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Body Temperature and Mortality in Patients with Acute Respiratory Distress Syndrome

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Abstract

Background—Little is known about the relationship between body temperature and outcomes in patients with acute respiratory distress syndrome (ARDS). A better understanding of this relationship may provide evidence for fever suppression or warming interventions, which are commonly applied in practice.

Objective—To examine the relationship between body temperature and mortality in patients with ARDS.

Methods—Secondary analysis of body temperature and mortality using data from the ARDS Network Fluid and Catheter Treatment Trial (n =969). Body temperature at baseline and on study day 2, primary cause of ARDS, severity of illness, and 90-day mortality were analyzed by using multiple logistic regression.

Results—Mean baseline temperature was 37.5°C (SD, 1.1°C; range, 27.2°C-40.7°C). At baseline, fever (≥ 38.3°C) was present in 23% and hypothermia (< 36°C) in 5% of the patients. Body temperature was a significant predictor of 90-day mortality after primary cause of ARDS and score on the Acute Physiology and Chronic Health Evaluation III were adjusted for. Higher temperature was associated with decreased mortality: for every 1°C increase in baseline temperature, the odds of death decreased by 15% (odds ratio, 0.85; 95% CI, 0.73-0.98, P = .03).

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When patients were divided into 5 temperature groups, mortality was lower with higher temperature (*P* for trend=.02).

Conclusions—Early in ARDS, fever is associated with improved survival rates. Fever in the acute phase response to lung injury and its relationship to recovery may be an important factor in determining patients' outcome and warrants further study.

The relationship between body temperature alterations (both hypothermia and fever) in critically ill patients and outcomes is not well understood, despite the fact that clinicians often intervene to achieve normothermia in these patients.[1-6] Fever is common in critically ill patients and occurs as an adaptive response to inflammation that results from injury or infection.[7-9] Fever is defined as a regulated increase in body temperature above the normal thermal set point in response to injury and inflammation.[10] studies that have examined the relationship between fever and mortality in critically ill patients have yielded disparate results.[1,7,9,11-13] high fever, typically defined as 39.5°C or greater, has been associated with increased mortality in critically ill patients.[7-9,12]

A large multinational observational study evaluating the relationship between temperature and mortality in critically ill patients with and without infection showed a reduced risk of in-hospital mortality with fever relative to normothermia in critically ill patients with infection.[11] The noninfection group from this study also had reduced risk of mortality with elevated temperatures up to 39°C, after which mortality increased. hypothermia was associated with increased mortality in both infection and noninfection groups. In another recent multisite observational study,[9] the presence of fever on admission to the intensive care unit (ICU) had no significant association with ICU case-fatality among patients in medical and surgical ICUs.

In a large, randomized, double-blind, placebo-controlled trial evaluating the effects of ibuprofen on outcomes in critically ill patients with sepsis, body temperature was significantly reduced in the febrile group that received ibuprofen.[14] however, despite the significant reductions in fever, heart rate, lactate levels, and oxygen consumption values in the treatment group, no differences in oxygen delivery, organ failure–free days, or mortality were found. In a recent observational trial,[1] researchers investigated the association of fever and antipyretic interventions with mortality in critically ill patients with and without sepsis. In the cohort with sepsis, fever was an independent predictor of decreased mortality and use of acetaminophen and ibuprofen was an independent predictor of increased mortality. In the cohort without sepsis, only high fever (≥39.5°C) was independently associated with increased mortality, and no associations were found with use of antipyretic medication and mortality. Thus, robust evidence to guide management of fever in critically ill patients is lacking. Nonetheless, the use of antipyretic medications and physical cooling interventions to treat fever is widespread in clinical practice.[1-4]

Acute respiratory distress syndrome (ARDS) is one of several forms of critical illness characterized by the presence of the acute phase response, a series of complex neuroimmunologic reactions that include stimulation of fever and the release of cytokines and other immunologically activated proteins in response to injury or infection in an attempt to reestablish homeostasis.[15,16] The acute phase response stimulates leukocytosis,

complement activation, coagulation activation, opsonization, cytotoxicity, vascular permeability, and chemotaxis of monocytes, neutrophils, and T cells.[17] Fever is a hallmark sign of the acute phase response to infectious and noninfectious sources of tissue injury, so one would expect fever to be common in patients with ARDS. however, little is known about the incidence of fever in patients with ARDS and whether body temperature has an association with the trajectory of illness and recovery.

