Published in final edited form as:

J Trauma. 2008 March ; 64(3): 580–585. doi:10.1097/TA.0b013e31816543dd.

High Levels of Endogenous Estrogens are Associated With Death in the Critically Injured Adult

Lesly A. Dossett, MD, Brian R. Swenson, MD, MS, Daithi Heffernan, MD, Hugo Bonatti, MD, Rosemarie Metzger, MD, Robert G. Sawyer, MD, and Addison K. May, MD

From the Division of Trauma and Surgical Critical Care (L.A.D., D.H., A.K.M.), Department of Surgery, Vanderbilt University Medical Center; Nashville, Tennessee; and Department of Surgery (B.R.S., H.B., R.M., R.G.S.), University of Virginia Health System; Charlottesville, Virginia.

Abstract

Background: Sex hormones exhibit predictable changes in their physiologic patterns during critical illness. Endogenous estrogens are elevated in both genders as a result of the peripheral conversion of androgens to estrogens by the aromatase enzyme. Elevated endogenous estrogens have been associated with death in medical and mixed surgical intensive care unit (ICU) patients. Our objective was to determine the relationship between endogenous estrogens and outcomes in critically injured patients.

Methods: A prospective cohort of injured patients remaining in the ICU for at least 48 hours at two trauma centers was enrolled. Sex hormones (estradiol, progesterone, testosterone, prolactin, and dehydroepiandrosterone-sulfate) were assayed and mortality was assessed. A logistic regression model was used to determine the association between estradiol and death. The area under the receiver operating characteristic (AUROC) curve was used to estimate the accuracy of estradiol in predicting death.

Results: Nine hundred ninety-one patients were enrolled with a 13.4% mortality rate. Despite no detectable difference in mortality among genders, estradiol was significantly elevated in nonsurvivors (16 pg/mL vs. 35 pg/mL, $p < 0.001$). Estradiol was a marker for injury severity with the most severely injured patients exhibiting the highest levels. The ability of estradiol to predict death (AUROC = 0.65) was comparable with Trauma and Injury Severity Score (AUROC = 0.65) and superior to Injury Severity Score (AUROC = 0.54) in this cohort.

Conclusions: Serum estradiol is a marker of injury severity and a predictor of death in the critically injured patient, regardless of gender. Whether or not estradiol plays a causal role in outcomes is unclear, but estrogen modulation represents a potential therapy for improving outcomes in critically ill trauma patients.

Keywords

Sex hormones; Estrogens; Outcomes

Trauma-related deaths occurring days to weeks after injury are complex events frequently secondary to sepsis or multiple organ failure. These events, which reflect the magnitude of the original insult, are often the result of dysfunctions of the normally homeostatic immune and

Address for reprints: Lesly A. Dossett, MD, 404 Medical Arts Building, 1211 21st Avenue South, Nashville, TN 37212; email: lesly.dossett@vanderbilt.edu..

Portions of this data were presented as a poster at the 66th Annual Meeting of the American Association for the Surgery of Trauma, September 27–29, 2007, Las Vegas, Nevada.

inflammatory systems. A number of demographic, clinical, and genetic factors influence the magnitude of the inflammatory response, which ranges from ineffective (predisposing the patient to infectious complications) to exaggerated (leading to inflammatory induced organ failure). One demographic variable that seems to be important in this regard (at least in animal models) is gender. Specifically, the immune and inflammatory properties of endogenous estrogens and testosterone are thought to underlie the differential outcomes related to gender observed in animal models. In these models, the estrus state is associated with an intact immune response and a survival advantage after trauma-hemorrhage, whereas men and ovariectomized women have depressed immune systems and higher mortality rates.¹⁻⁶

The relationship between gender and outcomes after critical injury in humans remains unclear despite multiple observational studies.⁷⁻²⁰ Most studies have been unable to detect a difference in overall survival, even when adequately powered.^{7,8,10,12-15,18} An important difference between humans and animal models with regards to sexual dimorphism is the unique mechanisms of estrogen biosynthesis during stress that is present in humans (and other primates). Despite hypothalamic-pituitary-gonadal (HPG) suppression, endogenous estrogens are elevated in response to various types of critical illness (sepsis, trauma, postmyocardial infarction) regardless of gender.^{6,8,20-24} In a validated model of the endocrine response to stress, Spratt et al.²⁵ demonstrated that increased peripheral aromatization, not decreased metabolism or clearance, is the source of the increased estrogens.

