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Cigarette Smoke Exposure and the Acute Respiratory Distress Syndrome

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Objective: The association between cigarette smoke exposure and the acute respiratory distress syndrome in patients with the most common acute respiratory distress syndrome risk factors of sepsis, pneumonia, and aspiration has not been well studied. The goal of this study was to test the association between biomarker-confirmed cigarette smoking and acute respiratory distress syndrome in a diverse cohort.

Design: Prospective cohort.

Setting: Tertiary care center.

Patients: Four hundred twenty-six critically ill patients with acute respiratory distress syndrome risk factors (excluding trauma and transfusion)

Interventions: None.

Measurements and Main Results: We obtained smoking histories and measured urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (a biomarker of cigarette smoke exposure) on urine samples obtained at the time of study enrollment. The association between cigarette smoke exposure and acute respiratory distress syndrome differed based on acute respiratory distress syndrome risk factor ($p < 0.02$ for interaction). In patients with nonpulmonary sepsis as the primary acute respiratory distress syndrome risk factor ($n = 212$), 39% of those with acute respiratory distress syndrome were current smokers by history compared with 22% of those without acute respiratory distress syndrome (odds ratio, 2.28; 95% CI, 1.24–4.19; $p = 0.008$). Likewise, cigarette smoke exposure as measured by urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol was significantly associated with acute respiratory distress syndrome in this group. The increased risk of acute respiratory distress syndrome in nonpulmonary sepsis was restricted to patients with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol levels consistent with active smoking and was robust to adjustment for other acute respiratory distress syndrome predictors. Cigarette smoke exposure as measured by history or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol was not associated with acute respiratory distress syndrome in patients with other risk factors (e.g., pneumonia and aspiration).

Conclusions: Cigarette smoking measured both by history and biomarker is associated with an increased risk of acute respiratory distress syndrome in patients with nonpulmonary sepsis. This finding has important implications for tobacco product regulation and for understanding the pathogenesis of acute respiratory distress syndrome. (*Crit Care Med* 2015; XX:00–00)

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

Despite advances in supportive care, the acute respiratory distress syndrome (ARDS) remains a major cause of morbidity and mortality in critically ill patients, with recent mortality rates of 20–40% (1). Furthermore, the search for specific pharmacologic therapies for this syndrome remains fruitless. As a result, increased attention has been focused on the development of preventative approaches, exemplified by the recent shift in focus of the National Institutes of Health's ARDS Clinical Trials Network to prevention and early treatment (2).

One approach to ARDS prevention is to focus on potentially modifiable risk factors ("first hits") that may increase the risk of developing noncardiogenic pulmonary edema in the setting of a "second hit" ARDS risk factor such as sepsis, pneumonia, aspiration, or trauma. In animal models and some human studies, cigarette smoke exposure causes significant alterations in lung epithelial and endothelial function similar to those observed in ARDS (3, 4). Likewise, cigarette smoking has potent effects on neutrophil trafficking and function, humoral and cell-mediated immunity, and alveolar macrophages that could contribute to ARDS development (5, 6). We previously reported that cigarette smoke exposure is associated with substantially increased risk of ARDS after severe blunt trauma or blood transfusion (7, 8). By contrast, the association between cigarette smoke exposure and ARDS in broader populations of at-risk patients, including those with the most common ARDS risk factors of sepsis, pneumonia, and aspiration, has not been well studied in rigorous, prospective analyses with quantitative measures of exposure.

Defining the association between smoking and ARDS also has significant implications for tobacco product regulation. Prior analyses of the economic and public health effects of smoking have not accounted for most short-term pulmonary effects of cigarette smoke exposure, including ARDS (9–11). With the large immediate health and financial burden of ARDS and the potentially rapid impact of regulation-related changes in cigarette smoke exposure on the incidence of ARDS, quantifying the association between smoking and ARDS may have important implications for the cost-benefit analysis of proposed regulations and their subsequent impact on health of the population (10, 12).

