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Gender Differences in Mortality in Patients with Severe Sepsis and Septic Shock

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Abstract

Background—Although the incidence of sepsis is higher in men than women, it is controversial whether there are gender differences in sepsis-associated mortality.

Objective—To test the hypothesis that hospital mortality is higher in men compared to women with severe sepsis or septic shock and requiring intensive care.

Methods—Retrospective cohort study of 18,757 intensive care unit (ICU) patients, including 8,702 women (46%), with severe sepsis or septic shock in the Cerner Project IMPACT database.

Results—Hospital mortality was higher in women vs. men (35% vs. 33%, $p = 0.006$). After adjusting for differences in baseline characteristics and processes of care, women had a higher likelihood of hospital mortality than men (OR = 1.11, 95% CI = 1.04 – 1.19, $p = 0.002$). Women were less likely than men to receive deep venous thrombosis prophylaxis (OR = 0.90, 95% CI = 0.84 – 0.97), invasive mechanical ventilation (OR = 0.81, 95% CI = 0.76 – 0.86), and hemodialysis catheters (OR = 0.85, 95% CI = 0.78 – 0.93). Women were more likely than men to receive red blood cell transfusions (OR = 1.15, 95% CI = 1.09 – 1.22) and code status limitations (OR = 1.31, 95% CI = 1.18 – 1.47).

Conclusions—In this large cohort of ICU patients, women with severe sepsis or septic shock had a higher risk of dying in the hospital than men. This difference remained after multivariable adjustment. We also found significant gender disparities in some aspects of care delivery, but these did not explain the higher mortality in women.

Keywords

gender; sex distribution; sepsis; infection; shock; critical care

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INTRODUCTION

Animal studies indicate that females have advantageous immunologic[1, 2] and cardiovascular responses[3] during infectious challenge. Epidemiological studies consistently report higher sepsis incidence in males compared to females, suggesting the advantageous female response to infection is also present in humans[4–9]. In contrast, clinical sepsis studies evaluating gender-mortality relationships are inconsistent, showing no gender difference [6, 10–12], higher risk in men[13, 14], or higher risk in women[9, 15]. The inconsistency may result from differences in study design, including the use of billing codes for diagnosis[6, 9, 10, 12, 14], limited sample size[11, 13, 15], limited risk adjustment[9, 10, 12], inclusion of non-ICU patients[6, 9, 10, 12, 14], or inclusion of patients without severe sepsis or septic shock[10, 12, 14].

The sepsis spectrum includes patients with widely varying mortality risks, and most patients who die have either severe sepsis or septic shock and require intensive care unit (ICU) admission[16]. Studies focused in the ICU could provide unique insights about gender-mortality relationships in critically ill patients with severe sepsis / septic shock. Identifying an association between gender and mortality in severe sepsis / septic shock would provide impetus for investigating biological and environmental causes of these disparities.

The purpose of our study was to test our hypothesis that the experimentally-demonstrated protective effects of female sex are manifested by lower mortality in women vs. men with severe sepsis / septic shock and requiring ICU admission.

MATERIALS AND METHODS

This retrospective cohort study used the Cerner Project IMPACT, Inc. (Bel Air, Maryland) database (CPI), and included patients from 98 ICUs in 71 U.S. hospitals and 4 Canadian or Brazilian hospitals. Each contributing ICU employs trained staff and standardized software to prospectively collect data on 50–100% of its ICU patients. Personnel at each site undergo training and certification to ensure uniform application of database-specific definitions and accurate data entry. The Cerner Project IMPACT software used at all participating centers has built-in checks for inconsistent or invalid entries. Only entries passing these validation checks are included in the Cerner Project IMPACT database. Data are transferred quarterly from participating sites to a central site where they are aggregated and undergo additional extensive quality control checking. The Cerner Project IMPACT database has been validated and used extensively since its creation by the Society of Critical Care Medicine in 1996[17–19]. A random sample of admitted patients was selected for ICUs enrolling <100% of their patients.

Severe sepsis / septic shock patients ≥ 16 years of age hospitalized from mid-2003 (coincident with the release of the CPI version prospectively identifying severe sepsis cases) through 2006 were eligible. The CPI diagnostic criterion for severe sepsis was development of at least one severe acute organ dysfunction within 3 days of a presumed infection. Patients were excluded if gender, age, or hospital mortality was missing. For each patient, only data from the first ICU admission was analyzed. The University of Rochester Institutional Review Board provided exemption from informed consent.

Statistical Methods

Gender was the primary independent variable and hospital mortality was the primary outcome variable. Variable definitions are provided in the Appendix. Normally distributed variables are presented as mean ± standard deviation (S.D.) and skewed variables are presented as median (interquartile range [IQR]).

Available covariates were evaluated for associations with gender and hospital mortality using chi-square testing for categorical variables and student's t-test or Kruskal-Wallis test for continuous variables, as appropriate. Variables associated with gender or hospital mortality ($p \leq 0.05$) were included in the base logistic regression model. Interaction terms with gender were included if a variable showed > 30% departure from additive and multiplicative model predictions[20].

Covariates were sequentially eliminated from the base model if the likelihood ratio test comparing nested models was insignificant ($p > 0.10$) and the odds ratios involving gender changed < 10% after exclusion. The model excluded 439 patients (2.3%) because of missing values. Model performance was assessed using the C statistic and Hosmer-Lemeshow test[21], and model diagnostics included leverage and Pregibon's delta beta plots[22]. Standard errors were calculated with robust variance estimators and ICU-level clustering, allowing for correlations between observations within ICUs[23].

