 49).

In conclusion, we provide biochemical evidence that active cigarette smoking is more prevalent among ARDS patients than the general population and that smoking history obtained from healthcare surrogates results in markedly lower estimates of exposure compared to urine NNAL. Furthermore, ARDS patients with NNAL levels consistent with active smoking were younger and had lower severity of acute illness and less septic shock compared with nonsmokers; despite these differences, smokers and nonsmokers had similar severity of lung injury. Future studies are needed to determine whether cigarette smoke exposure increases susceptibility to ARDS in a more general population and whether smoking cessation would change clinical outcomes.

REFERENCES

1. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533

2. Zambon M, Vincent JL: Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest* 2008; 133: 1120–1127
3. Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 353:1685–1693
4. Mikkelsen ME, Christie JD, Lanken PN, et al: The adult respiratory distress syndrome cognitive outcomes study: Long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med* 2012; 185:1307–1315
5. Herridge MS, Tansey CM, Matté A, et al; Canadian Critical Care Trials Group: Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; 364:1293–1304
6. Dusser DJ, Minty BD, Collignon MA, et al: Regional respiratory clearance of aerosolized 99mTc-DTPA: Posture and smoking effects. *J Appl Physiol (1985)* 1986; 60:2000–2006
7. Hoshino Y, Mio T, Nagai S, et al: Cytotoxic effects of cigarette smoke extract on an alveolar type II cell-derived cell line. *Am J Physiol Lung Cell Mol Physiol* 2001; 281:L509–L516
8. Xu H, Ferro TJ, Chu S: Cigarette smoke condensate inhibits ENaC alpha-subunit expression in lung epithelial cells. *Eur Respir J* 2007; 30:633–642
9. Olivera DS, Boggs SE, Beenhouwer C, et al: Cellular mechanisms of mainstream cigarette smoke-induced lung epithelial tight junction permeability changes in vitro. *Inhal Toxicol* 2007; 19:13–22
10. Raupach T, Schäfer K, Konstantinides S, et al: Secondhand smoke as an acute threat for the cardiovascular system: A change in paradigm. *Eur Heart J* 2006; 27:386–392
11. Barnoya J, Glantz SA: Cardiovascular effects of secondhand smoke: Nearly as large as smoking. *Circulation* 2005; 111:2684–2698
12. Calfee CS, Matthay MA, Eisner MD, et al: Active and passive cigarette smoking and acute lung injury after severe blunt trauma. *Am J Respir Crit Care Med* 2011; 183:1660–1665
13. Toy P, Gajic O, Bacchetti P, et al; TRALI Study Group: Transfusion-related acute lung injury: Incidence and risk factors. *Blood* 2012; 119:1757–1767
14. Diamond JM, Lee JC, Kawut SM, et al; Lung Transplant Outcomes Group: Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2013; 187:527–534
15. Bonser RS, Taylor R, Collett D, et al; Cardiothoracic Advisory Group to NHS Blood and Transplant and the Association of Lung Transplant Physicians (UK): Effect of donor smoking on survival after lung transplantation: A cohort study of a prospective registry. *Lancet* 2012; 380:747–755
16. Iribarren C, Jacobs DR Jr, Sidney S, et al: Cigarette smoking, alcohol consumption, and risk of ARDS: A 15-year cohort study in a managed care setting. *Chest* 2000; 117:163–168
17. Van Rompaey B, Elseviers MM, Schuurmans MJ, et al: Risk factors for delirium in intensive care patients: A prospective cohort study. *Crit Care* 2009; 13:R77
18. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease prevention and Health Promotion, Office on Smoking and Health: *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, GA, Centers for Disease Control and Prevention, 2006
19. Goniewicz ML, Eisner MD, Lazcano-Ponce E, et al: Comparison of urine cotinine and the tobacco-specific nitrosamine metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and their ratio to discriminate active from passive smoking. *Nicotine Tob Res* 2011; 13:202–208
20. Hecht SS, Hoffmann D: Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis* 1988; 9:875–884