This study was designed to test the hypothesis that cigarette smoke exposure is associated with an increased risk of ARDS in a diverse sample of critically ill patients with a variety of common ARDS risk factors. Because cigarette smoke exposure histories in critically ill patients may be inaccurate (13), we supplemented smoking history with quantitative measurement of urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a well-validated marker of cigarette smoke exposure (14). Some of these data have been previously presented in the form of an abstract (15).

METHODS

Subjects

This analysis was a prospective substudy within the Validation of biomarkers in Acute Lung Injury for Diagnosis (VALID) study (16), a prospective cohort of critically ill patients at Vanderbilt University Medical Center, a tertiary medical center in Nashville, TN. The inclusion and exclusion criteria for VALID have been described previously (16) and are summarized in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/B313). The informed consent process has also been described previously (16). The study was approved by the Vanderbilt Institutional Review Board.

For this substudy, we included patients with an identified risk factor for ARDS who were enrolled in VALID within 1 week of hospital admission between September 2007 and December 2009 and had a urine sample available for NNAL measurement ($n = 896$). We excluded patients whose primary ARDS risk factor was severe trauma ($n = 362$) or blood transfusion ($n = 108$) because of the established link between cigarette

smoke exposure and ARDS in these populations (7, 8) and potential clinical and biological differences between trauma-associated ARDS and other forms of ARDS, leaving 426 patients for analysis (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B313) (17).

ARDS and Risk Factor Definitions
Risk factors for ARDS were categorized as sepsis, pneumonia, aspiration, pancreatitis, near drowning, drug overdose, or other and were adjudicated by the VALID principal investigator (L.B.W.). Sepsis was defined by consensus definitions (18). Patients with sepsis due to pneumonia were classified as having pneumonia as their ARDS risk factor. ARDS was assessed daily through ICU day 5 using American European Consensus Conference definitions (i.e., Pao_2/Fio_2 ratio < 300) by two-physician review of radiographs and charts to exclude pure cardiogenic pulmonary edema (19). Both mechanically ventilated and not mechanically ventilated patients with ARDS were included. If an arterial blood gas was not available, the Spo_2/Fio_2 ratio was used to assess the level of hypoxemia (20).

Smoking and Alcohol History
Smoking and alcohol use histories, including administration of the Alcohol Use Disorders Identification Test, were obtained from patients or surrogates as detailed in the supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/B313). If patients or surrogates were unable or unavailable to provide this history, it was obtained from the medical record.

Urine NNAL
NNAL is a metabolite of NNK (nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, or nicotine-derived nitrosamine ketone), a potent carcinogen found only in tobacco products. Urine NNAL is a well-established, highly specific marker of NNK uptake with a half-life of 10–18 days (21–23). Because of its long half-life, NNAL detects tobacco exposure for many weeks and serves as an integrated marker of exposure over time. NNAL levels were measured in urine collected at study enrollment using liquid chromatography-tandem mass spectrometry (24). Urine NNAL levels greater than or equal to 47.3 pg/mL were considered consistent with active smoking, and NNAL levels less than 47.3 pg/mL but above the limit of quantitation (1 pg/mL) were considered consistent with passive smoke exposure, based on the finding in 601 outpatients that a urine NNAL cutoff of 47.3 pg/mL accurately distinguishes active from passive smokers (sensitivity, 87.4%; specificity, 96.5%) (14). Because the urine may be variably concentrated in critical illness, as a sensitivity analysis, NNAL levels were normalized to urine creatinine, for which a cutoff of 64 pg NNAL/mg Cr was used to distinguish active from passive exposure (25).

Statistical Analysis
Full details of the statistical methods are in the supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/B313). Because NNAL is not normally distributed,

NNAL levels were log-transformed or classified into a categorical variable for regression analysis. Multivariable logistic regression was performed to adjust the association between smoking (as measured by either history or NNAL) and ARDS for established predictors of ARDS, specifically diabetes, race-ethnicity, alcohol abuse, and severity of illness (26). In addition, we controlled for time elapsed between hospital admission and enrollment because NNAL levels decline over time.