The biological role of increased estrogens during critical illness in humans is uncertain, but elevated estradiol has been linked to adverse outcomes in medical Intensive Care Unit (ICU) patients with severe infection⁸ and in a mixed surgical ICU population.²⁶ Although estrogens may simply reflect global illness rather than be part of the causal pathway, their association with outcomes in the trauma population is unknown. Our hypothesis was that endogenous estrogens would be associated with mortality in critically injured patients, regardless of gender. Our objective was to test this hypothesis in a cohort of critically ill trauma patients and to determine whether or not serum estradiol could accurately predict death in this population.

PATIENTS AND METHODS

Study Population

A two-institutional, prospective cohort of critically injured patients was enrolled. Patients 18 years of age or older, admitted to the Trauma ICUs of Vanderbilt University Medical Center (Nashville, TN) and the University of Virginia Health Sciences Center (Charlottesville, VA) were eligible for enrollment. To select a population at high risk of mortality and morbidity (organ dysfunction, infectious complications, etc) patients who remained alive and in the ICU for 48 hours were eligible for enrollment. This time point served to eliminate those dying of uncontrolled hemorrhage or overwhelming events (nonsurvivable traumatic brain injury) and those with less severe injuries not requiring extended critical care. This high-risk population allowed for increased power while limiting the number required for enrollment. Pregnant women were excluded.

Data Collection

Gender, age, body mass index (BMI), date of hospital and ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Injury Severity Score (ISS), Trauma and Injury Severity Score (TRISS), and in-hospital mortality were recorded. Illness and injury severity scores were calculated based on the worst physiologic parameters at the time of hospital admission. Menopausal status was obtained by patient (after recovery) or family member interview. Postmenopausal was defined as having had no menstrual cycle in the previous 12 months or having undergone bilateral oophorectomy. Patient care was at the

discretion of the attending physician according to established critical care protocols. Both hospitals use standard protocols for ventilator management and weaning, hemodynamic support with vasoactive agents, nutrition support, diagnosis of infectious complications and antibiotic usage, and appropriate prophylaxis.

Hormonal Assays

One 10-mL blood sample was collected at study entry for analysis of hormones. Plasma was separated from whole blood and stored at -70°C until analysis. 17β -estradiol, progesterone, total testosterone, and prolactin assays were performed at the University of Virginia General Clinical Research Center. Estradiol was measured by kit EIA utilizing a competitive immunoassay strategy and alkaline phosphatase/p-Npp chromogenic reaction (Estradiol, catalog # 90108, Assay Designs, Inc., Ann Arbor, MI). Total testosterone, prolactin, and progesterone were measured by ELISA kits and manufacturer's directions (testosterone EIA, catalog # 700C-081; prolactin EIA, catalog # 30MC-009; progesterone EIA, catalog # 700C-079; Alfa Scientific Designs, Inc., San Diego, CA).

Statistical Analysis

Normally distributed continuous variables were summarized by reporting the mean and SD and compared using two sample *t* tests for independent samples. Continuous variables that were not normally distributed were presented by reporting the median and interquartile ranges (IQR) and compared using the Wilcoxon's rank sum test. Differences in proportions were compared using a χ^2 or Fischer's exact test. A logistic regression model was performed to determine the relationship between estradiol and the log-odds of death. Restricted cubic spline covariates were used in the regression model since this nonlinear model proved more accurate than the simple logistic regression model. Spline covariates were derived using five knots located at the default values recommended by the *rc_spline* program of the statistical package.

