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Gender disparities in the Intensive Care Unit

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Summary. Several studies have explored the existence of a potential gender preference in access to intensive care units (ICUs). Patients with more severe illness should have a greater chance of being hospitalized in ICUs regardless of gender. If there is a gender difference in the severity of illness on admission to ICUs, horizontal inequity arises. Conversely, if the patients of one gender show greater severity on admission and greater mortality at discharge, it might be concluded that the greatest needs have not been met (vertical inequity). The gender disparities of patients admitted to ICU may be due to the fact that some diseases can affect both sexes with different frequency or may assume a different expression of severity: sepsis and septic shock are more common in men, while subarachnoid haemorrhage has a prevalence among women. Sex hormones may influence the immune response following sepsis and great importance has been ascribed to the protective effect of female sex hormones, in particular oestrogens that appear to have a neuro-protective action in acute injury. Findings suggest an increased frequency of admission to ICU for males. Although there are no differences in outcome, there is a strong suspicion that older women receive aggressive therapies to a lesser extent. To improve the treatment of specific diseases such as sepsis and neurological emergencies, it is necessary to explore the pathophysiological hypotheses that lead to gender and sex disparities eliminating the confounding factors (comorbidities and risk factors) and exploring the existence of gender bias in healthcare workers.

Key words: vertical inequity, horizontal inequity, gender differences, gender bias, sex differences.

Disparità di genere in terapia intensiva

Riassunto. Diversi studi hanno esplorato l'esistenza di una potenziale preferenza di genere nell'accesso alla terapia intensiva (TI). I pazienti più gravi dovrebbero avere una maggiore probabilità di essere ricoverati in TI indipendentemente dal sesso. Se c'è una differenza di genere nella gravità della malattia al ricovero, si realizza una iniquità orizzontale. Al contrario se i pazienti di un sesso mostrano una maggiore gravità al ricovero e una maggiore mortalità alla dimissione si potrebbe ritenere che i maggiori bisogni non siano stati soddisfatti (iniquità verticale). La disparità di genere dei pazienti ricoverati in TI deve tener conto del fatto che alcune patologie possono colpire entrambi i sessi con una frequenza differente o possono assumere una diversa espressione di gravità: la sepsi e lo shock settico sono più comuni negli uomini, mentre l'emorragia subaracnoidea ha una prevalenza femminile. Una potenziale spiegazione delle differenze sessuali osservate nella sepsi è che gli ormoni sessuali femminili possano influenzare la risposa immunitaria che segue la sepsi e che questa risposta sia geneticamente influenzata. Grande importanza è stata data all'effetto degli ormoni sessuali femminili, in particolare agli estrogeni che sembrano agire come agente neuro protettivo del danno cellulare e della distruzione della barriera emato-encefalica. Le evidenze disponibili mostrano una maggiore frequenza di ricovero in TI per il sesso maschile. Anche se non ci sono differenze sull'outcome, c'è però il forte sospetto che siano le donne più anziane a ricevere terapie aggressive in misura inferiore. Per migliorare il trattamento di patologie specifiche come la sepsi e le emergenze neurologiche è necessario esplorare le ipotesi fisiopatologiche che portano alle disparità di genere e di sesso nella manifestazione della malattia, eliminando i fattori confondenti (comorbidità e fattori di rischio) ed esplorando l'esistenza d pregiudizi di genere negli operatori.

Parole chiave: disuguaglianza orizzontale, disuguaglianza verticale, differenze di genere, pregiudizio di genere, differenze sessuali.

Introduction

Intensive care units (ICUs) are involved in the care of patients with acute diseases and medical conditions that put them at risk for survival. It is therefore assumed that ICU admission is a response to the clinical needs of a patient, while the socio-demographic characteristics are not able to influence access to the ICU.

However, in recent years several studies have explored the potential existence of a gender preference in the use of healthcare resources[1-3].

The influence of sex on the incidence and outcome of critically ill patients has been proven among patients with cardiovascular disease. Some authors have reported that women are less likely to be evaluated and to receive invasive treatment for cardiovascular disease and have a higher rate of early mortality after acute myocardial infarction[4-11]. However, beyond the studies done on cardiac patients, little is known about gender disparities in the ICU.