RESULTS

Study Subjects
Overall, there were no differences in baseline demographics between patients with and without ARDS (**Table 1**). As in prior studies, ARDS subjects had higher severity of illness and a lower prevalence of diabetes than those without ARDS. Although the proportion of patients with a history of current smoking was numerically higher in those with ARDS than those without ARDS (36% vs 29%), this difference was not significant ($p = 0.12$).

In keeping with the diverse nature of this cohort, there were significant differences in source of ICU admission between those with and without ARDS ($p = 0.01$). Specifically, those with ARDS were more likely to have been admitted to the ICU from the hospital floor and less likely to have been admitted from the emergency department. Similarly, there were substantial differences in ARDS risk factor between those with and without ARDS ($p < 0.001$), with pneumonia and aspiration making up a larger proportion of those with ARDS than those at risk for ARDS.

Prevalence of Cigarette Smoke Exposure by NNAL
NNAL levels were consistent with active smoking (≥ 47.3 pg/mL) in 38% of the cohort, passive smoking (above Limit of Quantitation [LOQ] to 47.3 pg/mL) in 28%, and no cigarette smoke exposure in 34% (below LOQ). For reference, the prevalence of cigarette smoking in Tennessee in 2008 was 23% (27). The distribution of NNAL levels by smoking history is shown in **Figure 1**. As in our prior studies (7, 13), subjects identified by history as current smokers were highly likely to be confirmed as active smokers by NNAL; in addition, NNAL levels consistent with active smoking were not uncommon in subjects identified by history as nonsmokers or former smokers or whose smoking status was unknown.

Association of Cigarette Smoke Exposure With ARDS
In the overall cohort of 426 patients, there was no statistical association between NNAL levels and ARDS. This finding was consistent whether NNAL was analyzed as a continuous variable ($p = 0.67$) or as a categorical variable ($p = 0.89$).

Because there were significant differences in ARDS risk factors between subjects with and without ARDS, we tested for the presence of multiplicative interaction between cigarette smoke exposure and ARDS risk factors. There was a strong interaction between nonpulmonary sepsis as an ARDS risk

TABLE 1. Description of Study Population (*n* = 426) Stratified by Acute Respiratory Distress Syndrome

Characteristic	Patients With ARDS (*n* = 216)	Patients Without ARDS (*n* = 210)	*p*
Age	56±16	56±15	0.86
Male gender, *n* (%)	114 (53)	102 (47)	0.54
White race, *n* (%)	191 (88)	170 (81)	0.23
Acute Physiology and Chronic Health Evaluation II score	28±8	26±8	0.003
Comorbidities,[a] *n* (%)			
Diabetes	61 (28)	82 (39)	0.02
Chronic liver disease	14 (7)	17 (8)	0.52
Chronic kidney disease	30 (14)	34 (16)	0.51
History of current smoking, *n* (%)	77 (36)	60 (29)	0.12
Charted alcohol abuse, *n* (%)	42 (19)	43 (21)	0.79
Current alcohol abuse,[b] *n* (%)	24 (11)	37 (12)	0.66
Smokeless tobacco use, *n* (%)	3 (1.4)	3 (1.4)	0.44
Source of ICU admission, *n* (%)			
Emergency department	70 (32)	94 (45)	
Floor	65 (30)	37 (18)	0.01
Outside hospital	59 (27)	51 (24)	
Operating room	19 (9)	25 (12)	
Primary ARDS risk factor, *n* (%)			
Nonpulmonary sepsis	86 (40)	126 (60)	
Pneumonia	74 (34)	42 (20)	
Pancreatitis	1 (0.5)	9 (4)	< 0.001
Drug overdose	2 (1)	13 (6)	
Aspiration	44 (20)	20 (10)	
Other	9 (4)	0 (0)	

ARDS = acute respiratory distress syndrome.

