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Sex- and Diagnosis-Dependent Differences in Mortality and Admission Cytokine Levels Among Patients Admitted for Intensive Care

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Abstract

Objectives—To investigate the role of sex on cytokine expression and mortality in critically ill patients.

Design—A cohort of patients admitted to were enrolled and followed over a 5-year period.

Setting—Two university-affiliated hospital surgical and trauma ICUs.

Patients—Patients 18 years old and older admitted for at least 48 hours to the surgical or trauma ICU.

Interventions—Observation only.

Measurements and Main Results—Major outcomes included admission cytokine levels, prevalence of ICU-acquired infection, and mortality during hospitalization conditioned on trauma status and sex. The final cohort included 2,291 patients (1,407 trauma and 884 nontrauma). The prevalence of ICU-acquired infection was similar for men (46.5%) and women (44.5%). All-cause in-hospital mortality was 12.7% for trauma male patient and 9.1% for trauma female patient (p = 0.065) and 22.9% for nontrauma male patients and 20.6% for nontrauma female patients (p =

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Drs. Swenson, Evans, Chaudry, Pruett, May, and Sawyer conceived and designed the study. Drs. Swenson, Tache-Léon, Hranjec, and Sawyer analyzed and interpreted the data. All authors drafted the manuscript for important intellectual content.

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0.40). Among trauma patients, logistic regression analysis identified female sex as protective for all-cause mortality (odds ratio, 0.57). Among trauma patients, men had significantly higher admission serum levels of interleukin-2, interleukin-12, interferon-γ, and tumor necrosis factor-α, and among nontrauma patients, men had higher admission levels of interleukin-8 and tumor necrosis factor-α.

Conclusions—The relationship between sex and outcomes in critically ill patients is complex and depends on underlying illness. Women appear to be better adapted to survive traumatic events, while sex may be less important in other forms of critical illness. The mechanisms accounting for this gender dimorphism may, in part, involve differential cytokine responses to injury, with men expressing a more robust proinflammatory profile.

Keywords

Acute Physiology and Chronic Health Evaluation II; critical care; gender; hospital mortality; hospitalization/statistics and numerical data; humans; infection; logistic models; man; risk factors; sex; sex factors; treatment outcome; woman

Over 20 million critical care inpatient days are provided in the United States each year, representing 4.2% of national healthcare expenditures and 0.56% of the United States gross domestic product (1). The mortality of all patients admitted to American ICUs is significant. Many studies have suggested sex-based differences in outcomes from critical illness, including the prevalence of and mortality from ICU-acquired infection. Animal models also suggest a strong gender dimorphism, generally favoring females (2–5). These studies suggest that male patients have a more proinflammatory cytokine response than female patients and that this may account for differing rates of mortality. These relationships remain unclear in clinical practice, however, with some human studies suggesting a disadvantage for men in terms of rates of infection and survival (6–18) and others implying the opposite (19–26).

We previously reported that women with pneumonia had a significantly higher mortality than men in a hospitalized, mixed surgical, and trauma patient population, even after controlling for other variables (27). That conclusion, however, was based on the retrospective analysis of a prospectively collected dataset from a single institution. The aim of this study, therefore, was to retest our hypothesis that sex is an important determinant of infectious outcomes in the ICU in a more rigorous, prospective, multicenter, multi-ICU manner. We also sought to evaluate associations between admission cytokine levels and clinical outcomes.

PATIENTS AND METHODS

Study Design and Participating Centers

The study was a prospective, longitudinal cohort study, conducted at the University of Virginia Health System (UVA) and Vanderbilt University Medical Center (VU) with approval of each local institutional review board. At UVA, the need for informed consent was waived due to the observational nature of the study and rigorous de-identification of patient data after complete collection. At VU, assent was obtained from a surrogate prior to

data collection with informed consent of the patient after resolution of critical illness. Patients 18 years old and older admitted for at least 48 hours to the surgical-trauma ICU at UVA or the surgical ICU or the trauma ICU at VU from October 2001 to May 2006 were prospectively followed for the occurrence of infection and clinical outcomes. The minimum stay of 48 hours was intended to identify 1) substantiate critically ill patients who were 2) at high risk of infectious complications and 3) who were not too critically ill to survive early admission. Patients discharged from the ICU before 48 hours are at lower risk of infectious complication and mortality. Thus, this increases the power of the study by selecting patients likely to remain in the ICU for greater than 3 days. Patients with burns as the primary indication for admission were excluded.

