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ORIGINAL RESEARCH

Sex Differences in Short- and Long-Term Survival Among Critically Ill Patients with Sepsis

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Background: Currently, there have been studies showing a correlation between sex differences and prognosis. Nevertheless, the conclusions of clinical studies on sex-based differences are controversial. We aimed to evaluate the effect of sex on the short- and long-term survival of critically ill patients with sepsis.

Methods: We use the critical care database of the healthcare information mart. Cox models were conducted to determine the relationship of 28-day and 1-year mortality with a different sex. Interaction and stratified analyses were conducted to test whether the effect of sex differed across age and sequential organ failure assessment (SOFA) score subgroups.

Results: A total of 12,321 patients were enrolled in this study. The Cox regression analysis showed that the 28-day and 1-year mortality rates of female patients were significantly lower than those of male patients by 10% and 8%, respectively (hazard ratio [HR]=0.90, 95% confidence interval [CI] 0.83–0.98, and HR=0.92, 95% CI 0.87–0.97, respectively). The effects of the association between sex and 28-day and 1-year mortality were broadly consistent for age and the SOFA subgroup variables. Only age was observed to have significant interactions in the 1-year mortality (P=0.0177). Compared with male patients, female patients aged <50 years had a long-term survival advantage (HR=0.77, 95% CI 0.62–0.95). In contrast, we did not find sex-based differences in the short- and long-term survival for patients aged ≥50 years.

Conclusion: In the current retrospective large database review, the 28-day and 1-year mortality were significantly lower in females than in male patients among critically ill patients with sepsis. Notably, there was an interaction between age and sex, and whether female-associated hormones or other contributing factors affect the clinical outcomes of patients with sepsis needs to be further researched.

Keywords: critical care, sepsis, sex, prognosis

Introduction

Sepsis, a severe organ dysfunction induced by infection, is one of the leading causes of intensive care unit (ICU) admissions.[1] It is among the most expensive conditions to treat and a leading cause of death in United States hospitals. Sepsis affects more than 19 million people each year.[2] In 2014, approximately 174,000 adults in the United States were hospitalized for sepsis, 69.9% of whom were aged 60 years or older.[3,4]

Sex is one of the many factors postulated to affect the outcomes of sepsis in patients, with a hypothesis that females have better immune system activity and lower mortality rates than males. Indeed, several experimental and clinical studies have indicated such sex-based differences. In an animal model of sepsis, the

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survival rate and immune system response of pre-estrus female mice were significantly higher than those of male mice.[5] Similarly, the survival rate of male mice with sepsis significantly increased after androgen receptor blockade.[6] In contrast to animal research, numerous clinical studies have found no sex-based differences[7–9] or a higher mortality risk in males[10,11] or in females.[12–14] At present, the conclusions of clinical studies on sex-based differences are controversial. Therefore, determining the association between sex and mortality in sepsis could provide an impetus for exploring its pathophysiological mechanism. If such an association exists, the hormonal status (ie, androgen and estrogen) of a patient with sepsis should be considered. In addition, this knowledge could lead to development of potential therapies. Although many studies have explored the association between sex and the prognosis of sepsis, it should be investigated in different populations in order to obtain more convincing evidence. In the present study, we aimed to determine the effect of sex on the clinical outcomes of critically ill patients with sepsis.

Patients and Methods

Patient Data

We conducted this study in the Medical Information Mart for Intensive Care III database (version: 1.4).[15] The institutional review boards of Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates authorized access to the database (Shan Lin, Record ID: 33,460,949). Due to the anonymized nature of the data, the informed consent of the patient was not required.

All patients (≥18 years) with a diagnosis of sepsis based on a sequential organ failure assessment (SOFA) score ≥2 and suspected infection within the first day of ICU admission were included, and the extraction code for sepsis-3 we used was identified by Johnson et al[1,16]. Patients whose follow-up were less than one day were excluded. Only the data from the first ICU admission were analyzed. In keeping with our previous studies, we extracted data using structured query language (SQL) with Navicat.[17–19] The code is also readily available on the publicly accessed website.[20]

Outcomes

The primary outcomes were the 28-day and 1-year mortality rates after ICU admission.