Two sensitivity analyses were performed. The CPI severe sepsis diagnostic criterion differs slightly from published American College of Chest Physicians / Society of Critical Care Medicine consensus conference criteria ("consensus criteria")[24]. We applied consensus criteria to each patient in the dataset, then re-computed the model excluding patients who did not meet both CPI and consensus criteria. The second sensitivity analysis re-computed the model after excluding influential observations (leverage or Pregibon's delta beta ≥ 99th percentile).

Using an expected mortality in women of 28%[6], the calculated sample size was 7,903 patients of each gender to detect a ≥ 2% difference in hospital mortality with 80% power and two-sided alpha (α) = 0.05. Statistical analyses were performed using Stata/ SE version 9.2 (Stata Corp., College Station, TX).

RESULTS

18,846 patients met CPI criteria for severe sepsis. Seven subjects were excluded because age was missing or < 16 years, and 82 were excluded because of missing hospital mortality, leaving 18,757 patients (10,055 [54%] men and 8,702 [46%] women). At least 97% of patients were from U.S. hospitals. Hospitals had 496 (IQR = 350–615) beds and ICUs had 17 (IQR = 12–21) beds.

Gender comparisons are shown in Table I. Women were older and more likely to have dependent functional status at ICU admission than men. African-American race was the only racial / ethnic category associated with female gender, so the categories were collapsed into African – American race vs. other races in subsequent analyses. Men and women had similar Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Simplified Acute Physiology Score (SAPS) II-predicted mortality, and similarly short delays between hospital and ICU admission (0 days, interquartile range 0–1). The most common index organ dysfunctions were cardiovascular and respiratory (see Appendix for definitions of organ dysfunction). Over 50% of patients experienced cardiovascular dysfunction, defined as refractory hypotension (see Appendix), and therefore met criteria for septic shock. There were gender differences in the frequency of specific organ dysfunctions, but the number of dysfunctional organs did not differ by gender ($\chi^2 = 5.49$, $p = 0.48$, Figure 1). There were gender differences in the sources of infection (Table I).

Regarding ICU processes of care, women were more likely to have code status limitations and receive packed red blood cell (PRBC) transfusions, and men were more likely to receive invasive mechanical ventilation at ICU admission, deep venous thrombosis (DVT) prophylaxis, and hemodialysis catheters (Table I).

Hospital mortality was significantly higher in women vs. men (35% vs. 33%, $p = 0.006$, Table II). Women also had a higher ICU mortality rate and a lower likelihood of independence upon hospital discharge when compared to men (Table II). Hospital length of stay (LOS) was shorter in women (women = 12 [IQR 7–21] days vs. men = 13 [IQR 7–23] days, $p = 0.0001$) even when excluding hospital non-survivors (women = 14 [IQR 9–23] days vs. men = 15 [IQR 9–25] days, $p < 0.0001$), so this was not simply because of shorter hospital survival in women.

Many covariates were associated with hospital mortality (Table III). No variables met criteria for effect-modification on either the additive or multiplicative scale. The possible interaction between gender and age categories was of particularly importance in this regard, since previous studies in critically ill patients suggest that the higher risk of mortality in women is limited to patients > 50 years of age[25, 26]. In contrast, we found that the association between female gender and death was similar in subgroups of patients < 50 years (OR = 1.13, 95% CI = 0.96 – 1.32) and ≥ 50 years (OR = 1.06, 95% CI = 1.00 – 1.14), with the Mantel-Haenszel age category-adjusted OR = 1.07 (95% CI = 1.01 – 1.14, $p = 0.02$) and no evidence of interaction between age categories and gender in predicting mortality (p value for Breslow-Day test of homogeneity = 0.50).

Results of the final multiple logistic regression model are shown in Table III. Female gender remained significantly associated with hospital mortality after adjustment (OR = 1.11, 95% CI = 1.04 – 1.19, $p = 0.002$). The model had excellent discrimination (C statistic = 0.7989) and calibration (Hosmer Lemeshow statistic = 7.14, $p = 0.52$). Sensitivity analyses showed minimal change in gender risk after excluding 1,401 patients (7% of the sample) not meeting both sets of diagnostic criteria (OR = 1.13, 95% CI = 1.05 - 1.22, $p = 0.001$), or after excluding the 797 most influential observations (OR = 1.13, 95% CI = 1.06 - 1.22, $p = 0.001$).

The multiple logistic regression analysis was repeated without any process of care covariates (i.e., fresh frozen plasma transfusion, mechanical ventilation, hemodialysis catheter placement, stress ulcer prophylaxis, DVT prophylaxis, code status limitations, and critical care medicine specialty coverage were removed). The gender risk was similar (OR = 1.11, 95% CI = 1.03 – 1.19, $p = 0.004$), reinforcing the conclusion that these care processes were not responsible for higher mortality in women.

We performed exploratory bivariate analyses to determine whether gender disparities in care processes (Table I) were explained by other clinically relevant variables (Table IV). For example, more frequent code status limitations among women might stem from their older age or more impaired functional status. However, Table IV shows that gender differences in code status persisted within strata of functional status and in the subgroup of patients > 65 years. Likewise, women were more likely to receive PRBC transfusions during the first 24 hours of ICU care when nadir hematocrit (Hct) was > 31% (a potentially deleterious practice[27]), less likely to receive invasive mechanical ventilation regardless of respiratory infection or dysfunction, and less likely to receive hemodialysis catheters regardless of acute renal failure.