To compare the predictive ability of serum estradiol versus other variables, the area under the receiver operating characteristic (AUROC) curve was calculated. The ROC curve describes graphically the sensitivity and specificity of a given diagnostic test. As the AUROC curve approaches 1.0, the test becomes more accurate; as the area approaches 0.5, it becomes random and of little diagnostic value.

Stata version 9.2 (Stata Corp., College Station, TX) was used for the analysis. Tests for statistical significance were two sided with a level of significance of 0.05. The Institutional Review Boards of both Vanderbilt University Medical Center and the University of Virginia Health Sciences Center approved the study. All data are maintained in a secure, password-protected database that is HIPAA-compliant and all patient information is de-identified before analysis and reporting.

RESULTS

A total of 991 critically injured patients were enrolled. The overall in-hospital mortality rate was 13.4% (133 deaths). The demographics, clinical characteristics, and hormone levels by outcome are displayed in Table 1. Approximately 75% of patients were men, a proportion that was similar among survivors and nonsurvivors. Survivors and nonsurvivors did not differ by BMI or mechanism of injury (blunt vs. penetrating). Not surprisingly, survivors were younger and were less severely injured than nonsurvivors (APACHE II [16 ± 6 vs. 22 ± 6 , $p < 0.001$] and TRISS [0.72 ± 0.30 vs. 0.55 ± 0.35 , $p < 0.001$]). ISS was higher in nonsurvivors, but this difference was not statistically significant.

Median serum estradiol levels were within the physiologic range for all hormonal groups (men, pre- and postmenopausal women), but approximately 50% of patients had levels above the upper limit of physiologic normal. This degree of estradiol elevation was related to illness severity as estimated by APACHE II (Fig. 1). Median serum estradiol levels were significantly elevated in nonsurvivors (median of 16 [IQR, 10–44] pg/mL in survivors and 35 [IQR, 10–85] pg/mL in nonsurvivors, $p < 0.001$). This difference was present in both men (median of 14 [IQR, 10–40] pg/mL in survivors and 38 [IQR, 10–88] pg/mL in nonsurvivors, $p < 0.001$) and women (median of 20 [IQR, 10–57] pg/mL in survivors and 33 [IQR, 14–71] pg/mL in nonsurvivors, $p = 0.04$) subsets. The mortality rate for patients in the lowest quartile of estradiol was 8.3% whereas the mortality rate for patients with levels in the highest quartile was 23.4%. To further evaluate the relationship of estradiol to mortality, logistic regression modeling was performed. A restricted cubic spline analysis yielded a better model than simple logistic regression ($p = 0.03$), indicating a nonlinear relationship between estradiol and mortal risk. As shown in Figure 2, the predicted probability of death is lowest within the physiologic range of estradiol (0–54 pg/mL for men and postmenopausal women), but increases sharply outside of this range.

The predictive value of these logistic regression models (as determined by the AUROC) was compared with the predictive value of several of the parameters individually. Serum estradiol was a comparable predictor with TRISS (AUROC 0.65 vs. 0.65, respectively), and a better predictor of death than ISS (AUROC, 0.54) (Fig. 3). The best overall predictor of mortality was a multivariate regression model combining the spline covariates of estradiol, age, and APACHE II (AUROC = 0.83). The levels of progesterone, testosterone, and DHEA-S were also statistically higher in nonsurvivors, but their ability to accurately predict death was considerably lower than estradiol. Additionally, the differences in testosterone levels by outcome are not present in the male subgroup.

DISCUSSION

This study confirms the known sex hormone response to critical illness and injury—HPG suppression resulting in decreased testosterone with concurrent increases in serum estradiol related to injury severity. Although this relationship is well established,²⁷ there have been no large studies relating sex hormones to outcomes in the trauma population. In this cohort, serum estradiol was independently associated with death after controlling for age, gender, and BMI ($p < 0.001$). The median estradiol level for survivors was 16 pg/mL, which falls within the normal range for all patients, whereas the median estradiol level for nonsurvivors was almost twice that level (35 pg/mL). This difference was present in all subgroups (men, women, old, young, severely injured, less severely injured, etc). The mortality rate for patients with estradiol levels in the highest quartile was three times the mortality rate of those in the lowest quartile.