Statistical Analysis

Data were presented as mean±standard deviation or median (interquartile range, IQR) for continuous variables and as numbers and percentages for categorical variables. Characteristics of the participants in male and female groups were compared using the Chi-square test for categorical variables and Fisher's exact test or Kruskal–Wallis test for continuous variables. Different Cox regression models were conducted to determine the independent relationships of 28-day and 1-year mortality rates with a different sex. In the model I, covariates were adjusted for age, infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, Elixhauser Comorbidity Index (SID30).[21] In model II, the same as model I, but we replaced SID30 with specific comorbidities, including congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse. In model III, we used propensity score for adjustment calculated by age, infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse. The results of the main analysis were used with multivariate Cox regression models. Interaction and stratified analyses were conducted to test whether the effect of sex differed across subgroup variables classified by age (<50 and ≥50) and SOFA (<5, 5–10, 10–15, ≥15). EmpowerStats(R) (www.empowerstats.com, X&Y solutions, Inc., Boston, MA, USA) and R (http://www.R-project.org, version 3.4.3) were used for data analysis. *P*-values <0.05 were considered significant.

Results

Characteristics of Participants

We included 12,321 patients in this study. As shown in Table 1, there were 6493 male and 5828 female patients, accounting for 52.7% and 47.3%, respectively. Female patients were older than male patients (68.99±16.46 vs 65.42±16.20, *P*<0.001). Statistical differences were found between male and female patients in the SID30, infection site, and the need for mechanical ventilation or renal replacement therapy on the first day of ICU admission. The median SOFA scores were the same in the two groups,

Table 1 Characteristics of Participants

Variables	All (N=12,321)	Male (N=6493)	Female (N=5828)	*P*-value
Age (years)	67.10±16.42	65.42±16.20	68.99±16.46	<0.001
SOFA	5.00 (3.00–7.00)	5.00 (3.00–7.00)	5.00 (3.00–7.00)	<0.001
Elixhauser Comorbidity Index (SID30)	17.00 (8.00–26.00)	17.00 (8.00–26.00)	16.00 (8.00–25.00)	0.005
Infection site				<0.001
Bloodstream	5440 (44.15%)	2966 (45.68%)	2474 (42.45%)	
Pulmonary	807 (6.55%)	459 (7.07%)	348 (5.97%)	
Abdominal	265 (2.15%)	137 (2.11%)	128 (2.20%)	
Urinary tract	2596 (21.07%)	1210 (18.64%)	1386 (23.78%)	
Others	3213 (26.08%)	1721 (26.51%)	1492 (25.60%)	
Mechanical ventilation on first day	6132 (49.77%)	3357 (51.70%)	2775 (47.61%)	<0.001
Renal replacement therapy on first day	604 (4.90%)	349 (5.38%)	255 (4.38%)	0.010
Length of ICU stay (days)	3.33 (1.83–7.86)	3.55 (1.83–8.57)	3.18 (1.82–7.14)	<0.001
Length of hospital stay (days)	10.85 (6.36–19.04)	11.68 (6.74–20.36)	10.04 (6.07–17.84)	<0.001
28-year mortality, n (%)	2263 (18.37%)	1206 (18.57%)	1057 (18.14%)	0.531
1-year mortality, n (%)	4615 (37.46%)	2418 (37.24%)	2197 (37.70%)	0.601
Comorbidities, n (%)				
Congestive heart failure	4168 (33.83%)	2226 (34.28%)	1942 (33.32%)	0.260
Chronic pulmonary disease	2716 (22.04%)	1458 (22.45%)	1258 (21.59%)	0.245
Valvular disease	1747 (14.18%)	909 (14.00%)	838 (14.38%)	0.547
Peripheral vascular disease	1411 (11.45%)	720 (11.09%)	691 (11.86%)	0.182
Hypertension	6522 (52.93%)	3385 (52.13%)	3137 (53.83%)	0.060
Diabetes	3509 (28.48%)	1817 (27.98%)	1692 (29.03%)	0.198
Liver disease	1258 (10.21%)	669 (10.30%)	589 (10.11%)	0.718
Renal failure	2226 (18.07%)	1149 (17.70%)	1077 (18.48%)	0.259
AIDS	180 (1.46%)	94 (1.45%)	86 (1.48%)	0.897
Lymphoma	309 (2.51%)	163 (2.51%)	146 (2.51%)	0.985
Tumor	647 (5.25%)	337 (5.19%)	310 (5.32%)	0.749
Obesity	708 (5.75%)	335 (5.16%)	373 (6.40%)	0.003
Alcohol abuse	923 (7.49%)	490 (7.55%)	433 (7.43%)	0.806
Drug abuse	405 (3.29%)	220 (3.39%)	185 (3.17%)	0.506

