

Propensity-Score Analysis Reveals that Sex is Not a Prognosis Factor for Mortality in Intensive Care Unit-Admitted Patients with Sepsis

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Abstract

Purpose: Classically, men have been considered to have a higher incidence of infectious diseases, with controversy over the possibility that sex could condition the prognosis of the infection. The aim of the present work was to explore this assumption in patients admitted to the ICU with sepsis using a robust statistical analysis.

Methods: Retrospective analysis (2006-2017) in patients with microbiologically confirmed bacteremia (n=440) by majoritarian bacterial pathogens. Risk of ICU and in-hospital mortality in males respect to females was compared by an univariant analysis and a propensity score correspondence analysis integrating their clinical characteristics.

Results: Relevant differences were related to the infection source: urinary origin for females (28.7% vs 19.8%) and abdominopelvic surgery for males (8.8% vs 4.8%). Sepsis occurred more frequently in males (80.2% vs 76.1%) as well as in-hospital (48.0% vs 41.3%) and ICU (39.9% vs 36.5%) mortality. *Escherichia coli* was 2 times more frequent in survivors whereas *Staphylococcus aureus* was 3 times more frequent in deceased patients. Univariate analyses showed that males had a higher Charlson comorbidity index, a poorer McCabe prognostic score; however the propensity score in 296 patients demonstrated that females had higher risk of both ICU (OR 0.72; 95% CI 0.46 to 1.13), and in-hospital mortality (OR 0.84; 95% CI 0.55 to 1.30) but without statistical significance.

Conclusion: Men with sepsis have worse clinical characteristics when admitted to the ICU, but sex has no influence on the prognosis of mortality. Our data contributes to help reduce the sex-dependent gap present in health care provision.

Introduction

Sepsis is currently defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Microorganisms trigger the systemic immune response with direct cytopathic injury after release of proinflammatory mediators, resulting in endothelial injury, microvascular thrombosis and ultimately tissue ischemia. The cellular damage leads to organ dysfunction that can eventually result in septic shock and death. Sepsis-related mortality has been estimated at 18%-35% [2], being higher in patients admitted to intensive care units (ICUs) [3]. The assessment of the global sepsis impact remains undetermined for developed countries; however the World Health Organization estimates an incidence of 30 million cases and 6 million deaths per year, which represents a major public health concern with a high economic burden [4, 5].

One of the major challenges for ICU clinicians is to identify the prognostic factors that can predict the clinical course and outcome of sepsis. In this sense, the patient's sex has recently been hypothesized as a possible mortality prognostic factor in sepsis of ICU-admitted patients [6]. Both sex (biological and physiological factors specific to male or female) and gender (the social role, the activities attributed to men and women) can influence the acquisition, progression and prognosis of infectious diseases [7].

Examples of how sex differences could constrain the susceptibility to infective agents and the severity of the clinical presentation are those related to the immune system [8], and to pregnancy-related hormonal changes [9, 10]. In the same way, gender-related differences, such as the smoking use to be more common among men, making them more susceptible to respiratory tract infections [11]. It has been classically established by empirical evidence that males are at higher risk of sepsis than females [12], but it is still poorly understood whether sex differences could influence sepsis outcome.

Some studies have specifically assessed the role of sex or gender as a prognostic factor in patients with sepsis, yielding contradictory results [13]. Such differences could be attributed to methodological heterogeneity, lack of consideration of potential confounding factors and to setting (local or country) related factors influencing sepsis outcome. This was a retrospective observational study designed to analyze the impact of sex on the prognosis of ICU-admitted patients with sepsis, only considering the microbiologically confirmed cases by the most common pathogens, and adjusting for a wide set of potential confounding factors through a propensity score matching analysis.

Methods

Case selection strategy

Our institution is a tertiary hospital comprising 7 independent ICUs attending a metropolitan area with more than 1 million of inhabitants. We included all adult (≥ 18 years old) ICU-admitted patients with laboratory-confirmed bacteremia over an 11-year period (2006–2017), stratifying by etiological agent and excluding those caused by sporadic microorganisms ($< 1\%$ frequency). This sampling scheme allowed the inclusion of each microorganism as an individualized factors in the subsequent statistical analysis.

Only cases that fulfilled the current definitions of sepsis or septic shock were selected ($n = 731$). Trained personnel performed a complete and exhaustive review of the clinical charts of the selected patients from ICU admission until death or hospital discharge. Only the first ICU admission of each patient was included, and the recorded variables included demographic data (age, sex), comorbidities measured by the updated Charlson comorbidity index [14], reason for admission, diagnosis, McCabe prognosis index, outcome and length of hospital stay. Other information regarding the bacteremia episode was also documented, including clinical presentation (no sepsis, sepsis, or septic shock), origin (community or nosocomial), primary focus, source control measures, causal agent and antimicrobial susceptibility of the causing isolates (multiresistant or not). The distinction between gender and sex is often difficult, and for this work we have used the sex (male/female), as previously recommended [15]. The primary considered outcomes were mortality in the ICU and in-hospital mortality.

