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Sex and gender differences in intensive care medicine

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Keywords:

Sex disparities, Critical illness, Sex and gender differences, ARDS, AKI, Post-intensive care syndrome, Cardiogenic shock, Septic shock

Abstract

Despite significant advancements in critical care medicine, limited attention has been given to sex and gender disparities in management and outcomes of patients admitted to the intensive care unit (ICU). While “sex” pertains to biological and physiological characteristics, such as reproductive organs, chromosomes and sex hormones, “gender” refers more to sociocultural roles and human behavior. Unfortunately, data on gender-related topics in the ICU are lacking. Consequently, data on sex and gender-related differences in admission to the ICU, clinical course, length of stay, mortality, and post-ICU burdens, are often inconsistent. Moreover, when examining specific diagnoses in the ICU, variations can be observed in epidemiology, pathophysiology, presentation, severity, and treatment response due to the distinct impact of sex hormones on the immune and cardiovascular systems. In this narrative review, we highlight the influence of sex and gender on the clinical course, management, and outcomes of the most encountered intensive care conditions, in addition to the potential co-existence of unconscious biases which may also impact critical illness. Diagnoses with a known sex predilection will be discussed within the context of underlying sex differences in physiology, anatomy, and pharmacology with the goal of identifying areas where clinical improvement is needed. To optimize patient care and outcomes, it is crucial to comprehend and address sex and gender differences in the ICU setting and personalize management accordingly to ensure equitable, patient-centered care. Future research should focus on elucidating the underlying mechanisms driving sex and gender disparities, as well as exploring targeted interventions to mitigate these disparities and improve outcomes for all critically ill patients.

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Introduction

Over the last years, sex and gender differences in diagnosis, clinical care, and outcomes have become an increasing concern in medicine and critical care research [1, 2]. Inequalities in medical care were first described via several landmark publications in the early 1990s which revealed that women often received inequitable treatment compared to men, often resulting in worse outcomes. Bernadine Healy famously termed this phenomenon the “Yentl Syndrome” after the heroine of Isaac Bashevis Singer’s story, in which a young Jewish woman pretended to be a man, aiming to receive equal education as men [3]. Historically, research has widely disregarded sex differences, with women being underrepresented in clinical trials and experimental research, leading to a lack of understanding of their specific healthcare needs and differences in outcomes [4]. Addressing sex differences in critical care medicine is particularly challenging given the heterogeneity of patients and diagnoses in the intensive care unit (ICU) [1, 5]. Biological factors (sex) and sociocultural factors (gender) have been increasingly investigated and both have been held responsible for sex disparities in disease manifestation, provision of medical care, and outcomes [6, 7]. However, while biological sex comprises differences in hormonal status, sex chromosomes and physiology, gender refers to socially constructed norms, behaviors, expressions, and identities of women and men (Fig. 1).

Regarding the specific nature of sex, many anatomical and physiological characteristics partly explain some of these differences (Fig. 2 and Table 1).

Over the last decade, advances have been made to better understand the complex interplay of sex and gender in diseases, to guide clinicians' decision-making when incorporating sex and gender into patient centered medicine, and to support a more systematic approach in the reporting of sex and gender across disciplines and in research by releasing the SAGER (Sex and Gender Equity in Research) guidelines [8, 9] (Fig. 3) and with the development of gender scores to make gender "measurable" [10, 11]. Current evidence indicates that gender-related variables allow for the characterization of individuals beyond biological sex and its impact on clinical outcomes. However, limitations remain given the multidimensional aspects and complexity of gender and the co-existence of unconscious biases.

In this narrative review, based on a comprehensive, critical, and objective analysis of the current literature, our aim is to summarize the current evidence of sex and gender differences in the provision of critical care, including treatment and outcomes with a focus on sex disparities in the most common critical illnesses.

