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

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ABSTRACT

Objective: Men have been considered to have a higher incidence of infectious diseases, with controversy over the possibility that sex could influence the prognosis of the infection. This study aimed to explore this assumption in patients admitted to the intensive care unit (ICU) with septic bacteremia.

Methods: A retrospective analysis (2006-2017) of septic patients with microbiologically confirmed bacteremia (n=440) was performed. Risk of ICU and in-hospital mortality in males versus females was compared by univariate analysis and a propensity score analysis integrating their clinical characteristics.

Results: Sepsis more frequently occurred 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. Univariate analyses showed that males had a higher Charlson comorbidity index and worse McCabe prognostic score. However, the propensity score in 296 matched patients demonstrated that females had higher risk of both ICU (OR 1.39; 95% CI 0.89-2.19) and in-hospital mortality (OR 1.18; 95% CI 0.77-1.83), but without statistical significance.

Conclusion: Males with sepsis had worse clinical characteristics when admitted to the ICU, but sex had no influence on mortality. These data contribute to helping reduce the sex-dependent gap present in healthcare provision.

Introduction

Sepsis is currently defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [Singer et al., 2016]. 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% [Perner et al., 2016], being higher in patients admitted to intensive care units (ICUs) [Mayr et al., 2014]. Assessment of the global sepsis impact remains undetermined for developed countries; however, the World Health Organization (WHO) estimates an incidence of 30 million cases and 6 million deaths per year, which represents a major public health concern with high economic burden [Taeb et al., 2017; Álvaro-Meca et al., 2018].

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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 risk factor for ICU mortality in septic ICU-admitted patients [Shankar-Hari et al., 2016]. Both sex (biological and physiological factors specific to males or females) and gender (the social role, the activities attributed to men and women) can influence the acquisition, progression and prognosis of infectious diseases [Miller, 2012]. 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 [Wizemann & Pardue, 2001] and to pregnancy-related hormonal changes [Littauer et al., 2017; Pérez-Gracia et al., 2017]. An example of gender-related differences is smoking used to be more common among men, making them more susceptible to respiratory tract infections [Torres et al., 2013]. It has been classically established by empirical evidence that males are at higher risk of sepsis than females [Campanelli et al., 2018], 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 [Papathanassoglou et al., 2017]. 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.

The current study was a retrospective observational study designed to analyze the impact of sex on the prognosis of ICU-admitted patients with sepsis, only considering microbiologically confirmed cases by the most common pathogens, and adjusting for a set of potential confounding factors through propensity score matching analysis.

Methods

Case selection strategy

The current institution is a tertiary hospital comprising seven independent ICUs attending a metropolitan area with more than 1 million inhabitants. This study 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 factor 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 [Quan et al., 2011], 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 (multi-resistant or not). The distinction between gender and sex is often difficult, and this study decided to use sex (male/female), as previously recommended [Heidari et al., 2016]. The primary considered outcomes were mortality in the ICU and in-hospital mortality.

Definitions

To consider a bacteremic 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.* in 2016. 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 multi-resistant bacteria are those without *in vitro* phenotypic susceptibility to first-line antimicrobial therapy and with resistance to at least three 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

First, and to characterize the population, a descriptive analysis stratified by sex (male/female) was undertaken. Categorical variables were expressed as absolute and relative frequencies, and continuous variables as means and standard deviation or medians and interquartile ranges. Thereafter, a univariate analysis was performed evaluating all potential factors likely associated with the two 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. Normality of the continuous variables was assessed using the Shapiro-Wilk test. Subsequently, a propensity score analysis was performed to assess the effect of sex on primary outcomes while adjusting for the imbalance in the patient's characteristics observed between males and females [Austin, 2011]. To obtain the propensity score, a logistic regression model was fitted with sex as a binary dependent variable and the potential confounders as independent variables. A propensity score was used to match females to males, without replacement in a ratio of 1:1. Matched pairs were chosen using a caliper of 0.2 of the standard deviation of the propensity score (logit scale). Standardized differences for all variables included in the propensity score before and after matching were computed to assess the effect of matching on the imbalance. A 10% standardized difference was deemed to be the limit for a correct balance. After matching, mortality (ICU and in-hospital) between females and males was compared using a generalized estimating equations model to account for matched data. Stata (V.15; StataCorp. 2017) software was used for the statistical analysis. In addition, sensitivity analyses were carried out on two sub-populations: including only patients who received vasopressors (severe cases) and excluding females aged <50 years (to limit the influence of female sex hormones).

