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

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Abstract

Objective—Cigarette smoke exposure has recently been found to be associated with increased susceptibility to trauma- and transfusion-associated acute respiratory distress syndrome (ARDS).

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We sought to determine 1) the prevalence of cigarette smoke exposure in a diverse multi-center sample of ARDS patients, and 2) whether cigarette smoke exposure is associated with severity of lung injury and mortality in ARDS.

Design—Analysis of the Albuterol for the Treatment of ALI (ALTA) and Omega ARDS Network studies.

Setting—Acute Respiratory Distress Syndrome Network hospitals.

Patients—Three hundred eighty one patients with ARDS.

Interventions—None.

Measurements—NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), a validated tobacco-specific marker, was measured in urine samples from subjects enrolled in two NHLBI ARDS Network randomized controlled trials.

Main Results—Urine NNAL levels were consistent with active smoking in 36% of ARDS patients and with passive smoking in 41% of nonsmokers (vs 20% and 40% in general population, respectively). Patients with NNAL levels in the active smoking range were younger and had a higher prevalence of alcohol misuse, fewer comorbidities, lower severity of illness, and less septic shock at enrollment compared to patients with undetectable NNAL 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 ARDS patients, we found that active cigarette smoke exposure was significantly more prevalent among ARDS patients compared to population averages. Despite their younger age, better overall health, and lower severity of illness, smokers by NNAL had similar severity of lung injury as patients with undetectable NNAL. These findings suggest that active cigarette smoking increases susceptibility to ARDS in younger, healthier patients.

Keywords

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

INTRODUCTION

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 prevalence 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 days) (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 prevalence 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 NHLBI ARDS Network randomized controlled trials.

METHODS

Patients

Subjects who were enrolled in the ARDS Network Albuterol for the Treatment of ALI (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 (25, 26). Both studies were stopped early for futility, after the enrollment of 272 and 282 patients respectively (37 co-enrolled). The Institutional Review Board of the University of California at San Francisco approved the research protocol for this secondary analysis.

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 to 2 mL of urine (27). The limit of quantification (LOQ) of urine NNAL was 1 pg/mL for 0.5mL. 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%, AUC 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 (see Online Supplement). 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 or AUDIT) (28). Alcohol use was defined using validated gender-specific cutoffs in AUDIT scores (29) (Supplement Table S1).

Statistical Analysis

Statistical significance was defined as $p \leq 0.05$, using two-tailed tests of hypotheses. Categorical data were analyzed by chi-squared 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 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 step-wise 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), APACHE III score (33), 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 COPD). 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 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

Prevalence 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 prevalence of

smokers by history and similar 60-day mortality (Supplement Table S2). 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 prevalence 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 prevalence 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 Figure S1). 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 prevalence of mild to severe alcohol misuse and unknown alcohol history, and had fewer comorbidities than nonsmokers by NNAL. Specifically, the prevalence of immune suppression, diabetes, prior myocardial infarction, hypertension, congestive heart failure, prior stroke with sequelae, and dementia were lower in patients with NNAL in the active smoking range compared to patients with NNAL in the undetectable range ($p<0.05$). In addition to these pronounced differences in the prevalence 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 to 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 prevalence 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 (PaO2/FiO2, PEEP, compliance, and CXR 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 PaO2/FiO2 and oxygenation index (37) on study days 1 to 7 between the three groups (Supplement Table S3).

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 to 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 non-smoking OR 0.58, 95% CI 0.28–1.22, p=0.15; passive smoking vs non-smoking OR 1.00, 95% CI 0.49–2.02, p>0.99). In the full initial model, before backward selection (Supplement Table S4) these OR's 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 similar (Supplement Tables S5 and S6).

DISCUSSION

To our knowledge, this analysis is the first to investigate the prevalence 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 prevalence 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 to 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 to 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 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 have fewer other cardiovascular risk factors compared to nonsmokers (39).

The high prevalence 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 prevalence 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 prevalence levels (41% vs 40%) (18). It is possible that these data may underestimate the prevalence 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 prevalence of exposure in critically ill patients compared to 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 to 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 to smoking history by surrogate report.