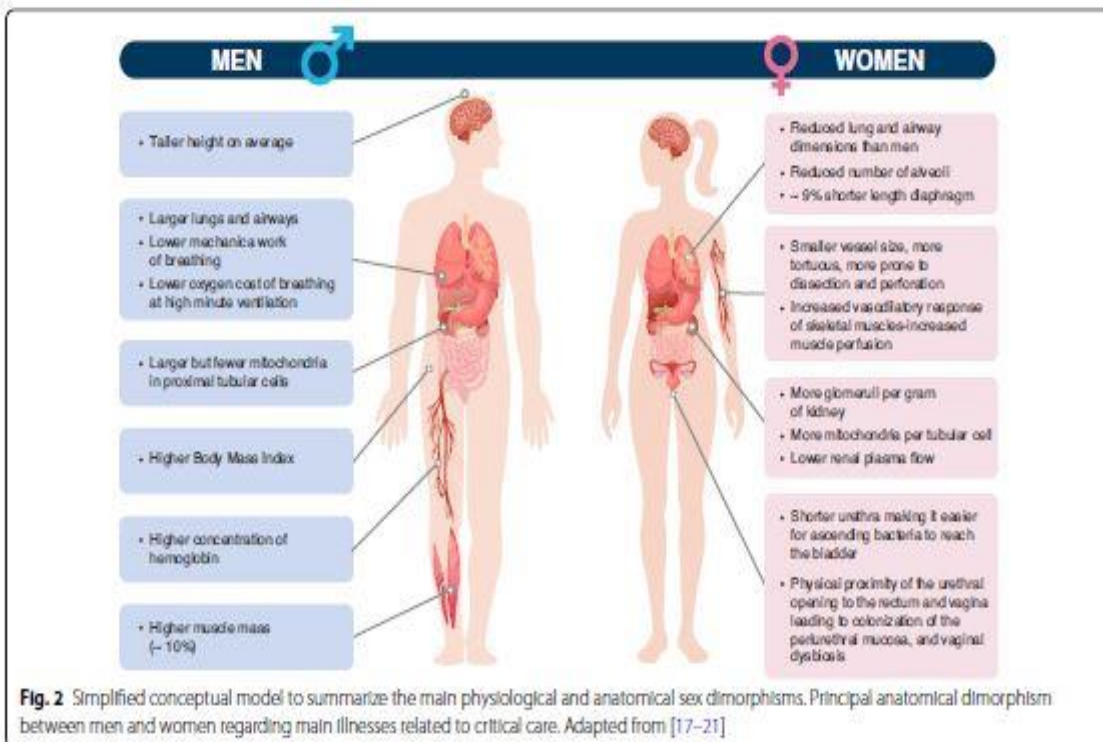
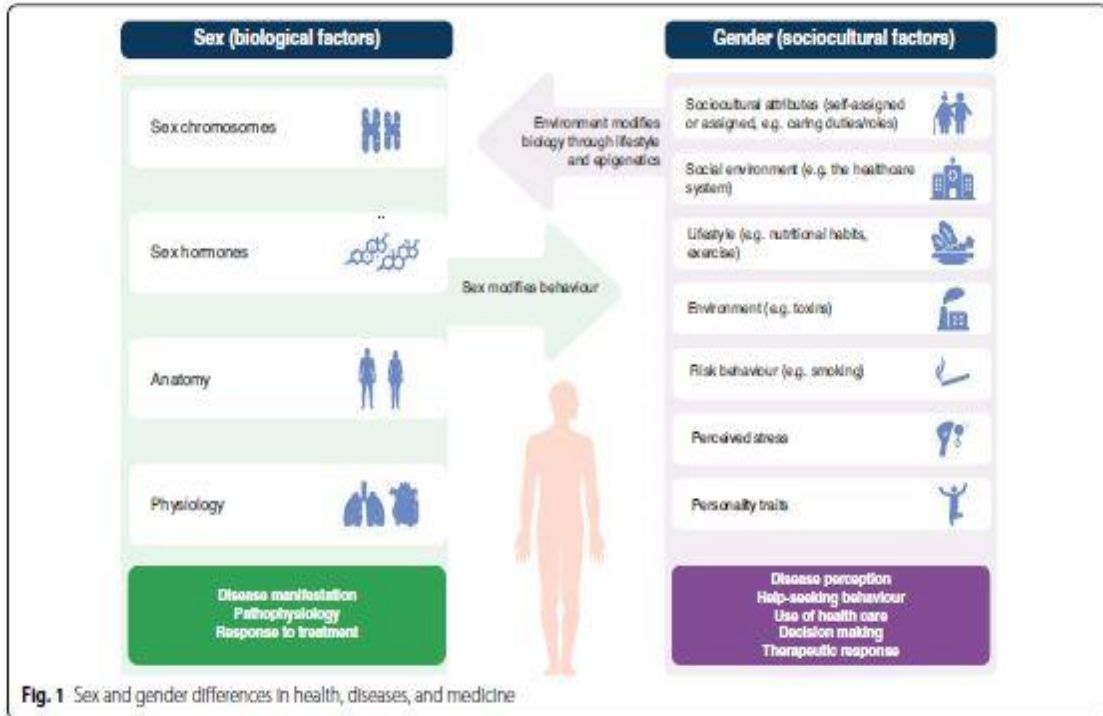
Influence of sex and gender on ICU admission

Intensive care unit admission is provided less frequently to women compared to men [12] within most diagnostic groups. This flies in the face of data supporting that women outlive men everywhere in the world, and accordingly, a higher percentage of women should be represented particularly in the aging ICU population [13]. While a male predominance in the overall ICU population is seen worldwide, an exemption with a female preponderance is observed in metabolic disorders, deliberate self-poisoning, and non-traumatic subarachnoid hemorrhage [14, 15]. Besides, among the main comorbidities, there appears to be some differences between men and women at ICU admission. For instance, cardiovascular morbidity (dyslipidemia, coronary artery disease), chronic obstructive pulmonary disease (COPD), and acquired immunodeficiency syndrome (AIDS), tend to be less prevalent in women [5, 16].

There is an ongoing debate regarding the sex imbalance in the provision of intensive care. Most studies, including large meta-analyses, have demonstrated that the severity of illness on ICU admission is similar [16, 22] or higher in women [5, 23]. The latter was confirmed in a recent meta-analysis including 505,138 patients across all ICU admission diagnoses [5]. Similarly, Todorov et al. demonstrated in a nationwide database of 450,948 cardiovascular or neurovascular patients that the likelihood of women being admitted to ICU was significantly lower compared to men, despite higher estimates of illness severity [23]. Conversely, some studies report an overall lower severity of the disease in women, probably related to lower average age than men at admission to ICU [24, 25]. However, sex predilection toward certain diagnoses may also impact illness severity and outcomes: higher illness severity and mortality for women have been reported in diagnostic groups with a lower percentage of women and points toward the fact that sex distributions within diseases, diagnoses, and age groups should be considered [25].