Results

Case selection

The 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 National Healthcare Safety Network-Centers for Disease Control and Prevention (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/fungemia were attributed to major pathogens such as *Escherichia coli* (24%), *Candida* spp. (13%), *Staphylococcus aureus* (12%), *Enterococcus faecalis* (10%), *Pseudomonas aeruginosa* (10%), *Klebsiella pneumoniae* (10%), and *Streptococcus pneumoniae* (7%). It also detected 14% polymicrobial episodes. Finally, 440 of the 731 patients initially selected met the criteria of sepsis or septic shock, and were ultimately used for statistical analysis (Figure 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, with females (66.3±14.2) being older than males (63.9±14.8). The males had a higher Charlson comorbidity index and worse McCabe prognostic score compared with females. Regarding the etiology of bacteremia, 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 differences between female and male patients 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 was more common in males (80.2% *vs* 76.1%), and hospital (48.0% *vs* 41.3%) and ICU (39.9% *vs* 36.5%) mortality was also higher in males.

Univariate analysis

Factors significantly associated ($p<0.05$) with the two selected outcomes (ICU and in-hospital mortality) were Charlson index, source of infection (higher rates of nosocomial origin among deceased patients), clinical presentation (higher septic shock rates in deceased patients), and the presence of an antibiotic multidrug-resistant bacteria (Table 2). The anatomical focus of the bacteremia was significantly associated with mortality; the urinary tract was approximately three times more frequent in survivors than in deceased patients, and endocarditis was seven 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 twice more frequent in survivors, to *S. aureus* that was three times more frequent in deceased patients.

Propensity score matching and risk estimation

Significant variables associated with mortality in the univariate 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 performing 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 misbalance (Table 1 and Figure 2).

The risk of sex difference in both ICU and in-hospital mortality were calculated in the matched cohort (Table 3). The results showed that the risk of both ICU (OR 1.39; 95% CI 0.89 to 2.19) and in-hospital mortality (OR 1.18; 95% CI 0.77 to 1.83) were higher in females. Sensitivity analysis including only females aged >50 years (n=124) and their respective counterparts (n=124) also pointed to a higher risk for both ICU (OR 1.59; 95% CI 0.99-2.57) and in-hospital mortality (OR 1.40; 95% CI 0.88-2.24) in the female group. The same trend was observed if only including subjects receiving vasopressors (n=188) (ICU mortality: OR 1.57; 95% CI 0.86-2.86; and in-hospital mortality: OR 1.35; 95% CI 0.77-2.39). Although there was no statistical significance in the paired analysis for ICU or in-hospital mortality, these findings contradict the results of univariate analysis showing that males have a higher ICU (39.9% *vs* 36.5%) and in-hospital (48.0% *vs* 41.3%) mortality risk.

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 [Campanelli et al., 2018]. Previously published studies focused on sepsis have obtained contradictory results [Papathanassoglou et al., 2017], making it worthwhile to evaluate the actual sex and gender impact on sepsis prognosis, and validate it in each country or geographical area. This is the first study from Spain regarding this topic, where propensity score matching was used to mitigate potential confounding factors. This study on ICU patients with sepsis revealed, after propensity score matching, that ICU and hospital mortality rates were slightly higher for females, and this result is opposite to that observed in univariate analysis, reinforcing the need to adapt the analytical strategy for each situation. However, given that this observation had no statistical significance, it can only be concluded 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 work [Angstwurm et al., 2005; Esper el at., 2006; Jacobson et al., 2012; Mahmood et al., 2012; Madsen et al., 2014; Samuelsson et al., 2015; van Vught et al., 2017]. Also, as occurred in other series [Zellweger et al. 1997; van Vught et al., 2017], the 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 [Esper et al., 2006].

Experimental studies have been performed to unravel the physiological mechanisms that could explain these observations and to validate sex at a prognostic level. In animal studies, females have more advantageous immunological and cardiovascular responses against severe infections such as sepsis [Zellweger et al., 1997; Diodato et al., 2001] by the direct effect of their estradiol [Sakiani et al., 2013; Yu & Chaudry, 2009; Zhu et al., 2009]. Moreover, genetic aspects, such as the female X chromosome mosaicism, could confer a diversification of leukocyte responses during endotoxemia [Chandra et al., 2010]. In contrast, the 5a-dihydrotestosterone present in males appears to exert a deleterious effect, weakening cardiovascular functions [Kuebler et al., 2003] and promoting the cytokine-mediated response [Aulock et al., 2006; Frink et al., 2007; Oberholzer et al., 2000]. Several experiments in sepsis have demonstrated the therapeutic utility of the administration of the estrogen precursor dehydroepiandrosterone (DHEA), and the blockage of androgen-related adverse effects through administration of androgen receptor antagonists such as flutamide [Angele et al., 2014].