Definitions

To consider a bacteremia episode as laboratory-confirmed, the culture and identification of a recognized pathogen (an organism not included on the National Healthcare Safety Network common commensal

list), from at least one blood culture was required. Cultures were performed in both aerobic and anaerobic blood culture bottles (BD BACTEC™ Plus Aerobic/F and BD BACTEC™ Lytic/10 Anaerobic/F, respectively) that were incubated in a BACTEC™ FX instrument (Becton & Dickinson, Belgium) following the manufacturer's instructions. Sepsis and septic shock status were assessed following the criteria agreed upon by Singer *et al.* [1]. Sepsis is defined as an acute change in the total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points consequent to the infection, whereas septic shock corresponds to a subset of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥ 65 mm Hg and a serum lactate level > 2 mmol/L despite adequate volume for resuscitation. Nosocomial acquisition is designated when a patient has a positive blood culture from 48 hours after their hospital admission, whereas community-acquired sepsis refers to a positive blood culture that occurs within the first 48 hours of hospital admission. Control measures correspond to key interventions in primary focus, including surgery, debridement, drainage and removal of a potentially infected device. Antibiotic multiresistant bacteria are those without *in vitro* phenotypic susceptibility to first-line antimicrobial therapy and with resistance to at least 3 antibiotic families. ICU mortality was defined as death before ICU discharge, and in-hospital mortality as that occurring within the period of hospitalization.

Statistical analysis

Firstly and to characterize our population, a descriptive analysis stratified by sex (male/female) were realized. We expressed categorical variables as absolute and relative frequencies and continuous variables as means and standard deviation or medians and interquartile ranges. Thereafter, we performed a univariate analysis evaluating all potential factors likely associated with the 2 primary outcomes (ICU and in-hospital mortality). Categorical data were compared by chi-squared tests, whereas Student's t-tests were used for sex comparison of continuous variables when normal distribution could be assumed or by Mann-Whitney U test otherwise. We assessed normality of the continuous variables using the Shapiro-Wilk test. Subsequently, we performed a propensity score analysis to assess the effect of sex on primary outcomes while adjusting for the imbalance in the patient's characteristics observed between males and females [16]. To obtain the propensity score, we fitted a logistic regression model, with sex as a binary dependent variable and the potential confounders as independent variables. A propensity score was used to match female to male, without replacement in a ratio 1:1. Matched pairs were chosen using a caliper of 0.2 of the standard deviation of the propensity score (logit scale). We computed standardized differences for all variables included in the propensity score before and after matching to assess the effect of matching on the imbalance. We deemed a 10% standardized difference as the limit for a correct balance. After matching, we compared mortality (ICU and in-hospital) between females and males using a generalized estimating equations model to account for matched data. Stata (V.15; StataCorp. 2017) software was used for the statistical analysis.

Results

Case selection

Our retrospective search yielded 5,520 positive blood cultures from 2,063 adult ICU patients during the selected 11-year period. Patients with bacteremia exclusively caused by microorganisms included in the NHSN-CDC common commensal list and by sporadic microorganisms were excluded (n = 1,288), as were duplicated episodes from the same patient (n = 44). The remaining 731 patients/episodes of bacteremia were attributed to major pathogens such as *Escherichia coli* (24%), *Candida* sp. (13%), *Staphylococcus aureus* (12%), *Enterococcus faecalis* (10%), *Pseudomonas aeruginosa* (10%), *Klebsiella pneumoniae* (10%), and *Streptococcus pneumoniae* (7%). It was also detected 14% polymicrobial episodes. Finally, 440 out of the 731 patients initially selected met the criteria of sepsis or septic shock, and were ultimately used for statistical analysis (Fig. 1).

Descriptive Analysis

Data obtained from the clinical charts reviewed from the 440 patients (62% males and 38% females) are summarized in Table 1. The mean age of the patients was 64.8 ± 14.6 years, being females (66.3 ± 14.2) older than males (63.9 ± 14.8). The males had a higher Charlson comorbidity index and poorer McCabe prognostic score compared with the females. Regarding the bacteremia etiology, a greater presence of *E. coli* (40.7% vs 32.6%) was observed in females, whereas *S. aureus* (14.3% vs 6.6%) and *P. aeruginosa* (10.3% vs 5.4%) were more frequent in males, who also presented more resistance to the therapeutic first-line antibiotics (19.1% vs 12.6%). The major between-sex differences were related to the focus of the infection, urinary origin was more frequent in females (28.7% vs 19.8%), whereas abdominopelvic surgery as an infection source was more common in males (8.8% vs 4.8%). Finally, septic shock occurred more frequently in males (80.2% vs 76.1%) as well as in-hospital (48.0% vs 41.3%) and ICU (39.9% vs 36.5%) mortality.