The UVA surgical and trauma ICU includes 16 beds and accepts admissions from the general, transplant, and trauma surgery services. The VU surgical ICU includes 21 beds, accepting patients from the general oncologic and transplant surgery services. A separate VU trauma ICU with 14 beds accepts non-burn trauma patients.

Data Collection

Clinical data were prospectively collected by full-time research nurses at each facility. Information sources included the patients and their families, nursing flow sheets, paper and electronic medical records, and healthcare providers. These data were entered into a custom computer database designed specifically for this project.

Patient- or family-described race and premorbid medical history were recorded at ICU admission. Acute Physiology and Chronic Health Evaluation (APACHE) II score (28, 29), the Marshall or Multiple Organ Dysfunction (MOD) score (30), and the McCabe score (31) were calculated and recorded at the time of ICU admission and at the onset of any new episode of infection. The Injury Severity Score (ISS) (32) and the accompanying Trauma Score-Injury Severity Score (TRISS) probability of survival (33) were calculated for trauma patients at the time of hospital admission. Additionally, World Health Organization (WHO) performance scores (22) were recorded at the time of ICU admission for all patients and at hospital discharge for survivors.

Patient- or family-reported menopausal status was recorded when available. When not available by interview, menopausal status was estimated by patient age (< 45 yr premenopausal, 45–55 yr perimenopausal, and > 55 yr postmenopausal). Poststudy analysis revealed that this age group categorization accurately predicted menopausal status in 86% of cases where menopausal status was known.

Pulmonary infection was diagnosed when a predominant organism was isolated from an appropriately obtained culture in the setting of purulent sputum production, a new or changing infiltrate on chest radiograph, and systemic evidence of infection. Quantitative endotracheal suction was routinely used at UVA ($> 10^5$ organisms per milliliter considered positive), and quantitative bronchoalveolar lavage was routinely used at VU ($> 10^4$ organisms per milliliter considered positive). Bloodstream infections were diagnosed by the isolation of organisms from a blood culture from any site, with the exception of *Staphylococcus epidermidis* or other coagulase-negative staphylococci, which required

isolation from two different sites. Criteria for urinary tract infection included isolation of more than 10^5 organisms per milliliter of urine or more than 10^4 organisms per milliliter of urine and accompanying dysuria. Criteria for catheter-related infection included isolation of 15 or more colony-forming units from catheter tips by semiquantitative roll plate technique in the setting of suspected infection. Cellulitis, peritoneal infections, and surgical site infections were diagnosed clinically, frequently without obtaining cultures.

The patient's body mass index (BMI) was calculated at the time of ICU admission using National Institutes of Health variables (34).

Statistical Analysis

Statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC). Due to previously noted differences in outcomes based on subgroups, trauma and nontrauma patients were a priori chosen for separate analyses. Demographic and past medical information, severity of illness, functional status scores, and outcomes were tabulated. Categorical variables were analyzed using chi-square or Fischer exact test where appropriate. Student *t* test was used for continuous parametric data, whereas the Wilcoxon rank-sum test was used for continuous nonparametric data. Gender-based differential effects of each categorical variable on key outcomes were then evaluated by calculating risk ratios with corresponding 95% CIs for men and women in both the trauma and nontrauma groups. A similar comparison was made between continuous variables by calculating the mean variable difference between category members with and without the outcome of interest and the corresponding 95% CI.

A series of logistic regression analyses were performed. The outcomes studied were acquisition of an infection in the ICU, in-hospital mortality following diagnosis of an ICU-acquired infection, and all-cause in-hospital mortality. Again, separate models were created for trauma and nontrauma patients. Variables which were found to have statistically significant associations ($p < 0.05$ or variable estimates outside of the 95% CI of the comparison group) with the outcome of interest were selected for inclusion in the regression model. To remove any effects that may obscure gender-specific differences in mortality due to variations in ICU course, only admission variables were included in the regression analyses for all-cause mortality relative to subgroup. As the variable of interest, gender was included in all models.

RESULTS

The final cohort contained 2,291 patients and comprised 1,407 trauma and 884 nontrauma patients. Seven hundred eighty patients (34.0%) were followed at UVA, whereas 1,512 (66.0%) were enrolled at VU. The VU enrollment rate was 92%. Modest variability was seen between institutions in terms of demographics and severity of illness scores. Details of the institutional comparisons are listed in Supplemental Table A (Supplemental Digital Content 1, http://links.lww.com/CCM/A794). Trauma patients at VU had a higher APACHE II score, ISS, and raw in-hospital mortality. When included in logistic regression analysis for survival, however, institution was not found to be an associated factor.