DISCUSSION

Our retrospective cohort study of ICU patients with severe sepsis / septic shock indicates that women have approximately 10% greater risk of hospital mortality than men; this is true in both bivariate analysis and multiple logistic regression analysis controlling for numerous potential confounding variables. We also find subtle but significant gender differences in processes of care, although these do not account for the mortality difference.

Our results are derived from CPI, a database designed to measure outcomes of critically ill patients. Severe sepsis was diagnosed prospectively by staff trained to achieve consistent data collection[17–19], and over 90% of patients also met published diagnostic consensus criteria[24]. The standardized, prospective data collection and diagnostic confirmation are important strengths of this study.

Possible mechanisms of higher severe sepsis mortality in women

Our hypothesis, that hospital mortality would be lower in women than men with severe sepsis / septic shock, was based on laboratory evidence indicating an estrogen-mediated female survival advantage during experimentally-induced sepsis[1, 3]. Our contrary findings suggest that this hypothesis was overly simplistic, a conclusion supported by divergent results of human studies measuring gender-specific responses to endotoxin[28, 29], paradoxically higher estrogen concentrations in elderly vs. younger critically ill women, elevated estrogen concentrations in critically ill men, and the association of higher estrogen levels with higher mortality in both women and men[30, 31]. Elevated estrogen levels may simply be a surrogate for severity of illness, because in critical illness estradiol concentrations are primarily determined by the adrenal stress response and peripheral aromatase activity[31]. However, estrogens also have physiologic actions that could be detrimental in sepsis[32]. Unfortunately we cannot determine whether higher estrogens concentrations are associated with higher mortality in women because gonadal hormone levels are not available in this dataset.

Non-biological explanations for our findings must also be considered. We found significant gender-differences in processes of care, consistent with previous studies[25, 33, 34]. These differences could originate from gender differences in treatment preferences or gender bias in clinical care[35]. For example, gender variation in code status limitations could stem from less aggressive treatment preferences by women (or their surrogates)[36, 37], or the influence of health care providers who affect end-of-life decisions yet often misperceive patient wishes[38, 39]. Importantly, our analysis showed that the observed disparities in care did not account for higher female mortality. Nevertheless, further investigation is required to determine whether these disparities are associated with other adverse clinical outcomes, and whether gender disparities exist in other care processes. Gender differences in numerous other observed covariates (e.g., age, sites of infection, functional status, and comorbid conditions, see Table III for full list) also cannot explain the observed mortality difference, since multivariable analysis adjusted for all of them.

Gender-based differences in symptoms[40], presentation of illness[41], or diagnostic bias[42] are additional potential explanations for both the hospital mortality and infection site differences we observed between men and women. Gender differences in sites of infection have been observed previously[12, 13, 43], but like the hospital mortality difference, it is unclear whether they originate from gender differences in biology[1–3], comorbidity[12, 13], or medical assessment and care[40–42].

Clinical implications of higher severe sepsis mortality in women

The clinical implications of our findings will largely depend on elucidation of the underlying mechanisms. For example, novel gender-targeted therapeutic strategies could be developed if women are found to have greater aromatase activity that is associated with higher estradiol levels and excess mortality. New policies may ensure equal application of therapy if gender disparities are discovered in other care processes that affect important clinical outcomes. Finally, educational efforts may be helpful if additional work uncovers gender differences in clinical presentation of illness. By establishing the presence of gender-disparities in sepsis mortality, our findings provide a catalyst for these additional investigations.

Comparison with previous studies

Recent landmark epidemiologic sepsis studies did not find gender differences in mortality[6, 10, 12]. Martin et al[10] identified over 10 million sepsis cases from 1979–2001 and found that septic women were older than men, but there was no mortality difference. Angus, et al[6] identified nearly 200,000 severe sepsis cases from 1995 and found that men had higher mortality, but this gender difference disappeared after adjusting for age, comorbidity, and infection site.

In comparison to these studies, our discrepant findings are best explained by differences in methodology and case-mix. Both Martin et al[10] and Angus et al[6] used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) billing codes. While they included nested validation analyses showing that ICD-9-CM coding successfully identified sepsis in a fraction of their patients, diagnostic accuracy could not be confirmed in the majority. In contrast, over 90% of our patients met both CPI and consensus criteria for severe sepsis; we confirmed our results by repeating the analysis using only these dually-confirmed cases. In addition, Martin et al[10] and Angus et al[6] included substantial fractions of non-ICU patients. Indeed, approximately 70–80% of patients studied by Martin et al[10] did not have any organ dysfunction. In contrast, 100% of our patients had at least one acute organ dysfunction and required ICU care, and over 50% met criteria for septic shock. We speculate that factors responsible for higher female mortality may be accentuated in a more severely ill cohort. Finally, we employed a systematic and comprehensive approach to risk adjustment, beginning with all available covariates sharing a bivariate association with either the risk factor of interest (gender) or the outcome of interest (hospital mortality). This inclusive model was pared down to the parsimonious model using objectively-defined methods. In contrast, multivariable risk adjustment was not employed by Martin et al[10]. In a subsequent multivariable analysis of this database the authors found that male gender was an independent predictor of mortality[14]. However, they were unable to include severity of illness and process of care variables in their analysis, model calibration and discrimination were not reported, and the effect of influential observations was not assessed. Angus et al[6] did not provide details of their multivariable analysis.

A more recent French study by Adrie et al found 25% lower risk of hospital mortality in 608 women vs. 1,000 men with severe sepsis / septic shock matched by propensity score[13]. National differences in population demographics or health-care delivery, and / or differences in statistical methods may contribute to the contrary results. Our large sample size permitted multiple logistic regression as the primary statistical approach[21].