Table 1

Data obtained from the review of clinical charts stratified by sex. Percentage of bias (setting male group as reference) is also showed. Continuous variables are expressed either as mean and standard deviation or as median and quartiles p25-p75, whereas categorical variables as absolute and relative frequencies

Variable	Before matching			After matching		
	Male	Female	% bias	Male	Female	% bias
	273 (62.0)	167 (38.0)		148 (50.0)	148 (50.0)	
Age						
mean ± sd	63.9 ± 14.8	66.3 ± 14.2	-16.5	65.6 ± 13.9	65.5 ± 14.6	0.8
Charlson comorbidity index						
mean ± sd	2.8 ± 2.3	2.1 ± 1.8	36.9	2.1 ± 1.8	2.2 ± 1.8	-5.3
McCabe prognostic score (n (%))						
Non-fatal	182 (66.9)	124 (74.3)	-16.1	114 (77.0)	110 (74.3)	5.9
Ultimately fatal	47 (17.3)	22 (13.2)	11.4	19 (12.8)	21 (14.2)	-3.8
Rapidly fatal	28 (10.3)	5 (3.0)	29.6	3 (2.0)	5 (3.4)	-5.5
Not applicable	15 (5.5)	16 (9.6)	-15.4	12 (8.1)	12 (8.1)	0.0
Acquisition (n (%))						
Nosocomial	158 (57.9)	82 (49.1)	17.6	75 (50.7)	75 (50.7)	0.0
Community	115 (42.1)	85 (50.9)	-17.6	73 (49.3)	73 (49.3)	0.0
Clinical presentation (n (%))						
Sepsis	54 (19.8)	40 (24.0)	-10.1	33 (22.3)	28 (18.9)	-8.2
Septic shock	219 (80.2)	127 (76.1)	10.1	115 (77.7)	120 (81.1)	8.2
Etiologic agent (n (%))						
<i>Escherichia coli</i>	89 (32.6)	68 (40.7)	-16.9	62 (41.9)	59 (39.9)	4.2
<i>Candida sp.</i>	28 (10.3)	22 (13.2)	-9.1	15 (10.1)	15 (10.1)	0.0
<i>Staphylococcus aureus</i>	39 (14.3)	11 (6.6)	25.3	13 (8.8)	11 (7.4)	4.4
<i>Pseudomonas aeruginosa</i>	28 (10.3)	9 (5.4)	18.2	4 (2.7)	9 (6.1)	-12.6

Variable	Before matching			After matching		
	Male	Female	% bias	Male	Female	% bias
	273 (62.0)	167 (38.0)		148 (50.0)	148 (50.0)	
<i>Klebsiella pneumoniae</i>	29 (10.6)	14 (8.4)	7.6	14 (9.5)	14 (9.5)	0.0
<i>Streptococcus pneumoniae</i>	25 (9.2)	18 (10.8)	-5.4	16 (10.8)	17 (11.5)	-2.3
<i>Enterococcus faecalis</i>	6 (2.2)	5 (3.0)	-5.0	6 (4.1%)	4 (2.7%)	8.5
Polymicrobial	29 (10.6)	20 (12.0)	-4.3	18 (12.2)	19 (12.8)	-2.1
Multiresistant	52 (19.1)	21 (12.6)	17.8	19 (12.8)	21 (14.2)	-3.7
Primary focus (n (%))						
Respiratory	65 (23.8)	40 (24.0)	-0.3	36 (24.3)	38 (25.7)	-3.2
Urinary	54 (19.8)	48 (28.7)	-21.0	42 (28.4)	40 (27.0)	3.2
Vascular or catheter-related	21 (7.7)	15 (9.0)	-4.7	12 (8.1)	8 (5.4)	9.8
Abdominal	53 (19.4)	32 (19.2)	0.6	29 (19.6)	31 (20.9)	-3.4
Abdominopelvic surgery	24 (8.8)	8 (4.8)	15.9	7 (4.7)	8 (5.4)	-2.7
Thoracic or head/neck surgery	6 (2.2)	3 (1.8)	2.9	3 (2.0)	3 (2.0)	0.0
Endocarditis	11 (4.0)	4 (2.4)	9.3	7 (4.7)	4 (2.7)	11.5
Meningitis	3 (1.1)	3 (1.8)	-5.8	3 (2.0)	2 (1.4)	5.6
Others	13 (4.8)	4 (2.4)	12.7	2 (1.4)	4 (2.7)	-7.3
Unknown	23 (8.4)	10 (6.0)	9.4	7 (4.7)	10 (6.8)	-7.8
Source control measures (n (%))						
Yes	86 (31.5)	63 (37.7)	-13.1	52 (35.1)	48 (32.4)	5.7
Length of stay at ICU (days)						
median (p25;p75)	7 (2;18)	7 (3;18)	-	7 (3;18)	7 (3;21)	-