Thus, a better understanding of the impact of body temperature on outcomes for ARDS patients can inform future research. specifically, because the relationship between body temperature and patients' outcomes is unknown, it is unclear whether temperature-altering interventions are beneficial, detrimental, or neutral in patients with ARDS. The purpose of this study was to examine the relationship between body temperature in early ARDS and mortality.

Methods

We conducted a secondary analysis of body temperature by using data from the National Heart, Lung and Blood Institute (NHLBI) ARDS Network Fluid and Catheter Treatment Trial.[18,19] This multi-center factorial study randomized patients with acute lung injury for 48 hours or less to receive a central venous catheter or a pulmonary artery catheter and to receive either liberal or conservative fluid management strategies per protocol.[19-21] The institutional review boards of participating centers and the NHLBI approved the original study. written consent was obtained from the patient participants or their legal surrogates in the original study. Certification from the institutional review board at the investigators' center was obtained for this secondary analysis.

Adult patients who met the American-European Consensus criteria for acute lung injury for 48 hours or less were eligible for study enrollment. with the exception of 0.2% of this study's sample, patients met the recently published criteria for the Berlin definition of ARDS.[16] Exclusion criteria included presence of ARDS for more than 48 hours, presence of a pulmonary artery catheter before study enrollment, presence of chronic conditions that could influence compliance with the study protocol or ventilator weaning, and terminal conditions with estimated 6-month mortality of greater than 50%. Because of missing data on body temperature and score on the Acute physiology and Chronic health Evaluation (APACHE) III, 31 patients were excluded from the original sample of 1000 patients.

Measurement of Variables

The sources of baseline measurements of body temperature in the original study included rectal, tympanic, and axillary sites. Baseline temperature was obtained from the 4-hour period preceding randomization, which occurred immediately after consent was obtained. Body temperature was measured at the same time each day from rectal, tympanic, axillary, or pulmonary artery catheter sites and recorded for up to 7 days. Temperature ranges used to create 5 groups were selected on the basis of definitions of moderate to deep hypothermia (< 34°C), mild hypo -thermia (34°C-35.9°C), normothermia (36°C-38.2°C), fever (38.3°C-39.4°C), and high fever (≥39.5°C).[9,20-22]

patients were followed up for 90 days after study enrollment or until death, whichever occurred first. The APACHE III score was calculated from patients' baseline data.[23] One of the following causes of primary lung injury was selected for each patient: trauma, sepsis, multiple transfusions, pneumonia, aspiration, or other causes.

Statistical Analysis

An independent-samples *t* test was conducted to compare baseline temperatures for survivors and nonsurvivors. In order to control for potential confounding variables, multiple logistic regression was performed to assess the impact of 3 factors on the likelihood of mortality at 90 days in patients with ARDS. The 3 factors in the model were baseline temperature, primary cause of ARDS, and severity of illness, measured by the APACHE III score. These variables were included because of their potential physiological and clinical significance as well as their significant association with mortality in univariate analyses. In addition, as a sensitivity analysis to explore whether hypothermia influenced the results of the study, the multiple logistic regression was repeated with exclusion of patients with body temperatures less than 36°C. Multiple logistic regression was also repeated using temperature from day 2 of the study in place of baseline temperature to determine whether the relationship was sustained at another time point early in the ARDS trajectory.

To better understand the relationship between body temperature and mortality, we used 5 categories of baseline temperature (moderate to deep hypothermia, mild hypothermia, normothermia, fever, and high fever) and used logistic regression to test for a trend in the mortality among the temperature groups. Baseline characteristics were compared among the 5 temperature groups by using 1-way analysis of variance for continuous variables and χ^2 analysis for categorical variables.

Because temperature is part of the APACHE III score calculation, correlation analyses and collinearity diagnostics of the independent variables were completed, and low correlations ruled out concern about multicollinearity issues. The Hosmer-Lemeshow test was used to assess the goodness of fit of the model.[24] Odds ratios and 95% confidence intervals were calculated. statistical tests were 2-sided and differences were considered significant at *P* less than .05. data were analyzed with SPSS computer software, version 21 (SPSS, Inc).

Results

Characteristics of the 969 participants with baseline temperature data available are presented by temperature group in Table 1. Mean body temperature at baseline was 37.5°C (SD, 1.1°C; range, 27.2°C-40.7°C). Mean body temperature on day 2 was 37.4°C (SD, 0.9°C; range, 34.5°C-40.6°C). At baseline, fever was present in 227 patients (23%) and hypothermia in 48 patients (5%). The overall 90-day mortality rate of the sample was 267/969 (28%). Baseline temperatures were compared between survivors (n=702) and nonsurvivors (n=267). Mean body temperature showed a modest but statistically significant difference between survivors and nonsurvivors (37.6°C [SD, 1°C] vs 37.3°C [SD, 1.2°C], $P < .001$).

