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Gender and mortality in sepsis: do sex hormones impact the outcome?

Associação entre sexo e mortalidade em pacientes com sepse: os hormônios sexuais influenciam o desfecho?

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ABSTRACT

Objective: Comparative assessment of the mortality rates of two septic patients' ages and/or gender subgroups, admitted to the intensive care unit of a university hospital.

Methods: From December 2005 to April 2008, from a total of 628 patients, 133 were admitted to the intensive care unit with sepsis and included into two age subgroups: (G1) 14 - 40 years old and (G2) more than 50 years old. Patients aged between 41 and 50 years old (n = 8) were excluded. Demographic data, prognostic indicators (APACHE II score, organ dysfunction and circulatory shock) and outcome (mortality) were analyzed.

Results: Of the G1 patients (n = 44), 27 were female (61.4%), and in G2 (n = 81), 40 were female (49.4%). For both groups, mean APACHE II scores, multi-organ dysfunction and progression to circulatory shock rates were not significantly different between female and male patients. For G1, overall mortality rate was lower in female than in male patients (p = 0.04), while for G2, the opposite trend was observed.

Conclusions: In this sample, reproductive age female patients younger than 40 years old showed lower mortality rates compared with age-matched male patients; for patients older than 50 years old, male patients had lower mortality rates than female patients.

Keywords: Gonadal hormones; Sepsis/mortality; Prognosis; Sex factors; Female

INTRODUCTION

Sepsis is a complex systemic response to infection characterized by multifactorial and interrelated defects in cardiopulmonary function and tissue metabolism.[1] Hemodynamic, systemic oxygen delivery and pulmonary gas exchange disorders have been intensively investigated, but the mechanisms behind gender-based differences in immune and hormonal sepsis-induced changes remain poorly understood.[2-5]

Gender has long been known to contribute to the incidence and progression of immune system disorders. More recently, several clinical and experimental studies have demonstrated gender dimorphism in immune responsiveness and in shock, sepsis and trauma susceptibility.[6-11]

Cumulative data provide a potential explanation of the mechanism

by which estrogens have immunoenhancing effects. Favorable effects have been shown to be provided via nuclear and extra-nuclear receptors. Estrogen rapidly activates several protein kinases and phosphatases as well as the release of calcium in different cell types. These effects are an example of the promising effects that estrogen treatment may have on adverse pathophysiological conditions following acute injury.[3-5]

This study's objective was to clarify the impact of sex hormones on sepsis prognosis.

METHODS

This retrospective study included all consecutive patients admitted from December 2005 to April 2008 to a six-bed medical intensive care unit (ICU) in a university hospital. The protocol complied with the ethical standards of our hospital's Committee for the Protection of Human Subjects. The study was approved by the Committee under number 054.08.08, and the need for informed consent was waived due to its observational nature. Sepsis patients were divided into two subgroups according to age: (G1) 14 - 40 years old and (G2) older than 50 years old. Patients aged between 41 and 50 years old were excluded to avoid changing hormone levels (early menopause) and inaccurate information about hormone replacement therapy. As recorded by ICU admission, the G1 women were premenopausal, and the G2 women were post-menopausal and used no hormone replacement therapy.

Sepsis was defined as a systemic response to infection featuring two or more of the following conditions: body temperature >38ºC or <36ºC; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg; and white blood cell count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms.[1] Severe sepsis patients (sepsis associated with organ dysfunction) and patients with septic shock (sepsis-induced hypotension despite appropriate fluid resuscitation) were also included in the study.[1] The following data were recorded upon admission to the ICU: age, gender, organ dysfunctions (respiratory, neurological, hematological, cardiovascular, hepatic and renal) according to the SOFA (Sepsis-related Organ Failure Assessment) score,[12] the APACHE II (Acute Physiology and Chronic Health disease Classification System II) score[13] and ICU outcomes (mortality, ICU length of stay).

The data for continuous variables are expressed as the means ± standard deviations (SD) or medians and interquartile ranges (IQR), according to their distribution patterns. The categorical variables were expressed as n (%). For comparing continuous variables, Student's t test and the Mann-Whitney U test were used as appropriate; categorical variables were compared using the chi-squared test. Univariate and multivariate analysis were performed to evaluate the independent risk factors associated with increased mortality in each subgroup; the results were considered statistically significant if $p < 0.05$.

