

# Sex or gender differences in treatment outcomes of sepsis and septic shock

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Gender disparities in intensive care unit (ICU) treatment approaches and outcomes are evident. However, clinicians often pay little attention to the importance of biological sex and sociocultural gender in their treatment courses. Previous studies have reported that differences between sexes or genders can significantly affect the manifestation of diseases, diagnosis, clinicians' treatment decisions, scope of treatment, and treatment outcomes in the intensive care field. In addition, numerous reports have suggested that immunomodulatory effects of sex hormones and differences in gene expression from X chromosomes between genders might play a significant role in treatment outcomes of various diseases. However, results from clinical studies are conflicting. Recently, the need for customized treatment based on physical, physiological, and genetic differences between females and males and sociocultural characteristics of society have been increasingly emphasized. However, interest in and research into this field are remarkably lacking in Asian countries, including South Korea. Through this review, we hope to enhance our awareness of the importance of sex and gender in intensive care treatment and research by briefly summarizing several principal issues, mainly focusing on sex and sex hormone-based outcomes in patients admitted to the ICU with sepsis and septic shock.

**Key Words:** intensive care units; sepsis; septic shock; sex

## INTRODUCTION

Sex and gender are essential in epidemiologic data in almost all clinical research papers. However, most clinicians ignore the distinction between these two terms and often pay little attention to the clinical importance of sex and gender when they treat patients. Sex is a term that describes biological differences between sexes, reflecting sex chromosomes, sex hormones, and anatomical structures between males and females and resulting differences in physiological characteristics, while gender is a term that reflects sociocultural factors, such as differences in gender identity (man and woman, boy and girl), societal roles and status, and behavioral patterns of genders [1]. With a sociocultural base, gender reflects differences in gender-specific medical demand, accessibility to medical services, and service provision methods [2].

Previous studies have reported that biological and sociocultural differences between males and females can significantly affect the diagnosis of diseases, clinicians' decisions about treat-

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ment, scope of treatment, and the incidence and manifestations of disease [3,4]. In the intensive care field, it has been reported that the complex interaction between sex and gender has a significant impact on disease manifestations, treatment responses, and patient outcomes [3]. While most studies on sex or gender differences in disease presentation and treatment behaviors in intensive care units (ICUs) have been conducted in western countries, studies conducted in Asian countries with a Confucian culture, such as South Korea, are scarce. However, as the demand for customized treatment based on individual characteristics increases, researchers and clinicians are paying more attention to sex and gender as essential variables. Reflecting this, in 2016, the United States National Institutes of Health (US NIH) recommended that sex be included as an essential biological variable in all animal or cell research [5,6]. The Canadian Institutes of Health Research also published guidelines emphasizing the importance of sex and gender in biomedical research [1].

Male sex is a well-known possible risk factor for sepsis and septic shock. Sepsis is more prevalent in men than in women, showing an annual relative risk of 1.3 times that of women [7]. In addition, among septic shock patients admitted to ICUs, males were more prevalent than females. Men also showed longer length of ICU stay, longer duration of hospitalization, higher ICU mortality, higher likelihood of readmission within 90 days and 1 year, and more frequent death at 1 year after the event of sepsis [8,9]. Although the possible mechanism explaining sex difference in manifestation of sepsis remains unclear, beneficial roles of many genes and their products expressed from a silent X chromosome in women and sex hormones such as estrogen in the regulation of immune responses in sepsis have been suggested [10,11].

Through this review, we hope to enhance awareness of the importance of sex and gender in intensive care treatment and research by briefly summarizing principal issues, mainly focusing on sex and sex hormone-based differences in treatment outcomes of patients admitted to the ICU with sepsis and septic shock.