Population characteristics, conditioned on sex, are given in Table 1. When compared with nontrauma patients, trauma patients were younger, were more likely to be men, had fewer underlying diseases, had a lower BMI, and had lower APACHE II scores. The proximate cause for admission to the ICU for trauma patients was blunt injury in 71.5%, penetrating injury in 8.8%, and admission secondary to complications of hospitalization in 19.7%, most commonly new-onset respiratory failure or sepsis. Additional data are given in Supplemental Table B (Supplemental Digital Content 1, http://links.lww.com/CCM/A794).

Clinical outcomes for both patient groups are given in Table 2. The majority of patients (≥ 87%) in all groups required mechanical ventilation during their ICU stay. Although trauma patients had shorter ICU and hospital lengths of stay, there were no sex-dependent differences noted for these outcomes. No differences were observed between sexes in the overall proportion of patients diagnosed with ICU-acquired infection. For trauma patients, men were more likely to receive treatment for ICU-acquired pneumonia and be discharged to home versus a rehabilitation facility. For nontrauma patients, men trended toward an increased risk for developing pneumonia although this difference did not achieve statistical significance ($p = 0.062$). All-cause inpatient mortality was higher in nontrauma patients, and traumatized women had a trend toward lower crude in-hospital mortality than traumatized men ($p = 0.065$).

Risk of ICU-Acquired Infection

Age, a history of dialysis dependence, higher APACHE II score, higher MOD score, higher ISS (for trauma patients), and duration of ICU stay were associated with the acquisition of infection (Supplemental Table C, Supplemental Digital Content 1, http://links.lww.com/CCM/A794). Patient sex was not associated with the acquisition of overall infections for any group. ICU courses complicated by infection were associated with higher mortality, more likely disposition to a location other than home, and diminished WHO functional status at discharge. Similar to our previous findings, men were more susceptible to ICU-acquired pneumonia (35). Overall, pneumonia developed in 34.6% of men and 25.4% of women in the ICU (univariate odds ratio [OR] for women, 0.64; 95% CI, 0.53–0.78; $p < 0.0001$). Supplemental Figure A (Supplemental Digital Content 2, http://links.lww.com/CCM/A795) illustrates comparisons in prevalence and mortality related to ICU-acquired pneumonia, stratified by trauma status.

Pneumonia rates were higher among younger patients for both men (37.0% for men < 50 yr old, 31.8% for men ≥ 50 yr old, $p = 0.034$) and women (28.9% for women < 50 yr old, 22.9% for women ≥ 50 yr old, $p = 0.057$). As expected, sex affected rates of urinary tract infection: 6.6% of men and 17.6% of women acquired a urinary tract infection in the ICU (OR for women, 3.01; 95% CI, 2.29–3.96; $p < 0.0001$).

All-Cause In-Hospital Mortality

For all patients, age, multiple comorbidities, menopausal status (for women), McCabe score, APACHE II score, MOD score, and do-not-resuscitate (DNR) status at ICU admission were associated with all-cause in-hospital mortality (Table 3). Additionally, trauma patient mortality was associated with race distribution, WHO score, ISS and TRISS probability of

survival, and hospital length of stay. Additional nontrauma associations included blood product transfusion, longer ICU length of stay, and ICU-acquired infections. A trend toward female survival in trauma patients was observed (28% vs 21%, $p = 0.065$). Additional data are given in Supplemental Table D (Supplemental Digital Content 1, http://links.lww.com/CCM/A794).

To assess gender as an independent predictor of outcomes, a series of logistic regression analyses were performed, controlling for ICU admission factors found to have statistically significant associations with mortality by univariate analysis for each subgroup and sex. Results are given in Table 4 for trauma patients and Table 5 for nontrauma patients. Female sex was independently predictive of survival after trauma, while gender had no effect on mortality for nontrauma patients. These findings appeared to be similar across all age ranges (Supplemental Figures B and C, Supplemental Digital Content 2, http://links.lww.com/CCM/A795). Other factors also found in both analyses to independently predict mortality included APACHE II score, MOD score, ISS, and DNR status.

Admission Cytokine Data

Admission cytokine levels for men and women stratified by trauma status are listed in Table 6. Rates of undetectable levels conditioned on diagnosis and sex are given in Supplemental Table E (Supplemental Digital Content 1, http://links.lww.com/CCM/A794). For trauma patients, admission levels of interleukin (IL)-2, IL-12, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α were significantly higher for men. For nontrauma patients, men had significantly higher IL-8 and TNF-α levels. None of the counterregulatory cytokines differed between genders.