Note: Data were presented as mean±standard deviation or median (interquartile range, IQR) for continuous variables and as numbers and percentages for categorical variables.

Abbreviations: ICU, intensive care unit; SOFA, sequential organ failure assessment; AIDS, acquired immune deficiency syndrome.

Table 2 Cox Regression Analysis for Sex Differences with 28-Day and 1-Year Mortality

Clinical Outcome				
28-Day Mortality	**Sex**	**HR**	**95% CI**	***P*-value**
Crude	Male Female	1.0 0.98	– 0.90–1.06	– 0.6248
Model I	Male Female	1.0 0.97	– 0.89–1.05	– 0.4093
Model II	Male Female	1.0 0.90	– 0.83–0.98	– 0.0148
Model III	Male Female	1.0 0.91	– 0.83–1.00	– 0.0450
1-Year Mortality	**Sex**	**HR**	**95% CI**	***P*-value**
Crude	Male Female	1.0 1.01	– 0.96–1.07	– 0.6413
Model I	Male Female	1.0 0.95	– 0.90–1.01	– 0.1155
Model II	Male Female	1.0 0.92	– 0.87–0.97	– 0.0048
Model III	Male Female	1.0 0.94	– 0.89–1.00	– 0.0474

Notes: Model I adjust for: age (years), infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, SID30. Model II adjust for: age (years), infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse. Model III was adjusted by propensity score calculated by age (years), infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse.
Abbreviations: HR, hazard ratio; CI, confidence interval.

but the median SID30 score was higher in male than in female patients. In all patients, the most common infection site was the bloodstream, and female patients had a higher rate of urinary tract infections than male patients. There were significantly more male than female patients who required mechanical ventilation and renal replacement therapy on the first day of ICU admission. Hypertension was the most common comorbidity among all patients, accounting for 52.93%. Other detailed results are listed in Table 1.

Clinical Outcomes of Participants

In terms of clinical outcomes, the median length of hospital and ICU stay was greater in male than in female patients. The 28-day mortality rate was slightly higher (18.57% vs 18.14%), and the 1-year mortality rate was slightly lower in male patients than in female patients (37.24% vs 37.70%); however, these differences were not statistically significant (all $P>0.05$; Table 1).

Associations Between Sex-Based Differences and Short- and Long-Term Survival

The multivariable Cox regression analysis showed that the 28-day and 1-year mortality rates of female patients were significantly lower than those of male patients by 10% and 8%, respectively (hazard ratio [HR]=0.90, 95% confidence interval [CI] 0.83–0.98, $P=0.0148$ and HR=0.92, 95% CI 0.87–0.97, $P=0.0048$, respectively; Table 2).

In the stratified analysis, the effects of the association between sex and 28-day and 1-year mortality were broadly consistent for age and the SOFA subgroup variables (Table 3 and Figures 1–4). Only age was observed to have significant interactions in the 1-year mortality ($P=0.0177$). Compared with male patients, female patients aged <50 years had a long-term survival advantage (HR=0.77, 95% CI 0.62–-0.95, $P=0.0163$; Figure 3). In contrast, we did not find sex-based differences in the short- and long-term survival for patients aged ≥50 years.