The nonlinear relationship demonstrated by the restricted cubic spline analysis further supports the notion that while estrogens may be beneficial within the normal physiologic range, markedly elevated levels can be detrimental. There is physiologic basis for this observation with a similar relationship being observed between estrogens and insulin resistance. Postmenopausal women (very low estrogens) develop insulin resistance, which improves with hormone replacement therapy (“normal” levels), but the excess estrogen associated with pregnancy again induces insulin resistance. In basic science models of the relationship between E2 and insulin resistance, this same dose-dependent relationship is observed.²⁸

The source of elevated serum estrogens in critically ill patients is related to increased peripheral conversion of androgens to estrogens via aromatase activity.^{29–32} These peripheral sites of aromatization account for the majority of estrogens in men and postmenopausal women and are the primary source of estrogens production during critical illness. In a recent study of

elective cardiac surgery patients, Spratt et al. demonstrated the elevation in estrogens present postoperatively was because of increased peripheral aromatase activity and not related to changes in metabolism or clearance.²⁵ Importantly, the aromatase enzyme is under site specific regulation. Whereas the gonadal production of estrogens is regulated by the HPG axis via follicle stimulating hormone and luteinizing hormone—and *inhibited* by class I cytokines and tumor necrosis factor alpha—the peripheral production of estrogens is *stimulated* by class I cytokines. Thus, while the inflammatory response to injury would inhibit the central mediated production of estrogens it stimulates peripheral biosynthesis.

Whether elevated estradiol contributes physiologically to adverse outcomes in critically injured patients or simply serves as a biomarker for overall injury severity is unknown. Some data do support a pathophysiologic role in adverse outcomes. Estradiol is a well-documented immunomodulator,^{22,35} altering monocyte and macrophage function and life span³⁴ and cytokine and chemokine production. These changes have translated into early survival in animal models, but they could lead to an exaggerated inflammatory response later in the clinical course. In addition to its inflammatory properties, estradiol has also been shown to induce and activate nitric oxide synthase in endothelial cells which may contribute to low peripheral resistance in response to shock.³⁵ As already mentioned, estrogens are known to modulate insulin resistance, an important contributor to outcomes after critical injury. Finally, the association with estrogens and hypercoagulability is well known, and a recent study confirmed the relationship between estradiol and the clotting cascade in trauma patients.³⁶ Perhaps the best evidence of the potential pathophysiologic role of estradiol in outcomes is that high doses of estradiol pretreatment in mice increases mortality from subsequent lethal challenge with lipopolysaccharide,³⁷ and that aromatase inhibitors decrease subsequent mortality from endotoxin in animals.³⁸

The strengths of this study include its large sample size and prospective nature. Additionally, the relationship between increased estradiol and death is stable across all subgroups and in patients from two institutions, all of which improve the ability to generalize this data. One limitation of this study is that patients who died or were discharged before 48 hours were excluded. In the trauma population deaths occurring before 48 hours are often the result of exsanguination or traumatic brain injury—events that are unlikely to be affected by the immune or inflammatory response. Similarly, patients discharged from the ICU before 48 hours have very low mortality rates. It is unknown, though, precisely how quickly estrogens are elevated and whether or not hospital admission panels would reveal similar elevations or if a relationship in other outcome measures could be demonstrated in patients with less severe illness. Another limitation is that this analysis is based off a single estradiol level drawn 48 hours after admission. Animal studies that demonstrate the protective effects of estrogens are based on measurements made in close proximity to the injury or insult. It is impossible to know from this data whether the observed increased mortality associated with elevated estrogens is a function of only this difference in timing of measurement. Finally, we did not measure follicle stimulating hormone or luteinizing hormone to confirm the well-documented HPG suppression.