Equity on admission to the ICU

The analysis of the differences in the case mix (age, severity, diagnosis) between males and females on admission to the ICU helps to understand if patients with the same severity receive the same level of care (equal use for equal needs) that is to say if there is "horizontal equity"[1].

When on admission for a given disease, individuals of the same sex have greater severity, we can assume the existence of horizontal inequity, because there is a higher clinical threshold for the hospitalization of individuals of that sex.

This inequity could be due to the tendency of clinicians to attribute a gender preference for certain diseases. For example, clinicians used to think that myocardial infarction affects men more and have the tendency to admit male patients with indices of severity lower than women. Similarly, since subarachnoid haemorrhage is thought to affect women more, female patients may be hospitalized with indices of severity lower than men.

There is "vertical equity" when the sickest patients receive more assistance (unequal use for unequal needs)[1]. When individuals of the same sex show a worse outcome than the other sex, we believe that the greatest needs were not met (vertical inequity). If there is a gender difference in the severity of illness on admission (horizontal inequity), vertical equity could be restored if mortality at discharge is the same.

Some studies have focused on gender differences in access to ICUs more than on the difference in diagnosis between sexes. In a large cohort of critically ill patients conducted in 31 ICUs in Austria, 58.3% of patients admitted were male and 41.7% female[12].

Other large-scale studies conducted with more than 10,000 critical patients have confirmed this prevalence in the admission to in ICUs[13-15].

This result is more surprising when you consider that in most Western countries the female population reaches 51% of the population.

In the study by Valentin et al.[12] male patients, though presenting with lower severity, received a higher level of care based on the number of applied invasive procedures. This different therapeutic approach in men did not translate into a better outcome. The authors rule out that this difference was due to the higher age (66.0 ± 17.4) of women than men (59.3 ± 16.8), because the increased likelihood of receiving procedures was found even in younger men. No gender-related difference in the severity of illness was found in this study, and the lower level of intensity of care in women was ascribed to a potential gender bias in healthcare workers.

These results agree with data presented by Asch et al.[16] on American Quality of Care. The authors revealed that women are more likely to receive treatment for chronic diseases, but less likely to receive recommended treatments for acute diseases.

Fowler et al.[13] also analysed the admission to ICUs of 24,778 patients (60.1% male, 39.9% female) and reported that women were less likely to be hospitalized in ICU and, if admitted, received less invasive procedures. In addition, in spite of similar age and severity of illness, women exhibited a higher mortality than men and were hospitalized mainly as a result of medical conditions while men for surgical disease.

Dodek et al.[14] found the same results showed by Valentin et al.[12] in the sex difference on admission to ICU (58.3% men vs 41.7% women). However, no gender difference in ICU and hospital mortality was found. The authors believe that the highest percentage of male admissions to ICU was related to clearer symptoms in men compared to women. In addition, they suggested the presence of gender bias on admission to ICU among healthcare workers.

According to the Fowler's results, Romo et al.[15] published the results of a study of 4,420 patients conducted in a single ICU (64.1% male vs. 35.9% female). Women showed a higher mortality rate than men. After age stratification a significantly higher mortality was reported in women older than 50 years, but not in younger. However, in this study the sex difference in the severity of disease on admission to the ICU was not reported.

Reinikainen et al.[17] investigated the impact of gender in Finnish ICUs. Once again, male patients were admitted more than female (61.7% vs 38.3%). An increased risk of hospital mortality was found for male patients in surgical ICUs but not in medical ICUs. Male patients were treated longer than female patients and approximately two-thirds of ICU resources were consumed by male patients. The authors suggested that female advantages may be due to sex hormones that have a protective role in immunomodulation, myocardial function and response to trauma.

In a study conducted in a single ICU, nevertheless, more male patients than female patients were admitted (64% vs 36%) with a lower mean age (57 ± 19 vs 62 ± 18). Vezzani et al.[18] did not identify differences in the severity of illness on admission to the ICU evaluated with SAPS II (Simplified Acute Physiology Score)[19]. Despite this inequity on admission, no gender difference was recognized on ICU and hospital outcome.