Table 3 Effect Size of Sex Difference in 28-Day and 1-Year Mortality in Prespecified and Exploratory Subgroups in Each Subgroup

	Adjusted Model					
	28-Day Mortality			1-Year Mortality		
Subgroup Variables	**HR (95% CI)**	***P*-value**	***P* for Interaction**	**HR (95% CI)**	***P*-value**	***P* for Interaction**
Age (years): <50						
Male	1.0	–	0.0653	1.0	–	0.0177
Female	0.77 (0.57–1.06)	0.1048		0.77 (0.62–0.95)	0.0163	
Age (years): ≥50						
Male	1.0	–		1.0	–	
Female	1.05 (0.96–1.14)	0.3098		1.04 (0.98–1.10)	0.2354	
SOFA: <5						
Male	1.0	–	0.2916	1.0	-	0.8577
Female	0.90 (0.78–1.04)	0.1668		0.95 (0.86–1.04)	0.2295	
SOFA: ≥5, <10						
Male	1.0	–		1.0	–	
Female	0.91 (0.80–1.03)	0.1186		0.92 (0.84–1.00)	0.0578	
SOFA: ≥10, <15						
Male	1.0	–		1.0	–	
Female	1.13 (0.92–1.38)	0.2448		1.01 (0.85–1.21)	0.8806	
SOFA: ≥15						
Male	1.0	–		1.0	–	
Female	1.03 (0.59–1.79)	0.9166		1.03 (0.62–1.69)	0.9200	

Notes: Adjust for age (years), infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse except for the subgroup variable.

Abbreviations: HR, hazard ratio; CI, confidence interval.

Figure 5 shows the effect of age (continuous variable) by sex on the 28-day and 1-year mortality in patients with sepsis. The results suggested that the 1-year mortality was predominantly lower in female than in male patients at different ages (Figure 5B), while between the age of 50 and 60 years, the 28-day mortality was slightly higher in female than in male patients (Figure 5A). Figure 6 shows the effect of different SOFA groups on the 28-day and 1-year mortality of patients with sepsis by sex, indicating that female patients had lower 1-year mortality than male patients in each SOFA group (Figure 6B); however, the 28-day mortality was slightly higher in female than in male patients with a SOFA score of 10 to 15 (Figure 6A).

Discussion

This retrospective cohort study including 12,321 patients compared the association between sex and the 28-day as well as 1-year mortality. To date, many studies have explored this association. However, there is still no consensus, which is confusing for clinicians. Therefore, it is necessary to perform such research in different populations, which would be particularly beneficial if using a large database. In our study, among critically ill patients with sepsis, female patients had significantly lower 28-day and 1-year mortality rates than male patients. Moreover, unlike previous studies, we found an interaction between age and sex, indicating that female patients aged <50 years had a survival advantage compared with male patients.

In humans, sex-based differences have been reported in many diseases, such as hypertension, atherosclerosis, lung disease, and cardiovascular disease.[22–27] However, sex-based differences in terms of infection and sepsis have remained controversial. A large retrospective study that enrolled 10,422,301 adult patients with sepsis indicated that male patients had higher mortality rates than female patients (odds ratio [OR]=1.09, 95% CI 1.05–1.14).[10] Similarly, a prospective study by Adrie et al involving 1692 patients with severe sepsis revealed that female patients had lower hospital mortality rates than male patients (OR=0.75, 95% CI 0.57–0.97), but such results

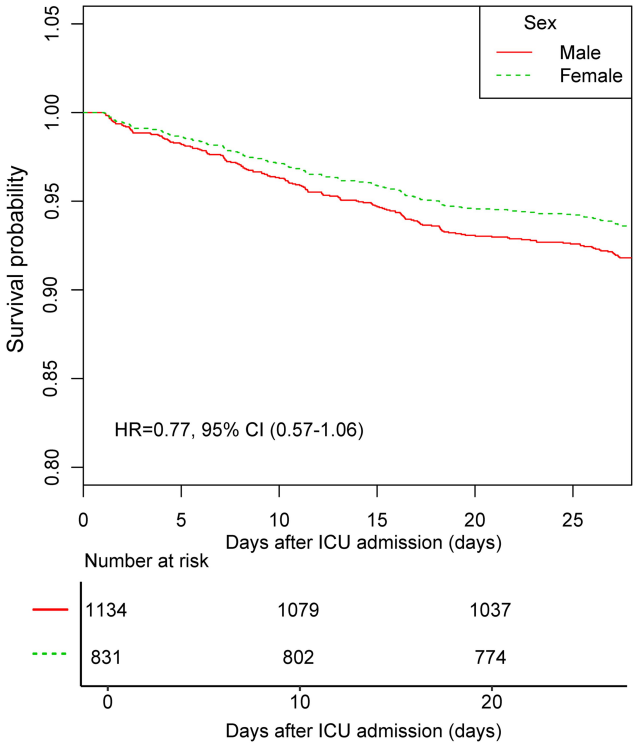

Figure 1 The 28-day survival curve of the Cox regression model for participants with age <50 years.