Notably, illness assessment tools such as the Simplified Acute Physiology Score (SAPS) and Acute Physiology and Chronic Health Evaluation (APACHE) scoring systems were initially implemented when knowledge of sex disparities was lacking and neither biological sex nor sex-adjusted thresholds of physiological parameters were considered [26–28]. It is not

surprising then, that risk assessment scores perform differently in women and men [29]. Indeed, adding sex in risk-assessment scores can improve their performance [30] and may have important implications for admission strategies in ICU patients and outcomes.



Gender differences in symptom perception may further contribute to under-representation of women in the ICU. It is well known that women with acute myocardial infarction (AMI) often present with atypical chest pain and remain underdiagnosed [31]. In addition, sociocultural factors such as lower socioeconomic status, limited formal education, higher stress levels, and limited access to healthcare tend to occur more frequently in women [10]. Women are still more frequently involved in traditional social roles such as family responsibilities or household chores and may, therefore, defer their needs, presenting with a delay at an advanced stage of illness.

Finally, women may more often set limitations on life sustaining therapies (advance directives), particularly in higher age groups or when divorced or widowed [32]. This may additionally impact ICU resource allocation or yield a bias where clinicians assume subsets of women may prefer less-aggressive care. Similarly, unconscious or implicit/explicit bias such as attitudes about race, ethnicity, abilities, age and gender may influence our decision-making in a discriminatory way, contributing to a delay in diagnosis and a delay or even denial of care [36]. Altogether, sociocultural rather than biological factors in addition to implicit and explicit bias seem to drive gender inequalities in the provision of intensive care (Fig. 4).

Influence of sex and gender on sepsis and septic shock

Male sex has been identified as a possible risk factor for sepsis. Indeed, epidemiological studies consistently report a higher prevalence of sepsis in men relative to women [37]. Men are more likely to develop infectious diseases than women, with a mean annual relative risk of 1.3 [37] and an almost 1.6 times higher risk of sepsis hospitalization [38]. Similarly, one meta-analysis reported a significant predominance of men (61%) among ICU septic shock patients [39]. This male overrepresentation is quite surprising since the sex ratio in the general population > 65 years old is around 0.8 male/female. Once in the surgical ICU, men also develop severe sepsis and septic shock more often than women. Although reports on the impact of sex on mortality from sepsis and septic shock have shown conflicting results, a recent analysis of a single-center large database study of more than 6000 patients admitted with sepsis reported an increased ICU length of stay (LOS) and mortality in men [38]. Similarly, men hospitalized for sepsis had a higher likelihood of death at 1 year, longer duration of hospital, and ICU stay. They were also more commonly readmitted to hospital within 90 days and 1 year after the incident sepsis hospitalization [38]. After admission, therapeutic strategies may be discrepant. For example, sex-based differences have been found in the emergency department management of critically ill patients with sepsis and septic shock, with men having 1-h sepsis bundles completed 38% more often than women, and with a 34% faster median time to antibiotic administration [40].

