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Original article

Sex-specific outcomes and management in critically ill septic patients

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ABSTRACT

Background: : Female and male critically ill septic patients might differ with regards to risk distribution, management, and outcomes. We aimed to compare male versus female septic patients in a large collective with regards to baseline risk distribution and outcomes.
Methods: : In total, 17,146 patients were included in this analysis, 8781 (51%) male and 8365 (49%) female patients. The primary endpoint was ICU-mortality. Baseline characteristics and data on organ support were documented. Multilevel logistic regression analyses were used to assess sex-specific differences.
Results: : Female patients had lower SOFA scores (5 ± 5 vs. 6 ± 6; $p<0.001$) and creatinine (1.20 ± 1.35 vs. 1.40 ± 1.54; $p<0.001$). In the total cohort, the ICU mortality was 10% and similar between female and male (10% vs. 10%; $p = 0.34$) patients. The ICU remained similar between sexes after adjustment in model-1 (aOR 1.05 95% CI 0.95–1.16; $p = 0.34$); model-2 (aOR 0.91 95% CI 0.79–1.05; $p = 0.18$) and model-3 (aOR 0.93 95% CI 0.80–1.07; $p = 0.29$). In sensitivity analyses, no major sex-specific differences in mortality could be detected.
Conclusion: : In this study no clinically relevant sex-specific mortality differences could be detected in critically ill septic patients. Possible subtle gender differences could play a minor role in the acute situation due to the severity of the disease in septic patients.

1. Introduction

Sepsis is a life-threatening condition triggered by an "out-of-proportion" immune response to an infection [1]. Septic patients have low survival rates, and research to refine and individualize treatment in septic patients is ongoing and warranted [1]. However, survival rates in sepsis remain low and, also, long-term morbidity in survivors is a significant public health challenge [2-5].

Human male and female biologic responses to infection differ regarding both cellular and humoral immune responses due to genetics [6, 7]. Also, in an American epidemiologic study, sepsis incidence was higher in men compared to women [8].

The literature regarding gender-specific mortality in patients with sepsis is contradictory. Nachtigall et al. reported higher mortality in female septic patients [9]. However, in another study, Nasir et al. reported higher survival and lower interleukin-6 plasma levels in females [10]. A recent study reported data from Medical Information Mart for Intensive Care-III supported the link between female sex and lower mortality [11]. Other studies reported similar outcomes in both male and female septic patients [12].

Sex-specific differences in outcomes were also observed for other acute diseases [13-16]. Some studies reported sex-specific differences in ICU patients [16-19]. Female and male critically ill patients were reported to differ regarding baseline risk distribution, and these disparities could lead to distinct outcomes [20, 21]. In elderly critically ill patients with sepsis, male sex was linked to decreased survival [8, 21]. A trend towards lower mortality in women compared to male patients was observed in a sub-study of the FROG-ICU study, which evaluated elderly critically ill patients [22].

However, most of these studies were single-centered and analyzed relatively few patients. The eICU Collaborative Research Database is a multi-center ICU database, including over 200 000 admissions [23]. We aimed to compare male versus female septic patients in this large collective regarding baseline risk distribution, management, and

Keymessage: No clinically relevant sex-specific disparities in management and outcomes could be observed.

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outcomes.

2. Methods

2.1. Study subjects

The eICU Collaborative Research Database is a multi-center intensive care unit (ICU) database, including over 200,000 admissions of 335 ICUs from 208 hospitals across the USA in 2014 and 2015 [23]. We extracted baseline characteristics and organ support on day one. The database is released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. This study included patients of the eICU database diagnosed with sepsis based on the method established by Angus et al., which identifies patients via billing codes [24]. Management strategies were defined as the use of vasopressors and mechanical ventilation. The type of primary infection site and the ethical background were extracted.

2.2. Statistical analysis

Continuous data points are expressed as median ± interquartile range. Differences between independent groups were calculated using Mann Whitney *U test* accordingly. Categorical data are expressed as numbers (percentage). The Chi-square test was applied to calculate univariate differences between groups.