Notes: The Cox regression model for 28-day mortality in female patients <50 years of age compared to male patients had a result of HR=0.77 (95% CI 0.57–1.06), after adjusting for age (years), infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse.

Abbreviations: HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; SOFA, sequential organ failure assessment; AIDS, acquired immune deficiency syndrome.

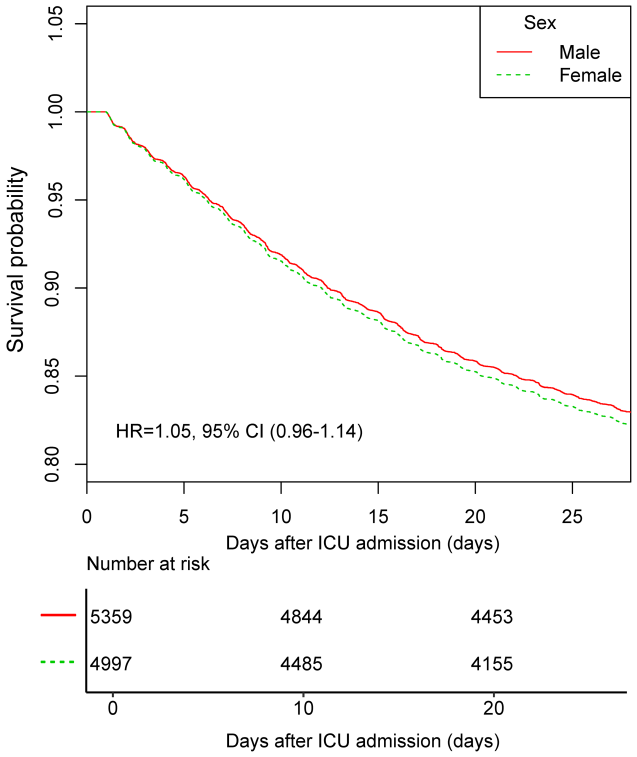

Figure 2 The 28-day survival curve of the Cox regression model for participants with age ≥50 years.

Notes: The Cox regression model for 28-day mortality in female patients ≥50 years of age compared to male patients had a result of HR=1.05 (95% CI 0.96–1.14), after adjusting for age (years), infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse.

Abbreviations: HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; SOFA, sequential organ failure assessment; AIDS, acquired immune deficiency syndrome.

were only observed in patients over the age of 50 (OR=0.69, 95% CI 0.52–0.93).[11] This may be attributed to the fact that there were only 127 female and 222 male patients under 50 years of age in the study population. Additionally, the female sex hormone, ie, estrogen, exhibits a modulatory effect on the immune system that may contribute to the benefit of females during sepsis; however, its levels start decreasing after the age of 50.[28–30] In our study, the results of the subgroup analysis were contrary to those of Adrie et al; namely, we found that only female patients under the age of 50 had a survival advantage compared with male patients.

A prospective study with 327 patients with sepsis found in the subgroup analysis that an increase in mortality was related to the female sex.[12] Eachempati et al also suggested that female sex was an independent index of increased mortality in critically ill patients.[13] However, both of these studies had small sample sizes.[12,13] Another large retrospective cohort study including 18,757 patients with severe sepsis/septic shock demonstrated that female patients had higher in-hospital mortality rates than male patients. Nonetheless, the subgroup analysis found that, compared with male patients, female patients younger than 50 years did not have an increased risk of death, which is consistent with the findings of our study.[14] Additionally, some studies have demonstrated that no sex-based differences exist in patients with sepsis.[7–9]

Although the underlying physiological mechanisms for these sex-based differences are still not fully understood, there are several possible explanations. Theoretically based explanations focus on the differences in hormone levels between males and females. Namely, the balancing effect of estrogen on the regulation of the immune system and its protective effect on endothelial cells have been well documented.[28–32] Moreover, improved survival has been demonstrated after androgen receptor blockade in animal