Univariable Analysis

Factors significantly associated ($p < .05$) with the two selected outcomes, ICU and in-hospital mortality, were Charlson index, mode of acquisition (higher rates of nosocomial origin between deceased patients),

clinical presentation (higher septic shock rates in deceased patients), and the presence of an antibiotic multiresistant bacteria (Table 2). The anatomical focus of the bacteremia was significantly associated with mortality; the urological tract was approximately 3 times more frequent in survivors than in deceased patients and endocarditis was 7 times more frequent in the deceased than in survivors. Finally, the etiological agent was also associated with broad mortality differences, ranging from *E. coli*, which was 2 times more frequent in survivors, to *S. aureus* that was 3 times more frequent in deceased patients.

Table 2

Results from the univariable analysis to detect association of potential confounders with either hospital mortality or ICU mortality. Continuous variables are expressed either as mean and standard deviation or as median and quartiles p25-p75, whereas categorical variables as absolute and relative frequencies. Significant *p* values (< .05) are marked in bold

Variable	ICU mortality		<i>p</i> value	Hospital mortality		
	YES	NO		YES	NO	<i>p</i> value
	170 (38.6)	270 (61.4)		200 (45.5)	240 (54.5)	
Age						
mean ± sd	65.2 ± 14.2	64.6 ± 14.9	.716	65.2 ± 14.1	64.5 ± 15.1	.654
Charlson comorbidity index						
mean ± sd	3.2 ± 2.2	2.1 ± 2.0	<.001	3.1 ± 2.2	2.0 ± 1.9	<.001
McCabe prognostic score (n(%))						
Non-fatal	109 (64.1)	197 (73.0)	<.001	126 (63.0)	180 (75.3)	<.001
Ultimately fatal	35 (20.6)	34 (12.6)		41 (20.5)	28 (11.7)	
Rapidly fatal	22 (12.9)	11 (4.1)		28 (14.0)	5 (2.1)	
Not applicable	4 (2.4)	27 (10.0)		5 (2.5)	26 (10.9)	
Acquisition (n(%))						
Nosocomial	115 (67.7)	125 (46.3)	<.001	133 (66.5)	107 (44.6)	<.001
Clinical presentation (n(%))						
Septic shock	145 (85.3)	201 (74.4)	.007	168 (84.0)	178 (74.2)	.012
Etiologic agent (n(%))						
<i>Escherichia coli</i>	41 (24.1)	116 (43.0)	<.001	50 (25.0)	107 (44.6)	<.001
<i>Candida</i> sp.	30 (17.7)	20 (7.4)		36 (18.0)	14 (5.8)	
<i>Staphylococcus aureus</i>	33 (19.4)	17 (6.3)		34 (17.0)	16 (6.7)	

Variable	ICU mortality		p value	Hospital mortality		
	YES	NO		YES	NO	p value
	170 (38.6)	270 (61.4)		200 (45.5)	240 (54.5)	
<i>Pseudomonas aeruginosa</i>	15 (8.8)	22 (8.2)		19 (9.5)	18 (7.5)	
<i>Klebsiella pneumoniae</i>	13 (7.7)	30 (11.1)		16 (8.0)	27 (11.3)	
<i>Streptococcus pneumoniae</i>	12 (7.1)	31 (11.5)		12 (6.0)	31 (12.9)	
<i>Enterococcus faecalis</i>	3 (1.8)	8 (3.0)		5 (2.5)	6 (2.5)	
Polymicrobial	23 (13.5)	26 (9.6)		28 (14.0)	21 (8.8)	
Antibiotic multiresistant agent (n(%))						
Yes	36 (21.2)	37 (13.7)	.040	44 (22.0)	29 (12.1)	.005
Focus (n(%))						
Respiratory	50 (30.0)	54 (20.0)		53 (26.5)	52 (21.6)	<.001
Urinary	19 (11.2)	83 (30.7)		25 (12.5)	77 (32.1)	
Vascular or catheter-related	16 (9.4)	20 (7.4)		23 (11.5)	13 (5.4)	
Abdominal	25 (14.7)	60 (22.2)		34 (17.0)	51 (21.3)	
Abdominopelvic surgery	12 (7.1)	20 (7.4)	<.001	13 (6.5)	19 (7.9)	
Thoracic or head/neck surgery	4 (2.4)	5 (1.9)		4 (2.0)	5 (2.1)	
Endocarditis	12 (7.1)	3 (1.1)		12 (6.0)	3 (1.3)	
Meningitis	4 (2.4)	2 (0.7)		4 (2.0)	2 (0.8)	
Others	8 (4.7)	9 (3.3)		10 (5.0)	7 (2.9)	
Unknown	19 (11.2)	14 (5.2)		22 (11.0)	11 (4.6)	
Source control measures (n(%))						