## THE ROLE OF ESTROGEN IN REGULATING INFLAMMATORY RESPONSE

Estrogen is a sex hormone that regulates the development and function of the female reproductive system. Before menopause, estrogen is mainly synthesized in the ovaries. After menopause, it is produced in adipose tissues (breasts), brain, kidneys, liver, and bones [12]. In men, estrogen is produced primarily in

### KEY MESSAGES

- As the demand for customized treatment based on individual characteristics increases, researchers and clinicians should increase their awareness of the critical role of biological sex and sociocultural gender.
- Although the possible mechanism explaining sex-different manifestations and outcomes of sepsis remains unclear, the beneficial roles of gene expression from a silent X chromosome and sex hormones in regulating immune responses in sepsis have been suggested.
- Future research targeting intensive care unit care must reflect characteristics of biological sex and sociocultural gender based on sociocultural background.

the testes. The proportion of estrogen produced in secondary tissues is relatively higher in men than in women [13]. Among four types of estrogens (estrone, estradiol, estriol, and etestrol), estradiol is the most potent. It can bind to estrogen receptors in the nucleus, plasma membrane, and endoplasmic reticulum and exert its functions through genomic and non-genomic mechanisms [14,15]. There are currently three known estrogen receptors: estrogen receptor alpha (ER $\alpha$ ), estrogen receptor beta (ER $\beta$ ), and guanine nucleotide-binding protein-coupled estrogen receptor 1 (CPR1/CPR30) [16]. Estradiol participates in the regulation of proinflammatory signaling/pathways in the immune system. It acts mainly as an anti-inflammatory agent through ER $\alpha$  and CPR1 [17,18] and has various anti-inflammatory and proinflammatory functions through ER $\beta$  [19,20]. Diverse effects of estrogen on inflammation are believed to be due to various expression levels of estrogen receptor based on cell type and physiological state [21].

## DIFFERENT EFFECTS OF SEX HORMONES ON THE OUTCOMES OF SEPSIS IN ANIMAL STUDIES

### Protective Effects of Estrogen Against Sepsis

Evidence supporting the protective effects of estrogen has been accumulating for several decades. Most of these data are associated with dampening the hyperinflammatory state of sepsis by reducing expression levels of circulating proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$  [21].

Experiments using proestrus female mice in a cecal ligation sepsis model demonstrated that immune functions of preserved splenocytes are associated with better survival [22].

Addition of 17 $\beta$ -estradiol to splenocytes from ovariectomized female mice normalized immune functional capacities in a trauma-hemorrhage model [23]. Another study performed with a mouse model of hemorrhage and subsequent sepsis showed a greater increase in plasma proinflammatory cytokines including IL-6, TNF- $\alpha$ , and prostaglandin E2 in male mice than proestrus female mice. They also showed a survival advantage of female sex hormones against subsequent septic challenge [24]. In addition, less pronounced cardiac dysfunction was seen in female mice than in male mice in a cecal ligation and puncture (CLP) sepsis model [25]. In that study, female mice showed decreased production of TNF- $\alpha$ , IL-6, and inducible nitric oxide synthase. Cardioprotective effects were shown in ovariectomized female mice after administration of landiolol in a CLP sepsis model. Such effects were assumed to be due to overexpression of genes involved in calcium influx. In contrast, inactivation of the  $\beta$ -adrenergic and a calcium efflux pathway was seen in control females [25]. The protective effect of estrogen against liver damage in sepsis has also been observed in a lipopolysaccharide (LPS)-induced sepsis model. Female septic mice showed liver damage with increased serum aspartate aminotransferase and alanine aminotransferase levels as well as extensive necrosis, and both were more severe in male septic mice. In addition, ovariectomy-aggravated sepsis-induced liver damage and activation of the pyroptosis signaling pathway could be alleviated by estrogen [26].