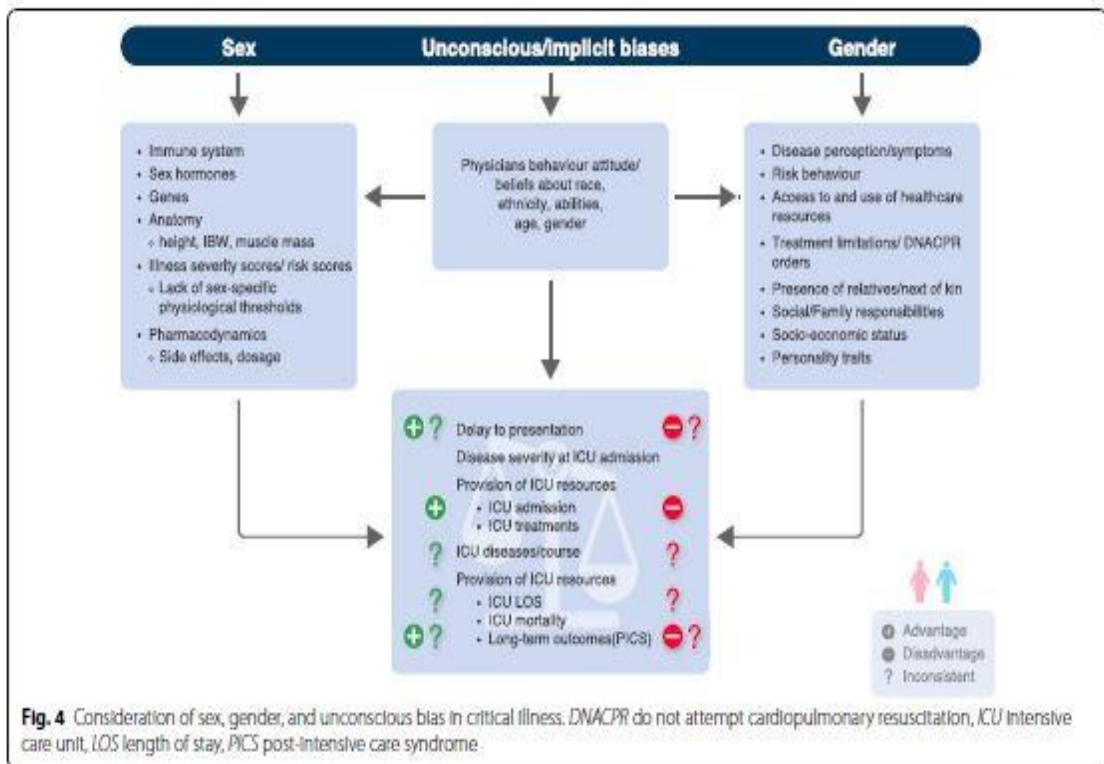
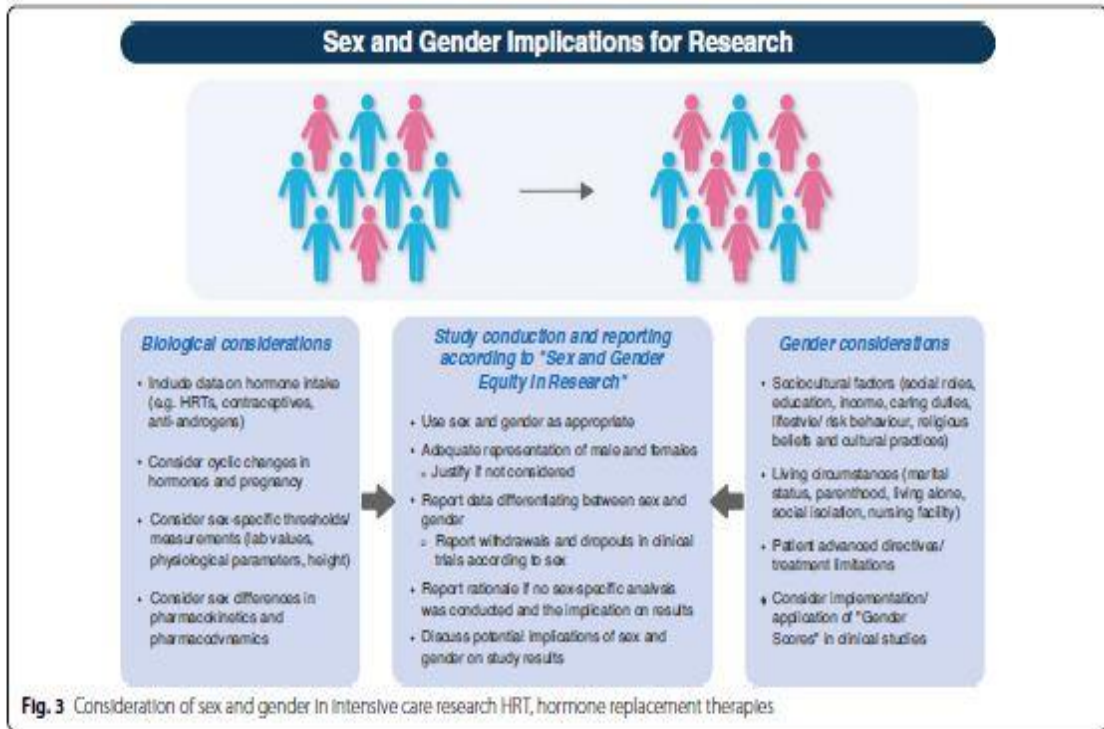
Potential mechanisms underlying sex differences in sepsis are manifold. Men and women differ in their innate immune responses. Notably, sex differences begin at conception with women having two X chromosomes that harbor many genes that regulate immune function such as some interleukin and Toll-like receptors [17]. Although one X chromosome is randomly silenced in each cell, up to one-third of genes may escape silencing and are expressed at higher levels in women than in men [17]. In addition, by binding to specific receptors expressed in immune cells such as lymphocytes, macrophages, and dendritic cells, sex steroids can affect immune responses and impact bacterial metabolism, growth, and expression of virulence factors [17]. Estrogens, for example, can directly stimulate B lymphocytes immunoglobulin production, increasing the humoral immune response in women [41]. Anatomy and urinary microbiome also explain why women are more prone to genital

and urinary tract infections, though these are typically less severe in women than in men [17]. Behavioral factors associated with gender may also alter the risk. Historically, smoking, alcohol, and substance misuse were more prevalent in men and associated with an increased risk of community-acquired pneumonia, particularly *Streptococcus pneumoniae* [42] and bloodstream infections [43]. More men were also traveling and more often exposed to *Legionella pneumophila* [44].

Table 1 Main differences in pharmacokinetic parameters in women as compared to men

Parameter	Men	Women	Sex difference	Example
Oral absorption	Faster	Slower	Women have reduced gastric acid secretion and gastric emptying, and a slower gastrointestinal transit time, which can delay drug absorption	Drugs that require an acidic environment for absorption have lower bioavailability in women. Women also exhibit delayed gastric emptying, meaning the interval between eating/taking medications that must be absorbed on an empty stomach must be extended
Distribution	Wider	Tighter	Body composition in women is characterized by a lower body surface area, organ size, and blood flow, as well as lower total body water content, plasma volume, cardiac output, lung volume, and functional capacity. However, women have a higher body fat content than men In women, plasma protein binding is characterized by a lower percentage of albumin and α_1 -acid glycoprotein, and a higher percentage of globulins	Women require a higher infusion rate of common lipid-soluble hypnotics such as midazolam or propofol due to a larger volume of distribution. In contrast, water-soluble drugs, such as neuromuscular blocking agents, have lower volumes of distribution in women, and need lower doses for the same effect
Drug transporters	Higher	Lower	Expression of permeability-glyco-protein, organic cation transporter (OCT2), and anion-transporting polypeptides (OATP1B1-3) is lower in women than in men	Reduced efflux transporters, such as permeability-glyco-protein in women may limit morphine entry into the brain, reducing analgesia
Metabolism	Faster	Slower	Phase I metabolism in women: Reduced activity of some cytochromes P450 such as CYP1A2, CYP2C9, CYP2D6, CYP2C19, and CYP2E1 Increased activity of some cytochromes P450 such as CYP2A6, CYP2B6, CYP2D6, and CYP3A4 Phase II metabolism in women: Reduced activity of N-acetyl/sulfo/methyl/UDP-glucuronosyl-transferases, alcohol dehydrogenase, and thiopurine S-methyltransferase (TPMT) Increased activity of xanthine-oxidases	Women have higher biotransformation of amiodarone and calcium channel blockers and reduced biotransformation of clopidogrel
Excretion	Faster	Slower	Renal blood flow, estimated glomerular filtration rate, and tubular secretion and/or reabsorption are lower in women	Aminoglycosides, vancomycin, angiotensin-converting enzyme inhibitors, and digoxin have a slower clearance rate in women, that may increase the risk of side effects