As shown in Table 2, multiple logistic regression showed that baseline temperature and APACHE III score made significant contributions to the model. Baseline temperature was a significant predictor of mortality when the cause of ARDS and APACHE III score were controlled for. Remarkably, for every 1°C increase in temperature, the odds of death at 90 days decreased by 15% (odds ratio, 0.85 per 1°C increase in temperature; 95% CI, 0.73-0.98, *P*= .03).

To test whether the hypothermic patients significantly influenced our finding, we performed a sensitivity analysis with those patients excluded from the logistic regression. when patients with hypothermia (< 36°C, n=48) were excluded from the analysis, baseline temperature remained a significant predictor of mortality after the cause of ARDS and the APACHE III score were controlled for, with higher baseline temperature being associated with decreased mortality (odds ratio, 0.82 per 1°C increase in temperature; 95% CI, 0.69-0.98, *P*= .03). similarly, our findings were unchanged when the data were analyzed without the participant who had an extremely low body temperature (27.2°C).

To test whether the relationship between body temperature and mortality was significant at another early time point in the ARDS trajectory, we repeated the multiple logistic regression analysis using temperature from the second study day (Table 3). Body temperature on study day 2 was also a significant predictor of mortality, when APACHE III score and the cause of ARDS were controlled for (odds ratio, 0.82 per 1°C increase in temperature; 95% CI, 0.69-0.98; *P*= .03).

As shown in the Figure, a significant trend toward lower mortality in the fever and high fever groups was apparent (23% and 19%, respectively) compared with in the normothermia (29%) and mild hypothermia group (36%) and the moderate to deep hypothermia group (67%; *P* for trend=.02). Although patients in the moderate to deep hypothermia group were older and had higher APACHE III scores, no statistically significant differences in baseline characteristics were found among the 5 temperature groups as shown in Table 1.

Discussion

The presentation of body temperature alterations, both fever and hypothermia, and the impact on physiologic and recovery outcomes in patients with ARDS are not well understood. This study adds to the literature on temperature abnormalities in critically ill patients with ARDS and is 1 of 2 new studies to investigate the association between temperature and mortality in this subgroup of critically ill patients. Netzer et al[25] recently published findings from their secondary analysis of 450 patients from the Improving Care of Acute Lung Injury patients study cohort. The frequency of temperature alterations in their study was higher than in our sample. They found at least 1 febrile day (≥38.0°C) in the first 3 days of ARDS onset in 65% of their sample, and 46% of their sample had at least 1 hypothermic day (< 36°C). Febrile days in early ARDS in their study were not associated with increased in-hospital mortality in their multivariable model, yet 2 or more days of hypothermia were found to be associated with increased risk of in-hospital mortality. The incidence of body temperature alterations in our sample is more similar to the incidence reported in an observational study[8] of 493 medical and surgical critical care patients, of

whom 28% had fever and 9% had hypothermia as defined using the same temperature thresholds used in our study. however, similar to our findings, in that study, hypothermia, rather than fever, was associated with an increased risk of death.

Laupland et al[9] prospectively studied temperature on admission and outcomes in 10962 patients (75% medical and 25% surgical admission types) from French ICUs in 10 years. Body temperatures at admission were hypothermia (16%), normothermia (55%), fever (26%), and mixed hypothermia and fever (3%). Although it is unclear whether ARDS was present, in the patients who required mechanical ventilation (n = 5019), 27% had fever and 23% had hypothermia at admission. After severity of illness and other confounders were controlled for, fever was not associated with increased ICU mortality. Indeed, hypothermia was a significant independent predictor of ICU mortality in the medical subgroup. These findings are consistent with the increased odds of mortality as body temperature decreased that we are reporting here. similar to our study, their study also lacked evaluation of temperature-altering interventions (antipyretics and warming), limiting interpretation of their potential confounding effects.

In a study by Bernard et al,[14] administration of ibuprofen did not significantly alter the rates of organ failure and mortality in a large sample (n=455) of patients with sepsis, of whom 29% had ARDS. They evaluated whether this cyclooxygenase inhibitor affected fever and the increased metabolic demands of sepsis. That study included febrile and hypothermic patients and excluded patients with normothermia. A significant reduction in body temperature was achieved in the ibuprofen group compared with the placebo group. however, the use of acetaminophen and physical cooling methods for fever reduction was not controlled for, and patients in both placebo and treatment groups received acetaminophen before and during the study.