[a]No difference in metastatic malignancy, leukemia, chronic obstructive pulmonary disease, asthma, organ or bone marrow transplantation, HIV, and coronary artery disease.

[b]Charted alcohol abuse includes current or former. Current alcohol abuse includes charted history of current abuse or high score on Alcohol Use Disorders Identification Test questionnaire.

factor and cigarette smoke exposure that was present whether cigarette smoke exposure was classified by smoking history (*p* = 0.01) or by NNAL (*p* = 0.004). Specifically, in patients
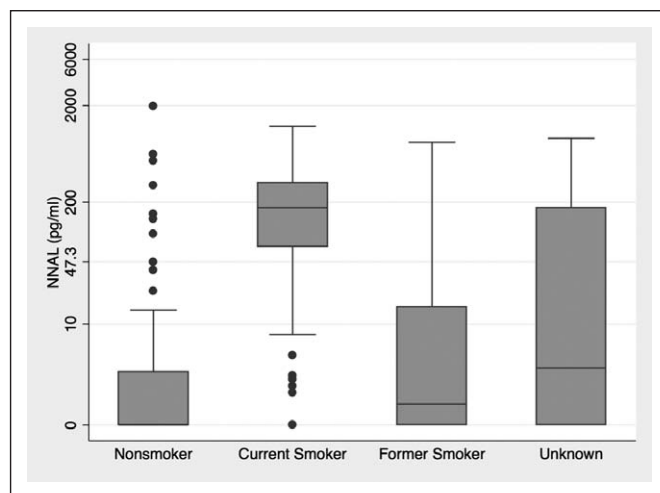
Figure 1. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) levels by smoking history in entire cohort (*n* = 426). Urine NNAL levels ≥ 47.3 pg/mL were considered consistent with active smoking.

with nonpulmonary sepsis (*n* = 212, excluding pneumonia and aspiration), both current smoking by history (odds ratio [OR] for ARDS, 2.28; 95% CI, 1.24–4.19; *p* = 0.008) and increasing NNAL levels (OR per one-log increase, 1.13; 95% CI, 1.00–1.27; *p* = 0.047) were associated with development of ARDS. In this group, 39% of subjects with ARDS were current smokers by history compared with 22% of subjects without ARDS. These patients are further described in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/B313). In patients with other ARDS risk factors, there was no association between ARDS and either a history of smoking (OR, 0.79; 95% CI, 0.45–1.40; *p* = 0.42) or urine NNAL (OR, 0.91; 95% CI, 0.82–1.02; *p* = 0.11).

Multivariable Models

To determine whether the association between smoking and ARDS in nonpulmonary sepsis could be confounded by demographic or clinical factors associated with ARDS, we created multivariable logistic models to adjust for other ARDS predictors. The association between NNAL and ARDS in patients with nonpulmonary sepsis was not significantly attenuated by adjustment for severity of illness as measured by Acute Physiology and Chronic Health Evaluation (APACHE) II score, race-ethnicity, diabetes, or alcohol abuse (**Table 2**). Analyses using categorized NNAL as the primary predictor showed similar results (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B313). Likewise, the association between smoking history and ARDS was robust to adjustment for these predictors (**Table 3**).

Of note, using previously validated NNAL cutpoints, the risk of ARDS was restricted to active smoking in both unadjusted and adjusted models (Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/B313). A smoothed Lowess scatterplot of the association between NNAL levels and ARDS is shown in **Figure 2**. This analysis suggests that increased ARDS risk may begin at levels of NNAL consistent with moderate to heavy passive smoke exposure.