It is generally assumed that males have a higher incidence of severe forms of sepsis [Adrie et al., 2007; Sakr et al., 2013] and

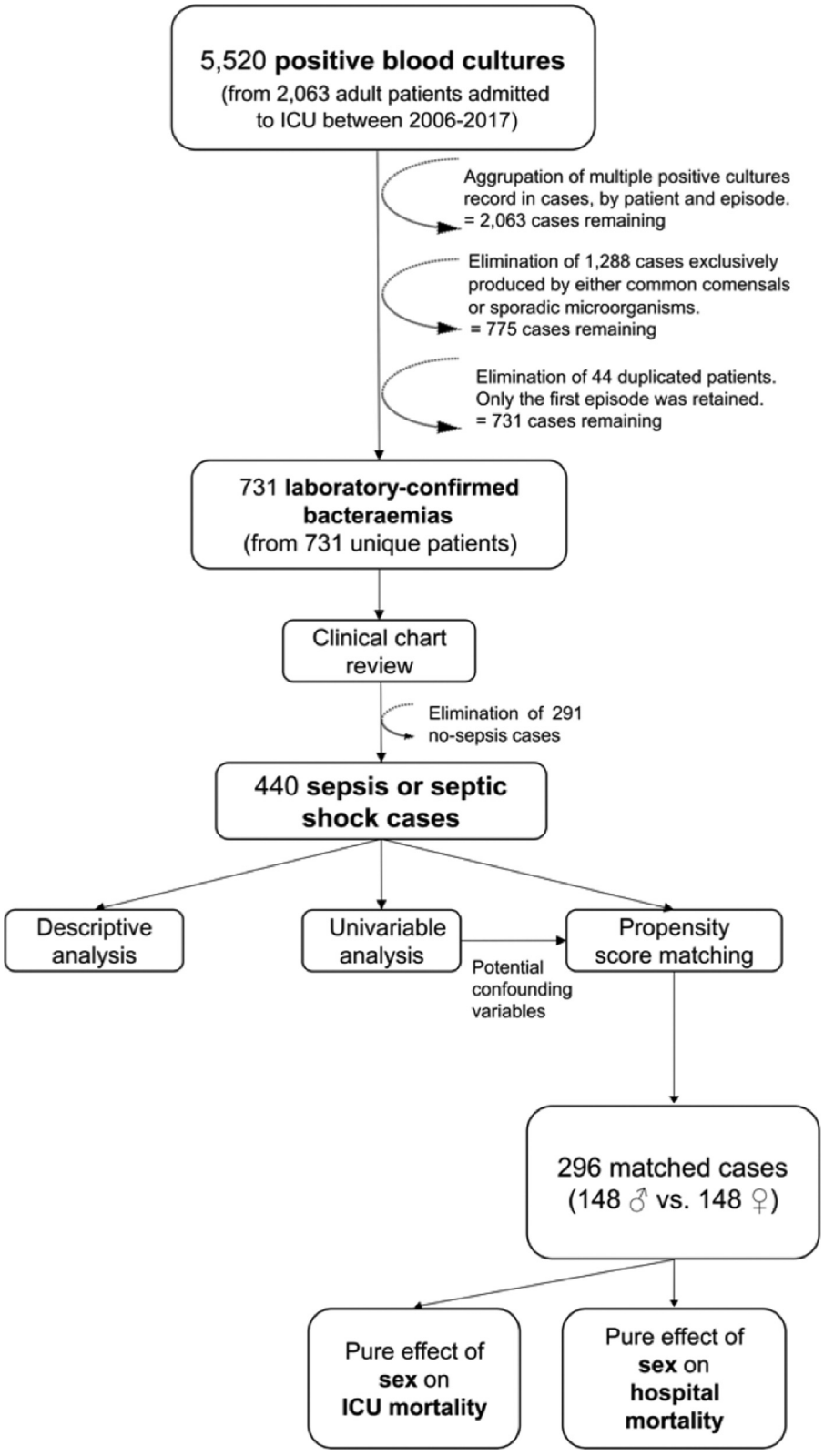

Figure 1. Flowchart from case selection to statistical analysis.

more organ failure [Esper et al. 2006; Jacobson et al. 2012], 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 included 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,

Table 1
Data obtained from the review of clinical charts stratified by sex.

