Association of sex with clinical outcomes in COVID-19 patients: A retrospective analysis of 1190 cases

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ABSTRACT

Background: The outbreak of COVID-19 caused by SARS-CoV-2 has been a pandemic. The objective of our study was to explore the association between sex and clinical outcomes in patients with COVID-19.
Methods: Detailed clinical data including clinical characteristics, laboratory tests, imaging features and treatments of 1190 cases of adult patients with confirmed COVID-19 were retrospectively analyzed. Associations between sex and clinical outcomes were identified by multivariable Cox regression analysis.
Results: There were 635 (53.4%) male and 555 (46.6%) female patients in this study. Higher rates of acute kidney injury (5.5% *vs.* 2.9%, p = 0.026), acute cardiac injury (9.1% *vs.* 4.3%, p = 0.001), and disseminated intravascular coagulation (2.5% *vs.* 0.7%, P = 0.024) were observed in males. Compared with female patients, male patients with COVID-19 had a higher inhospital mortality rate (15.7% *vs.* 10.3%, p = 0.005). However, Cox regression analysis showed that sex did not influence inhospital mortality of COVID-19 patients.
Conclusions: Male sex was associated with a worse prognosis of COVID-19, but it seems not to be an independent prognostic factor.

1. Background

The outbreak of novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], has rapidly turn into a pandemic. To 26 July 2020, it has affected more than 15,700,000 cases and claimed more than 640,000 lives (https://covid19.who.int). Although the disease is now better contained in China, the prevalence in other parts of the world remains serious. Researches on underlying mechanism of COVID-19 outcomes become urgent worldwide.

Published studies from multiple countries on clinical characteristics of the disease have indicated that males appear with higher incidence and mortality of COVID-19 than females [2–5]. One study of 44672 patients with confirmed COVID-19 in Mainland China, carried out by the Novel Coronavirus Pneumonia Emergency Response Epidemiology

Team, found the male-to-female ratio in China overall was 1.06:1, case fatality rate for males was 2.8% and for females was 1.7% [3]. In a study of 1099 patients with COVID-19 from 552 hospitals in 30 provinces in China, the male-to-female ratio was 1.39:1 [4]. Italian epidemiologic data showed the male-to-female ratio was up to 3:1 for SARS-CoV-2 infection [5].

Given the sex-based disparity in incidence and hospitalization, as well as in mortality, the clinical characteristics of the disease need to be stratified by sex. In the present study, we analyzed 1190 adult patients with confirmed COVID-19 in Wuhan Infectious Disease Hospital, to explore the association between sex and clinical outcomes of COVID-19 in Chinese population.

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Abbreviation

COVID-19	corona virus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
ACE2	angiotensin-converting enzyme 2
SOFA	sequential organ failure assessment
APACHE II	acute physiology and chronic health evaluation II
ARDS	acute respiratory distress syndrome
COPD	chronic obstructive pulmonary disease
AKI	acute kidney injury
AHI	acute hepatic injury
ACI	acute cardiac injury
DIC	disseminated intravascular coagulation
MV	mechanical ventilation
FDPs	fibrin/fibrinogen degradation products
PT	prothrombin time
APTT	Activated-partial thromboplastin time
TT	thrombin time
TBIL	total bilirubin
ALT	alanine-aminotransferase
AST	aspartate-aminotransferase
BUN	blood urea nitrogen
SCr	serum creatinine
CK-MB	creatine kinase isoenzyme
hsCRP	hyper-sensitive C-reactive protein
PCT	procalcitonin
SAA	serum amyloid protein A
IL	interleukins

2. Methods

2.1. Patient population

This study was approved by the Medicine Institutional Review Board of Wuhan Infectious Disease Hospital (KY-2020-03.01). Patients between the ages of 18 and 94 years with confirmed COVID-19 admitted to Wuhan Infectious Disease Hospital from December 29, 2019 to February 28, 2020 were enrolled. The clinical outcomes were monitored up to March 2, 2020, the final date of follow-up.