Gomez et al.[20] evaluated gender differences on admission to trauma centres: female patients were less likely to be transferred to a regional trauma centre. The authors suggested a conscious or unconscious gender bias among operators. This different perception of benefit to women than men, regardless of whether the lesions were equivalent, could lead medical personnel to categorize women as less urgent or to deliver a treatment that does not include the transfer to a trauma centre.

Gender disparities in critical illness

ICUs may have different configurations: exclusively medical, surgical or mixed. Surgical ICU may be general postoperative or specialized in neurosurgery, cardiac surgery and trauma. This leads to make decisions on admission to ICU that are not related to patient sex and age, but depends on the specific configuration of the ICU.

The gender difference of patients admitted to ICU may be due to the fact that some diseases can affect both sexes with a different frequency or may assume a different expression of severity: sepsis and septic shock are more common in men, while subarachnoid haemorrhage (SAH) has a female prevalence. This makes it more difficult to evaluate if there is a real gender disparity in critical care medicine.

A large observational study investigated the association of gender to outcome, coronary angiography and adverse events in comatose, out-of-hospital cardiac arrest treated with mild induced hypothermia: male gender was associated with improved survival but not with neurological outcome[21].

A recent meta-analysis[22] assessed the influence of sex on outcomes among trauma patients, including injury severity, medical resource utilisation, complications, and mortality. This study strongly supports the protective effect of female sex on outcomes of trauma patients, including mortality, hospital length of stay and fatal complications.

Many observational and experimental studies investigated the effects of gender and sex hormones on incidence, response to treatment and outcome of sepsis in critically ill patients with conflicting results. In a review, Fowler et al. suggested the potential mechanisms leading to sexual differences related to ICU admission, treatment and outcome of critical illness[23].

Men are more likely to develop sepsis[24] than women and male gender was identified as an independent risk factor for surgical infection[25]. In surgical sepsis a better outcome was observed in female patients aged up to 30 years[26-27]. Mahmood K. et al. showed women less than 50 years of age to have a lower ICU mortality compared to men, while women aged 50 years or over did not show a significant difference compared to men[28].

In a large cohort of patients, higher mortality was identified in men >50 years of age compared to same-age postmenopausal women[29].

Women appear to be at increased risk for death from hospital-acquired pneumonia, including after controlling for other comorbidities in a study conducted in surgical units[30].

Similarly, another observational study reported that older female patients with postoperative abdominal sepsis were more likely to die than male patients of the same age[31].

In the prospective multicenter study EPISEPSIS[32], hospital mortality was similar in both sexes while in the SOAP study (Sepsis Occurrence in Acutely Ill Patients)[33] female gender was found to be an independent risk factor for mortality in ICU after the elimination of some confounding factors.

These observational studies do not allow drawing final conclusions, albeit they point to potential gender disparities in critically ill patients with sepsis. However, it is yet to be determined whether there are differences in diagnosis, comorbidities, response to illness or decisions taken for certain types of acute diseases.

A potential explanation of sex differences observed in sepsis is that female sex hormones may influence the immune response following sepsis and that this response is genetically influenced[13,34,35]. In addition, studies of sepsis have revealed a close genetic influence on the expression of inflammatory mediators and the genetics of an individual has been demonstrated to be the major determinant of death after infectious disease[36].

Gender differences in neurological emergency

Cerebral ischemic and haemorrhagic events are a leading cause of lethal and disabling conditions and patients with stroke are frequently admitted to ICU. Only in recent years, the impact of gender on epidemiology, pathophysiology, incidence and outcome of cerebrovascular disease has been explored, but much remains to be done to understand the real differences found in both sexes.

Ischemic stroke

Men have a higher incidence of stroke until 45 years, but with the onset of menopause and the fall in levels of oestrogen, incidence begins to rise in women, becoming similar in both sexes after age 55[37]. Women over 85 years have more stroke events than men. Mortality does not show significant differences in the two sexes, and higher mortality in older women results from their disproportionate representation in the population[38].