Our findings support those of Dombrovskiy et al[9], who found higher age-adjusted case-fatality rates in women vs. men over a 10 year time interval. Our results are also consistent with several smaller studies indicating that female gender is an independent risk factor for mortality in sepsis and infection[15, 44–47].

Study limitations

This study has several limitations. First, the CPI database does not include a random sample of ICUs, potentially introducing selection bias. However, a database containing detailed clinical information from a random sample of U.S. ICUs does not currently exist. Second, if the likelihood of hospital discharge in situations of imminent or expected death (e.g., to hospice) was greater in men, the hospital mortality results could be biased. We were unable to specifically address this concern because the hospital discharge destination was unknown in approximately 40% of patients and 30- or 60-day mortality rates were not available. However, this bias seems unlikely since men had longer hospitalizations and were more likely to be independent upon hospital discharge than women (Table II). Third, we were

unable to control for baseline hormonal status because menopausal status, estrous status, and information on chronic use of hormone replacement therapy were not available in this dataset. Our stratified analysis showed that women under age 50 (the approximate median age of menopause of women in the U.S.[48]) were not spared from the higher mortality risk, in contrast with previous studies of unselected critically ill patients[25, 26]. Although these data suggest that the findings are independent of menopausal status, they are clearly insufficient to fully evaluate the effect of baseline hormonal status. Finally, other non-observed covariates could confound our results. In this respect, it is notable that our processes of care analyses were limited to variables available in CPI. Future research should evaluate whether there are gender disparities in the use of validated sepsis therapies (e.g., early appropriate antibiotics [49] and goal-directed therapy [50]) that could explain our results.

CONCLUSIONS

In our retrospective analysis of a large, prospectively collected dataset of ICU patients with severe sepsis / septic shock, women had significantly higher hospital mortality than men. This difference persisted after adjustment for baseline characteristics and gender differences in some processes of care. Further research should investigate the causes of gender-based differences in hospital mortality and gender disparities in care.

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APPENDIX

Appendix: Definition of Variables

Covariate	Definition
Index infection	Infection present at the time of organ dysfunction or up to 3 days before onset of organ dysfunction
Hospital mortality	Death in hospital before discharge
ICU mortality	Death in ICU
Independent functional status at hospital discharge	“Independent” vs. “other” functional status. “Independent” is defined when the patient is discharged home and independent in activities of daily living. “Other” functional status includes categories of partially dependent, fully dependent, or dead.
Hospital length of stay	Number of consecutive days in current acute care hospital

Covariate	Definition
ICU length of stay	Number of consecutive days in ICU. Only the duration of the first ICU stay during hospitalization is counted.
Age	Age of the patient in years
Gender	Male or female
SAPS II* score	Calculated from the necessary variables provided in the CPI dataset according to the methods of LeGall, et al [1]
SAPS II predicted mortality	Calculated from the necessary variables provided in the CPI dataset according to the methods of LeGall, et al [1]
APACHE II score	Calculated from the variables provided in the CPI dataset according to the methods of Knaus, et al [2]
Origin prior to hospital admission	Admission from the community vs. a health-care associated facility, the latter including another location within the hospital or transfer from another hospital
Previous ICU admission	Previous ICU admission within the same hospitalization
Acute renal failure	Creatinine > 1.5 mg/dL evident < 48 hours before ICU admission and associated with oliguria
CPR within 24 hours of ICU admission	Self-expanatory
Functional status on hospital admission	“Independent” vs. “other” functional status. The “other” category includes partially dependent and fully dependent.
Code status on ICU admission	Full vs. “limited.” The “limited” category included no CPR, limited interventions/ withholding therapy, or withdrawing therapy/ comfort care code status.
Medicine service vs. surgery	Surgical category includes elective and emergent surgical admissions
Index infection	Current infection present at or up to 3 days prior to the time when acute organ dysfunction was detected. At least one of the following conditions must be met: antibiotics started for presumed infection; antibiotics administered for a known active infection (not for antibiotic prophylaxis); purulent drainage from wound or catheter site; radiological evidence of infiltrates and sputum production; white blood cells present in a normally sterile body fluid.
Intra-abdominal infection	Infection in the abdominal compartment and pelvis. Includes peritoneal fluid, abscess drainage, and fluid from surgical drain.
Bloodstream infection	Bloodstream infection not due to vascular access site
Chest infection	Infection of lungs, pleura, pleural fluid, or drainage around chest tube site
CNS infection	Infection of brain, meninges, CSF, spine, or drainage from or around invasive CNS device
Sinus infection	Infection of fluid in cranial or facial sinus cavity
Surgical infection	Infection of any surgical wound site regardless of location
Urinary infection	Infection of kidney, bladder, urethra, drainage around invasive device, or perinephric abscess
Vascular infection	Infection related to invasive vascular catheter
Other infection	Infection of any other known site
Unknown infection	Signs of infection present but unknown site (this category is not chosen if there is a clinically suspected site)
Index organ dysfunction	Organ dysfunction occurring within ± 3 days of a presumed infection
Acute cardiovascular dysfunction	Any one of the following persisting for ≥ 1 hour despite adequate fluid resuscitation: systolic blood pressure (SBP) < 90 mmHg unless known baseline SBP <90 mmHg ; SBP > 40 mmHg below baseline SBP; mean arterial pressure (MAP) < 70mmHg; vasopressor (if dopamine, > 5 mcg/ kg/ min) requirement to maintain SBP > 90 or MAP > 70 mmHg
Elevated serum lactate	Serum lactate value above the normal range in combination with acute cardiovascular dysfunction on the same day