Variable	ICU mortality		p value	Hospital mortality		
	YES	NO		YES	NO	p value
	170 (38.6)	270 (61.4)		200 (45.5)	240 (54.5)	
Yes	51 (30.0)	98 (36.3)	.174	61 (30.5)	88 (36.7)	.174
Length of stay at ICU (days)						
median (p25;p75).	14.7 (18.1)	13.7 (18.6)	0.792	15.98 (19.3)	12.53 (17.5)	0.280
U MannWhitney test						

Propensity Score Matching And Risk Estimation

Significant variables associated with mortality in the univariable analysis were further selected to perform propensity score matching. After a pairing algorithm, a total of 296 cases (148 from each sex) were matched. Figure 2 shows the standardized differences by sex, before and after perform the matching. After matching, only endocarditis as the primary focus in men and *P. aeruginosa* as the etiologic agent for women remained with a minor disbalance (Table 1 and Fig. 2).

The between-sex difference in risks for both ICU and in-hospital mortality were calculated in the matched cohort (Table 3). Our results showed that the risk of ICU mortality was 28% lower in males (OR 0.72; 95% CI 0.46 to 1.13), as well as the risk of in-hospital mortality, which was 16% lower in males (OR 0.84; 95% CI 0.55 to 1.30). Although there was no statistical significance in the matched analysis for either ICU or in-hospital mortality, these findings contrast with the univariate results in which men presented higher a ICU (39.9% vs 36.5%) and in-hospital (48.0% vs 41.3%) mortality risk.

Table 3

Comparison of hospital and ICU mortality risk by sex, and odds ratio after the propensity score matching. Male group has been taken as reference for the odds ratio calculation

Hospital mortality	Male (n = 148)	Female (n = 148)	Total (n = 296)
No. of events	56	62	118
Risk (%)	37.8%	41.9%	39.9%
Odds Ratio, adjusted (95% CI)	0.84 (0.55; 1.30)	-	-
ICU mortality			
No. of events	45	56	101
Risk (%)	30.4%	37.8%	34.1%
Odds Ratio, adjusted (95% CI)	0.72 (0.46; 1.13)	-	-

Table 4

Characteristics of studies that specifically assessed the role of sex/gender on mortality in septic patients admitted to ICU (literature search period: last 15 years)

Reference/Country	Research strategy	Statistical approach	Study sample	Mortality definitions	Main results
Angstwurm <i>et al.</i> (2005) Germany [17]	Prospective observational study	Univariable analysis. Stratification by hormonal levels.	n = 308 Severe infection/sepsis	Hospital mortality	Equal risk of hospital mortality
Adrie <i>et al.</i> (2007) France [35]	Prospective observational nested case-control study	Propensity score matching / Stratification	n = 1.692 Severe sepsis	ICU and hospital mortality	More risk of ICU and hospital mortality in men (only in > 50 year-old group)
Pietropaoli <i>et al.</i> (2010) USA, Canada, Brazil [42]	Retrospective cohort study	Multivariable logistic regression analysis	n = 18.757 Severe sepsis and septic shock	Hospital mortality	More risk of hospital mortality in women
Nachtigall <i>et al.</i> (2011) Germany [37]	Prospective observational study	Multivariable logistic regression analysis	n = 327 Sepsis	ICU mortality	More risk of ICU mortality in women
De Oliveira Couto <i>et al.</i> (2011) Brazil [41]	Retrospective comparative study	Matching by age	n = 133 Sepsis	ICU mortality	More risk of ICU and hospital mortality in men (only in < 40 year-old group)
Jacobson <i>et al.</i> (2012) Sweden [19]	Prospective observational cohort study	Multivariable backward stepwise logistic regression analysis	n = 127 Severe sepsis and septic shock	Three-month, 6-month, and 2-year mortality	Equal risk of hospital mortality
Sakr <i>et al.</i> (2013) Italy [36]	Retrospective cohort study	Multivariable logistic regression analysis / Stratification	n = 305 Severe sepsis and septic shock	ICU mortality	More risk of ICU mortality in women (only in severe sepsis group)

Reference/Country	Research strategy	Statistical approach	Study sample	Mortality definitions	Main results
Madsen <i>et al.</i> (2014) USA [40]	Retrospective observational study	Multivariable logistic regression analysis	n = 814 Severe sepsis and septic shock	Hospital mortality	Equal risk of hospital mortality
van Vught <i>et al.</i> (2017) Netherlands [23]	Prospective observational cohort study	Multivariable logistic regression analysis / Stratification	n = 1.815 Sepsis	ICU, hospital, 30-day, 60-day, 90-day, and 1-year mortality	Equal risk of 90-day mortality (in all groups tested)
Xu <i>et al.</i> (2019) China [43]	Retrospective observational cohort study	Multivariable logistic regression analysis	n = 6.134 Severe sepsis and septic shock	Hospital, 90-day, and 1-year mortality	More risk of 1-year mortality in men