TABLE 2. Association Between 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (Continuous) and Acute Respiratory Distress Syndrome, Unadjusted and Adjusted, in Patients With Nonpulmonary Sepsis (n = 212)

Predictors of ARDS	OR for ARDS (95% CI)	p
Unadjusted model		
Log-NNAL, per one-log increment	1.13 (1.00–1.27)	0.047
Multivariable model[a]		
Log-NNAL, per one-log increment	1.16 (1.01–1.33)	0.037
Acute Physiology and Chronic Health Evaluation II score	1.09 (1.04–1.13)	< 0.001
African-American race	0.34 (0.13–0.91)	0.03
Hispanic ethnicity	0.31 (0.03–3.20)	0.33
Current alcohol abuse	1.77 (0.62–5.08)	0.29
Diabetes	0.65 (0.35–1.23)	0.19
Time elapsed between admission and enrollment	1.19 (0.99–1.44)	0.06

ARDS = acute respiratory distress syndrome, OR = odds ratio, NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.
[a]Referent ethnicity is white.

TABLE 3. Association Between Smoking History and Acute Respiratory Distress Syndrome, Unadjusted and Adjusted, in Patients With Nonpulmonary Sepsis (n = 212)

Predictors of ARDS	OR for ARDS (95% CI)	p
Unadjusted model		
Current smoker by history[a]	2.28 (1.24–4.19)	0.008
Multivariable model[b]		
Current smoker by history[a]	2.15 (1.07–4.32)	0.03
Acute Physiology and Chronic Health Evaluation II score	1.08 (1.04–1.13)	< 0.001
African-American race	0.38 (0.14–1.01)	0.053
Hispanic ethnicity	0.38 (0.04–3.97)	0.42
Current alcohol abuse	1.77 (0.62–5.08)	0.29
Diabetes	0.69 (0.37–1.30)	0.25
Time elapsed between admission and enrollment	1.18 (0.98–1.42)	0.09

ARDS = acute respiratory distress syndrome, OR = odds ratio.
[a]Referent group is all current nonsmokers by history, including former smokers, and those with unknown smoking history.
[b]Referent race-ethnicity is white.

Cigarette Smoke Exposure and ARDS Outcomes

As a secondary analysis, we tested whether cigarette smoke exposure was associated with severity of lung injury and/or clinical outcomes in subjects with ARDS. In both the nonpulmonary sepsis subset and the overall cohort, cigarette smoke exposure as measured by NNAL was not associated with ARDS severity (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B313). Furthermore, as in our prior study of the association between NNAL levels and ARDS outcomes (28), cigarette smoke exposure as measured by NNAL was associated with significantly lower mortality in ARDS patients (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B313). Also as in our prior work, the association between smoking and lower mortality was no longer statistically significant after adjusting for other predictors of mortality, including age, APACHE score, comorbidities, code status at ICU admission, and shock (**Table S5**, Supplemental Digital Content 1, http://links.lww.com/CCM/B313).

Sensitivity Analysis Correcting NNAL for Creatinine

As described in the *Methods* section, because the urine may be variably concentrated in critical illness, urine NNAL levels were normalized to urine creatinine for sensitivity analysis. These analyses revealed no substantive differences in results (data not shown).

DISCUSSION

To our knowledge, this analysis is the first to examine prospectively the risk of ARDS associated with biomarker-confirmed cigarette smoke exposure in critically ill subjects with a variety of ARDS risk factors. Cigarette smoke exposure as assessed by either smoking history or urinary NNAL levels was associated with approximately double the odds of developing ARDS in subjects with nonpulmonary sepsis, even after controlling for other ARDS predictors, including alcohol abuse, diabetes, and severity of illness. No association was detected in subjects at risk for ARDS from pneumonia or aspiration. As sepsis is both common and increasing in incidence, these findings have important implications for ARDS prevention, public health, regulation of tobacco products, and the global burden of disease attributable to tobacco.