Acknowledgements

Supported by a National Institutes of Health Grant—RO1 AI49989-01 (Clinical Trials.gov identifier NCT00170560) and an Agency for Healthcare Research and Quality grant—T32 HS 013833.

REFERENCES

1. Zellweger R, Wichmann MW, Ayala A, Stein S, DeMaso CM, Chaudry IH. Females in proestrus state maintain splenic immune functions and tolerate sepsis better than males. *Crit Care Med* 1997;25:106–110. [PubMed: 8989185]

2. Samy TS, Knoferl MW, Zheng R, Schwacha MG, Bland KI, Chaudry IH. Divergent immune responses in male and female mice after trauma-hemorrhage: dimorphic alterations in T lymphocyte steroidogenic enzyme activities. *Endocrinology* 2001;142:3519–3529. [PubMed: 11459798]
3. Mizushima Y, Wang P, Jarrar D, Cioffi WG, Bland KI, Chaudry IH. Estradiol administration after trauma-hemorrhage improves cardiovascular and hepatocellular functions in male animals. *Ann Surg* 2000;232:673–679. [PubMed: 11066139]
4. Knoferl MW, Jarrar D, Angele MK, et al. 17 beta-Estradiol normalizes immune responses in ovariectomized females after trauma-hemorrhage. *Am J Physiol Cell Physiol* 2001;281:C1131–C1138. [PubMed: 11546648]
5. Knoferl MW, Angele MK, Diodato MD, et al. Female sex hormones regulate macrophage function after trauma-hemorrhage and prevent increased death rate from subsequent sepsis. *Ann Surg* 2002;235:105–112. [PubMed: 11753049]
6. Majetschak M, Christensen B, Obertacke U, et al. Sex differences in posttraumatic cytokine release of endotoxin-stimulated whole blood: relationship to the development of severe sepsis. *J Trauma* 2000;48:832–839. [PubMed: 10823526]
7. Wichmann MW, Inthorn D, Andress HJ, Schildberg FW. Incidence and mortality of severe sepsis in surgical intensive care patients: the influence of patient gender on disease process and outcome. *Intensive Care Med* 2000;26:167–172. [PubMed: 10784304]
8. Angstwurm MW, Gaertner R, Schopohl J. Outcome in elderly patients with severe infection is influenced by sex hormones but not gender. *Crit Care Med* 2005;33:2786–2793. [PubMed: 16352961]
9. Romo H, Amaral AC, Vincent JL. Effect of patient sex on intensive care unit survival. *Arch Intern Med* 2004;164:61–65. [PubMed: 14718323]
10. Gannon CJ, Pasquale M, Tracy JK, McCarter RJ, Napolitano LM. Male gender is associated with increased risk for postinjury pneumonia. *Shock* 2004;21:410–414. [PubMed: 15087816]
11. George RL, McGwin G Jr, Metzger J, Chaudry IH, Rue LW III. The association between gender and mortality among trauma patients as modified by age. *J Trauma* 2003;54:464–471. [PubMed: 12634524]
12. Valentin A, Jordan B, Lang T, Hiesmayr M, Metnitz PG. Gender-related differences in intensive care: a multiple-center cohort study of therapeutic interventions and outcome in critically ill patients. *Crit Care Med* 2003;31:1901–1907. [PubMed: 12847381]
13. Bowles BJ, Roth B, Demetriades D. Sexual dimorphism in trauma? A retrospective evaluation of outcome. *Injury* 2003;34:27–31. [PubMed: 12531373]
14. Croce MA, Fabian TC, Malhotra AK, Bee TK, Miller PR. Does gender difference influence outcome? *J Trauma* 2002;53:889–894. [PubMed: 12435939]
15. Napolitano LM, Greco ME, Rodriguez A, Kufera JA, West RS, Scalea TM. Gender differences in adverse outcomes after blunt trauma. *J Trauma* 2001;50:274–280. [PubMed: 11242292]
16. Oberholzer A, Keel M, Zellweger R, Steckholzer U, Trentz O, Ertel W. Incidence of septic complications and multiple organ failure in severely injured patients is sex specific. *J Trauma* 2000;48:932–937. [PubMed: 10823539]
17. Eachempati SR, Hydo L, Barie PS. Gender-based differences in outcome in patients with sepsis. *Arch Surg* 1999;134:1342–1347. [PubMed: 10593332]
18. Crabtree TD, Pelletier SJ, Gleason TG, Pruett TL, Sawyer RG. Gender-dependent differences in outcome after the treatment of infection in hospitalized patients. *JAMA* 1999;282:2143–2148. [PubMed: 10591336]
19. Offner PJ, Moore EE, Biffl WL. Male gender is a risk factor for major infections after surgery. *Arch Surg* 1999;134:935–938. [PubMed: 10487586]
20. Schroder J, Kahlke V, Staubach KH, Zabel P, Stuber F. Gender differences in sepsis human. *Arch Surg* 1998;133:1200–1205. [PubMed: 9820351]
21. Klaiber EL, Broverman DM, Haffajee CI, Hochman JS, Sacks GM, Dalen JE. Serum estrogen levels in men with acute myocardial infarction. *Am J Med* 1982;73:872–881. [PubMed: 7148879]
22. Fourrier F, Jallot A, Leclerc L, et al. Sex steroid hormones in circulatory shock, sepsis syndrome, and septic shock. *Circ Shock* 1994;43:171–178. [PubMed: 7895322]