All patients enrolled in this study were diagnosed according to World Health Organization interim guidance [6]. Nasal and pharyngeal-swab specimens from patients with history of epidemiology and characteristics of virus pneumonia in chest computed tomographic (CT) or X-ray were obtained. Patients with positive results from high-throughput sequencing or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens were confirmed with COVID-19.

2.2. Data collection

Epidemiological, demographic, clinical, laboratory and radiological data, treatments and outcomes data were extracted from medical records. The data were reviewed by a trained team of physicians. Information collected included age, sex, comorbidities, exposure history, laboratory findings, chest CT and x-ray scans, respiratory support during hospitalization, therapeutic strategy and outcomes.

Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition [7]. Acute kidney injury (AKI) was identified according to the Kidney Disease: Improving Global Outcomes definition [8]. Acute cardiac injury (ACI) was defined if the serum levels of cardiac biomarkers were above the 99th percentile upper reference limit or new abnormalities were shown in electrocardiography and echocardiography [9]. Acute hepatic injury (AHI) was identified as total bilirubin increase by 51.3 μmol/L and alanine aminotransferase increase to five times the upper reference limit. Platelet counts, prothrombin time test, and the levels of fibrin/fibrinogen degradation products (FDPs) were components in the major sets of diagnostic criteria of disseminated intravascular coagulation (DIC) [10]. The sequential organ failure assessment (SOFA) and acute physiology and chronic health evaluation II (APACHE II) scores were determined on admission.

2.3. Statistical analysis

Continuous variables were described as mean (95% confidence interval), or as median (interquartile range 25–75% [IQR]), and compared using Student's t-test or Mann-Whitney U test. Categorical variables were described as number (percentage), and compared using chi-square test or Fisher exact test, as appropriate. The association between sex and inhospital mortality in COVID-19 patients were explored by Cox proportional hazard regression model and displayed as hazard ratios (HR) and 95% confidence intervals (CI). The model was adjusted on priori–decided baseline variables of clinical interest and on those with a p value of less than 0.05 in the univariate analysis. The included variables were: age, sex, comorbidity, SOFA sore, lymphocyte, platelet, D-dimer, glucocorticoid and antiviral drugs. A two-sided p value less than 0.05 was defined as statistically significant for all the analyses.

All statistical analyses were performed using SPSS (version 24.0, SPSS Inc., Chicago, IL, USA) and SAS (version 9.4, SAS Institute, Cary, NC).

3. Results

3.1. Demographic and clinical characteristics

1190 adult patients with confirmed COVID-19 were recorded in Wuhan Infectious Disease Hospital during the study period. Of these 1190 patients, 635 (53.4%) were male and 555 (46.6%) were female. Clinical characteristics for males versus females are shown in Table 1. The age distribution as well as clinical symptoms and vital signs on admission had no difference between the two groups. The frequencies of smoking (8.8% *vs.* 0%, p < 0.001) and drinking (8.8% *vs.* 0.2%, p < 0.001) were much higher in males. Besides hypertension (males 28.6% *vs.* females 23.3%, p = 0.037), the comorbidities were similar in the two groups. More female health care workers were infected through occupational exposure than males (2.2% *vs.* 0.7%, p = 0.025).

3.2. Laboratory and radiologic findings and treatments

There were numerous differences in laboratory findings between male and female patients (Table 2), including higher leucocyte and neutrophil counts, lower lymphocyte and platelet counts, lower CD4/CD8 ratio, longer PT and APTT, higher levels of organ function parameters like TBIL, ALT, AST, BUN, SCr and CK-MB, as well as higher levels of infection or inflammation markers like hsCRP, PCT, serum amyloid A, serum ferritin and IL-6 in males. Stratification by age group revealed that males of all ages had higher levels of organ and coagulation function parameters (*e.g.* TBIL, ALT, AST, SCr, CK-MB and PT) than those in the age-matched females (Fig. 1).

We also analyzed sex differences in chest radiological findings and therapies during hospitalization. The radiological findings were similar in males and females. However, male patients were more likely to receive glucocorticoids during hospitalization than female patients (30.7% *vs.* 20.6%, p < 0.001).