21. Benowitz NL, Schultz KE, Haller CA, et al: Prevalence of smoking assessed biochemically in an urban public hospital: A rationale for routine cotinine screening. *Am J Epidemiol* 2009; 170:885–891
22. Yuan JM, Gao YT, Murphy SE, et al: Urinary levels of cigarette smoke constituent metabolites are prospectively associated with lung cancer development in smokers. *Cancer Res* 2011; 71:6749–6757
23. Hsieh SJ, Ware LB, Eisner MD, et al: Biomarkers increase detection of active smoking and secondhand smoke exposure in critically ill patients. *Crit Care Med* 2011; 39:40–45
24. Goniewicz ML, Havel CM, Peng MW, et al: Elimination kinetics of the tobacco-specific biomarker and lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. *Cancer Epidemiol Biomarkers Prev* 2009; 18:3421–3425
25. Matthay MA, Brower RG, Carson S, et al: Randomized, placebo-controlled clinical trial of an aerosolized beta(2)-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med* 2011; 184:561–568
26. Rice TW, Wheeler AP, Thompson BT, et al: Initial trophic vs full enteral feeding in patients with acute lung injury: The EDEN randomized trial. *JAMA* 2012; 307:795–803
27. Jacob P III, Havel C, Lee DH, et al: Subpicogram per milliliter determination of the tobacco-specific carcinogen metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in human urine using liquid chromatography-tandem mass spectrometry. *Anal Chem* 2008; 80:8115–8121
28. Reinert DF, Allen JP: The Alcohol Use Disorders Identification Test (AUDIT): A review of recent research. *Alcohol Clin Exp Res* 2002; 26:272–279
29. Rubinsky AD, Kivlahan DR, Volk RJ, et al: Estimating risk of alcohol dependence using alcohol screening scores. *Drug Alcohol Depend* 2010; 108:29–36
30. Moss M, Mannino DM: Race and gender differences in acute respiratory distress syndrome deaths in the United States: An analysis of multiple-cause mortality data (1979-1996). *Crit Care Med* 2002; 30:1679–1685
31. Stapleton RD, Wang BM, Hudson LD, et al: Causes and timing of death in patients with ARDS. *Chest* 2005; 128:525–532
32. Clark BJ, Williams A, Feemster LM, et al: Alcohol screening scores and 90-day outcomes in patients with acute lung injury. *Crit Care Med* 2013; 41:1518–1525
33. Cooke CR, Kahn JM, Caldwell E, et al: Predictors of hospital mortality in a population-based cohort of patients with acute lung injury. *Crit Care Med* 2008; 36:1412–1420
34. Centers for Disease Control and Prevention: Current cigarette smoking prevalence among working adults–United States, 2004–2010. *MMWR Morb Mortal Wkly Rep* 2011; 60:1305–1309
35. Centers for Disease Control and Prevention: Vital signs: Nonsmokers' exposure to secondhand smoke–United States, 1999–2008. *MMWR Morb Mortal Wkly Rep* 2010; 59:1141–1146
36. Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720–723
37. Seeley E, McAuley DF, Eisner M, et al: Predictors of mortality in acute lung injury during the era of lung protective ventilation. *Thorax* 2008; 63:994–998
38. Eisner MD: Smoking and adult asthma: A healthy smoker effect? *Am J Respir Crit Care Med* 2002; 165:1566; author reply 1566–1567
39. Ruiz-Bailén M, de Hoyos EA, Reina-Toral A, et al; ARIAM Group: Paradoxical effect of smoking in the Spanish population with acute myocardial infarction or unstable angina: Results of the ARIAM Register. *Chest* 2004; 125:831–840
40. Mant J, Murphy M, Rose P, et al: The accuracy of general practitioner records of smoking and alcohol use: Comparison with patient questionnaires. *J Public Health Med* 2000; 22:198–201
41. Woo JG, Pinney SM: Retrospective smoking history data collection for deceased workers: Completeness and accuracy of surrogate reports. *J Occup Environ Med* 2002; 44:915–923
42. Agrawal A, Matthay MA, Kangelaris KN, et al: Plasma angiopoietin-2 predicts the onset of acute lung injury in critically ill patients. *Am J Respir Crit Care Med* 2013; 187:736–742
43. 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
44. Guidot DM, Modelska K, Lois M, et al: Ethanol ingestion via glutathione depletion impairs alveolar epithelial barrier function in rats. *Am J Physiol Lung Cell Mol Physiol* 2000; 279:L127–L135