DISCUSSION

The contribution of sex to outcomes from critical illness remains a matter of debate. This controversy arises to a great extent from past studies that have generally been retrospective, small, based on post hoc subgroup analysis, or derived largely from administrative datasets. We had previously reported an increased mortality for women with hospital-acquired pneumonia (27) analyzing prospective data that were not, however, collected expressly for that purpose. The current study, designed specifically to examine this question, was intended to determine prospectively the role of sex in morbidity and mortality suffered by patients requiring intensive care and to explore possible differences in inflammatory mediators at admission that might be associated with discrepancies in outcomes and is the largest study of its type to date. Globally, it appeared that female sex was protective for death for patients admitted after trauma but not for patients admitted with non-traumatic diagnoses (comprised mostly of patients with a higher premorbid state and postoperative respiratory failure or intra-abdominal infections). These findings may be partially explained by recently published data examining outcomes in over 4,000 trauma patients, where premenopausal women (age, 14–44 yr) had lower initial lactate levels compared with men despite similar severity of illness, although the overall mortality was not different by sex (36). Lower lactate level and presently reported lower proinflammatory cytokine expression profile may indicate a less severe systemic response by women to traumatic injury that portends a lower mortality.

Ample precedent exists for the importance of the trauma versus nontrauma dichotomy in outcomes in the ICU (37). In addition, the majority of preclinical animal research demonstrating a protective effect for female sex has been performed using models of trauma or hemorrhage, meant to replicate trauma and sepsis (38, 39). Although it is tempting to attribute better outcomes for women to the obvious differences in sex hormone expression, the overexpression of estradiol after admission may actually be associated with worse outcomes for both sexes (40–42). Although our previous publications (35, 41, 42) from this study imply an association between increased estradiol expression, a proinflammatory cytokine phenotype, and mortality, the exact causal relationships between these phenomena cannot be ascertained from our purely observational dataset.

The current study demonstrated that sex does not appear to play a major role in the overall rate of acquisition of an infection in the ICU, although pneumonia and urinary tract infection have differences in rates associated with sex. A relationship between male sex and susceptibility to hospital-acquired pneumonia has been described several times before, including by our group (35). In addition, Kropec et al (11) analyzed 756 patients in a mixed medical/surgical ICU over a 2-year period and found male sex (relative risk, 2.7; 95% CI, 1.2–6.3) to be one of eight independent risks factors for the development of hospital-acquired pneumonia. Gannon et al (43), using population-based data on 26,231 blunt trauma patients from the Commonwealth of Pennsylvania, found that male sex was an independent predictor of acquiring pneumonia, along with ISS, injury type, admission Revised Trauma Score, admission respiratory rate, history of cardiac disease, and history of cancer. Similarly, Croce et al (9) noted an increased prevalence of pneumonia among male patients with blunt trauma in a cohort of 18,133 patients. Thus, among major, life-threatening ICU-acquired infections, men do appear to be more susceptible to pulmonary infections.

Even though men were more susceptible to pneumonia, mortality on a per case basis was nearly identical for men and women after accounting for admission diagnosis, leading us to believe that the excess mortality among women following hospital-acquired pneumonia that we previously reported (27) was due to a lack of stratification by trauma versus nontrauma diagnosis and the skewed sex distribution in those groups. In our previous study, men were relatively overrepresented in the trauma group (which had a lower mortality following pneumonia for both men and women), and without correcting for this maldistribution, men spuriously appeared to have a lower mortality following pneumonia.

Although we report the largest set of admission cytokine values to date among critically ill and traumatized patients, the results do not contribute much clarity to the clinical outcomes we observed. Previous animal studies had implied that traumatized females have a more robust Th1 response related to greater production of IL-2 and IFN-γ and lesser production of IL-10, leading to an enhanced resistance to infection and death (2). Two clinical studies, on the other hand, reported higher early IL-6 production among traumatized men (44, 45), and one also suggested higher levels of IL-8 and IL-10 among men, as well (44). Our data suggested another pattern, with greater early expression of IL-2, IL-12, IFN-γ, and TNF-α among traumatized men and IL-8 and TNF-α among nontraumatized men compared with women. The small differences in absolute values, frequency of patients with undetectable levels, the large overlap in levels between genders, the lack of similarity between cytokines

found to be different between men and women and those we have previously identified as independently predicting mortality (46), and the lack of consistency between multiple animal and human studies led us to question the relevance of cytokine levels in the critically ill population based on sex. Our observations are limited by the detection ability of the assay. However, we believe that differences in cytokine expression below this level are unlikely to be clinically significant. We suggest, therefore, that gender-based differences in levels of circulating cytokines at admission may be subtle and are unlikely to completely explain differences in clinical outcomes between men and women.