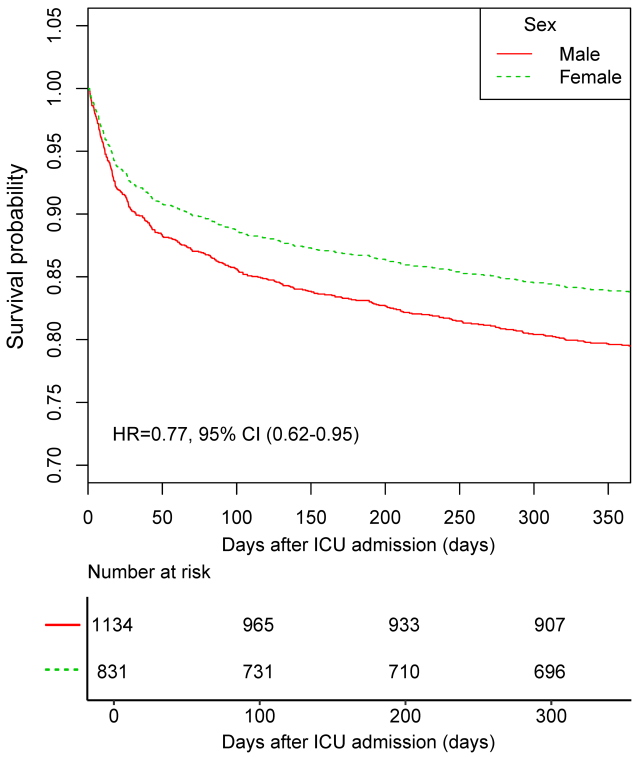

Figure 3 The 1-year survival curve of the Cox regression model for participants with age <50 years.

Notes: The Cox regression model for 1-year mortality in female patients <50 years of age compared to male patients had a result of HR=0.77 (95% CI 0.62–0.95), after adjusting for age (years), infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse.

Abbreviations: HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; SOFA, sequential organ failure assessment; AIDS, acquired immune deficiency syndrome.

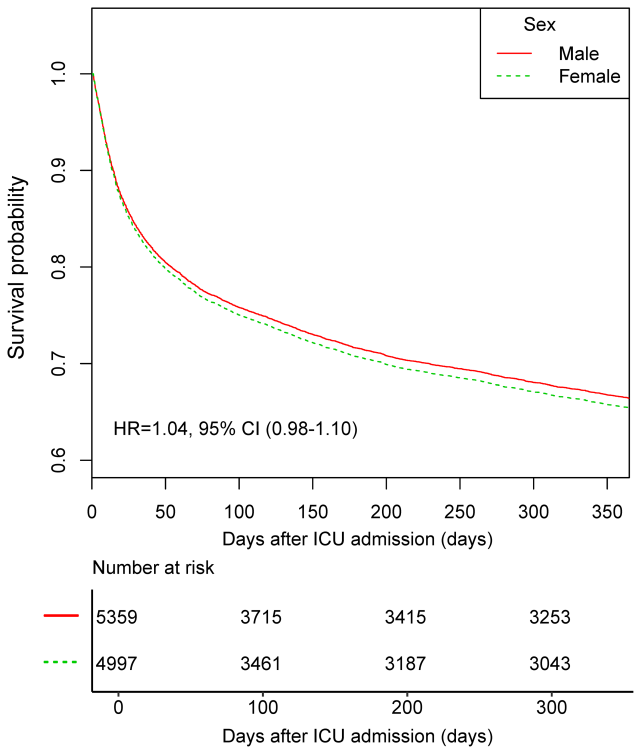

Figure 4 The 1-year survival curve of the Cox regression model for participants with age ≥50 years.

Notes: The Cox regression model for 1-year mortality in female patients ≥50 years of age compared to male patients had a result of HR=1.04 (95% CI 0.98–1.10), after adjusting for age (years), infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse.