Using data presented in the original study by Bernard et al,[14] we calculated mortality rates in the subgroup of febrile patients in the 2 arms of the study: mortality in the ibuprofen and placebo groups was the same at 35%. Although the study intervention was not targeted to fever suppression, these results suggest that at a minimum there is no mortality benefit to fever suppression. Furthermore, the 54% mortality rate of the ibuprofen-treated hypothermic subgroup was significantly lower than the 90% mortality in the placebo-treated hypothermic subgroup (P= .02), although both mortality rates were higher than the mortality rates in the febrile patients. The finding that mortality rates were lower in patients who had a fever rather than hypothermia at admission is consistent with our results, where mortality was lowest in the febrile group. In our study, this association remained significant, even after severity of illness and primary cause of ARDS were adjusted for.

In a large (n=1425), multisite observational study,[1] findings for fever and mortality and for antipyretic intervention use and mortality differed between the cohort with sepsis and the cohort without sepsis. Those researchers reported that fever is an independent predictor of decreased mortality in patients with sepsis but is not a predictor in patients without sepsis. This result suggests that future investigations evaluate the risk and use of antipyretic interventions with respect to the cause of the fever. Although ARDS was not a specified patient characteristic in that study, a large number of patients received mechanical

ventilation (67%) and had respiratory/thoracic disease as the reason for admission (38%). In our study, 71% of the sample had sepsis (n=228) or pneumonia (n=458) as the primary cause of their ARDS. Therefore, the importance of fever in the acute phase response to infection, which is often associated with acute lung injury, and its relationship to recovery may be underestimated.

Researchers who have examined the relationship between fever and outcomes including mortality in critically ill patients have reported mixed results.[7-9,14,26] however, experimental animal studies suggest that febrile-range hyperthermia in lung injury models worsens lung function and increases mortality, although the mechanisms are not well understood.[27-29] Induced hypothermia has been used as a therapeutic strategy in critically ill patients after cardiac arrest and with acute liver failure to optimize outcomes.[30,31] A recent randomized controlled trial[32] compared the effects of fever suppression using external cooling versus no cooling for 48 hours on vasopressor dose reduction in febrile patients with septic shock. In that study, in which 70% had pneumonia as the primary source of infection, there was a significantly higher occurrence of a 50% reduction in vasopressor dose from baseline to 12 hours in the cooling group, but significance was not sustained to their primary end point of 48 hours. Although the study was not powered to detect significant differences in mortality, they reported a lower 14-day mortality rate in the cooling group but that rate was no longer significant at ICU or hospital discharge.

Earlier, in the first known study examining the relationship of mortality to body temperature in ARDS patients, Villar and slutsky[33] reported an association between induced hypothermia and survival. They conducted a case-controlled prospective trial to evaluate whether induced hypothermia affected clinical outcomes in 19 patients with moribund sepsis and ARDS. In contrast to our results, they found a significant increase in survival in the hypothermia intervention group as well as reductions in intrapulmonary shunt, heart rate, and oxygen tension–based indices. Interestingly, they found no difference in oxygen consumption between the groups, and whether induced hypothermia initiated a protective mechanism is unclear.

In spite of the positive results, their study had several limitations, including small sample size, the moribund condition of the sample, the potential for historical bias, and the lack of a standard evaluation of severity of illness. Furthermore, it is important to distinguish between induced hypothermia and spontaneous hypothermia as well as induced normothermia when reviewing publications on thermoregulation. Mechanisms of spontaneous hypothermia include impaired heat production, excessive heat loss, and/or impaired thermoregulation and may be the result of exposure or metabolic/endocrine, neurologic, or toxic disease states. It is unclear whether the occurrence of hypothermia in early ARDS is a sign of disease severity or of discordant thermoregulatory response to severe inflammation, and/or if the hypothermia adversely affects lung recovery and patients' survival.

A prospective clinical trial[26] comparing infection and mortality rates in 85 critically ill trauma patients randomized to permissive fever or aggressive fever suppression groups was stopped after an interim analysis because more deaths were occurring in the aggressive fever suppression group. Although the target sample size was not achieved, this raises the question

of whether clinicians should routinely intervene to suppress fever in critically ill patients. Along the same lines, our study, which shows an association of lower mortality with higher baseline and day 2 body temperatures, supports the rationale for a randomized clinical trial that compares the effects of permissive fever versus the common practice of fever suppression on the recovery and outcomes of critically ill patients including patients with ARDS.