Covariate	Definition
Acute respiratory dysfunction	PaO2 / FiO2 ratio ≤ 300 or PEEP requirement > 5 cm H20 in patients with acute lung injury (patients with cardiogenic pulmonary edema are excluded)
Acute renal dysfunction	Creatinine remains increased by > 1 mg/dL after adequate fluid resuscitation or creatinine ≥ 2 mg/dL in the absence of known baseline (patients on chronic dialysis excluded)
Acute hematologic dysfunction	Platelet (plt) count half of the highest value in last 3 days, or plt count <100,000mm3, or PT/PTT >1.5 times control in absence of anticoagulant
Acute hepatic dysfunction	Acute rise in serum total bilirubin to a level > 2 mg/dL
Acute neurological dysfunction	Acutely altered sensorium and all of the following: no known CNS injury, presence of sedation holiday, and Glasgow coma score (GCS) ≤ 12
fresh frozen plasma transfusion	Any transfusion of fresh frozen plasma during the ICU stay
Packed red blood cell (PRBC) transfusion	Any transfusion of PRBCs during the first 21 days of ICU stay
Intravenous nutrition	Any administration of intravenous nutrition during the ICU stay
Stress ulcer prophylaxis	Any administration of stress ulcer prophylaxis during the ICU stay
Hemodialysis catheter	Placement of a hemodialysis catheter during the ICU stay
Deep venous thrombosis (DVT) prophylaxis	Administration of any of the following prophylactic treatments during the ICU stay: unfractionated, low-molecular weight, or synthetic heparin or spontaneous compression devices
Invasive mechanical ventilation	Administration of invasive mechanical ventilation upon ICU admission
Chronic liver disease	Any of the following: biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; prior episodes of hepatic failure/ encephalopathy/ coma
Chronic cardiovascular disease	New York Heart Association Class IV symptoms and one or more of the following: severe coronary artery disease; severe valvular heart disease; severe cardiomyopathy
Chronic respiratory disease	Any of the following: chronic restrictive, obstructive or vascular disease resulting in severe mobility restriction; respiratory dependency; chronic hypoxia, hypercapnea, secondary polycythemia or severe pulmonary hypertension (>40 mmHg)
Chronic renal disease	A history of chronic renal compromise with most recent creatinine > 2.0 mg/dL
Immunocompromise	Any of the following: AIDS, immunosuppressive drugs, radiation or chemotherapy within 1 year of ICU admission, documented immuno-humoral or cellular immune deficiency state
Active cancer within 5 years	Any of the following in the past 5 years: solid organ tumor, hematological malignancy, lymphoma, or proven metastases
Race	African American / African European / Haitian) vs. “other.” The “other” category includes White / Caucasian, American Indian/ Alaska Native, Australian Aborigine, Asian/ Pacific Islander, Latin/ Hispanic, , other, or unknown.
Payment source	Medicaid insurance (including Medicaid managed care) or self-pay vs. other insurance. The other insurance category includes managed care, commercial/ indemnity insurance, Medicare, Medicare managed care, government insurance, national health service, or other.
Critical care medicine (CCM) management	A critical care medicine physician was responsible for the overall care of the patient for all or a portion of the patient’s ICU stay
Hospital beds	Number of licensed hospital beds
Academic hospital	Academic vs. “other” hospital. The “other” category includes city/ county, state, Veteran’s Administration, community/ for profit, and community/ not for profit.
Medical school	The hospital is the primary teaching hospital of an accredited medical school

Covariate	Definition
CCM fellowship program	The hospital is the primary location of an accredited Critical Care Medicine fellowship
Residency program	The hospital is the primary location of an accredited residency program

APPENDIX REFERENCES

1. LeGall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/ North American multicenter study. *JAMA* 1993;270:2957–2963.

2. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: A severity of disease classification system. *Crit Care Med* 1985;13:818–829.