Abbreviations: HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; SOFA, sequential organ failure assessment; AIDS, acquired immune deficiency syndrome.

studies.[5,6] Finally, differences in the response of the male and female immune systems to endotoxin and an association of female hormone levels with the clinical outcome have been identified in clinical studies.[33–35] On the other hand, of perhaps even greater importance are the medical interventions received during the hospitalization of the patients, as well as the progression and management of comorbidities after discharge. Indeed, it was observed in our study that the need for mechanical ventilation and renal replacement therapy on the first day of ICU admission was significantly higher in male than in female patients.

To the best of our knowledge, we showed for the first time that female patients less than 50 years of age had a long-term survival advantage compared with male patients through interaction and stratified analysis for age (≥50 and <50 years; the median age of menopause in the United States).[36] Although no statistical difference was observed in the interaction for age and 28-day mortality, a reduction in 28-day mortality was almost certain in female patients younger than 50 years. Whether this is a crucial clue to a better prognosis due to female hormones or other factors needs further verification. Therefore, research on sex-based differences in patients with sepsis is worthy of attention.

Limitations remain to be pointed out, although a sufficiently large sample was included in our study. First, although previous studies have suggested that female hormones are associated with the immune system and endothelial cell function, we were unable to extract indicators related to hormone levels, inflammatory mediators, and cell function, making it impossible for us to assess the relationships. Second, the management of post-discharge comorbidities may have an impact on the long-term prognosis of patients; however, data on the treatment

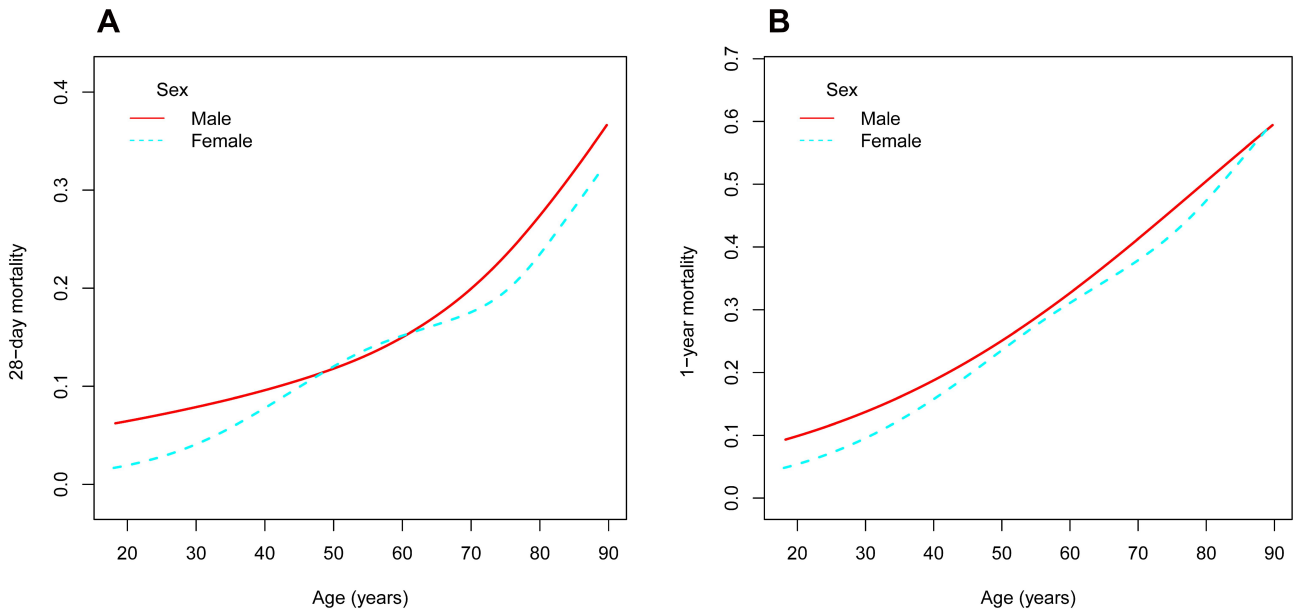

Figure 5 (**A**) Association of age with 28-day mortality in males and females. (**B**) Association of age with 1-year mortality in males and females.
Notes: Adjust for infection site, SOFA, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse.
Abbreviations: SOFA, sequential organ failure assessment; AIDS, acquired immune deficiency syndrome.