45. Zhang YL, Li QQ, Guo W, et al: Effects of chronic ethanol ingestion on tight junction proteins and barrier function of alveolar epithelium in the rat. *Shock* 2007; 28:245–252
46. Goniewicz M, Peyton J, Havel C, et al: Application of urine cotinine to NNAL ratio in tobacco smoke exposure assessment. 2009 Joint Conference of Society for Research on Nicotine and Tobacco and SNRT-Europe. Dublin, Ireland; 2009. POS4–78
47. Centers for Disease Control and Prevention: State-Specific Prevalence of Cigarette Smoking and Smokeless Tobacco Use Among Adults --United States, 2010; 59: No. 43. Available at: http://www.cdc.gov/tobacco/data_statistics/mmwrs/byyear/2010/mm5943a2/highlights.htm. Accessed May 9, 2014
48. Cooke CR, Erickson SE, Watkins TR, et al: Age-, sex-, and race-based differences among patients enrolled versus not enrolled in acute lung injury clinical trials. *Crit Care Med* 2010; 38:1450–1457
49. Glassberg AE, Luce JM, Matthay MA; National Heart, Lung, and Blood Institute Clinical Trials Network: Reasons for nonenrollment in a clinical trial of acute lung injury. *Chest* 2008; 134:719–723

APPENDIX 1: National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network Participants