Discussion

The possible link between sex and infectious diseases has classically been debated, and males are often attributed as having a greater predisposition for infection and a poorer prognosis [12]. Previously published works focused on sepsis have obtained contradictory results [13], making it worthwhile to deeply evaluate the actual sex and gender impact on sepsis prognosis, and validating it in each country or geographical area. This is the first study from our country regarding this topic, and we performed an exhaustive analysis to mitigate confounding factors by propensity score matching. Our study on ICU patients with sepsis revealed, after propensity score matching, that ICU and hospital mortality rates are slightly lower for males, and this result is opposite to that observed in the univariable analysis, reinforcing the need to adapt the analytical strategy for each situation. However, given this observation had not statistical significance, we can only conclude that both ICU and in-hospital mortality rates of ICU patients with sepsis or septic shock are not significantly influenced by sex. This conclusion is consistent with other previously published works [17–23]. Also, as occurs in other series [23, 24], our male patients had more comorbidities, higher septic shock incidence and both ICU and in-hospital mortality. On the contrary, women were associated with urinary primary focus of sepsis and a lower incidence of Gram-positive bacteremia, which has been widely reported [18].

Experimental studies have been performed to unravel the physiological mechanisms that could explain these observations and also to validate sex at a prognostic level. In animal studies, females have more advantageous immunological and cardiovascular responses against severe infections such as sepsis [24, 25] by the direct effect of their estradiol [26–28]. Moreover, genetic aspects, such as the female X chromosome mosaicism, could confer a diversification of leukocyte responses during endotoxemia [29]. In contrast, the 5 α -dihydrotestosterone present in males appears to exert a deleterious effect, weakening

cardiovascular functions [29] and promoting the cytokine-mediated response [31–33]. Several experiments in sepsis have demonstrated the therapeutic utility of the administration of the oestrogen precursor dehydroepiandrosterone (DHEA), and the blockage of androgen-related adverse effects through the administration of androgen receptor antagonists such as flutamide [34].

It is generally assumed that males have a higher incidence of severe forms of sepsis [35, 36] and more organ failure [18, 19], which spurred the interest to evaluate whether females have milder symptoms and better outcomes during a septic episode. However, clinical studies attempting to evaluate the relationship between sex and sepsis prognosis have failed to achieve consistent results. All the recently published studies (in the last 15 years) that include an evaluation of the influence of sex on the outcome of ICU patients with sepsis among their primary objectives are summarized in Table 4. Several reasons could explain the disparity of results, the most evident being the geographic location of the studies, which implies socio-economic and racial differences of the enrolled population, as well as differences in diagnostic accuracy and therapeutics. Case definitions are also relevant; given some studies include a mix of surgical and medical ICU patients, or only patients with severe sepsis or septic shock. Importantly, the definitions of gender and sex were not clear in some studies, so the results could be misleading. There are also important differences in study design, outcome endpoint, statistical approach (i.e. which methodology was used to control for confounding factors) and which studies were selected. The latter point is critical, given the difficulty in identifying true confounders. For instance, there is accumulated evidence indicating that males receive both more invasive procedures and earlier antimicrobial therapy than females. A recent systematic review and meta-analysis aimed to evaluate gender-related mortality risk in ICU patients with sepsis [13]. The authors found a slightly higher risk of mortality in women, although this result was considered inconclusive given the heterogeneity of the results obtained in each of the separately selected studies.

The strengths of our study include the fact that is the first work in which the latest sepsis criteria have been applied [1]; the selection of the patients was made for the first time on the basis of microbiological data, selecting only episodes caused by the most prevalent and relevant pathogens; and the use of a propensity score matching approach allowed us to obtain 2 groups carefully matched on a large set of confounding factors. Finally, this study is the first to assess the effect of sex on sepsis mortality for the Spanish population.

Our main limitations include the retrospective nature of the study, the inclusion of a single center, and the fact that we were unable to control for hormonal status and the immunological host-response. We did not perform stratification by age to separate premenopausal and postmenopausal women, contrary to what was performed in some previous studies [23, 36, 41]. Finally, we matched in the propensity score by focus and etiologic agent, due to the aforementioned differences obtained by sex. These factors could also be observed as true drivers of the pathophysiology of sepsis; thus matching by them could have biased the true sex mortality differences observed in the present work. Despite our efforts to adjust for a number of possible confounders of the association between sex and survival, we cannot disregard the possibility that residual confounding is still present due to unobserved variables.