23. Christeff N, Auclair MC, Dehennin L, et al. Effect of the aromatase inhibitor, 4 hydroxyandrostenedione, on the endotoxin-induced changes in steroid hormones in male rats. *Life Sci* 1992;50:1459–1468. [PubMed: 1573977]
24. Scheingraber S, Dobbert D, Schmiedel P, Seliger E, Dralle H. Gender-specific differences in sex hormones and cytokines in patients undergoing major abdominal surgery. *Surg Today* 2005;35:846–854. [PubMed: 16175466]
25. Spratt DI, Morton JR, Kramer RS, Mayo SW, Longcope C, Vary CP. Increases in serum estrogen levels during major illness are caused by increased peripheral aromatization. *Am J Physiol Endocrinol Metab* 2006;291:E631–E638. [PubMed: 16670151]
26. May AK, Dossett LA, Norris PR, et al. Estradiol is associated with mortality in critically ill trauma and surgical patients. *Crit Care Med* 2007;36:62–68. [PubMed: 18090358]
27. Spratt DI, Cox P, Orav J, Moloney J, Bigos T. Reproductive axis suppression in acute illness is related to disease severity. *J Clin Endocrinol Metab* 1993;76:1548–1554. [PubMed: 8501163]
28. Gonzalez C, Alonso A, Gueso NA, et al. Role of 17beta-estradiol administration on insulin sensitivity in the rat: implications for the insulin receptor. *Steroids* 2002;67:993–1005. [PubMed: 12441184]
29. Simpson ER, Merrill JC, Hollub AJ, Graham-Lorence S, Mendelson CR. Regulation of estrogen biosynthesis by human adipose cells. *Endocr Rev* 1989;10:136–148. [PubMed: 2666116]
30. Simpson ER, Michael MD, Agarwal VR, Hinshelwood MM, Bulun SE, Zhao Y. Cytochromes P450 11: expression of the CYP19 (aromatase) gene: an unusual case of alternative promoter usage. *FASEB J* 1997;11:29–36. [PubMed: 9034163]
31. Simpson ER. Aromatase: biologic relevance of tissue-specific expression. *Semin Reprod Med* 2004;22:11–23. [PubMed: 15083377]
32. Simpson ER, Ackerman GE, Smith ME, Mendelson CR. Estrogen formation in stromal cells of adipose tissue of women: induction by glucocorticosteroids. *Proc Natl Acad Sci USA* 1981;78:5690–5694. [PubMed: 6946508]
33. Homo-Delarche F, Fitzpatrick F, Christeff N, Nunez EA, Bach JF, Dardenne M. Sex steroids, glucocorticoids, stress and autoimmunity. *J Steroid Biochem Mol Biol* 1991;40:619–637. [PubMed: 1958562]
34. Vegeto E, Belcredito S, Eteri S, et al. Estrogen receptor-alpha mediates the brain antiinflammatory activity of estradiol. *Proc Natl Acad Sci USA* 2003;100:9614–9619. [PubMed: 12878732]
35. Florian M, Lu Y, Angle M, Magder S. Estrogen induced changes in Akt-dependent activation of endothelial nitric oxide synthase and vasodilation. *Steroids* 2004;69:637–645. [PubMed: 15465108]
36. Gee AC, Sawai RS, Differding J, Muller P, Underwood S, Schreiber MA. The influence of sex hormones on coagulation and inflammation in the trauma patient. *Shock*. 2007
37. Christeff N, Auclair MC, Thobie N, Fertil B, Carli A, Nunez EA. Effect of estradiol on endotoxin-induced changes in steroid hormone levels and lethality in male rats. *Circ Shock* 1994;44:154–159. [PubMed: 7600639]
38. Schneider CP, Nickel EA, Samy TS, et al. The aromatase inhibitor, 4-hydroxyandrostenedione, restores immune responses following trauma-hemorrhage in males and decreases mortality from subsequent sepsis. *Shock* 2000;14:347–353. [PubMed: 11028555]