Variable	Before matching Male 273 (62.0)	 Female 167 (38.0)	 % bias	After matching Male 148 (50.0)	 Female 148 (50.0)	 % bias
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
Source (n (%))						
Nosocomial	158 (57.9)	82 (49.1)	17.6 -17.6	75 (50.7)	75 (50.7)	0.0
Community	115 (42.1)	85 (50.9)		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
Etiological agent (n (%))						
Escherichia coli	89 (32.6)	68 (40.7)	-16.9	62 (41.9)	59 (39.9)	4.2
Candida spp.	28 (10.3)	22 (13.2)	-9.1	15 (10.1)	15 (10.1)	0.0
Staphylococcus aureus	39 (14.3)	11 (6.6)	25.3	13 (8.8)	11 (7.4)	4.4
Pseudomonas aeruginosa	28 (10.3)	9 (5.4)	18.2	4 (2.7)	9 (6.1)	-12.6
Klebsiella pneumoniae	29 (10.6)	14 (8.4)	7.6	14 (9.5)	14 (9.5)	0.0
Streptococcus pneumoniae	25 (9.2)	18 (10.8)	-5.4	16 (10.8)	17 (11.5)	-2.3
Enterococcus faecalis	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
Multi-resistant	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
Bloodstream or CRB	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 surgical site	24 (8.8)	8 (4.8)	15.9	7 (4.7)	8 (5.4)	-2.7
Thoracic head/neck surgical site	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 (IQR)	7 (2;18)	7 (3;18)	-	7 (3;18)	7 (3;21)	-

Percentage of bias (setting male group as reference) is showed. Continuous variables are expressed either as mean and standard deviation or as median and quartiles p25-75, whereas categorical variables as absolute and relative frequencies.
CRB: catheter-related bloodstream; ICU, intensive care unit

which implies socioeconomic and racial differences in the enrolled population as well as differences in diagnostic accuracy and therapeutics. Case definitions are also relevant, given that 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 unclear 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 accumulating 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 [Papathanassoglou et al., 2017]; the authors found a slightly higher risk of mortality in

Table 2
Results from the univariate analysis to detect association of potential confounders with either hospital mortality or ICU mortality.

Variable	ICU mortality YES 170 (38.6)	NO 270 (61.4)	*p*-value	Hospital mortality YES 200 (45.5)	NO 240 (54.5)	*p*-value
Age						
mean±SD	65.2±14.2	64.6±14.9	0.716	65.2±14.1	64.5±15.1	0.654
Charlson comorbidity index						
mean±SD	3.2±2.2	2.1±2.0	**<0.001**	3.1±2.2	2.0±1.9	**<0.001**
McCabe prognostic score (n(%))						
Non-fatal	109 (64.1)	197 (73.0)	**<0.001**	126 (63.0)	180 (75.3)	**<0.001**
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)	
Source, n (%)						
Nosocomial	115 (67.7)	125 (46.3)	**<0.001**	133 (66.5)	107 (44.6)	**<0.001**
Clinical presentation, n (%)						
Septic shock	145 (85.3)	201 (74.4)	**0.007**	168 (84.0)	178 (74.2)	**0.012**
Etiological agent, n (%)						
Escherichia coli	41 (24.1)	116 (43.0)	**<0.001**	50 (25.0)	107 (44.6)	**<0.001**
Candida spp.	30 (17.7)	20 (7.4)		36 (18.0)	14 (5.8)	
Staphylococcus aureus	33 (19.4)	17 (6.3)		34 (17.0)	16 (6.7)	
Pseudomonas aeruginosa	15 (8.8)	22 (8.2)		19 (9.5)	18 (7.5)	
Klebsiella pneumoniae	13 (7.7)	30 (11.1)		16 (8.0)	27 (11.3)	
Streptococcus pneumoniae	12 (7.1)	31 (11.5)		12 (6.0)	31 (12.9)	
Enterococcus faecalis	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 multi-resistant agent (n(%))						
Yes	36 (21.2)	37 (13.7)	**0.040**	44 (22.0)	29 (12.1)	**0.005**
Focus, n (%)						
Respiratory	50 (30.0)	54 (20.0)		53 (26.5)	52 (21.6)	**<0.001**
Urinary	19 (11.2)	83 (30.7)		25 (12.5)	77 (32.1)	
Bloodstream or CRB	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 surgical site	12 (7.1)	20 (7.4)	**<0.001**	13 (6.5)	19 (7.9)	
Thoracic head/neck surgical site	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(%))						
Yes	51 (30.0)	98 (36.3)	0.174	61 (30.5)	88 (36.7)	0.174
Length of stay at ICU (days)						
median (IQR). Mann-Whitney U test	14.7 (18.1)	13.7 (18.6)	0.792	15.98 (19.3)	12.53 (17.5)	0.280