One major weakness of this study is that it analyzed two discrete and relatively different populations: critically ill traumatized and nontraumatized surgical patients. Given this stratification, subtle differences in gender-based outcomes may be obscured due to potential underpowering. Extrapolation to nonsurgical patients or patients outside of the ICU is problematic. Also, menopausal status was not specifically used for most analyses despite the fact that it may be an important predictor of outcome for other states, for example, cardiovascular disease. This was done for two reasons. First, accurate data were not available for up to one third of women, particularly those in the perimenopausal age group, since an accurate history could not be obtained from either the patient (due to mental status changes) or the family. Second, and more importantly, for women with accurate data, age and menopausal status were strongly correlated (age-predicted menopausal status in 86% of cases), to the extent that in all logistic regression models that included age, menopausal status was never found to be an independent predictor of outcomes. It is possible that important but unmeasured patient characteristics affecting mortality were excluded from our modeling, although the final c statistics were high, including 0.83 for the model demonstrating the independent relationship between female sex and survival among trauma patients. Similarly unmeasured patient- or disease-specific characteristics affecting cytokine expression are a potential source of confounding. Furthermore, as patients present to the ICU at various stages of acute illness, cytokine levels measured at admission may have limited value, and a lack of longitudinal data may obscure gender-based differences in cytokine expression patterns. Finally, repeated analysis of cytokine data may increase the likelihood of a type II error.

Overall, we have demonstrated that sex can influence outcomes following critical illness, in this instance, among severely traumatized patients. The magnitude of this effect is less than other factors (e.g., APACHE II score) and is far from universal. A better understanding of the effects on sex on outcomes in other populations may suggest therapeutic interventions based on the physiologic mechanisms at the root of findings in this study. We have also identified specific proinflammatory cytokines with greater expression in men that may modulate these observations. With further investigation, it is possible that interventions can be designed to manipulate the immunopathology of critical illness and improve outcomes for both men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline Patient Characteristics of 2,291 Patients Admitted for Surgical/Trauma Intensive Care

	Trauma			Nontrauma		
Variables	**Men (*n* = 1,024)**	**Women (*n* = 383)**	***p*[a]**	**Men (*n* = 471)**	**Women (*n* = 413)**	***p***
Age, mean (SD), yr	42.2 (18.1)	47.0 (19.4)	< 0.0001	59.4 (13.5)	57.7 (15.8)	0.082
Race, %						
White	80.7	87.2	0.016	84.3	86.0	0.73
Black	12.5	8.4		12.1	10.4	
Other	6.8	4.4		3.6	3.6	
Pre-ICU admission medical history, %						
No listed comorbidities	66.3	57.4	0.0021	11.5	11.6	0.94
Diabetes mellitus	7.2	10.7	0.034	27.8	29.3	0.63
Cardiac disease	11.9	14.1	0.27	34.3	30.8	0.27
Dialysis dependence	0.2	0.8	0.13	6.4	4.1	0.13
Malignancy	2.5	2.1	0.62	30.0	19.6	0.0004
Hepatic dysfunction	3.8	2.9	0.40	22.1	13.8	0.0034
Chronic corticosteroid use	0.8	1.8	0.14	7.9	9.2	0.48
Menopausal status, %						
Premenopausal	NA	44.4	NA	NA	17.4	NA
Perimenopausal	NA	15.4	NA	NA	12.8	NA
Postmenopausal	NA	40.2	NA	NA	69.7	NA
Solid-organ transplants, %	0.2	0.3	> 0.99	17.0	12.1	0.041
Trauma mechanism, %						
Blunt	86.9	93.9	0.0002	NA	NA	NA
Penetrating	13.1	6.1		NA	NA	NA
Patients with infections present at the time of ICU admission, %	66 (6.4)	24 (6.3)	0.90	167 (35.5)	164 (39.7)	0.19
World Health Organization score at ICU admission, mean (SD)	0.15 (0.52)	0.25 (0.65)	0.0093	1.3 (1.2)	1.2 (1.2)	0.56

	Trauma			Nontrauma		
Variables	**Men (*n* = 1,024)**	**Women (*n* = 383)**	***p*[a]**	**Men (*n* = 471)**	**Women (*n* = 413)**	***p***
McCabe score at ICU admission, mean (SD)	0.22 (0.46)	0.24 (0.47)	0.43	1.2 (0.8)	1.0 (0.7)	< 0.0001
Acute Physiology and Chronic Health Evaluation II score, mean (SD)	15.9 (6.4)	16.8 (5.9)	0.012	19.6 (6.9)	18.4 (6.5)	0.013
Marshall or Multiple Organ Dysfunction score, mean (SD)	7.5 (3.6)	7.2 (3.6)	0.16	7.8 (4.7)	7.0 (4.5)	0.015
Injury Severity Score, mean (SD)	30.2 (12.5)	29.7 (12.0)	0.55	NA	NA	NA
Probability of trauma survival, mean (SD)	0.68 (0.32)	0.71 (0.30)	0.26	NA	NA	NA
Do-not-resuscitate status at time of ICU admission, %	1.1	0.8	0.77	1.9	1.7	0.81

NA = not applicable.