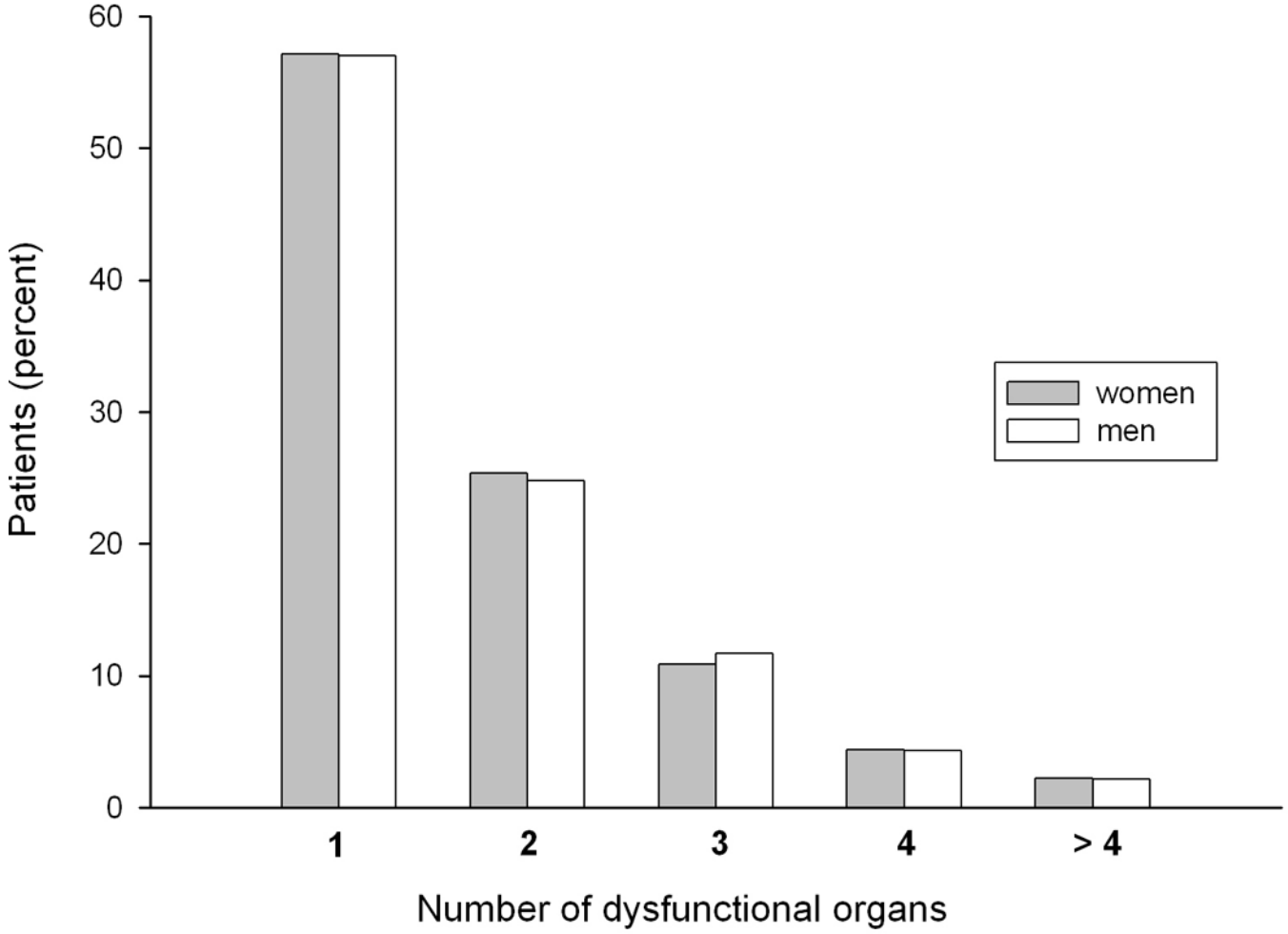

Figure 1.
Number of dysfunctional organs in men and women

Table I

Bivariate Association Between Other Independent Variables and Gender

Covariate	Women (n = 8,702)	Men (n = 10,055)	OR (95% CI)	*p* value
Patient characteristics				
Age (years)	68 (54 – 75)*	65 (52 – 76)*	--	0.0001
Dependent functional status at admission†	44%	36%	1.39 (1.31 – 1.48)	<0.0001
Race / Ethnicity				
Caucasian	74%	75%	0.94 (0.88 – 1.01)	0.08
African-American	14%	12%	1.18 (1.09 – 1.29)	0.0001
Latin/ Hispanic	5%	6%	0.87 (0.77 – 0.99)	0.04
Asian or Pacific Islander	1%	1%	0.93 (0.72 – 1.20)	0.55
American Indian	< 1%	< 1%	0.65 (0.39 – 1.08)	0.08
Other or unknown	5%	5%	1.02 (0.89 – 1.17)	0.79
Admitted from health care facility‡	53%	52%	1.03 (1.00 – 1.06)	0.06
Previous ICU admission this hospitalization	4.3%	4.7%	0.91 (0.79 – 1.05)	0.18
CPR within 24 hours of ICU admission	4.8%	5.0%	0.96 (0.84 – 1.10)	0.57
Medical patient (vs. surgical)	82%	82%	1.00 (0.92 – 1.08)	0.88
Medicaid or self-pay vs. other insurance §	15%	15%	1.00 (0.92 – 1.08)	0.92
Comorbidity				
Chronic liver disease	3%	4%	0.73 (0.63 – 0.86)	0.0001
Active cancer within 5 years	14%	17%	0.81 (0.75 – 0.88)	<0.0001
Chronic cardiovascular disease	6%	7%	0.80 (0.71 – 0.90)	0.0002
Chronic renal disease	6%	6%	0.90 (0.80 – 1.02)	0.10
Chronic respiratory disease	10%	10%	1.04 (0.94 – 1.14)	0.45
Immunocompromise	13%	13%	0.99 (0.91 – 1.08)	0.80
Severity of illness variables				
Neurologic dysfunction	7%	5%	1.32 (1.17 – 1.49)	<0.0001
Cardiovascular dysfunction	58%	54%	1.20 (1.13 – 1.27)	<0.0001
Respiratory dysfunction	43%	47%	0.83 (0.78 – 0.88)	<0.0001
Elevated serum lactate	10%	9%	1.15 (1.04 – 1.27)	0.0042
Acute renal failure	20%	18%	1.13 (1.05 – 1.22)	0.0012