Many studies report that women have worse quality of life after stroke. As a result, women remain dependent in their activities of daily living[39-41]. This may be due to the older age of women at the time of stroke, to higher rate of depression, and also to greater limitation in muscle function that affects physical recovery[41].

Great importance has been ascribed to the protective effect of female sex hormones, in particular to oestrogen that appears to have a neuro-protective action in acute injury. This hypothesis comes from animal studies that have confirmed the anti-inflammatory role of oestrogens[38,42-44]. In contrast to the protective effects of

oestradiol seen in animal studies, two studies found no benefit of hormone replacement therapy[45,46].

Some observational studies showed the presence of gender disparity in treatment[47]. Women have a lower likelihood of receiving treatment with rt-PA although they show greater benefit when undergoing treatment[48]. These disparities may be due to a higher frequency of non-traditional symptoms, older age and the presence of major comorbidities in women[49].

More women live alone than men and have an unwitnessed stroke. The delay reported in the hospitalization of women with stroke may contribute to gender differences in the outcome with a longer hospital stay for women[38].

Haemorrhagic stroke

Gender differences in haemorrhagic stroke have been little investigated and the results of currently available studies are conflicting. The incidence appears to be affected by the interaction between sex and other factors such as age, hypertension and alcohol abuse. Women are less likely to be hospitalized in ICU, more likely to have poorer functional outcome and a higher risk of death during the first 7 days of hospitalization[47,50-52].

Stroke and pregnancy

Although the overall incidence of stroke is extremely low, pregnancy and postpartum have a wide variety of risk factors for both ischemic and haemorrhagic stroke. Gestational diabetes, gestational hypertension or eclampsia, autoimmune diseases, hypercoagulable states and vasculitis are risk factors that can produce particularly severe clinical conditions and put the mother at risk of death and/or serious disability and may require the transfer of the mother in ICU[47].

Subarachnoid haemorrhage

Subarachnoid hemorrhage (SAH) accounts for approximately 5% of all cases of stroke, but the consequences may be disastrous with a high mortality rate, ranging from 30% to 60%, or severe disability. The incidence is higher for women, showing a female-to-male ratio ranging from 1.2:1 to 3.1:1 times, increasing with age. The reasons for the overall higher incidence in women are not clear[53]. The incidence of SAH in women increases with age and reaches the peak in the fifth and sixth decade when, due to menopause, oestrogen levels decline[54].

There are no conclusive studies on sex differences in mortality. Even if female sex has been associated with a worse outcome, studies on quality of life after SAH are conflicting[55,56].

In the most severe forms of neurological injury cardiomyopathy with left ventricular dysfunction, increased levels of troponin, cardiac failure and pulmonary oedema have been described. This type of cardiomyopathy is a variety of Takotsubo more frequently described in menopausal women suggesting the existence of sexual differences in complications and outcome in patients with SAH[57,58].

In patients treated earlier a higher likelihood of having minimal or no disability at discharge has been observed. Women show a higher probability than men to receive early treatment in aneurysm, whether surgical or endovascular treatment[53].

Conclusion

We cannot exclude the presence of potential gender inequity on admission to the ICU due to the tendency of clinicians to show gender preference for certain diseases. To improve the care of critically ill patients, including sepsis and neurological emergency, we need to understand the biological and physiological causes that lead to sex and gender differences in disease. To clarify the pathophysiology of the disease, we have to include sex-specific data analysis in study designs and encourage appropriate interpretation of the results.

Key messages

- Horizontal equity: patients of both sexes with equal clinical severity receive the same level of support with equal use of resources (equal use for equal needs).
- Vertical equity: the sickest patients receive more assistance regardless of gender (unequal use for unequal needs).
- All studies show that more male patients than female patients are admitted to ICU.
- Men are more likely to develop any form of sepsis. However, it is unclear whether there is a different susceptibility, an advantage in survival, or underreporting of cases of sepsis in women.
- Women are more likely to have a worse functional outcome after ischemic or haemorrhagic episodes of stroke.

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