[a] Student *t* test for continuous variables; chi-square test or Fisher exact test for categorical variables.

TABLE 2

Clinical Outcomes of 2,291 Patients Stratified by Admission Diagnosis and Sex for Patients Admitted for Surgical Intensive Care

	Trauma			Nontrauma		
Variables	**Men (*n* = 1,024)**	**Women (*n* = 383)**	***p*[a]**	**Men (*n* = 471)**	**Women (*n* = 413)**	***p***
Blood cell product transfusion, %	72.7	75.0	0.40	79.4	71.8	0.011
Mechanical ventilation						
Required, %	93.6	90.9	0.082	88.1	87.2	0.67
Duration, mean (SD), d	8.2 (6.2)	8.8 (6.2)	0.96	11.5 (8.1)	11.6 (7.9)	0.86
Length of stay						
ICU length of stay, mean (SD), d	11.8 (10.1)	11.2 (8.5)	0.34	14.4 (12.8)	16.6 (38.6)	0.27
Hospital length of stay, mean (SD), d	22.1 (29.1)	20.1 (15.9)	0.092	32.4 (33.7)	31.9 (43.3)	0.84
Infection						
Patients with infections acquired in the ICU, %	47.6	43.1	0.13	44.2	45.8	0.63
Patients treated for ICU-acquired pneumonia, %	38.1	29.5	0.0028	30.0	21.6	0.062
Mortality						
Inpatient mortality, %	12.7	9.1	0.065	22.9	20.6	0.40
Died after withdrawal of care, %	10.6	7.6	0.094	15.7	13.8	0.43
Surviving patient discharge disposition						
Home, %	34.5	22.0	< 0.0001	45.5	44.8	0.86
Rehabilitation facility, %	34.3	46.9	< 0.0001	20.3	19.9	0.88
Skilled nursing facility, %	10.8	12.3	0.44	12.4	16.1	0.17
Other hospital, %	14.0	14.7	0.78	14.7	9.8	0.054
Functional status at discharge						
WHO functional status, mean (SD)	2.8 (1.0)	2.9 (1.0)	0.058	2.5 (1.1)	2.6 (1.1)	0.87
Change in WHO functional status from admission, mean (SD)	2.7 (1.1)	2.7 (1.1)	0.61	1.3 (1.4)	1.4 (1.3)	0.24

WHO = World Health Organization.

[a]Student *t* test for continuous variables; chi-square test or Fisher exact test for categorical variables.

TABLE 3

Preadmission Factors, Outcomes, and Their Relationship to All-Cause In-Hospital Mortality

	Trauma			Nontrauma		
Variable	**Lived (*n* = 1,242)**	**Died (*n* = 165)**	***p***	**Lived (*n* = 691)**	**Died (*n* = 193)**	***p***
Age, mean, (SD), yr	42.3 (17.9)	52.8 (20.6)	< **0.0001**	57.1 (14.3)	64.1 (14.6)	< **0.0001**
Sex, female, %	28.0	21.2	0.065	47.5	44.0	0.40
Race, %						
White, non-Hispanic	81.6	89.1	**0.036**	85.7	82.9	0.39
Black	11.8	8.5		11.1	11.9	
Other	6.7	2.4		3.2	5.2	
Pre-ICU admission medical history, %						
No comorbidities	34.0	52.1	< **0.0001**	12.7	7.3	**0.035**
Diabetes mellitus	7.7	11.5	0.095	30.0	23.3	0.071
Cardiac disease	10.8	25.5	< **0.0001**	30.7	39.4	**0.023**
Pulmonary disease	9.4	12.7	0.18	25.4	23.8	0.66
Chronic renal insufficiency	0.7	4.2	< **0.0001**	11.0	13.0	0.45
Chronic corticosteroid use	0.9	2.4	0.089	7.3	13.0	**0.012**
Hypertension	19.1	24.9	0.081	50.9	44.6	0.12
Hepatic dysfunction	2.9	8.5	**0.0003**	17.4	21.2	0.22
Malignancy	2.3	3.6	0.28	22.3	35.2	**0.0003**
Solid organ transplant, %	0.2	0.6	0.31	14.6	15.0	0.89
Menopausal status (women only), %						
Premenopausal	47.1	3.5	**0.0027**	19.8	8.2	**0.014**
Perimenopausal	14.4	25.7		13.2	9.4	
Postmenopausal	38.5	57.2		66.5	82.4	
National Institutes of Health weight classification, %						
Underweight (BMI, < 18.5)	5.0	6.0	0.96	13.8	16.0	0.16
Normal weight (BMI, 18.5–24.9)	35.0	34.1		29.4	32.4	