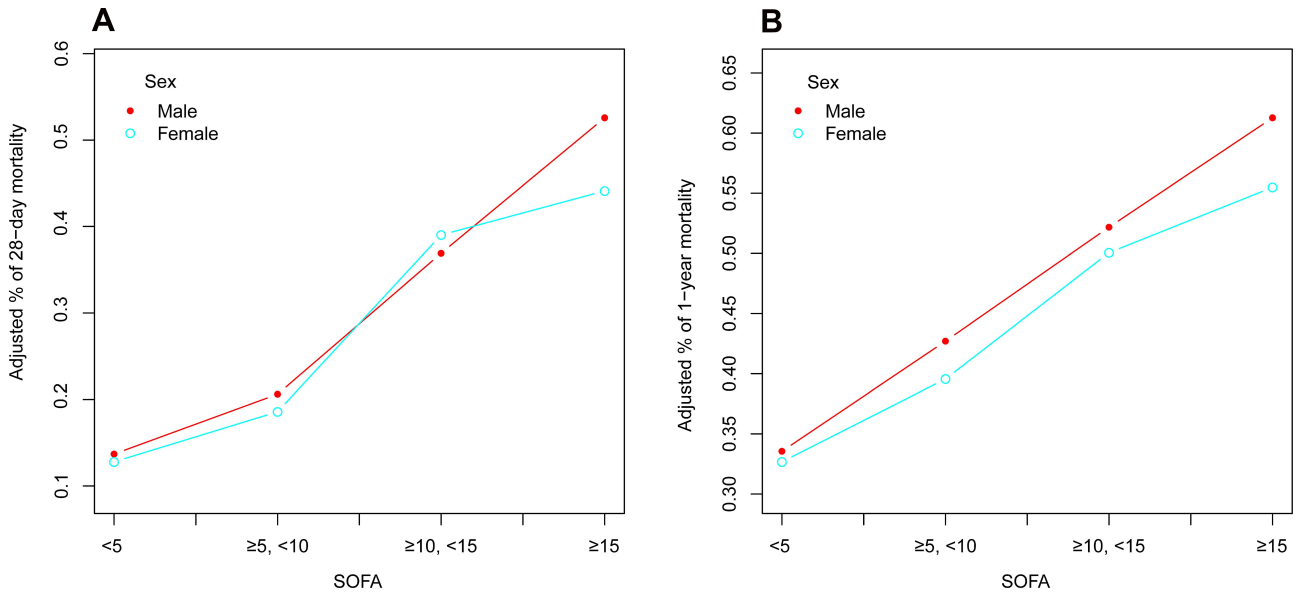

Figure 6 (**A**) Association of SOFA groups with 28-day mortality in males and females. (**B**) Association of SOFA groups with 1-year mortality in males and females.
Notes: Adjust for age (years), infection site, mechanical ventilation on first day, renal replacement therapy on first day, congestive heart failure, chronic pulmonary disease, valvular disease, peripheral vascular disease, hypertension, diabetes, liver disease, renal failure, AIDS, lymphoma, tumor, obesity, alcohol abuse, and drug abuse.
Abbreviations: SOFA, sequential organ failure assessment; AIDS, acquired immune deficiency syndrome.

and medication use for comorbidities are not available in the database. Therefore, we could not control for the confounding effect of these factors on the patients' outcomes. Third, selection bias is inherent in all retrospective studies. Nonetheless, the data in the database are independently measured and prospectively collected, making them not susceptible to manipulation. Forth, our findings should be interpreted with caution, since the results of the correlation analysis should not be misinterpreted as evidence of causality. Finally, the single-center study design may result in variation in external applicability.

Conclusions

Among critically ill patients with sepsis, the 28-day and 1-year mortality were significantly lower in females than in male patients. Notably, there was an interaction between age and sex. Nevertheless, whether female-associated hormones or other contributing factors affect the clinical outcomes of patients with sepsis needs to be further researched.

Abbreviations

ICU, intensive care unit; SID30, Elixhauser Comorbidity Index; SOFA, sequential organ failure assessment; AIDS, acquired immune deficiency syndrome; IQR, interquartile range; SQL, structured query language; HR, hazard ratio; CI, confidence interval.

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Disclosure

The authors have no conflicts of interest to declare.

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