RESULTS

Out of 628 patients admitted to the ICU during the study, 133 complied with the criteria for sepsis, and 8 were excluded due to having ages between 41 and 50 years old; G1 (n = 44) had 27 (61.4%) female patients, and G2 (n = 81) had 40 (49.4%) female patients. Of the 125 patients included, 12 had uncomplicated sepsis, and the remaining patients had severe sepsis. The incidence of septic shock was 32%. ICU patient admission characteristics (age, APACHE II score) and dysfunctions were similar for female and male patients in both subgroups. The ICU length of stay was longer in G2 female patients when compared with male patients in the same subgroup. No statistically significant differences were determined for supportive care (ventilation, vasoactive drugs, dialysis and blood components) between women and men in both subgroups (Table 1).

There were no statistically significant differences in the incidence of multi-organ dysfunctions ($p = 0.89$) or progression to circulatory shock ($p = 0.46$) between female and male patients in both subgroups. However, the overall mortality rate was lower in female patients compared to male patients in the G1 subgroup; for the G2 subgroup, a reverse trend was observed (Figure 1).

The univariate analysis showed that the APACHE II score was associated with higher mortality rates for the G1 and G2 subgroups (Table 2). However, the multivariate linear regression

Table 1 - Demographic data and therapeutic support used in patients with sepsis admitted to the intensive care unit

Subgroups	G1 (14 – 40 years old)	p value	G2 (> 50 years old)	p value
Demographic data				
Age¥				
Female	25.5 ± 5.8	0.158	68.1 ± 10.9	0.757
Male	29.0 ± 7.2		68.9 ± 12.3	
APACHE II¥				
Female	20.4 ± 9.0	0.401	22.8 ± 7.5	0.312
Male	22.6 ± 6.9		24.5 ± 9.4	
Length of stay (days)§				
Female	4.0 (1.0-12.0)	0.591	10.0(5.0-25.7)	0.010
Male	1.0 (1.0-12.7)		6.0 (1.0-15.0)	
Dysfunctions at admission (n)§				
Female	2.5 (1.0-3.0)	0.512	3.0 (2.0-4.0)	0.934
Male	3.0 (2.0-3.0)		3.0 (2.0-4.0)	
Supports£				
Respiratory				
Female	15 (55.6)	0.101	29 (67.4)	0.492
Male	13 (76.5)		24 (58.5)	
Blood components£				
Female	6 (22.2)	0.083	15 (34.9)	0.553
Male	8 (47.1)		17 (41.5)	
Dialysis£				
Female	4 (14.8)	0.278	16 (37.2)	0.449
Male	5 (29.4)		12 (29.3)	
Vasoactive drugs£				
Female	19 (70.4)	0.943	28 (65.1)	0.990
Male	12 (70.6)		27 (65.9)	

The results are expressed as the mean ± SD, medians (IQR) and n (%). APACHE II - Acute Physiology and Chronic Health Evaluation; ¥ Student's t test; § Mann-Whitney U test; £ chi-squared test; $p < 0.05$. Patients with ages between 41 and 50 years old were excluded.

analysis of continuous variables (age, APACHE II score, length of stay in the ICU and number of organ dysfunctions) showed the APACHE II score to be an independent risk factor associated with increased mortality only for G1 (adjusted Rsqr = 0.35, p = 0.005) but not for G2 subgroup (adjusted Rsqr = 0.05, p = 0.55).

The univariate and multivariate analyses of categorical variables showed that male gender and the use of respiratory support were risk factors for increased mortality during the ICU stay in G1 subgroup patients. However, in the G2 subgroup, only respiratory support persisted as a risk factor for an increased mortality rate (Tables 2 and 3).

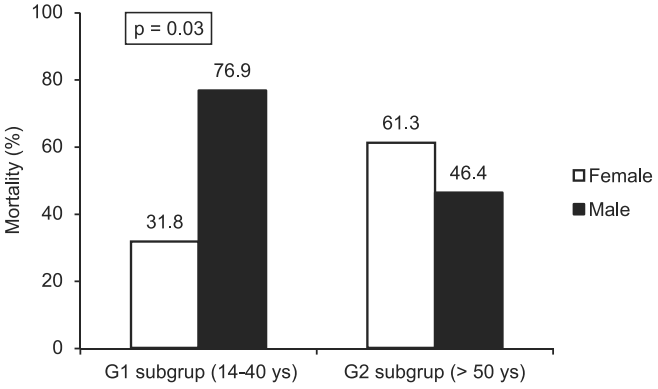

Figure 1 - Mortality rates in G1 (14 – 40 years old) and G2 (> 50 years old) subgroups of patients with sepsis admitted to the intensive care unit.