Variable	Trauma			Nontrauma		
	Lived (*n* = 1,242)	**Died (*n* = 165)**	***p***	**Lived (*n* = 691)**	**Died (*n* = 193)**	***p***
Overweight (BMI, 25.0–29.9)	48.3	51.0		46.1	47.3	
Obese (BMI, 30.0–39.9)	40.4	39.0		46.7	20.7	
Extremely obese (BMI, ≥ 40)	16.0	11.1		33.8	20.6	
Trauma mechanism, %						
Blunt	88.5	90.9	0.35	NA	NA	NA
Penetrating	11.5	9.1		NA	NA	NA
Abode prior to admission, *n* (%)						
Home	97.7	11.9	0.36	87.3	86.5	0.79
Skilled nursing facility	0.3	0.0	> 0.99	3.4	5.1	0.28
World Health Organization score at ICU Admission, mean (SD)	0.15 (0.5)	0.35 (0.7)	**0.0007**	1.2 (1.2)	1.4 (1.1)	0.18
McCabe score at ICU Admission, mean (SD)	0.19 (0.4)	0.46 (0.63)	< **0.0001**	1.0 (0.7)	1.3 (0.8)	< **0.0001**
Acute Physiology and Chronic Health Evaluation II score, mean (SD)	15.4 (5.9)	21.8 (6.3)	< **0.0001**	18.1 (6.4)	22.4 (6.9)	< **0.0001**
Marshall or Multiple Organ Dysfunction score, mean (SD)	7.2 (3.6)	8.9 (3.3)	< **0.0001**	7.5 (4.5)	7.5 (5.0)	0.90
Injury Severity Score, mean (SD)	28.9 (12.0)	15.1 (17.0)	**0.024**	NA	NA	NA
Probability of trauma survival, mean (SD)	0.71 (0.30)	0.52 (0.36)	< **0.0001**	NA	NA	NA
Do-not-resuscitate status at time of ICU admission, %	0.5	4.9	< **0.0001**	0.6	6.2	< **0.0001**
Blood cell product transfusion, %	72.8	12.5	0.25	73.6	84.3	**0.0031**
Required mechanical ventilation, %	92.5	95.2	0.22	87.3	89.1	0.49
Length of stay, mean (SD)						
ICU length of stay	11.5 (9.6)	10.2 (10.3)	0.091	13.3 (11.2)	21.2 (55)	**0.049**
Hospital length of stay	11.3 (27.1)	13.6 (15.1)	< **0.0001**	30.0 (28.1)	35.8 (62.1)	0.21
Infection, %						
Patients with infections acquired in the ICU	46.6	44.2	0.57	40.5	60.6	< **0.0001**
Patients treated for pneumonia acquired in the ICU	36.6	29.1	0.058	21.0	36.8	< **0.0001**

BMI = body mass index, NA = not applicable.

Statistically significant *p* values are in bold font.

TABLE 4

Logistic Regression Analysis of the Influence of Factors Predicting All-Cause In-Hospital Mortality for Trauma ICU Patients

Variable	OR	95% CI	Wald Chi-Square Estimate	*p*
Sex, female	0.59	0.38–0.92	5.48	0.019
Age, per year	1.02	1.01–1.04	12.39	0.0004
Race				
White, non-Hispanic[a]	1.00	NA	NA	NA
Black	0.77	0.40–1.48	0.60	0.44
Other	0.51	0.17–1.54	1.42	0.23
Pre-ICU admission medical history				
Any comorbidity	0.79	0.45–1.38	0.68	0.41
Cardiac disease	1.34	0.74–2.41	2.01	0.16
Diabetes	0.80	0.42–1.53	0.44	0.51
Chronic renal failure	1.27	0.39–4.12	0.15	0.69
Chronic steroid use	0.71	0.17–2.88	0.23	0.63
Hepatic dysfunction	2.53	1.08–5.92	4.58	0.03
Malignancy	0.54	0.19–1.57	1.27	0.26
Penetrating trauma mechanism	1.18	0.62–2.27	0.25	0.62
World Health Organization score at ICU admission, per point	1.15	0.85–1.57	0.83	0.36
McCabe score at ICU admission, per point	1.40	0.88–2.22	2.02	0.16
Acute Physiology and Chronic Health Evaluation II score, per point	1.13	1.10–1.17	57.05	< 0.0001
Marshall or Multiple Organ Dysfunction score, per point	1.08	1.02–1.14	8.15	0.004
Injury Severity Score, per point	1.02	1.00–1.03	5.02	0.025
Do-not-resuscitate status at time of ICU admission	3.67	1.08–12.48	4.35	0.037
Probability of trauma survival (Trauma Score-Injury Severity Score)	0.55	0.34–0.89	5.92	0.015