### Suppressive Effects of Testosterone on the Immune System in Sepsis

Sex-dependent differences in the incidence and severity of sepsis make males more susceptible to septic shock than females. Testosterone is a primary male sex hormone and has also been implicated in sex-dependent differences in sepsis. Testosterone has significant immunosuppressive effects on innate and adaptive immunity by reducing immunoglobulin, cytokine production, and lymphocyte proliferation [27,28]. LPS-induced TNF- $\alpha$  secretion in plasma was significantly enhanced in rats receiving neonatal androgen blockade with flutamide and in prepubertal orchietomies rats, suggesting testosterone's immunosuppressive role in inflammation [29]. Another study showed that orchietomized mice were significantly more susceptible to endotoxic shock, and that macrophages isolated from them had significantly higher toll-like receptor-4 cell surface expression than those derived from sham gonadectomized mice. However, these effects were dampened in orchietomized mice receiving exogenous testosterone [30]. Although the details of the under-

lying molecular mechanisms remain unclear, effects of androgen receptor blockade are thought to be partly attributable to the upregulation of estrogen receptors or enhanced estrogen receptor-related pathways [31-33].

## SEX DIFFERENCE IN MANIFESTATIONS AND OUTCOMES OF SEPSIS IN HUMAN STUDIES

### Epidemiologic Differences Based on Sex

A higher prevalence of sepsis in men than in women has been reported in various nationwide or individual hospital-based epidemiologic studies [34]. A longitudinal, population-based epidemiological study of sepsis from 2005 to 2012 using the Korean National Health Insurance Service-National Sample Cohort—a population-based cohort representing 2.2% of the Korean population—reported that 53.5% to 58.0% of a total of 22,882 sepsis cases were males. It also found that female sex was an independent favorable risk factor for 6-month mortality in multivariate logistic regression analysis, showing an odds ratio (OR) of 0.7 (95% confidence interval [CI], 0.66–0.76;  $P < 0.001$ ) [35]. Potential mechanisms explaining the higher prevalence of sepsis in men are unclear. However, the combination of biological sex differences, such as the immune system, sex hormones, gene expression from a silent X-chromosome, anatomical differences, and pharmacokinetics and dynamics for drugs [10,11,36,37], and sociocultural gender differences in disease perception, risk behavior, accessibility to and use of healthcare resources, and service provision methods are thought to play a critical role in sex disparities in sepsis [38-40].

### Sex Preference in the Source of Bacterial Infections

Sexual differences in bacterial infections have been reported in human and animal models. Diverse manifestations and outcomes of infections based on sex are intricately linked to genetic, biological, and behavioral differences, which are associated with gender preferences of specific bacterial infections, sex hormones, and immune responses by sex [41,42]. In general, men are more susceptible to gastrointestinal and respiratory bacterial diseases and sepsis, while women are more susceptible to genitourinary tract infections [43]. Recent studies have reported that tissue-specific expression of sex hormone receptors contributes to the sexual disparity in bacterial infections [43]. According to a prospective observational study on community-acquired severe sepsis and septic shock conducted in 12 university hospitals in South Korea, among a total of 1,192 patients, gastrointestinal (26.8% vs. 20.9%), respiratory (39.2%

vs. 19.2%), and skin and soft tissue (11.0% vs. 4.7%) infections as a source of primary infection were higher in men (men vs. women), while urinary tract infection (11.4% vs. 44.8%) was more prevalent in women ( $P < 0.05$  for each) [44].