Table 2 - Multivariate analysis of risk factors associated with mortality in G1 (14 – 40 years old) and G2 subgroups (> 50 years old) of patients with sepsis admitted to the intensive care unit

	Survivors	No survivors	p value
G1 subgroup			
Age¥	27.1 ± 6.5	26.7 ± 6.7	0.858
APACHE II¥	16.7 ± 6.4	28.0 ± 6.5	< 0.001
Length of stay (days)§	2.0 (1.0-12.2)	10.0 (5.0-17.0)	0.076
Dysfunctions at admission (n)§	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.350
Respiratory support£	36.8	94.1	< 0.0001
Blood components£	26.3	52.9	0.171
Dialysis £	10.5	35.3	0.113
Vasoactive drugs£	57.9	88.2	0.065
Male gender£	10.5	64.7	0.001
G2 subgroup			
Age¥	68.2 ± 11.2	68.8 ± 12.1	0.828
APACHE II§	20.0 (17.0-25.5)	24.0 (21.0-27.5)	0.028
Length of stay (days)§	4.5 (2.0-9.5)	5.0 (2.7-10.2)	0.705
Dysfunctions at admission (n)§	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.902
Respiratory support£	37.5	82.9	< 0.0001
Blood components£	30.0	40.4	0.372
Dialysis£	28.2	34.0	0.643
Vasoactive drugs£	62.5	65.9	0.823
Male gender£	52.5	48.9	0.830

The results are expressed as the mean ± S.D and n (%). APACHE II - Acute Physiology and Chronic Health Evaluation; ¥ Student's t test; § Mann-Whitney U test; £ chi-squared test; $p < 0.05$.

Table 3 - Multivariate analysis of risk factors associated with mortality in G1 (14 – 40 years old) and G2 subgroups (> 50 years old) of patients with sepsis admitted to the intensive care unit

	OR	95% CI	p value
G1 subgroup			
Respiratory support	0.04	0.002 - 0.068	0.026
Blood components	1.09	0.126 – 9.459	0.937
Dialysis	0.20	0.001 - 2.722	0.228
Vasoactive drugs	5.01	0.215 – 116.9	0.316
Male gender	0.06	0.005 - 0.084	0.003
G2 subgroup			
Respiratory support	0.08	0.08 - 0.02	< 0.001
Blood components	0.54	0.18 – 1.64	0.283
Dialysis	0.61	0.19 – 1.87	0.388
Vasoactive drugs	2.79	0.81 – 9.60	0.102
Male gender	0.99	0.37 – 2.67	0.997

OR = odds ratio; 95% CI = 95% confidence interval; $p < 0.05$.

DISCUSSION

In recent years, interest in gender influence on acute illness care and outcomes has grown. The response to sepsis in acutely ill patients has been found to be different for men and women; however, sex-based differences in clinical outcomes within this specific condition are less well established.[2]

Our study showed that in the G1 subgroup, with patients aged between 14 and 40 years old, the mortality rate was lower for women compared with men. This subgroup's women were likely to have sex hormones within the normal range. This finding is in agreement with the literature's clinical and experimental data. While gender-based differences in the development of protective or pathological adaptive host responses have been widely reported, it is becoming apparent that gender may also influence early acknowledgement of microbial insults and the production of inflammatory immune responses.[14] In this subgroup of patients, male sex and respiratory support were considered to be risk factors associated with higher ICU mortality rates. The limited sample size hindered better analysis of the interaction between these two factors in determining higher mortality rates.

In animal models of traumatic hemorrhage, splenic and peritoneal macrophages, as well as T-cell function, are depressed in male patients but not in female patients.[3] Other studies have also shown that the mortality

rate and induction of subsequent sepsis following traumatic hemorrhage are significantly higher in males and ovariectomized females compared with proestral females.[4] These data demonstrate that sex hormones provide a basis for this gender dichotomy and that the administration of estrogen can ameliorate immune depression and increase the survival rate after traumatic hemorrhage. Other studies have also indicated that androgens cause immunodepression following traumatic hemorrhage in males.[5] In contrast, female sex steroids apparently exhibit immunoprotective properties following trauma and severe blood loss.[3-5] Alternatively, indirect sex hormone effects, i.e., modulation of cardiovascular responses or androgen- and estrogen-synthesizing enzymes, might contribute to gender-specific immune responses.[2] Recent studies have indicated that sex hormones, such as dehydroepiandrosterone (DHEA), also modulate the function of peripheral blood mononuclear cells in surgical patients.[5] DHEA seems to have a protective immunologic effect in sepsis, and IL-6 might be involved in the DHEA-mediated reduction of postseptic complications.[15]

Although testosterone depletion, testosterone receptor antagonism, and estrogen treatment have been shown to prevent the depression of immune functions after traumatic hemorrhage, it remains to be established whether differences in the testosterone-estradiol ratio are responsible for immune dysfunction. Furthermore, sex hormone receptors have been identified in various immune cells, suggesting direct effects.[5,16]