Continuous variables are expressed either as mean and standard deviation or as median and interquartile range (p25-75), whereas categorical variables as absolute and relative frequencies. Significant *p* values (<0.05) are marked in bold.
CRB: catheter-related bloodstream; ICU, intensive care unit

Table 3
Comparison of hospital and ICU mortality risk by sex, and odds ratio after propensity score matching. Male group has been taken as reference for the odds ratio calculation.

	Male (n=148)	Female (n=148)	Total (n=296)
Hospital mortality			
No. of events	56	62	118
Risk (%)	37.8%	41.9%	39.9%
Odds ratio, adjusted (95% CI)	-	1.18 (0.77; 1.83)	-
ICU mortality			
No. of events	45	56	101
Risk (%)	30.4%	37.8%	34.1%
Odds ratio, adjusted (95% CI)	-	1.39 (0.89; 2.19)	-

women, although this result was considered inconclusive, given the heterogeneity of the results obtained in each of the separately selected studies.

The strengths of the current study included the fact that was the first work in which the latest sepsis criteria were applied [Singer et al., 2016]; 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 using a propensity score matching approach enabled two groups to be obtained that were carefully matched on potential confounding factors. In addition, age was stratified to minimize the influence of female sex hormones, as performed in some previous studies [Adrie et al., 2007; Sakr et al., 2013; van Vught et al, 2017], and by disease severity (in terms of use of vasopressors). Finally, this study was the first to assess the effect of sex on sepsis mortality for the Spanish population.

The main limitations included the retrospective nature of the study, inclusion of a single center, and the fact that it was unable to control for hormonal status and immunological host-response. In addition, it was decided to not include severity scores such as SOFA or SAPS II in the propensity score analysis, since previous work pointed out that such scores could be biased by sex [Nachtigall et al., 2011; Jacobson et al., 2012]; however, a recent study suggested the contrary [Nouri-Pasovsky et al., 2021]. Finally,