The primary exposure was sex (male or female), and the primary outcome was ICU-mortality. The secondary outcomes were the management strategies, mechanical ventilation, and vasopressor use. Three sequential random effects, multilevel logistic regression models were used to evaluate the impact of sex on ICU-mortality. First, a baseline model with sex as a fixed effect and ICU as random effect (model-1) was fitted. Second, to model-1, patient characteristics (age, SOFA score, BMI, infection source, ethnics) (model-2) were added to the model. Third, to model-2, management strategies (model-3) were added to the model. Model-1 and model-2 were used to evaluate the primary and secondary outcomes, whereas model-3 was only used to assess the primary outcomes. Adjusted odds ratios (aOR) with respective 95% confidence intervals (95%CI) were calculated. Multiple sensitivity analyses, analyzing only patients with creatinine above and below 2.0 mg/dL (arbitrary cut-off), lactate above and below 2.0 mmol/L (arbitrary cut-off), age above and below 65 years (arbitrary cut-off), and SOFA above and below 10 (arbitrary cut-off), with and without mechanical ventilation, with and without the vasopressor use and with pulmonary focus were performed.

All tests were two-sided, and a p-value of <0.05 was considered statistically significant. Stata/IC 16.1 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) was used for all statistical analyses.

3. Results

In total, 8365 (49%) female and 8781 (51%) male septic patients were included in this study. Baseline characteristics and risk distribution of the unadjusted cohort are shown in Table 1. There were no clinically relevant differences between male and female patients except for lower SOFA scores (5 ± 5 vs. 6 ± 6 points; $p<0.001$) and creatinine (1.20 ± 1.35 vs. 1.40 ± 1.54 mg/dL; $p<0.001$) in female patients. There were other differences, including age (66 ± 22 vs. 66 ± 21; $p = 0.04$), and lactate (1.80 ± 1.92 vs. 1.80 ± 1.80 mmol/L; $p = 0.006$). The most recent primary infection focus was the lung and the urinary tract. Male suffered significantly less from urinary tract infections (19% vs. 27%; $p<0.001$), while males were predominantly affected from pulmonary (40% vs. 35%; $p<0.001$) and cutaneous illnesses (10% vs. 8%; $p<0.001$; Table 1).

After the adjustment for the ICU cluster as random effect (model-1), there was no difference between both genders regarding the use of mechanical ventilation (aOR 1.03 95%CI 0.95–1.11; 0.52) and vasopressors (aOR 0.94 95%CI 0.88–1.01; 0.07) Table 2). After adding patient-specific confounders (model-2), males evidenced a lower odds for both the use of mechanical ventilation (aOR 0.78 95%CI 0.70–0.87; <0.001) and vasopressors (aOR 0.87 95%CI 0.79–0.97; 0.01; Table 2). This finding of lower odds for the use of mechanical ventilation in model-2 (aOR 0.67 95%CI 0.51–0.88; $p = 0.004$) persisted in the subgroup of patients with pulmonary focus.

In the total cohort, the ICU mortality was 10% and similar between female and male (10% vs. 10%; $p = 0.34$) patients. The ICU remained similar between sexes after adjustment in model-1 (aOR 1.05 95% CI 0.95–1.16; $p = 0.34$); model-2 (aOR 0.91 95% CI 0.79–1.05; $p = 0.18$) and model-3 (aOR 0.93 95% CI 0.80–1.07; $p = 0.29$). In sensitivity analyses, no major sex-specific differences in mortality could be detected (Fig. 1).

Table 1
Baseline characteristics in the total cohort, male versus female patients.

	Female	Male	p-value
	$n = 8365$	$n = 8781$	
BMI	28 (12)	27 (9)	<0.001
Age (years)	66 (22)	66 (21)	0.04
Age >65 years	4326 (52)	4617 (53)	0.26
SOFA score	5 (5)	6 (6)	<0.001
SOFA >10	976 (12)	1249 (14)	<0.001
Heart rate >110bpm	2106 (27)	2183 (27)	0.67
O2 saturation <90%	379 (5)	416 (5)	0.54
Body temperature >38 °C	886 (11)	1051 (13)	0.003
Creatinine (mg/dL)	1.20 (1.35)	1.40 (1.54)	<0.001
Creatinine >2.0 mg/dL	2084 (27)	2707 (33)	<0.001
Lactate (mmol/L)	1.80 (1.92)	1.80 (1.80)	0.006
Lactate >2.0 mmol/L	2128 (43)	2285 (44)	0.33
Focus			
UTI	2280 (27)	1679 (19)	<0.001
Pulmonary	2919 (35)	3512 (40)	<0.001
GI	1051 (13)	1058 (12)	0.31
Cutaneous	646 (8)	836 (10)	<0.001
Unknown	904 (11)	1083 (12)	0.002
Other	514 (6)	609 (7)	0.04
Gynecologic	51 (1)	4 (<1)	<0.001
Ethnic			
Caucasian	6566 (79)	6770 (77)	0.03
AfricanAmerican	833 (10)	974 (11)	0.02
Hispanic	333 (4)	330 (4)	0.45
Asian	140 (2)	128 (2)	0.27
Native American	82 (1)	62 (1)	0.54
Other	411 (5)	517 (6)	0.005
Length of stay (h)	53 (71)	54 (76)	0.55