Covariate	Women (n = 8,702)	Men (n = 10,055)	OR (95% CI)	*p* value
Hepatic dysfunction	8%	9%	0.87 (0.79 – 0.97)	0.011
Hematologic dysfunction	16%	17%	0.89 (0.83 – 0.97)	0.0047
APACHE II score	21 (15–27)*	21 (15–27)*	--	0.49
SAPS II predicted mortality	35% (15 – 64%)*	33% (14 – 64%)*	--	0.19
Source of infection				
Urinary infection	31%	19%	1.97 (1.84 – 2.10)	<0.0001
Intra-abdominal infection	12%	9%	1.33 (1.21 – 1.46)	<0.0001
Chest infection	37%	48%	0.63 (0.60 – 0.67)	<0.0001
Bloodstream infection	23%	24%	0.94 (0.88 – 1.00)	0.06
Unknown infection	3.8%	3.5%	1.10 (0.94 – 1.28)	0.23
Processes of care				
Code Status limitations **	9%	7%	1.31 (1.18 – 1.47)	<0.0001
Invasive mechanical ventilation	63%	68%	0.81 (0.76 – 0.86)	<0.0001
HD catheter	12%	14%	0.85 (0.78 – 0.93)	0.0002
PRBC transfusion	42%	39%	1.15 (1.09 – 1.22)	<0.0001
DVT prophylaxis	75%	77%	0.90 (0.84 – 0.97)	0.0034
Intravenous nutrition	18%	19%	0.93 (0.86 – 1.00)	0.06
FFP transfusion	17%	18%	0.94 (0.87 – 1.01)	0.10
Stress ulcer prophylaxis	43%	44%	0.96 (0.90 – 1.01)	0.12
CCM coverage	71%	72%	0.96 (0.90 – 1.02)	0.20
Hospital Characteristics				
Accredited residencies	69%	71%	0.89 (0.83 – 0.94)	0.0002
Accredited CCM fellowship	28%	30%	0.92 (0.85 – 0.96)	0.002
Academic hospital ††	21%	22%	0.92 (0.86 – 0.99)	0.02
Number of hospital beds (quartiles) ‡‡	--	--	0.97 (0.95 – 1.00)	0.02 §§
Urban hospital	60%	62%	0.94 (0.89 – 1.00)	0.05
Suburban hospital	26%	25%	1.06 (0.99 – 1.13)	0.10
Rural hospital	14%	13%	1.03 (0.95 – 1.12)	0.43
Medical school	21%	22%	0.94 (0.88 – 1.01)	0.10

*Numbers in parentheses represent interquartile range;

Gend Med. Author manuscript; available in PMC 2012 April 10.

[†] 206 missing values;

[‡] 46 missing values;

[§] 90 missing values;

[**] 191 missing values;

[††] 4 missing values;

[‡‡] 6 missing values;

[§§] Mantel Haenszel odds ratio per quartile increase in hospital beds.

Abbreviations: OR= odds ratio; CI = confidence interval; APACHE = acute physiology and chronic health evaluation score; SAPS = simplified acute physiology score; FFP = fresh frozen plasma; HD = hemodialysis; PRBC = packed red blood cells; DVT = deep venous thrombosis; CCM = critical care medicine

Table II

Unadjusted Outcome Differences by Gender

Outcome	Women (n = 8,702)	Men (n = 10,055)	OR (95% CI)	*p* value*
Hospital Mortality (n = 6,359)	35%	33%	1.09 (1.02 – 1.16)	0.006
ICU Mortality (n = 4,310)	24%	22%	1.09 (1.02 – 1.17)	0.01
Independent on hospital discharge (n = 3,620)	18%	20%	0.88 (0.82 – 0.95)	0.0006

* Chi-square test used for significance testing.

Table III

Associations Between Independent Variables and Hospital Mortality

Covariate	Bivariate analysis * OR (95% CI)	*p* value	Multivariable analysis † OR (95% CI)	*p* value
Patient characteristics				
Female gender	1.09 (1.02 – 1.16)	0.006	1.11 (1.04 – 1.19)	0.002
Age quintiles	1.27 (1.24 – 1.30)	< 0.001	1.20 (1.16 – 1.23)	< 0.001
Dependent functional status at admission	1.53 (1.43 – 1.62)	< 0.001	1.30 (1.18 – 1.43)	< 0.001
African-American race	0.95 (0.86 – 1.04)	0.24	0.89 (0.77 – 1.04)	0.137
Admitted from health care facility	1.38 (1.30 – 1.47)	< 0.001	1.49 (1.37 – 1.62)	< 0.001
Previous ICU admission this hospitalization	1.19 (1.03 – 1.37)	0.02	ns ‡	ns
CPR within 24 hours of ICU admission	3.22 (2.81 – 3.70)	< 0.001	1.81 (1.56 – 2.11)	< 0.001
Medical patient (vs. surgical)	1.23 (1.13 – 1.34)	< 0.001	1.55 (1.36 – 1.76)	< 0.001
Medicaid or self-pay vs. other insurance	0.71 (0.65 – 0.78)	< 0.001	ns	ns
Comorbidity				
Chronic liver disease	1.84 (1.57 – 2.15)	< 0.001	1.90 (1.55 – 2.34)	< 0.001
Active cancer within 5 years	1.87 (1.72 – 2.02)	< 0.001	1.34 (1.20 – 1.50)	< 0.001
Chronic cardiovascular disease	1.63 (1.44 – 1.83)	< 0.001	1.19 (1.01 – 1.40)	0.037
Chronic renal disease	1.48 (1.31 – 1.68)	< 0.001	ns	ns
Chronic respiratory disease	1.16 (1.05 – 1.29)	0.002	1.15 (1.04 – 1.28)	0.009
Immunocompromise	1.86 (1.71 – 2.04)	< 0.001	1.53 (1.34 – 1.75)	< 0.001
Severity of illness variables				
Neurologic dysfunction	1.47 (1.30 – 1.65)	< 0.001	1.23 (1.05 – 1.44)	0.01
Cardiovascular dysfunction	1.97 (1.85 – 2.10)	< 0.001	1.24 (1.11 – 1.40)	< 0.001
Respiratory dysfunction	1.26 (1.19 – 1.34)	< 0.001	ns	ns
Elevated serum lactate	2.64 (2.39 – 2.91)	< 0.001	1.14 (0.99 – 1.32)	0.067
Acute renal failure	2.67 (2.47 – 2.88)	< 0.001	1.36 (1.24 – 1.50)	< 0.001
Hepatic dysfunction	1.44 (1.29 – 1.60)	< 0.001	1.15 (0.97 – 1.35)	0.104
Hematologic dysfunction	1.60 (1.48 – 1.73)	< 0.001	1.36 (1.22 – 1.53)	< 0.001
APACHE II score (per 1 point increase in score)	1.11 (1.10 – 1.11)	< 0.001	ns	ns
SAPS II score (per 1 point increase in score)	1.06 (1.05 – 1.06)	< 0.001	1.04 (1.03 – 1.04)	< 0.001

Gend Med. Author manuscript; available in PMC 2012 April 10.

