CRITICAL CARE

COMMENTARY

Does gender influence outcomes in critically ill patients?

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See related research by Mahmood *et al.*, http://ccforum.com/content/16/3/R92

Abstract

Investigators continue to debate whether gender plays any role in patient outcome following injury/critical illness. We submit that age and hormonal milieu at the time of injury, rather than gender, are the critical factors influencing patient outcome under those conditions.

Mahmood and colleagues [1] performed a retrospective analysis, published in this issue of *Critical Care*, of 261,255 adult patients admitted to intensive care units (ICUs). The results indicate that women younger than 50 years old had lower ICU mortality in comparison with age-matched men, whereas mortality rate was similar in older patients. Female mortality, compared with male mortality, was increased following coronary artery bypass graft (CABG) surgery but decreased with chronic obstructive pulmonary disease (COPD) exacerbation. Gender-specific mortality rates were not evident for patients with acute coronary syndrome, sepsis, or trauma.

Numerous experimental studies report gender-specific immune and cardiovascular responses [2-4]. Male gender was associated with suppressed immune responses and impaired cardiovascular function as opposed to maintained responses in proestrus females in experimental models of trauma-hemorrhage or sepsis (cecal ligation and puncture). In diestrus mice, immunoprotection was not evident. Proestrus mice are characterized by elevated estrogen plasma levels in comparison with mice in other phases of the estrus cycle. Gender-specific immune responses were reversed in aged mice [2-4].

In contrast, the referenced study [1] did not demonstrate gender-specific outcome in septic and trauma patients in any age group. Similarly, other clinical studies failed to consistently reproduce experimental findings [5]; a large cohort of 22,332 patients with blunt injury did not demonstrate gender-specific outcome [6]. A retrospective analysis of blunt and penetrating trauma at the University of Alabama (Birmingham, AL, USA), however, showed a significantly increased mortality rate in males younger than 50 years of age [7]. Those results are supported by Deitch and colleagues [8], who conducted a prospective cohort analysis (n = more than 4,000 trauma patients) that showed that, despite higher Injury Severity Scores (ISSs), females younger than 50 years tolerated trauma better than males did. Higher proinflammatory cytokine levels appear to be responsible for diminished outcome in male victims of trauma [9]. In burn patients, however, young females had an increased mortality rate [10,11], suggesting that different trauma mechanisms (blunt versus burn trauma) alter gender-specific outcome.

In experimental studies, sex hormones have been shown to affect gender-specific immune responses. Male sex hormones are deleterious whereas female hormones are protective [2-4,12]. Hormonal status is not evaluated in most clinical studies. To define pre- versus postmenopausal by using a cutoff age of 50 years is inaccurate. Furthermore, the percentage of postmenopausal females on hormone replacement therapy is not defined. According to Hersh and colleagues [13], an estimated 21% of US women take hormone replacement medication. This should be taken into consideration when analyzing gender-specific outcomes in critically ill patients. Failure to measure hormone plasma levels significantly limits most clinical studies investigating gender differences. In summary, the prevailing hormonal milieu, and not gender, dictates immune and cardiovascular depression or maintenance following injury.

Different immune responses to various disease entities have been shown in experimental and clinical studies. Trauma and sepsis severity is known to affect pathophysiological mechanisms [2-4,12]. In the present study, diseases were categorized into five groups (acute

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coronary syndrome, CABG surgery, sepsis, trauma, and COPD exacerbation). Within those categories severity was based on APACHE (Acute Physiology and Chronic Health Evaluation) score. Specific scoring systems (that is, ISS for trauma) were not mentioned, possibly limiting the conclusiveness of the data.

In clinical conditions (in contrast to experimental conditions), genetic background and comorbidities vary between critically ill patients, certainly affecting outcome. In the present study, chronic health conditions (that is, AIDS, cirrhosis, hepatic failure, lymphoma and leukemia, and tumors with metastases) were registered. Potentially relevant comorbidities (for example, diabetes) were not included.

Long-term medication as well as ICU medication (that is, heparin, cyclooxgenase inhibitors, steroids, and immunosuppressants) may alter immune responses and should be considered potential confounders. In this study, however, only immunosuppressants were registered.

Most studies investigating gender-specific outcome and mortality are retrospective, involving data from large registries. Despite enrolling huge numbers of patients, those studies are subject to limitations and constraints. There is no control over comprehensiveness or detail of data recorded, and information important for gender analysis (that is, hormone plasma levels, state of the estrus cycle, and pre- versus postmenopausal status) is not documented. To enhance data relevance, consideration of those potential confounders would require prospective registration of gender-specific parameters.

Because clinical studies suggest that females require less ICU treatment in comparison with males [14], incorporating ICU patients may reflect a selection bias of females with reduced prognosis in comparison with the overall female population. It is also important to consider age and hormonal status when investigating outcome in critically ill patients. Specifically designed prospective studies are required to better define the exact role of gender and sex hormones in the clinical arena. Female gender itself cannot be considered a protective factor in critically ill patients. Continued research into potential sex hormone-based differences may close the gap between bench and bedside and ultimately promote therapeutic interventions to improve outcomes in males and females. In this respect, individualized estrogen treatment should be based on actual hormonal status immediately after injury.

Abbreviations

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ISS, Injury Severity Score.

Competing interests

The authors declare that they have no competing interests.

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