SOFA - Sepsis-related organ failure assessment; BMI – body mass index; UTI – urinary tract infection; GI - gastrointestinal.

4. Discussion

In this study we could not detect any significant gender-specific differences in ICU mortality based on multicenter data from critically ill septic patients on ICU. This result could be confirmed in several sensitivity analyses as well as after correction for several possible confounders.

In theory, both biological and non-biological factors could impact sex-specific outcomes after critical care. Biological factors include genetics, but also endocrine, neurohumoral and immunological factors [22, 30-32]. There was a numerical trend towards a higher age in men, but the proportion of patients over 65 years of age was similarly high in both sexes. Furthermore, in addition to clinical disease severity expressed as SOFA, creatinine concentration was higher in men. This finding is consistent with recent evidence showing that the male gender is per se associated with a higher baseline creatinine level. This higher concentration does not necessarily reflect lower kidney function [25]. However, in male kidney epithelial cells are also more susceptible to

Table 2
Associations of primary exposure (sex) with mortality and management strategies in three multilevel logistic regression models.

	Crude events Female (n = 8365) n (%)	Male (n = 8781) n (%)	Model 1 aOR (95%CI, p-value)	Model 2 aOR (95%CI, p-value)	Model 3 aOR (95%CI, p-value)
ICU mortality	836 (10)	906 (10)	1.05 (0.95–1.16; 0.34)	0.91 (0.79–1.05; 0.18)	0.93 (0.80–1.07; 0.29)
Management					
Mechanical ventilation	1110 (28)	1010 (25)	1.03 (0.95–1.11; 0.52)	0.78 (0.70–0.87; <0.001)	
Vasopressor use	1547 (38)	1427 (35)	0.94 (0.88–1.01; 0.07)	0.87 (0.79–0.97; 0.01)	

Model 1 - ICU cluster as random effect.
Model 2 - Model 1 plus patient level (SOFA, BMI, age, ethnics, infection focus, heart rate, lactate concentration).
SOFA - Sepsis-related organ failure assessment; BMI – body mass index.