### Sex Differences in Outcomes of Sepsis and Septic Shock

Numerous individual and nationwide studies have evaluated the relationship between sex and mortality from sepsis and septic shock. However, evidence showing an association of sepsis mortality with specific sex is conflicting. Although preclinical studies have suggested potential protective effects of estrogen on sepsis, some studies have shown higher mortality rates in women with sepsis [45-48]. In comparison, others have shown higher mortality rates in men with sepsis [49-51]. Furthermore, some studies have reported no difference in mortality rate from sepsis and septic shock between sexes [52-54]. According to a recently published meta-analysis including 13 studies with 80,520 participants, there were no sex-based differences in all-cause hospital mortality (OR, 1.02; 95% CI, 0.79-1.32; very low-certainty evidence) or all-cause ICU mortality (OR, 1.19; 95% CI, 0.79-1.78; very low-certainty evidence). Interestingly, however, females presented higher 28-day all-cause mortality (OR, 1.18; 95% CI, 1.05-1.32; very low-certainty evidence) and lower 1-year all-cause mortality (OR, 0.83; 95% CI, 0.68-0.98; low-certainty evidence) [55]. An epidemiologic study for severe community-acquired sepsis and septic shock conducted in South Korea reported that 28-day mortality (27.0% vs. 18.1%), in-hospital mortality (32.9% vs. 22.0%), and sepsis-related mortality (28.3% vs. 18.1%) were lower in females ( $P < 0.001$  for each) [44]. Several explanations have been suggested for these disparate findings in clinical studies of sex differences in sepsis and septic shock. The most critical issues were heterogeneous study designs (prospective vs. retrospective, single vs. multi-center or nationwide database), different definitions of sepsis, different baseline health statuses, comorbidities, severity of sepsis, age, and sociocultural differences affecting treatment attitudes for men and women [56]. Among these, age is a critical factor to consider when assessing the protective effects of estrogen against sepsis. Level of estradiol, the most potent estrogen, is highest in women between prepuberty and menopause. In contrast, the prevalence of sepsis and septic shock is significantly higher in patients over 60 years of age. Multiple comorbidities are also more common in these patients. Thus, when evaluating effects of sex factors on outcomes of sepsis, age stratification and control of confounding factors such as comorbidities should be considered [56]. In a study conducted

on 143 polytraumatized patients with injury severity score  $> 16$  and between 16 and 65 years old, the prevalence of multiorgan dysfunction syndrome and sepsis was significantly lower in females younger than 50 years with an injury severity score  $> 25$  than in age-matched males [57]. However, when focusing on clinical studies specifically examining sex hormones in connection to sepsis patients, results are again conflicting. Higher circulating estradiol levels were associated with higher mortality rates in both male and female patients, and elevated serum estradiol levels were associated with the severity of renal dysfunction and the development of acute kidney injury [58-60]. In addition, while levels of proinflammatory cytokines such as TNF- $\alpha$  and IL-6 were increased in male patients, anti-inflammatory cytokine IL-10, which was defined as a predictor for the severity of sepsis, was higher in female patients [28,61,62]. Thus, differences in study conclusions might be attributed to differences in sex steroid levels among patients rather than a difference in the type of sex hormones alone.

### GENDER DISPARITIES IN MEDICAL TREATMENT IN THE ICU

Many studies have reported that treatment opportunities in the ICU differ depending on gender. Most studies have pointed out that women have a lower tendency to receive advanced life-supporting measures, including early goal-directed treatment for sepsis, mechanical ventilatory support, renal replacement therapy, and other invasive procedures [63,64]. Pharmacokinetic and pharmacodynamic differences between male and female patients have also recently attracted attention from clinicians. Adverse events from medications used in the ICU were more prevalent in female patients.

Possible explanations include sex-associated anatomic and physiologic factors, such as lower body weight, higher proportion of fat compared with muscle, and lower plasma volume, which can easily lead to an over-concentration of medicine and toxicity in females [38]. However, considering different physical traits between western and Asian women and the differences in sociocultural attitudes toward female gender between western and Asian countries, gender differences in ICU treatment should be individually evaluated and interpreted based on each country's sociocultural background.

### CONCLUSIONS

Many studies have reported that sex or gender differences

can affect the perception and manifestation of the disease, treatment decision, response to treatment, and outcomes in patients admitted to the ICU. Among them, the immunomodulating effects of sex hormones and differences in sex-specific gene expression potentially play an important role in treatment outcomes of sepsis and organ dysfunction in animal studies. However, results in human studies are conflicting. In clinical research, sex or gender differences in outcomes of sepsis patients are further confused by the differences in diagnosis and treatment provision depending on sociocultural background. Even if the need for customized treatment based on an individual's characteristics has been increasingly emphasized based on physical, physiological, and genetic differences between women and men at a time when sociocultural considerations are necessary, interest and research in this field are remarkably lacking in Asian countries, including South Korea. Therefore, future research targeting septic patients in the ICU is needed to reflect characteristics of biological sex and sociocultural gender based on sociocultural background.

## CONFLICT OF INTEREST

Dohhyung Kim is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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