University of Washington, Harborview—L. Hudson*, S. Gundel, C. Hough, M. Neff, K. Sims, A. Ungar, T. Watkins; Baystate Medical Center—J. Steingrub*, M. Tidswell*, E. Braden, L. DeSouza, J. Germain, C. Kardos, D. Kelley, L. Kozikowski, K. Kozikowski, S. Ouellette; Baylor College of Medicine—K. Guntupalli, V. Bandi, C. Pope; Johns Hopkins Hospital—R. Brower*, H. Fessler, D. Hager, P. Mendez-Tellez, D. Needham, K. Oakjones; Johns Hopkins Bayview Medical Center—J. Sevransky, A. Workneh, S. Han, S. Murray; University of Maryland—C. Shanholtz, D. Herr, H. Howes, G. Netzer, P. Rock, A. Sampaio, J. Titus; Union Memorial Hospital—P. Sloane, T. Beck, H. Highfield, S. King; Washington Hospital Center—D. Herr, B. Lee, N. Bolouri; Cleveland Clinic Foundation—H. P. Wiedemann*, R. W. Ashton, D. A. Culver, T. Frederick, J. J. Komara, J. A. Guzman, A. J. Reddy; University Hospitals of Cleveland—R. Hejal, M. Andrews, D. Haney; MetroHealth Medical Center—A. F. Connors, S. Lasalvia, J. D. Thornton, E. L. Warren; University of Colorado Health Science Centers—M. Moss*, A. Benson, E. Burnham, B. Clark, L. Gray, C. Higgins, B. J. Maloney, M. Mealer; National Jewish Health—S. Frankel; St. Anthony's Hospital—T. Bost, P. Dennen, K. Hodgin; Denver Health Medical Center—I. Douglas, K. Overdier, K. Thompson, R. Wolken; Rose Medical Center—J. McKeehan; Swedish Medical Center—M. L. Warner; Saint Anthony's Hospital—T. Bost, C. Higgins, K. Hodgin; Duke University—N. MacIntyre*, L. Brown, C. Cox, M. Gentile, J. Govert, N. Knudsen; University of North Carolina—S. Carson, L. Chang, S. Choudhury, W. Hall, J. Lanier; Vanderbilt University—A. P. Wheeler*, G. R. Bernard, M. Hays, S. Mogan, T. Rice; Wake Forest University—R. D. Hite*, K. Bender, P. E. Morris, A. Howard, A. Harvey, Mary Ragusky; Moses Cone Memorial Hospital—P. Wright, S. Gross, J. McLean, A. Overton; University of Virginia—J. Truwit, K. Enfield, M. Marshall; LDS Hospital—P. Bailey, W. Beninati, L. Bezdijan, T. Clemmer, S. Rimkus, R. Tanaka, L. Weaver; Intermountain Medical Center—A. Morris*, A. Ahmed, A. Austin, S. Barney, S. Brown, N. Dean, J. Fergeson, A. Fitzpatrick, H. Gallo, T. Graydon, C. Grissom, E. Hirshberg, A. Jephson, N. Kumar, R. Miller, J. Orme, S. Pandita, G. Schreiber, A. Stow, L. Struck, F. Thomas, G. Thomsen, D. VanBoerum, D. Ward, L. Weaver, T. White, M. Zenger, D. Dienhart, P. Nelson, M. Goddard, J. Krueger, L. Napoli; McKay-Dee Hospital—C. Lawton, J. Baughman, T. Fujii, D. Hanselman, T. Hoffman, B. Kerwin, P. Kim, F. Leung; Utah Valley Regional Medical Center—K. Sundar, W. Alward, C. Bishop, E. Campbell, D. Eckley, T. Hill, B. Jensen, K. Ludwig, D. Nielsen, M. Pearce; University of California, San Francisco—M. A. Matthay*, C. Calfee, B. Daniel, M. Eisner, O. Garcia, E. Johnson, R. Kallet, K. Kordesch, K. Liu, N. Shum, H. Zhou; University of California, San Francisco, Fresno—M. W. Peterson, J. Blaauw, K. Van Gundy; University of California Davis—T. Albertson, B. Morrissey, E. Vlastelin; Mayo Foundation—R. Hubmayr*, D. Brown, M. Dubin, E. Festic, O. Gajic, R. Hinds, S. Holets, D. J. Kor, A. Lee, M. Passe, G. Simpson, J. Wright; Louisiana State University—B. deBoisblanc*, A. Antoine, D. Charbonnet, J. Hunt, P. Lauto, A. Marr, G. Meyaski, C. Romaine, R. Tejedor; Louisiana State University—Earl K. Long; Baton Rouge General Medical Center Mid-City and Baton Rouge General Medical Center Bluebonnet—S. Brierre, J. Byrne, T. Jagneaux, C. LeBlanc, K. Moreau, C. Thomas; Alton-Ochsner Clinic Foundation—D. Taylor, S. Jain, L. Seoane; Our Lady of the Lake Medical Center—C. Hebert, J. Thompson; Tulane University—F. Simeone, J. Fearon, J. Duchesne; Clinical Coordinating Center (Massachusetts General Hospital and Harvard Medical School)—D. Schoenfeld*, M. Aquino, D. Dorer, M. Guha, E. Hammond, N. Lavery, P. Lazar, I. Molina, R. Morse, C. Oldmixon, B. Rawal, N. Ringwood, A. Shui, E. Smoot, B. T. Thompson, R. Wilson; National Heart, Lung and Blood Institute—A. Harabin, S. Bredow, M. Waclawiw, G. Weinmann; Data and Safety Monitoring Board—R. G. Spragg (chair), A. Slutsky, M. Levy, B. Markovitz, E. Petkova, C. Weijer; Protocol Review Committee—J. Sznajder (chair), M. Begg, E. Israel, J. Lewis, P. Parsons.

*Denotes principal investigator.