Adapted from [33–35]



Influence of sex and gender on cardiac arrest

Cardiac arrest also occurs more often in men, with women accounting for 18–46% of patients in studies [45]. This seems to apply for both in-hospital cardiac arrests (IHCA) and out-of-hospital cardiac arrest (OHCA), though data are biased toward OHCA, which is reported more frequently [46]. Compared to men, women with OHCA are less likely to present with a

shockable rhythm [47] and are often older with more comorbidities (e.g., hypertension, diabetes, obesity) [48]. More women suffer from cardiac arrest in their home and are less likely to be witnessed [45]. Women are further disadvantaged since those who suffer an OHCA are less likely to receive bystander cardiopulmonary resuscitation (CPR), even in public locations [49]. Further, layperson bystanders may be reluctant to perform CPR in women for fear of being accused of sexual misconduct. This concern was emphasized in an American public survey that highlighted concerns about inappropriate touching and allegations of sexual assault as potential barriers to performing CPR on women in public [50]. Following return of spontaneous circulation, women are less likely to receive in hospital post-resuscitation therapies like percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), mechanical circulatory support (MCS) [51], and targeted temperature management [45].

Despite these variations in presenting features and management, many studies and registries corroborate comparable mortality rates and neurological outcomes in men and women. This paradox that men may be physically stronger with fewer disabilities and/or comorbidities but have substantially higher mortality at all ages has been termed the “gender paradox” or “male–female health-survival paradox.” This remarkable discrepancy is visible where women experience comparable survival outcomes to men, despite exhibiting inferior prognostic factors. Once again, sexual differences could partly explain this paradox. Women have higher chest wall compliance than men, making CPR efforts easier and more effective [52]. Further, evidence from preclinical investigations suggests that estrogen may exhibit anti-inflammatory and antioxidant effects, mitigating ischemia–reperfusion-induced injury [53]. Additionally, estrogen may also enhance the stability of the mitochondrial membrane and prevent the intracellular calcium and potassium influx that contributes to intracellular death after cardiac arrest [54].

Influence of sex and gender on acute respiratory distress syndrome

Limited evidence exists regarding the impact of sex and gender on acute respiratory distress syndrome (ARDS). Recent randomized controlled trials (RCT) and registries report a marked prevalence of males among ARDS patients, with the proportion of females ranging from 28% to 38% [55]. In contrast, following a trauma, women were more likely than men to develop ARDS [56]. In this study, a pro-inflammatory sex hormone profile (low testosterone, high oestradiol) was associated with ARDS in both men and women [56]. Though expectedly occurring less often in men, this hormone profile was also associated with ARDS in men, suggesting that sex-specific hormonal differences may impact ARDS. Interestingly, in prepubertal children, when hormone levels are expected to be uniformly low in both sexes, an equivalence of ARDS caused by non-septic factors is reported [57]. However, ARDS secondary to sepsis appears to be more common in boys, suggesting a biological basis for sex disparities in the susceptibility to ARDS, despite comparable hormone levels at this age. Similarly, among patients > 50 years, there is no notable elevation in the ratio of women to men, suggesting that the ARDS incidence in women does not increase after the hormonal changes of menopause [56].

Despite all these differences and conflicting data in presentation and management, most studies and registries report similar mortality rates in non-coronavirus disease 2019 (COVID-19) ARDS in men and women [58]. This is in the context of unique risk factors, where women with ARDS are more likely to be immunocompromised, and men with ARDS are more likely to have trauma, COPD, and chronic renal failure [56]. Regarding COVID-19

ARDS specifically, the latest data report a male bias in mortality [11]. However, despite intense research efforts, there is currently no consensus about the precise mechanisms by which female sex might protect against COVID-19 ARDS [59].

ARDS management may also differ between men and women. A study by Han et al. revealed that patients of shorter stature suffering from severe sepsis-related acute lung injury were less likely to receive lung-protective ventilation [60]. This is crucial as women with ARDS tend to be shorter and with a higher body mass index [61]. This concern has been validated in an analysis of ARDS network trials [62] and also in an ancillary analysis of the LUNG SAFE study, which showed that a higher proportion of women received non-protective lung ventilation. This resulted in higher plateau and driving pressures compared with men [61]. Indeed, height is often estimated incorrectly, especially in patients with shorter body length [63], further increasing the risk of women not receiving adequate lung-protective ventilation (Fig. 2). In contrast, more women than men received adjunctive measures, such as veno-venous extracorporeal membrane oxygenation and inhaled vasodilators [61].