Fig. 1. Relationship between APACHE II and serum estradiol. Regression model using restricted cubic spline covariates demonstrating predicted estradiol with increasing APACHE II.

Fig. 2.

Relationship between mortality and increasing serum estradiol. Regression model using restricted cubic spline covariates demonstrating probability of death with increasing serum estradiol levels (pg/mL). Although estradiol seems to be protective within the physiologic range (<54 pg/mL for men and postmenopausal women), the probability of death increases sharply with rising estradiol.

Fig. 3.

The receiver operating characteristic (ROC) curve for estradiol compared with other outcome predictors. The ROC curves for estradiol, ISS, and TRISS for predicting mortality are displayed. The curve for estradiol is comparable with TRISS and the area under the ROC curve (AUROC) is the same for these two variables.

Table 1
Demographic and Clinical Characteristics of Patients by Outcome

Variable	Survivors (n = 858)	Nonsurvivors (n = 133)	p Value
Males (%) [*]	73	80	NS
Age (yr) [†]	41 ± 17	52 ± 20	<0.001
BMI (kg/m ²) [‡]	28 ± 7	28 ± 7	NS
Blunt trauma (%) [*]	86	92	NS
APACHE II [†]	16 ± 6	22 ± 6	<0.001
ISS [†]	31 ± 11	33 ± 14	NS
TRISS [†]	0.72 ± 0.30	0.55 ± 0.35	<0.001
Estradiol (pg/mL) [‡]	16	35	<0.001
Progesterone (ng/mL) [‡]	0.75	0.92	<0.001
Prolactin (ng/mL) [‡]	14	12	NS
Testosterone (ng/mL) [‡]	30	70	<0.001
DHEA-S (μg/mL) [‡]	50	39	<0.001

Body mass index (BMI) is weight in kilograms divided by height in meters squared.

APACHE II, Acute Physiology and Chronic Health Evaluation II; ISS, Injury Severity Score; TRISS, Trauma and Injury Severity Score; DHEA-S, dehydroepiandrosterone-sulfate.

^{*} Proportion; compared using χ^2 test.

[†] Mean ± SD; compared using two sample *t* test.

[‡] Median; compared using Wilcoxon's rank sum test.