Conclusion

Evidence regarding sex-related differences in susceptibility and host-response to sepsis has not been consistently supported by clinical studies due to its heterogeneity and the difficulties to control for underlying biases. Our findings showed that males have a better prognosis of sepsis in the ICU compared with females, although the confidence interval prevents us from excluding a significant reduction or increase in mortality risk. Our group is currently working on a systematic review that aims to comprehensively assess the prognostic role of sex in critically ill adults with sepsis; protocol registered in PROSPERO as CRD42019145054 [44]. Accumulated knowledge in this area could lead to the development of sex-targeted therapies in sepsis, and to contributing to a reduction in the sex-dependent gap present in health care provision.

Abbreviations

ICU

Intensive Care Unit

SOFA

Sequential Organ Failure Assessment

NHSN-CDC

National Helathcare Safety Network-Centers for Disease Control and Prevention

Declarations

Ethics approval and consent to participate

The ethics committee for clinical research at our institution approved this study, considering that informed consent of the patients was not necessary due to the retrospective and non-interventional condition of the study.

Availability of data and material

All material used for this work are available.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Author’s contributions

MPA and BMFF designed the work and made the acquisition, analysis, and interpretation of the data and draft of the work. RC and AM designed the work and revised it. AH, MRD, and AMSD made the acquisition, analysis and interpretation of the data. JZ and RdC designed the work, interpreted the data and wrote the manuscript. All authors read and approved the final manuscript.

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Figures

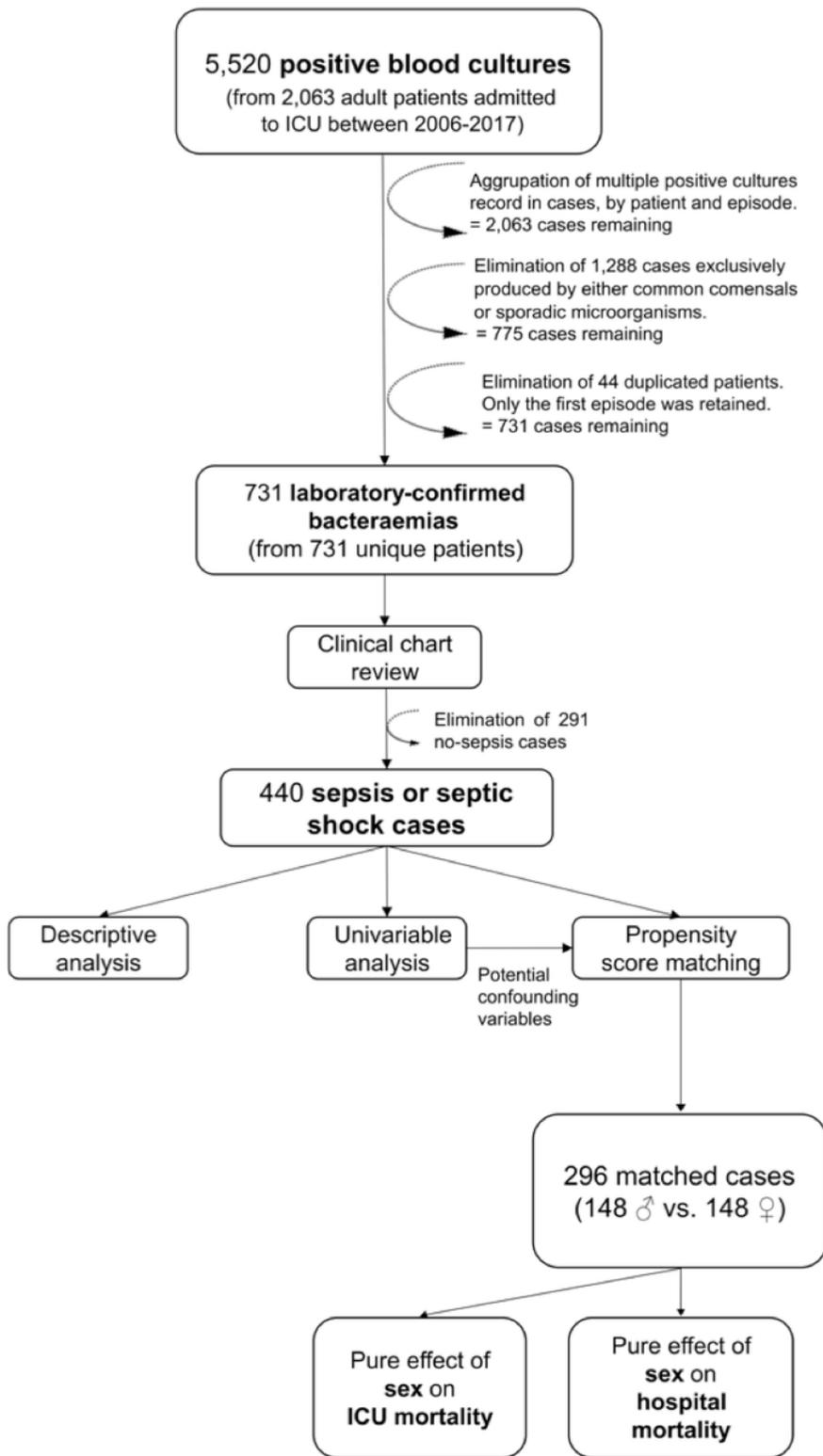


Figure 1

Flowchart from case selection to statistical analysis.