Our analyses had some limitations. The lack of standardized body temperature measurement methods could have resulted in patients being incorrectly categorized into the temperature groups used in our analysis of the 5 temperature groups. Although 51% of the sample had temperature measured by a pulmonary artery catheter for the study day 2 analysis, the rectal, tympanic, or axillary methods of measurement have varying levels of agreement with core temperature measured with a pulmonary artery catheter. data on temperature-altering interventions such as antipyretic medications, external cooling, and warming measures were not collected. we also did not have information regarding unit-based protocols or unit routines for managing hypothermia and fever, which can vary. These factors limit the interpretation of whether the study results are related to spontaneous body temperatures or temperatures altered by fever suppression or warming interventions. Nonetheless, the results suggest that, despite frequent use of antipyretic interventions in critically ill patients, there may be equipoise in support of a randomized clinical trial of such interventions to determine if they have any benefit.

Although not specific to the ARDS population, studies of the impact of fever and fever-suppression interventions on outcomes in critically ill patients are underway. In effort to evaluate the safety and feasibility of studying aggressive versus permissive temperature control and its effects on mortality and inflammatory biomarkers in critically ill patients with no neurologic injuries, a pilot randomized clinical trial[34] was recently conducted in Canada. Results of that pilot study indicated no difference in mortality or safety outcomes between the aggressive and permissive treatment groups, but they concluded the study with less than 50% of their targeted sample size because of enrollment challenges that informed their feasibility aim. The HEAT trial (permissive hypertherEmiaA Through avoidance of paracetamol in known or suspected infection in ICU trial), a multisite, randomized clinical trial to compare the effect of intravenous acetaminophen and placebo on survival, body temperature reduction, and organ injury in febrile critically ill patients with infection recently concluded enrollment of participants in Australia and New Zealand.[35]

Finally, because fever is a biomarker of the acute phase response, it is difficult to determine whether the favorable outcome of patients with fever is due to their ability to mount an appropriate acute phase response or is related to the fever response itself. Furthermore, it is unclear whether there is an ideal target temperature range that is optimal for lung recovery or that is protective against further lung injury in patients with ARDS. Therefore, the design of future studies evaluating temperature and outcomes should include measurement of temperature-altering interventions and biologic markers of the acute phase response such as cytokines and acute phase proteins, to optimize interpretation and testing of our results.

This study had the largest cohort of patients with ARDS ever used to evaluate alterations in body temperature. Fever was present in 23% of the sample at baseline, and a smaller proportion of patients had hypothermia early in their ARDS trajectory. Although fever was associated with improved survival even after severity of illness and cause of ARDS were accounted for, we cannot conclude that permissive fever or aggressive fever suppression influences mortality because of the aforementioned limitations of our study. The routine practice of fever suppression in patients with ARDS requires further research to test whether fever suppression has a harmful, helpful, or neutral effect on patients' outcomes. well-designed randomized controlled trials are warranted to test the therapeutic value of treating or not treating fever in patients with ARDS.

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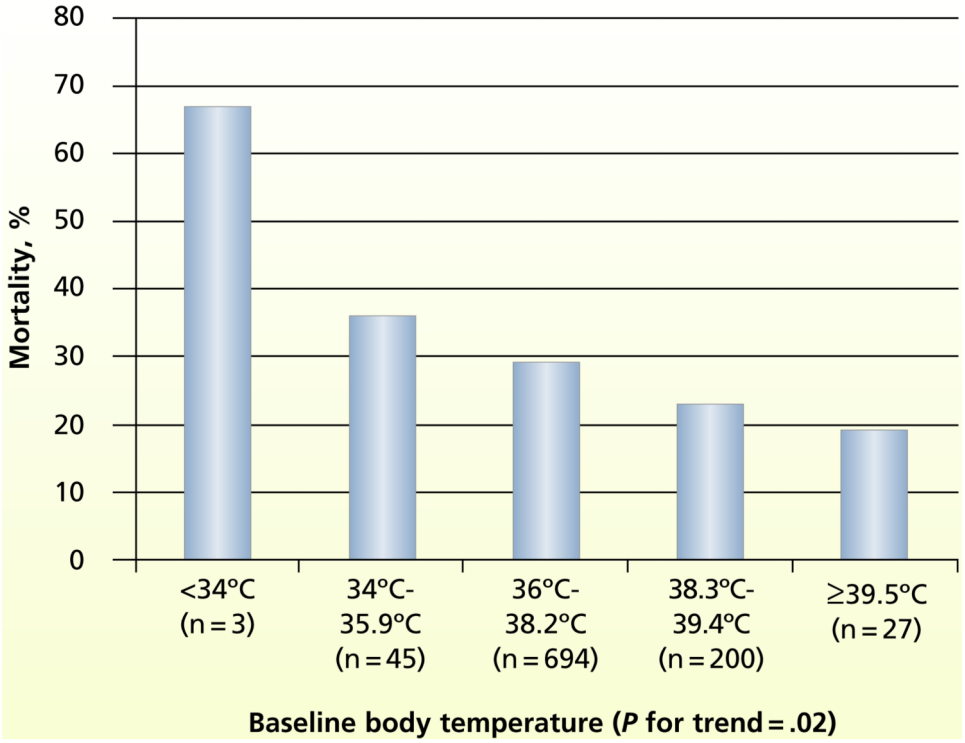