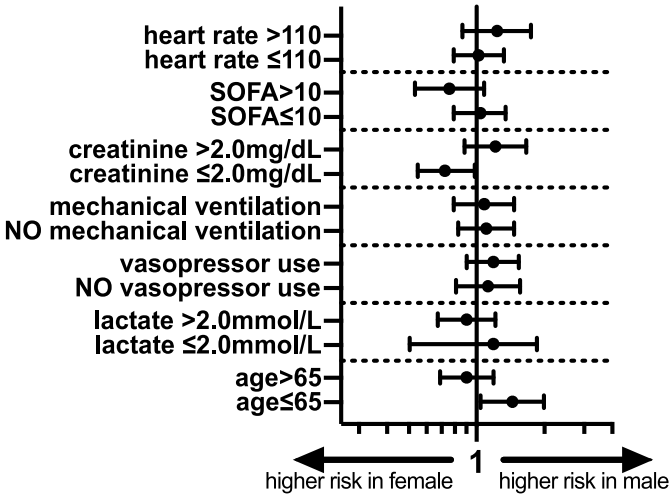

Fig. 1. Forest plot of OR of female versus male for different subgroups according to model-1 (aOR 95%CI). Neither in younger (>65 years; aOR 0.95 0.83–1.09) patients, patients with lactate ≤2.0 (aOR 1.09 95%CI 0.71–1.36) and lactate >2.0 (aOR 0.95 95%CI 0.82–1.10), patients with (aOR 1.09 95%CI 0.95–1.24) and without (aOR 1.06 95%CI 0.90–1.25) vasopressor use; with (aOR 1.04 95%CI 0.89–1.21) and without (aOR 1.05 95%CI 0.91–1.21); with creatinine ≤2.0 (aOR 0.85 95%CI 0.74–0.99) and with creatinine >2.0 (aOR 1.10 95%CI 0.94–1.29); with SOFA≤10 (aOR 1.02 95%CI 0.89–1.16) and SOFA>10 (aOR 0.87 95%CI 0.73–1.04); with a heart rate ≤110 (aOR 1.01 95%CI 0.89–1.15) and heart rate >110 (aOR 1.11 95%CI 0.93–1.32) sex-specific differences could be detected.
Only in older (≤65 years; aOR 1.20 95%CI 1.02–1.41) patients and in patients with creatinine ≤2.0 mg/dL (aOR 0.74 95%CI 0.74–0.99), a trend towards sex specific mortality could be detected.
SOFA - Sepsis-related organ failure assessment.

injury compared to female, which could also contribute to this laboratory finding [26]. However, even in the sensitivity analyses in patients with or without elevated creatinine levels, we could not detect any differences in mortality between the sexes. Thus, we interpret the observed difference in creatinine concentrations primarily as not clinically relevant. Furthermore, both model-2 and model-3 were corrected for creatinine levels.

The results of the present analysis confirm the FROG-ICU study, which observed no sex-related differences in outcomes in more than 2000 critically ill patients [22]. Also, no sex-specific difference was observed in a large Austrian cohort study on 25,998 patients without age-restriction after adjustment for illness [27]. However, Cillóniz et al. found in 1238 older patients (≥80 years) an increased risk for the development of a community-acquired pneumonic sepsis [21]. In this study, sensitivity analysis in the older patients (arbitrary cut-off at 65 years), revealed no differences in outcomes. Therefore, sex-specific differences in mortality reported in smaller cohorts could be due to lower patient numbers and consecutive selection bias [28].

Interestingly, after inclusion of the ICU level as random effect and several patient-specific factors (model 2), female patients evidenced higher rates of mechanical ventilation and vasopressor use. However, this difference in the management strategies did not lead to a change in the ICU-mortality (model 3). On the other hand, we could confirm the finding that the odds of using mechanical ventilation were lower in men, even in patients with pulmonary focus. This finding could, therefore, be a statistical random result on the one hand, or it could represent a real sex-specific difference in the management of critically ill patients [29]. Based on our data, this finding must remain descriptive, and the explanation of the causes remains speculative.

4.1. Limitations

This retrospective analysis has several limitations. The present study is limited to ICU-mortality as primary endpoint and some management strategies as secondary endpoints. Outcome differences in the long-term, or differences in functional outcomes could evidence sex-specific differences [33, 34]. However, these points are beyond the scope of the present study. Sepsis per se is a complex syndrome; its definition and diagnostic criteria underlie continuous changes and debates. This problem affects this retrospective diagnosis. The present study uses the established algorithm by Angus et al. [24]. Recently Johnson et al. compared five retrospective algorithms for a similar database in terms of diagnostic accuracy and mortality. In brief, the method established by Angus et al. shows both average capacities in identifying sepsis and predicting intra-hospital mortality. The agreement between all five criteria was acceptable [35]. Other algorithms for identifying septic patients could therefore identify slightly different patients. However, even in the subgroup with high lactate we could not detect any gender-specific differences. Therefore, we do not assume that the use of other algorithms to identify sepsis would have detected significantly different results. Further, it was not possible to extract microbiological data from the database. In order to at least partially correct our analysis for this limitation, the infection focus was taken into account in the model (model-2 and model-3). [36]. It was, however, not possible to check whether a primary eradication of the infection focus was performed. This study reports only on the acute disease state in terms of SOFA scores, but no information on chronic comorbidities.

Thus, while there are several relevant limitations to this data set and our results, we believe that the finding that there are no large sex-specific differences in ICU mortality in patients with sepsis is robust due to the large patient population.

4.2. Conclusion

In this study no clinically relevant sex-specific mortality differences could be detected in critically ill septic patients. Possible subtle gender differences could play a minor role in the acute situation due to the severity of the disease in septic patients.

5. Declarations

5.1. Competing interests

The authors declare that they have no competing interests.

5.2. Funding

No (industry) sponsorship has been received for this investigator-initiated study.

5.3. Availability of data and materials

All data relevant for this study will be given by the authors upon specific request. Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

5.4. Conflicts of interest

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

6. Financial disclosure statement

No (industry) sponsorship has been received for this investigator-initiated study.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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