The association between smoking and ARDS has strong biologic plausibility in light of considerable mechanistic research on the effects of smoking on inflammation and lung epithelial and endothelial function. Smoking enhances both lung epithelial and endothelial permeability (3, 4, 29), modifies the quantity and function of pulmonary neutrophils and alveolar macrophages (5, 6), and promotes platelet dysfunction (30), pathways central to the pathogenesis of ARDS. In 298 explanted human lungs rejected for transplantation, we found that smokers had more pulmonary edema as measured by lung weight than nonsmokers; furthermore, smokers with the highest level of exposure had impaired alveolar fluid clearance (31). These experimental studies provide supportive evidence that
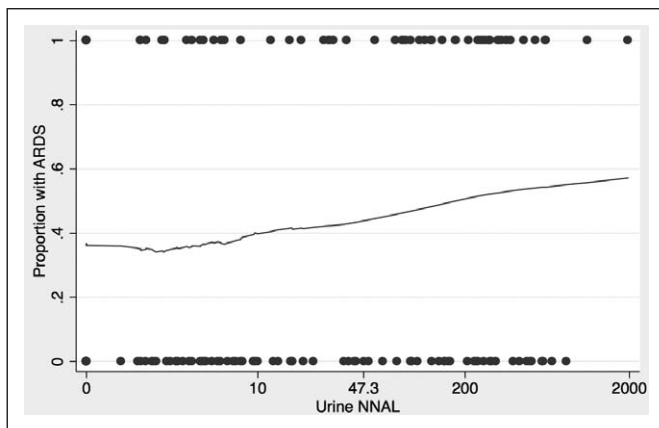
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Figure 2. Association between 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and acute respiratory distress syndrome (ARDS) in patients with nonpulmonary sepsis ($n = 212$). This figure demonstrates a locally weighted scatterplot smoothing (Lowess) analysis in which the continuous relationship between NNAL levels on the *x*-axis (log-scale) and development of ARDS on the *y*-axis is depicted (*line*). *Dots* represent individual patients; those at the top of the figure have ARDS and those at the bottom do not.

the association identified in this study between smoking and ARDS in nonpulmonary sepsis is important and likely to be causal.

Why might the association between smoking and ARDS differ based on ARDS risk factor? For one, ARDS due to nonpulmonary sepsis (an "indirect" lung injury) may be biologically different from ARDS due to "direct" lung injury (e.g., pneumonia and aspiration). We recently reported that ARDS due to indirect lung injury from nonpulmonary sepsis is characterized by more severe endothelial injury and inflammation when compared with ARDS due to direct lung injury, which is characterized by more severe lung epithelial injury (32). If smoking primes the lung to develop ARDS via enhanced endothelial permeability, as suggested by some experimental studies (3), the effects of smoking on ARDS susceptibility may be more pronounced in indirect lung injury, as in nonpulmonary sepsis. Alternatively, it may be that the effects of smoking on lung epithelial permeability (4, 29) combined with increased endothelial permeability due to severe sepsis culminate in poor barrier function across the alveolar-capillary interface and a higher propensity to develop the increased permeability pulmonary edema that characterizes ARDS.

A second potential explanation for the interaction between smoking and ARDS risk factors derives from reported associations between smoking and increased susceptibility to bacterial pneumonia and influenza (6). Since smoking is already associated with an increased risk of pneumonia, any smoking-associated increased risk of ARDS in pneumonia patients may either be negligible or difficult to detect. Further, because development of ARDS in patients with pneumonia leads to ICU admission, many patients with less severe pneumonia (and no ARDS) were likely never admitted to the ICU and therefore would not have been enrolled in this study, potentially obscuring associations between smoking and ARDS susceptibility. Larger studies in a broader cohort of hospitalized pneumonia

patients will be needed to further evaluate the association between smoking and ARDS in this subgroup.