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 to 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 to 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 prevalence 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, multi-center 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 Table S5 and S6) (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 health care 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 to 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.

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Table 1

Baseline characteristics by smoking exposure

Characteristic	Smoking Status by Urine NNAL			P-value
	Nonsmoker 0 pg/ml (N=143)	Passive smoker >0, <47.3 pg/ml (N=101)	Active smoker >=47.3 pg/ml (N=137)	
Age (years), 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
Non-smoker	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]*	0.0001
Time in hospital prior to urine collection (days), median [IQR]	1 [0, 3]	2 [0, 4]	1 [0, 3]	0.10
Comorbidities, n (%)				
Immune suppression	20 (14)	8 (8)	3 (2)*	0.001
Diabetes	49 (34)	28 (28)	26 (19)*	0.02
Prior myocardial infarction	15 (10)	5 (5)	4 (3)*	0.03
Hypertension	79 (55)	43 (43)†	33 (24)*	<0.001
Congestive heart failure	11 (8)	8 (8)	2 (1)*	0.02
Chronic pulmonary disease	13 (9)	2 (2)†	14 (10)	0.03
Prior stroke with sequelae	10 (7)	3 (3)	0 (0)*	0.002

	Smoking Status by Urine NNAL			
Characteristic	**Nonsmoker 0 pg/ml (N=143)**	**Passive smoker >0, <47.3 pg/ml (N=101)**	**Active smoker >=47.3 pg/ml (N=137)**	**P-value**
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
APACHE III score, mean ± SD	97 ± 29	91 ± 28	85 ± 26*	0.001
Vasopressor use at baseline, n (%)	84 (59)	50 (50)	56 (41)*	0.01
Septic shock at enrollment, n (%)	72 (50)	36 (36)†	42 (31)*	0.002

[a] Passive vs nonsmoker p≤0.05;

[b] Active smoker vs nonsmoker p≤0.05

[c] As defined by Alcohol Use Disorders Identification Test (AUDIT) scores (Online Supplement, Table S1)

Definition of abbreviations: APACHE III = Acute Physiology and Chronic Health Evaluation III

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-value
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
Non-smoker	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

Characteristic	Alive at day 60 (N=297)	Dead at day 60[a] (N=84)	p-value
APACHE 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
PaO2/FiO2 (mm Hg), mean ± SD	124 ± 66	125 ± 64	0.92
PEEP (cm H_2O), mean ± SD	9 ± 4	9 ± 4	0.64
Compliance (mL / cm H_2O), mean ± SD	34 ± 16	33 ±15	0.53
CXR quadrants with opacities, median [IQR]	4 [3, 4]	4 [3, 4]	0.64

[a] Sixty-day mortality is defined as death prior to discharge from a health care facility to home within 60 days from study entry

[b] As defined by Alcohol Use Disorders Identification Test (AUDIT) scores (Online Supplement, Table S1)

[c] Does not include AIDS

Table 3

Baseline severity of lung injury by urine NNAL level

	Smoking Status 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-value**
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
PEEP (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
CXR 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)	

Definition of abbreviations: FiO_2 = fraction of inspired oxygen; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; PaO_2 = partial pressure of oxygen in arterial blood; PEEP = positive end-expiratory pressure; SD = standard deviation

Table 4

Clinical outcomes by urine NNAL level

	Smoking Status Stratified by Urine NNAL			
Outcome	**Nonsmoker 0 pg/ml (N=143)**	**Passive smoker >0, <47.3 pg/ml (N=101)**	**Active smoker >=47.3 pg/ml (N=137)**	**p-value**
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

Definition of abbreviations: NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol

[a] Active smoker vs 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-value
Smoking status by urine NNAL			
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
APACHE III	1.02	1.01 – 1.03	<0.001

Definition of abbreviations: APACHE III = Acute Physiology and Chronic Health Evaluation III; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[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 Online Supplement Table S4.

[b] As defined by Alcohol Use Disorders Identification Test (AUDIT) scores (Online Supplement, Table S1)