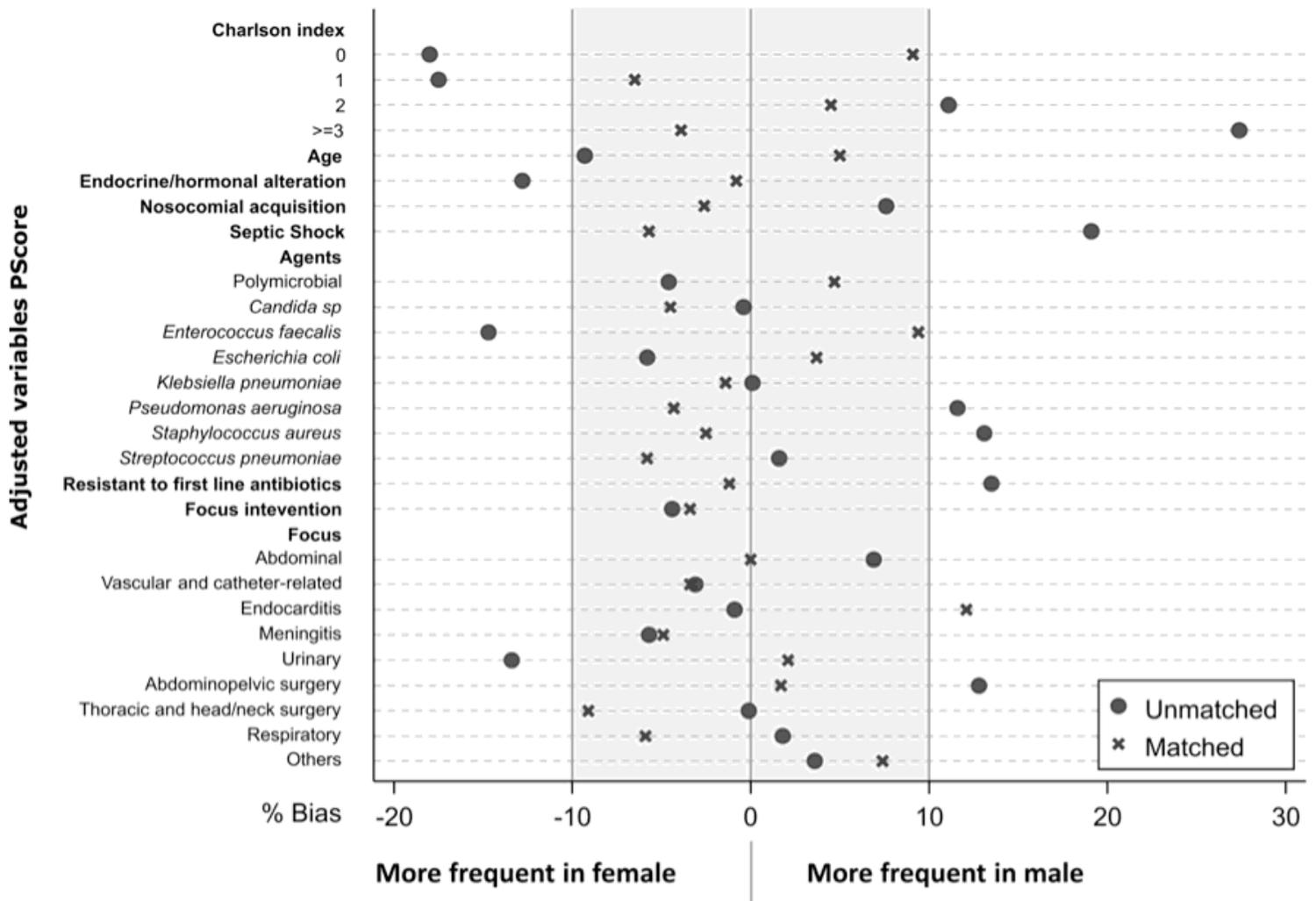


Figure 2

Comparison of the bias deviation (%) of potential confounding variables by sex, before (dots) and after (crosses) propensity score matching. Bias cut-off range is delimited by vertical bars, and only *P. aeruginosa* as etiological agent in females and endocarditis as infectious source in males remained above cut-off after matching.