Influence of sex and gender on cardiogenic shock

Given the association of cardiogenic shock (CS) with a high risk of morbidity and mortality, the impact of sex and gender on treatment and outcomes is poorly understood. In most recent studies on cardiogenic shock, women are consistently less represented than men, with a prevalence of about 33–40%. However, among patients with CS, women are more likely to present with non-ischemic (NI) CS than with AMI complicated by cardiogenic shock (AMI-CS) [64]. This could be partly explained by the fact that etiologies of NI-CS such as Takotsubo syndrome have a higher prevalence among women [65].

About 5–10% of AMI patients will develop AMI-CS [66] which is associated with in-hospital mortality rates ranging from 40% to 60% [67]. Post-menopause, decreasing oestrogen levels, and reduced vascular protective effects are associated with the development of microvascular damage after menopause [68], and may contribute biologically to an increased risk of developing more frequent complications after AMI [69].

Women who suffer from AMI frequently display an atypical clinical presentation and tend to delay seeking medical attention for their symptoms, leading to a longer total ischemia time and an increased risk of developing CS [70]. Despite sociocultural factors, the evidence from both RCT's and registries consistently indicates that women who experience CS are typically older and have a greater incidence of comorbidities, such as hypertension and diabetes than men [69]. Unfortunately, after presentation for AMI-CS, women again receive less-frequent guideline-recommended care including coronary angiography, PCI, CABG, and MCS [51, 71] compared with men. Similarly, in NI-CS, a recent study showed the same trend of lower MCS use among women [72]. Women are also less likely to receive guideline-recommended pharmacological therapies at discharge in AMI-CS [73]. Nonetheless, despite compelling differences in the features and management of CS, there seems to be an absence of sex disparities in long-term outcomes [69].

Influence of sex and gender on acute kidney injury

Although experimental models of ischemic acute kidney injury (AKI) have consistently demonstrated that female sex protects against the development of renal damage, the consensus view is that female sex is an independent risk factor for AKI in humans. There is growing

evidence that significant sex differences exist in the response of the kidney to injury [74]. They may be mediated by the effects of sex hormones on cellular processes instrumental in the pathogenesis of AKI. Differences also exist in the generation of nitric oxide, vascular response to endothelin-1, and in the renal hemodynamic response to angiotensin II [75].

A meta-analysis of 83 AKI studies from 1978 to 2018, including 6,758,124 patients, showed that the risk of developing hospital-associated AKI was significantly greater in men [odds ratio, OR, 1.23 (1.11, 1.36)] [76]. Furthermore, the association of male sex with AKI was strongest in patients undergoing non-cardiac surgery and critically ill patients in the ICU. In contrast, cardiac surgery-associated AKI and radiocontrast-induced AKI showed no sexual dimorphism, suggesting that sex differences impact the pathogenesis of AKI. However, there are many limitations to untangling the relationship between sex and AKI. Importantly, differences exist in the rate of creatinine generation, (given the usually greater muscle mass, creatinine levels are higher in men), the elimination of creatinine, and in its volume of distribution.

These features directly impact the diagnosis of AKI [28]. Further, sociocultural factors play a role, and processes of care may differ, including the use of nephroprotective medications or exposure to nephrotoxic factors. Finally, clinical AKI studies rarely report the menopausal status or the use of oral contraceptive or hormone therapy among participants and have not discerned how puberty, menopause, and transgender impact the susceptibility to AKI and risk of progression.

Influence of sex and gender on ICU delirium

Delirium is defined as a form of acute brain dysfunction with disturbance in awareness, attention, and cognition. It has been associated with worse outcomes such as higher mortality, longer LOS in ICU, post-ICU cognitive decline, and functional impairment after discharge [77]. Gender has not been consistently shown as a risk factor for ICU delirium, but a study by Mehta et al. reported that delirious patients were more likely to be men (61.1% vs 46.6%; $p=0.005$) [78]. Data regarding the influence of sex on ICU delirium duration are conflicting, with a study by Liu et al. demonstrating no difference [79]. Similarly, delirium severity in acutely ill hospitalized patients was similar between sexes [80]. Sex differences in delirium subtype (hypoactive, hyperactive, or mixed) are also unclear. Current literature reports a higher likelihood in women to suffer from hypoactive delirium as compared to men in acute medicine background [80], while other works have shown no sex differences in ICU delirium subtype [81]. Documented agitation and hyperactive delirium are reported to occur more frequently in men than in women, with a higher likelihood of men being initiated on antipsychotic medications due to higher visibility of hyperactive symptoms and safety issues associated with agitation [82]. Figure 5 demonstrates the impact of sex and gender on most common ICU diagnoses.

Influence of sex and gender on medical treatment

Evolving evidence has supported that women are undertreated in the ICU, despite higher illness severity. This comprises the application of organ support measures, including renal replacement therapy (RRT), mechanical ventilation, invasive procedures, and early goal directed therapies [1, 23, 40]. By neglecting sex-specific thresholds of creatinine or urea, a systematic bias in clinical routine and risk prediction/survival scores may contribute to an underestimation of renal impairment and thus, lower assignment to RRT, and less-frequent

transition to permanent dialysis access or organ transplantation in women [83–85]. As mentioned above, advanced directives are more prevalent in women and may confound treatment assignments.