OR = odds ratio, R^2 = 0.143, c statistic = 0.826, NA = not applicable.

[a]Referent group.

TABLE 5

Logistic Regression Analysis of the Influence of Factors Predicting All-Cause In-Hospital Mortality for Nontrauma Surgical ICU Patients

Variable	OR	95% CI	Wald Chi-Square Estimate	*p*
Sex, female	1.11	0.78–1.58	0.32	0.57
Age, per year	1.03	1.02–1.04	16.86	< 0.0001
Race				
White, non-Hispanic[a]	1.00	NA	NA	NA
Black	1.26	0.73–2.17	0.69	0.41
Other	1.99	0.83–4.77	2.39	0.12
Pre-ICU admission medical history				
Any comorbidity	0.80	0.41–1.57	0.41	0.52
Chronic steroid use	1.49	0.86–2.60	2.02	0.15
Malignancy	1.61	1.08–2.38	5.52	0.019
McCabe score at ICU admission, per point	1.38	1.08–1.77	6.57	0.010
Acute Physiology and Chronic Health Evaluation II score, per point	1.09	1.06–1.12	38.69	< 0.0001
Marshall or Multiple Organ Dysfunction score, per point	1.00	0.96–1.03	0.07	0.79
Do-not-resuscitate status at time of ICU admission	10.52	3.13–35.33	14.50	0.0001
Home as prior abode	1.16	0.69–1.95	0.32	0.57

OR = odds ratio, R^2 = 0.129, c statistic = 0.737, NA = not applicable.

[a]Referent group.

TABLE 6

Admission Cytokine Levels for Men and Women for Both Trauma and Nontrauma Populations

	Trauma			Nontrauma		
Variable	**Men (*n* = 1,024)**	**Women (*n* = 383)**	***p***	**Men (*n* = 471)**	**Women (*n* = 413)**	***p***
IL-1	2.7 (2.7–5.6)	2.7 (2.7–5.3)	0.48	2.7 (2.7–4.6)	2.7 (2.7–2.8)	0.27
IL-2	3.7 (2.7–14.9)	2.7 (2.7–9.8)	**0.0041**	3.3 (2.7–13.3)	2.7 (2.7–10.9)	0.37
IL-4	38.2 (6.7–214)	31.2 (5.9–214)	0.50	45.1 (4.9–223)	29.2 (6.1–160)	0.28
IL-6	149 (54.7–374)	164 (68.4–353)	0.61	153 (47.7–487)	134 (41.3–394)	0.38
IL-8	32.8 (13.5–67.3)	29.9 (12.5–64.4)	0.61	54.1 (20.9–120)	41.9 (13.1–99.0)	**0.036**
IL-10	53.0 (21.8–129)	51.4 (20.1–128)	0.72	68.7 (30.8–244)	86.9 (26.9–246)	0.70
IL-12	2.7 (2.7–10.8)	2.7 (2.7–6.6)	**0.0072**	2.7 (2.7–10.8)	2.7 (2.7–12.3)	0.71
Interferon-γ	3.7 (2.7–12.3)	2.7 (2.7–8.3)	**0.011**	2.7 (2.7–8.2)	2.7 (2.7–8.7)	0.84
Granulocyte macrophage-colony stimulating factor	4.6 (2.7–10.2)	3.5 (2.7–8.3)	0.058	2.9 (2.7–8.3)	2.7 (2.7–6.2)	0.087
Tumor necrosis factor-α	5.4 (2.7–10.3)	4.6 (2.7–8.3)	**0.038**	9.9 (3.3–17.9)	8.2 (2.7–15.6)	**0.018**

IL = interleukin.

Values reported as median (interquartile range). All values are pg/mL. For the purposes of statistical analysis, undetectable cytokine levels were replaced with the minimum level of detectability for each assay, which was 2.7 pg/mL. Statistically significant *p* values are in bold font.