In addition to identifying a link between smoking and ARDS in nonpulmonary sepsis, these analyses confirmed two of our prior findings regarding cigarette smoke exposure in critical illness. First, the prevalence of smoking in ICU patients and ARDS patients in this sample is higher than the population average (7, 13, 28). Since NNAL levels decline over time, and subjects were enrolled on average 1–2 days after hospital admission (and concomitant smoking cessation), the prevalence of smoking measured at admission might be even higher. Second, these data confirmed our prior finding that biomarker-confirmed smoking status is associated with lower unadjusted mortality in ARDS (28). In this study, as in our prior work, we found that this lower mortality in smokers seemed to be largely explained by younger age, fewer comorbidities, and lower severity of acute illness (Table S5, Supplemental Digital Content 1, http://links.lww.com/CCM/B313). A similar association, termed the "smoker's paradox," is observed in acute myocardial infarction (MI) and has been attributed in part to the younger age and relative paucity of comorbidities of smokers with acute MI compared with nonsmokers, similar to the pattern observed in ARDS (28, 33).

The finding that smoking is associated with development of ARDS in nonpulmonary sepsis has important implications for tobacco product regulation. The immediate effects of cigarette smoke exposure on acute cardiopulmonary disease costs and outcomes have not been well represented in economic models, including those used in the U.S. Food and Drug Administration's (FDA) cost-benefit analyses of cigarette warning labels (10) and its 2014 proposed "deeming" rule in which the FDA asserts jurisdiction over cigars, e-cigarettes, and other products (11). Because these models time-discount costs, inclusion of immediate changes in disease burden, such as posed by ARDS, may have a substantial effect on the discounted present value of reductions in smoking. Further research will be needed to define the dose-response curve and time course of the association between smoking and sepsis-associated ARDS to fully inform regulatory decisions.

This study has several strengths, including the use of a validated biomarker to quantify cigarette smoke exposure, measurement of alcohol use with a validated survey instrument, a diverse patient sample, and a prospective design focused on testing the hypothesis under study. This study also has some limitations. First, inclusion in this analysis was predicated on the urine availability, and anuric patients were excluded. The effect of acute kidney injury (AKI) on urine NNAL excretion is unknown. To mitigate this concern, we conducted sensitivity analyses using NNAL adjusted for urine creatinine, which produced similar results (not shown) and is consistent with approaches used to analyze other urine biomarkers in AKI (34). Furthermore, adjustment of the primary analyses for AKI or abnormal renal function did not substantively affect the results (not shown). Second, urine NNAL can be elevated by use of smokeless tobacco or other inhaled tobacco products. In this sample, 2% of subjects

had a history of using smokeless tobacco; exclusion of these subjects did not change the findings. However, it is possible that some elevations in urine NNAL were due to smokeless tobacco use not captured by history; the Centers for Disease Control recently estimated the prevalence of smokeless tobacco use in Tennessee at 6.4% (35). Third, the number of subjects with nonpulmonary sepsis and NNAL levels consistent with passive smoking is modest ($n = 58$); thus, whether passive smoking is associated with some increase in the risk for ARDS (as suggested by Fig. 2) or not (as suggested by data in Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/B313) remains unclear, and further study would require a larger group of patients. Fourth, although our focus on nonpulmonary sepsis was strongly supported by highly significant tests of interaction for both a history of smoking ($p = 0.01$) and NNAL levels ($p = 0.004$), as a subgroup analysis, it should be interpreted with some caution and would benefit from external validation in an independent cohort. Finally, while urine NNAL is clearly a useful biomarker for clinical research purposes, it does not at present have utility in clinical practice in the ICU.

In conclusion, in this prospective cohort of heterogeneous critically ill patients at risk for ARDS, cigarette smoking is associated with a substantial increase in the risk of developing ARDS in nonpulmonary sepsis, independent of other ARDS predictors. With the widespread prevalence of both smoking (particularly in the developing world) and sepsis, these findings have important implications for public health, tobacco product regulation, and the global burden of disease related to tobacco. Furthermore, these findings may have important implications for prevention of ARDS, particularly if the mechanisms by which smoking promotes the development of acute lung injury can be identified. Future research should focus on replicating and quantifying the association between smoking and ARDS in other diverse ARDS cohorts, including hospitalized non-ICU patients, and on identifying the underlying mechanisms of smoking-associated ARDS in order to facilitate targeted treatment strategies.

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