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COMMENT

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Sex matters: Is it time for a SOFA makeover?

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While sepsis affects individuals regardless of sex, emerging research has highlighted notable differences in how women and men experience, respond to, and recover from sepsis treated in intensive care units (ICU). These differences are influenced by a complex interplay of biological, hormonal, and sociocultural factors. As we explore sepsis management in ICU settings, it becomes evident that understanding the factors contributing to these sex-based variations is important for tailoring therapeutic approaches and improving overall patient outcomes. Moreover, for a nuanced interpretation of current evidence, it is worth noting the distinction between the terms gender and sex: gender refers to the socially constructed roles and behaviors that a given society considers appropriate, while sex pertains to biological characteristics.

The ICU sepsis patient population comprises individuals of all ages and with diverse comorbidities and clinical conditions, leading to acute organ failure. Efforts have been made to identify distinct phenotypes and establish correlations with host-response patterns and clinical outcomes [1]. As clinicians, it is increasingly clear that personalized treatment and prognostication strategies are essential for optimizing patient care, but somewhat limited by our current diagnostic and therapeutic tools. While patient sex is often a readily available characteristic, the extent to which we incorporate it as a variable into our comprehensive clinical assessments for critically ill sepsis patients could warrant further consideration and refinement. Are we taking it into account as thoroughly as we should? In their recent publication in this journal, Zimmermann and colleagues conducted a retrospective study on sex differences in the sequential organ failure assessment (SOFA) score among ICU patients with sepsis or septic shock, analyzing data from 85 ICUs across Switzerland [2]. They concluded that significant variations exist, although the full clinical implications remain to be elucidated. Notably, they found no disparity in ICU mortality rates between male and female patients. The authors suggested that reevaluation of sex-specific thresholds for SOFA score components could potentially refine future individualized classifications, addressing a current oversight in the consideration of patient sex within the SOFA scoring system.

Aligned with these findings, emerging insights into sepsis pathophysiology indicate that sex-based differences in host responses to pathogens may play an important role [3]. Animal models suggest that females exhibit lower susceptibility to sepsis and tend to recover more effectively than males. Distinct host responses to pathogens between females and males could be partly attributed to the sex-specific polarization of intracellular pathways responding to pathogen–cell receptor interactions [4]. Sex hormones are believed to play a role in these disparities and have been shown to target most immune cells, yet the full range of contributing factors remains a subject of ongoing investigation. Further exploration is warranted to fully understand how various factors beyond sex hormones influence the observed differences in immune reactions [3].

Current evidence does not allow for definitive conclusions regarding the association between patient sex and sepsis-related mortality. In recent years, the sepsis literature has reported more favorable outcomes for women,

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less favorable outcomes, or no differences between women and men [5]. Differences in mortality, favoring either women or men, have also been observed for other ICU diagnoses [6, 7]. Establishing substantive evidence linking sex differences in clinical outcomes from animal models has proven challenging. Moreover, beyond therapeutic efforts in the ICU, other factors important for disease severity and recovery can differ between women and men. For example, health-seeking behaviors, such as the timing of seeking medical care, can influence outcomes by affecting the severity of sepsis upon ICU admission. Additionally, the roles of caregiving and social support structures are crucial factors influencing recovery trajectories and psychological outcomes following an ICU stay. These multifaceted elements collectively shape the overall impact of sepsis and underscore the need for further research, while also highlighting the complexity of understanding and addressing sex-related disparities.

Since its introduction, the SOFA score has been crucial in intensive care settings and sepsis management by quantifying the severity of organ dysfunction [8]. In their publication, Zimmerman and colleagues reported sex-specific differences in SOFA, particularly in the laboratory-based components [2]. However, the data must be interpreted with some caution considering potential bias. For example, creatinine levels inherently vary between women and men, and including additional variables such as patient weight could enhance interpretations of the analyses. Nevertheless, their findings raise a difficult question: could potential discrepancies in scoring of organ dysfunction hamper clinical decision-making regarding the appropriate level of care?

There is an underlying assumption in society and healthcare that critically ill patients are admitted to an ICU based primarily on illness severity and comorbidities, with other variables considered less relevant. It is therefore troublesome that we do not fully understand the sex discrepancy in the ICU population, where the distribution is consistently found to be around 40% women and 60% men [9, 10]. Current evidence is weak to guide whether we are, in fact, treating the adequate proportions of women and men. Given women's longer life expectancy compared to men, yet often similar outcomes post-intensive care for sepsis, it prompts a reassessment of whether we are treating the appropriate proportions, also suggested by other authors [11, 12]. Should we consider admitting more, or fewer, women? Admittance patterns are inherently challenging to address in a scientific setting. Effort have been made in survey format to explore potential bias in admitting female versus male patients, but no detectable differences were found [13]. The results are obviously hindered by lack of sensitivity and a high risk of volunteer bias. Another interesting area for future research involves how age should be accounted for when addressing outcomes after intensive care, especially among older patients. Patient sex may influence age-associated outcomes, as has been discussed, for example, in the context of sepsis patients [14]. Considering sex-based differences in life expectancy, should equal mortality rates post-intensive care in older patients be interpreted as truly "equal", given women's longer life expectancy?

In conclusion, the complexities of sex-based differences in critically ill sepsis patients underscore the need for continued research to better understand these disparities, refine clinical scoring and prognostication, and optimize care for both women and men in the ICU.

Abbreviations

ICU	Intensive care unit
SOFA	Sequential organ failure assessment

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