While women less frequently receive mechanical organ support measures, medication-based treatments are primarily applied in equal measure to critically ill men and women. However, sex differences in the pharmacokinetics and pharmacodynamics of drugs can lead to overdosing and more adverse side effects in women (Table 1). For instance, women are more prone to develop Torsade de Pointes arrhythmias with QT-prolonging drugs (e.g., amiodarone) due to the effect of estrogens on lengthening the cardiac repolarization time [86]. Furthermore, women experience more side effects with loop diuretics based on 30–40% higher maximal serum concentrations than men, and experience more bleeding complications with unfractionated heparin [87]. Sex-associated factors, such as lower weight, higher average body fat, and lower plasma volume and blood flow in women may lead to higher maximum concentrations and thus, to the excess bleeding risk observed. Finally, treatment delays are more common in women, too. A gender-linked delay in presentation is seen in women presenting with an acute abdomen of non-obstetric cause, often primarily referred for a gynecology opinion, but also in women with chest pain, stroke, and cancer. Socio-economic status, responsibility for family duties, and sex differences in pain perception may contribute to these differences [88].

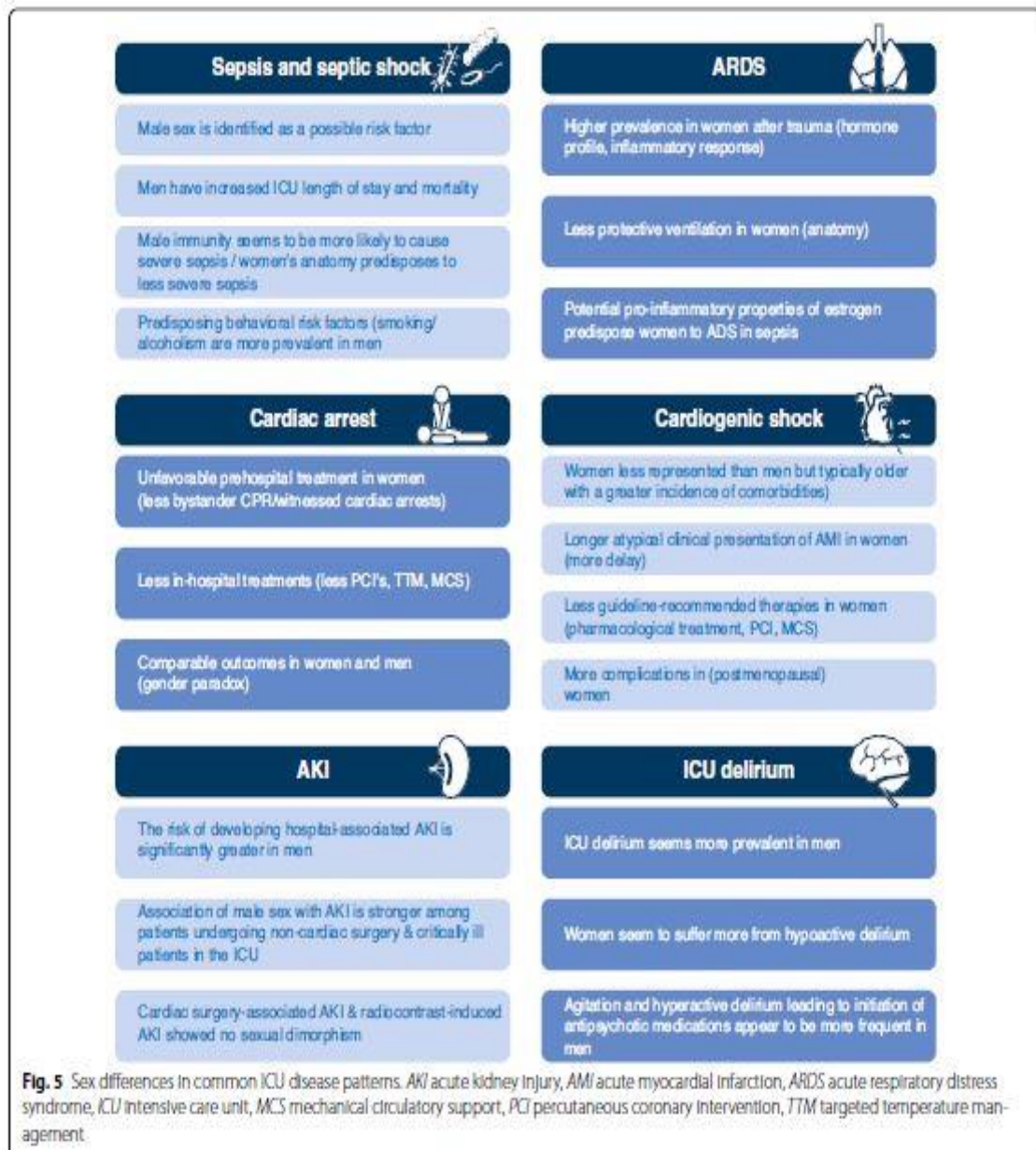
General outcomes in the ICU

Influence of sex and gender on ICU LOS and short-term mortality Data on ICU LOS and ICU mortality are inconsistent. Shorter ICU LOS has been reported in both women [22] and men [89]. In a pooled, adjusted (40,494 patients) analysis, a shorter ICU LOS was found in women, while no sex differences in hospital LOS were observed in a separate pooled dataset including 7 studies and 57,292 patients [1]. These disparate results may be related to differences in age/sex predominance (e.g., a higher percentage of elderly women), higher female mortality, and higher incidence of treatment limitations upon ICU admission, as previously discussed [90] (Fig. 4).