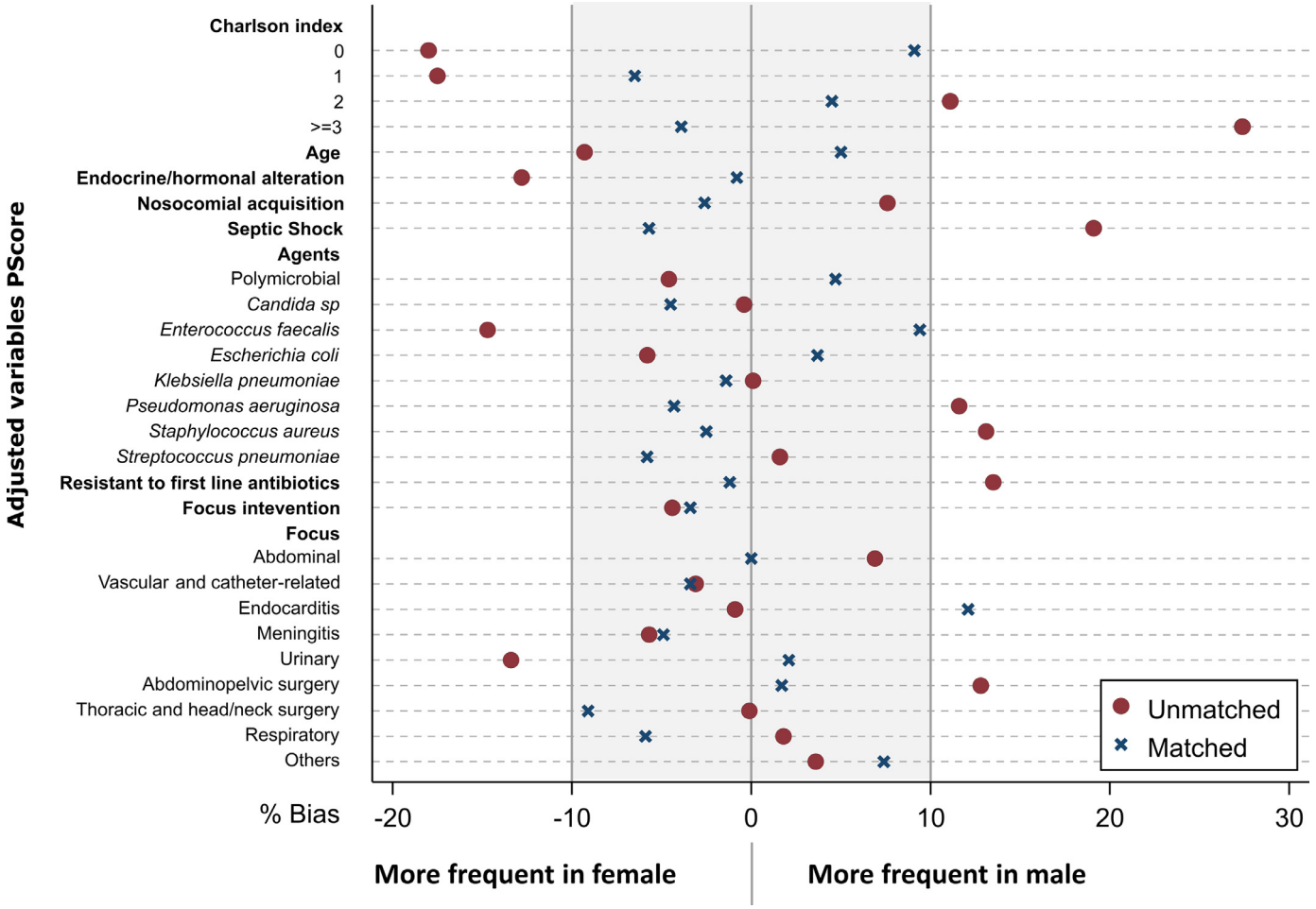

Figure 2. Comparison of the bias deviation (%) of potential confounding variables by sex, before (dots) and after (crosses) propensity score matching. Bias cut-off range is delimited by vertical bars, and only *Pseudomonas aeruginosa* as the etiological agent in females and endocarditis as the infectious source in males remained above the cut-off after matching.

the current study matched in the propensity score by focus and etiologic agent, due to the aforementioned differences obtained by sex. These could also be observed as true driving factors of the pathophysiology of sepsis; thus, matching by them could have biased the true sex mortality differences observed in the present work. Despite efforts to adjust for a number of possible confounders of the association between sex and survival, the possibility that residual confounding is still present, due to unobserved variables, cannot be disregard.

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 in controlling for underlying biases. These findings showed that males have a better prognosis of septic bacteremia in the ICU compared with females, although the confidence interval prevented exclusion of a significant reduction or increase in mortality risk. The absence of statistical significance being due to small sample size or the low power of the analysis cannot be ruled out. The 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 [Lopez-Alcalde et al., 2020]. 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 healthcare provision.

Ethics approval and consent to participate

The institutional ethics committee for clinical research 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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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 *et al.* (2005) Germany	Prospective observational study	Univariate analysis stratification by hormonal levels	n=308 Severe infection/sepsis	Hospital mortality	Equal risk of hospital mortality
Adrie *et al.* (2007) France	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 years group)
Pietropaoli *et al.* (2010) USA, Canada, Brazil	Retrospective cohort study	Multivariate logistic regression analysis	n=18.757 Severe sepsis and septic shock	Hospital mortality	More risk of hospital mortality in women
Natchtigall *et al.* (2011) Germany	Prospective observational study	Multivariate logistic regression analysis	n=327 Sepsis	ICU mortality	More risk of ICU mortality in women
De Oliveira Couto *et al.* (2011) Brazil	Retrospective comparative study	Matching by age	n=133 Sepsis	ICU mortality	More risk of ICU and hospital mortality in men (only in <40 years group)
Jacobson *et al.* (2012) Sweden	Prospective observational cohort study	Multivariate 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 *et al.* (2013) Italy	Retrospective cohort study	Multivariate 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)
Madsen & Napoli (2014) USA	Retrospective observational study	Multivariate logistic regression analysis	n=814 Severe sepsis and septic shock	Hospital mortality	Equal risk of hospital mortality
van Vught *et al.* (2017) Netherlands	Prospective observational cohort study	Multivariate 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 *et al.* (2019) China	Retrospective observational cohort study	Multivariate 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

way to achieve Europe" (ERDF). All authors report no conflict of interest relevant to this article. MPA was supported by a Rio Hortega contract (CM19/00069) from Instituto de Salud Carlos III.

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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