Covariate	Bivariate analysis * OR (95% CI)	*p* value	Multivariable analysis † OR (95% CI)	*p* value
Source of infection				
Urinary infection	0.86 (0.80 – 0.93)	< 0.001	0.83 (0.76 – 0.92)	< 0.001
Intra-abdominal infection	1.41 (1.28 – 1.55)	< 0.001	ns	ns
Chest infection	0.94 (0.89 – 1.00)	0.06	1.08 (1.00 – 1.17)	0.06
Bloodstream infection	1.23 (1.15 – 1.32)	< 0.001	ns	ns
Unknown infection	1.67 (1.43 – 1.96)	< 0.001	1.21 (1.00 – 1.47)	0.05
Processes of care				
Code status limitations	1.84 (1.65 – 2.06)	< 0.001	1.74 (1.51 – 2.01)	< 0.001
Invasive mechanical ventilation	2.37 (2.21 – 2.54)	< 0.001	2.19 (1.97 – 2.44)	< 0.001
HD catheter	1.69 (1.55 – 1.84)	< 0.001	1.23 (1.08 – 1.40)	0.002
PRBC transfusion	1.32 (1.24 – 1.41)	< 0.001	ns‡	ns
DVT prophylaxis	0.64 (0.60 – 0.69)	< 0.001	0.60 (0.54 – 0.67)	<0.001
Intravenous nutrition	1.24 (1.15 – 1.34)	< 0.001	ns	ns
FFP transfusion	2.23 (2.06 – 2.41)	< 0.001	1.57 (1.41 – 1.75)	< 0.001
Stress ulcer prophylaxis	0.54 (0.50 – 0.57)	< 0.001	0.60 (0.55 – 0.65)	<0.001
CCM coverage	1.28 (1.19 – 1.38)	< 0.001	1.16 (1.02 – 1.31)	0.019
Hospital Characteristics				
Accredited residencies	1.02 (0.96 – 1.10)	0.447	ns	ns
Accredited CCM fellowship	1.23 (1.15 – 1.32)	< 0.001	1.20 (1.03 – 1.40)	0.022
Academic hospital	1.27 (1.18 – 1.36)	< 0.001	1.17 (1.01 – 1.36)	0.041
Number of hospital beds (quartiles)	1.04 (1.02 – 1.07)	0.002	1.05 (0.99 – 1.11)	0.115
Urban hospital	1.07 (1.00–1.14)	0.04	ns	ns
Suburban hospital	0.98 (0.91 – 1.05)	0.58	ns	ns
Rural hospital	0.90 (0.82 – 0.99)	0.025	0.89 (0.74 – 1.07)	0.231
Medical school	1.33 (1.23 – 1.43)	< 0.001	ns	ns

*Chi-square test;

†Results of parsimonious multiple logistic regression model as described in Methods.

‡Covariates labeled “ns” (abbreviation for “not significant”) fell out of the logistic regression model during analysis (see Methods).

Gend Med. Author manuscript; available in PMC 2012 April 10.

Table IV

Subgroup Analyses of Processes of Care in Women Compared to Men *

Likelihood of women vs. men receiving code status limitations†	
Subgroups of patients with:	**Stratum-specific associations OR (95% CI)**
Impaired functional status	1.14 (1.00 – 1.31)
Non-impaired functional status	1.34 (1.09 – 1.63)
Age > 65 years	1.31 (1.15 – 1.49)
Age ≤ 65 years	1.02 (0.80 – 1.30)
Likelihood of women vs. men receiving mechanical ventilation at ICU admission	
Subgroups of patients with:	**Stratum-specific associations OR (95% CI)**
Chest infection	0.88 (0.79 – 0.98)
Other infection	0.92 (0.85 – 0.99)
Acute respiratory dysfunction	0.83 (0.71 – 0.96)
Other organ dysfunction	0.87 (0.80 – 0.94)
Likelihood of women vs. men receiving PRBC transfusion on 1st ICU day	
Subgroups of patients with:	**Stratum-specific associations OR (95% CI)**
Nadir hematocrit on 1st ICU day > 31%	1.19 (1.06 – 1.32)
Nadir hematocrit on 1st ICU day ≤ 31%	1.01 (0.93 – 1.09)
Likelihood of women vs. men receiving hemodialysis catheter placement	
Subgroups of patients with:	**Stratum-specific associations OR (95% CI)**
Acute renal failure present	0.84 (0.72 – 0.98)
Acute renal failure absent	0.82 (0.74 – 0.91)

* Each process of care is considered an outcome measure. The odds ratios refer to the likelihood of receiving the process of care in women vs. men, within the subgroup listed. For example, the odds ratio of 1.14 applies specifically to patients with impaired functional status, and indicates that women in this subgroup have a 14% higher likelihood of having code status limitations than men in this same subgroup.

† 191 missing values