Accordingly, data on ICU and short-time mortality show conflicting results. Some studies have found a higher risk-adjusted ICU mortality in women [22, 23], while others have refuted this association [24]. In a recent meta-analysis, sex differences in illness severity and mortality in 505,138 adult ICU patients (43.1% women) from 3 different continents were assessed. They found a significantly higher risk-adjusted ICU and 1-year mortality in women, while hospital and 30-day mortality did not differ between sexes [5]. However, when studies at high risk of bias were excluded, there were no statistically significant differences at any time point. Illness severity score discrepancies, mortality time-point differences, unique diagnostic groupings, and unequal sex representation therein all make data interpretation challenging.

An approach to overcome some of these limitations used a sex-balanced based analysis considering the sex distribution within each diagnostic subgroup of patients admitted to the ICU. In diagnostic groups with a lower female percentage (e.g., cardiovascular diseases, cardiac surgery), women were admitted with higher illness severity and were more likely to die. The same results were found in diagnostic groups with fewer men (e.g., metabolic disorders) [25]. Apart from illness-specific biological differences in each sex, a delay in recognition of low-probability conditions may contribute to the worse outcomes observed due

to unconscious and preconceived judgment (Figs. 2 and 5). Furthermore, sociocultural factors (lifestyle/risk behavior, physical environment, access to and the use of available healthcare systems, gender roles and relations, socioeconomic status) are increasingly recognized as modifiers of diseases and outcomes, mostly studied in women with cardiovascular diseases [7,10] (Fig. 4).



Influence of sex and gender on outcomes after critical illness

Outcomes after critical illness usually referred as the post-intensive care syndrome (PICS) [91] encompass a broad spectrum of issues, some of which are associated with sex differences in the frequency and presentation. ICU-acquired weakness (encompassing myosin-depletion myopathy and/or axonopathy) is nearly ubiquitous in long-stay ICU patients and female sex has consistently been identified as an independent risk factor in multiple international studies

and meta-analyses [92]. While the underlying mechanism is still unclear, this diagnosis has significant consequences for women's ability to regain functional independence, navigate care transitions, return to work, and reintegrate into the community [93].

Cognitive dysfunction is also highly prevalent after critical illness but has not been shown to have a consistent sex predilection across multiple international cohort studies. As demonstrated in the BRAIN-ICU study, its main determinants are the incidence and duration of delirium [94, 95].

Post-traumatic stress disorder (PTSD) occurs frequently in PICS, with a prevalence between 17 and 44% [96]. Sex differences in PTSD are debated; meta-analyses do not support differences (13 over 18 studies showed no association) [96]. Sex-related differences in ICU treatment may be a confounding factor in understanding this relationship. As one example, traumatic memories, a known PTSD risk factor, may increase with increasing doses of epinephrine in the cardiothoracic intensive care unit (CTICU), but only in men [97]. In contrast, metoprolol in the CTICU may decrease traumatic memory formation and later PTSD symptoms, but only in women [97]. Broadening from PTSD to all mental health diagnoses, women are more likely to have higher PTSD screening scores and are more at risk of new mental health diagnoses after critical care [93]. There may be an overarching bias in follow-up that fundamentally influences this literature and may be influenced by opportunity to participate based on access and responsibility for family caregiving and other restrictive social roles.

Summary and implications

Sex and gender differences impact the full spectrum of intensive care medicine, from critical care access to the severity of presentation, initial and ongoing management, and to short- and long-term outcomes. Biological differences in sex hormone profiles and immune responses seem to modify the trajectory of critical illness in common ICU diagnoses like sepsis or ARDS. However, evidence remains equivocal at this time, given the under-representation of women and the lack of information regarding hormonal status, hormone intake, and cyclic changes in many studies. Despite delayed (sepsis bundle) or inappropriate (ARDS lung-protective ventilation) treatments, short-term outcomes seem not to be impacted in female patients. Under treatment remains not to be limited to these diagnoses and affects the general female population, starting from less-frequent ICU admissions to less organ support measures—despite being equally ill. The underlying reasons for these inequalities remain unclear, but unconscious or implicit bias may influence the treating clinicians, leading to delays in diagnosis and care with harmful consequences. The latter is supported by the fact that ICU mortality of women is higher in diagnoses with a lower percentage of female patients. It underscores the importance of workforce diversity, educational measures and most importantly, male and female physicians' awareness that unconscious biases exist. Besides biology, gender factors influence critical illness at various stages. Socio-economic status, access and use of healthcare resources, social roles and personality traits may impact illness severity at presentation, ICU admission, treatment decisions (treatment limitation), and thus outcomes. The implementation of validated gender scores and the SAGER guidelines in critical care research may help to detangle the impact of biological and gender factors on critical illness.

Conclusion

Taken together, sex and gender differences in critical illness are complex and further challenged by unmeasurable existing biases. Current evidence is still scarce, and data remain conflicting. Healthcare providers and researchers need to be aware of these sex/gender differences and unconscious biases and work toward addressing them in their practice and clinical studies to improve ICU management for both, men and women, in a personalized, patient-centered manner. To further improve understanding, we encourage to use the terms sex and gender carefully to avoid confusion, to include information about hormonal status and to consider sociocultural factors as modifiers of diseases and outcomes.

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Declarations

Conflicts of interest

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