Considering the effects of 17-estradiol on the expression of the pattern recognition receptor on innate immune sentinel cells, which recognize bacterial endotoxins, the withdrawal of endogenous estrogens was shown to decrease both pro- and anti-inflammatory cytokine production, with a concomitant reduction in the circulating levels of lipopolysaccharide-binding protein and cell surface expression of Toll-like receptor 4 on murine macrophages.[6]

Our data showed no significant difference in G2 subgroup mortality rates, but mortality trended to be higher in women. Angstwurm et al. showed that in elderly patients with infections, the mortality rate was not gender-dependent but was correlated with increased 17-estradiol levels in both genders, with increased levels of progesterone in males and testosterone in females. Although progesterone and testosterone may be derived from the adrenals, cortisol levels are only moderately increased and are not associated with survival. Therefore, other sex steroid production pathways must be involved. The higher death rates found in the elderly female group may indicate loss of protective estradiol actions.[17]

Rettew et al. investigated the effects of 17-estradiol on endotoxin susceptibility in mice. Exogenous replacement of 17-estradiol, but not progesterone, significantly increased lipopolysaccharide-binding protein levels and cell surface expression of Toll-like receptor 4 and CD14 on macrophages. This effect corresponded to significantly higher inflammatory cytokine levels after in vivo lipopolysaccharide challenge and a marked increase in endotoxin-associated morbidity.[6]

The data supporting clinically relevant sexually dimorphic pathophysiologic responses to sepsis in humans are less clear than those in animal models. In an interesting parallel with previously described murine models, Schröder et al. demonstrated that male patients with sepsis had higher proinflammatory TNF-α levels, while female patients with sepsis had higher anti-inflammatory IL-10 levels.[18] Patients' underlying genetics and gender interact to influence the final phenotypic response to sepsis, as has been previously shown in animal models. Common polymorphisms in the lipopolysaccharide-binding protein genotypes may be associated with an increased risk of sepsis and decreased survival in this condition in male, but not in female, patients.[19]

Our study has some limitations. It was a retrospective study, with limited access to other ICU mortality risk factors, hormonal levels were not dosed, and only one site was involved; however, our study showed human clinical evidence that could be explored by other prospective studies to clarify the role of hormonal response in sepsis. The analysis of larger samples of patients with sepsis may help to better characterize premenopausal female protective effects.

CONCLUSION

Apparently, there are gender differences in critical care. Based on the existing observational data, no definitive answer on independent gender-related clinical outcome differences was provided. In our study, female sepsis patients who were younger than 40 years old, i.e., who were in their reproductive phase, had lower mortality rates, compared to male patients. Furthermore, a trend toward lower mortality was observed for men older than 50 years old, possibly due to dimorphic gender- and age-related immune and organ

responses. Further studies are required to elucidate the pathophysiology underlying gender-related differences in sepsis outcomes, enabling the development of gender-specific treatments and interventions able to improve outcomes for all septic patients.

RESUMO

Objetivo: Análise comparativa da mortalidade em dois subgrupos de pacientes com sepse, diferenciados pela idade e sexo, admitidos na unidade de cuidados intensivos de um hospital de ensino.

Métodos: De dezembro de 2005 a abril de 2008, de um total de 628 pacientes admitidos na unidade de cuidados intensivos, 133 tinham o diagnóstico de sepse e foram separados em dois subgrupos com base na idade: subgrupo G1, com idades entre 14 – 40 anos e subgrupo G2, com idade acima de 50 anos. Os pacientes com idades entre 41 e 50 anos (n = 8) foram excluídos. Os subgrupos foram caracterizados quanto aos dados demográficos, indicadores prognósticos (escore APACHE II, disfunção orgânica e choque circulatório) e desfecho (mortalidade).

Resultados: O subgrupo G1 (n = 44) tinha 27 (61,4%) pacientes do sexo feminino e o subgrupo G2 (n = 81) tinha 40 (49,4%) pacientes do sexo feminino. A média do escore APACHE II, incidência de disfunção de múltiplos órgãos e progressão para choque circulatório não foram estatisticamente diferente entre pacientes femininos e masculinos em ambos os subgrupos. A taxa de mortalidade geral foi menor em mulheres do que em homens do subgrupo G1 (p = 0,04); no subgrupo G2 foi observada uma tendência inversa.

Conclusões: Em pacientes com sepse, mulheres abaixo dos quarenta anos de idade, portanto em período fértil, tiveram menor mortalidade do que homens; houve uma tendência para menor mortalidade entre homens com mais de 50 anos.

Descritores: Hormônios gonadais; Sepse/mortalidade; Prognóstico; Fatores sexuais; Feminino

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