Figure.

Observed mortality according to 5 baseline body temperature groups in 969 patients with acute respiratory distress syndrome. Body temperature groups: moderate-deep hypothermia, <34°C; mild hypothermia, 34°C-35.9°C; normothermia, 36°C-38.2°C; fever, 38.3°C-39.4°C; high fever, ≥39.5°C.

Table 1

Baseline patient characteristics by body temperature group[a]

Characteristic[b]	Hypothermia (n = 3)	Mild hypothermia (n = 45)	Normothermia (n = 694)	Fever (n = 200)	High fever (n = 27)	*P*[c]
Age, mean (SD), y	59 (19)	48 (15)	50 (16)	47 (15)	47 (15)	.06
Male sex	67	49	52	60	63	.26
Ethnicity						
White	33	60	64	62	70	.22
Black	0	29	22	20	19	
Other	67	11	14	18	11	
Cause of ARDS						.48
Trauma	0	2	7	10	4	
Sepsis	33	29	23	21	33	
Multiple transfusion	0	0	1	2	0	
Pneumonia	33	51	47	48	52	
Aspiration	33	11	17	10	4	
Other	0	7	5	9	7	
APACHE III score, mean (SD)	123 (28)	103 (30)	94 (31)	91 (28)	96 (27)	.09

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome.

[a] Moderate-deep hypothermia, body temperature < 34°C; mild hypothermia, body temperature 34°C-35.9°C; normothermia, body temperature 36°C-38.2°C; fever, body temperature 38.3°C-39.4°C; high fever, body temperature ≥ 39.5°C.

[b] Values are percentage of patients unless indicated otherwise.

[c] $P < .05$ for statistical significance.

Table 2

Baseline body temperature, cause of acute respiratory distress syndrome, and APACHE III score as predictors of 90-day mortality[a]

Predictor variable	Odds ratio (95% CI)	*P*
Baseline body temperature[b]	0.85 (0.73-0.98)	.03
APACHE III score	1.03 (1.02-1.03)	<.001
Primary cause of lung injury[c]		.31
Trauma vs aspiration	0.51 (0.20-1.26)	.14
Sepsis vs aspiration	1.27 (0.76-2.13)	.37
Multiple transfusion vs aspiration	1.89 (0.44-8.07)	.39
Pneumonia vs aspiration	1.16 (0.72-1.86)	.55
Other causes vs aspiration	0.84 (0.38-1.83)	.65

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

[a] Hosmer-Lemeshow goodness of fit $P = .55$.

[b] Per 1°C increase in body temperature.

[c] Reference category for analysis was the aspiration group.

Table 3

Body temperature on day 2, cause of acute respiratory distress syndrome, and APACHE III score as predictors of 90-day mortality

Predictor variable	Odds ratio (95% CI)	*P*
Body temperature on day 2	0.82 (0.69-0.98)	.03
APACHE III score	1.03 (1.02-1.03)	<.001
Primary cause of lung injury		.31
Trauma vs aspiration	0.46 (0.18-1.19)	.11
Sepsis vs aspiration	1.20 (0.71-2.01)	.50
Multiple transfusion vs aspiration	1.85 (0.43-7.93)	.41
Pneumonia vs aspiration	1.16 (0.72-1.87)	.54
Other causes vs aspiration	0.83 (0.37-1.85)	.64

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.