Table 1
Clinical characteristics of patients with COVID-19 by gender category.

	All patients (n = 1190)	Males (n = 635)	Females (n = 555)	P value
Age, Median (IQR)-yr	57 (47,67)	56 (46,67)	58 (48,67)	0.176
Distribution-n (%)				0.106
<45 yr	240 (20.2)	144 (22.7)	96 (17.3)	
45~54 yr	266 (22.3)	142 (22.3)	124 (22.3)	
55~64 yr	305 (25.6)	146 (23.0)	159 (28.7)	
>65 yr	379 (31.9)	203 (32.0)	176 (31.7)	
Smoking-n (%)	45 (3.8)	45 (7.1)	0 (0)	<0.001
Drinking-n (%)	48 (4.0)	47 (7.4)	1 (0.2)	<0.001
Comorbidity-n (%)				
COPD	22 (1.9)	16 (2.6)	6 (1.1)	0.051
Diabetes	144 (12.2)	80 (12.7)	64 (11.6)	0.564
Hypertension	308 (26.1)	180 (28.6)	128 (23.3)	0.037
Chronic cardiac disease	86 (7.3)	51 (8.1)	35 (6.4)	0.247
Chronic kidney disease	30 (2.6)	20 (3.2)	10 (1.8)	0.140
Chronic liver disease	40 (3.4)	20 (3.2)	20 (3.6)	0.670
Stroke	39 (3.3)	23 (3.7)	16 (2.9)	0.481
Malignancy	34 (2.9)	16 (2.6)	18 (3.3)	0.452
Exposure history-n (%)				
Huanan seafood market	131 (11.4)	89 (14.6)	42 (7.8)	<0.001
Medical staff	16 (1.4)	4 (0.7)	12 (2.2)	0.025
SOFA	3 (1,5)	3 (1,5)	2 (1,5)	0.071
APACHEII	3 (1,6)	3 (1,6)	3 (2,6)	0.850

Abbreviation: chronic obstructive pulmonary disease, COPD; sequential organ failure assessment, SOFA; acute physiology and chronic health evaluation II, APACHE II.

3.3. Clinical outcomes

Calculations of clinical outcomes were stratified by sex and were summarized in Table 3. Among the 1190 patients, there were 100 male deaths accounted for 63.7% of all deaths, and 57 female deaths accounted for 36.3% of all deaths. The inhospital mortality rate of male patients was significantly higher than that of female patients (15.7% *vs.* 10.3%, p = 0.005). In male patients, we found significantly higher rates of acute kidney injury (5.5% *vs.* 2.9%, p = 0.026), acute cardiac injury (9.1% *vs.* 4.3%, p = 0.001) and DIC (2.5% *vs.* 0.7%, p = 0.024) than in female patients. However, there were no sex differences in incidence of ARDS, acute hepatic injury or shock. The median length of hospitalization for male patients was 11 days, while that for female patients was 10 days (p = 0.003). Considering that age represents an important issue on clinical outcomes, we compared organ failure and inhospital mortality between males and females in different age groups. As shown in Figs. 2 and 3, the rates of organ failure occurrence and mortality of males and females both increased with age. In patients older than 65 years, male patients had significantly higher incidences of organ failure and inhospital mortality over female patients.

3.4. Multivariable cox regression of inhospital mortality

Our multivariable Cox regression model revealed no relation between sex and inhospital mortality (Table 4). SOFA score on admission (HR 1.057, 95% CI 1.028–1.087, p < 0.001), lymphocytopenia (HR 1.249, 95% CI 1.054–1.479, p = 0.010), thrombocytopenia (HR 1.600, 95% CI 1.142–2.247, p = 0.006) and elevated D-dimer (HR 1.156, 95% CI 1.065–1.255, p < 0.001) were correlated with increased mortality risk during hospitalization. In addition, glucocorticoid and antiviral treatment was negatively associated with inhospital mortality (HR 0.618, 95% CI 0.521–0.735, p < 0.001 and HR 0.747, 95% CI 0.648–0.862, p < 0.001, respectively).

Table 2
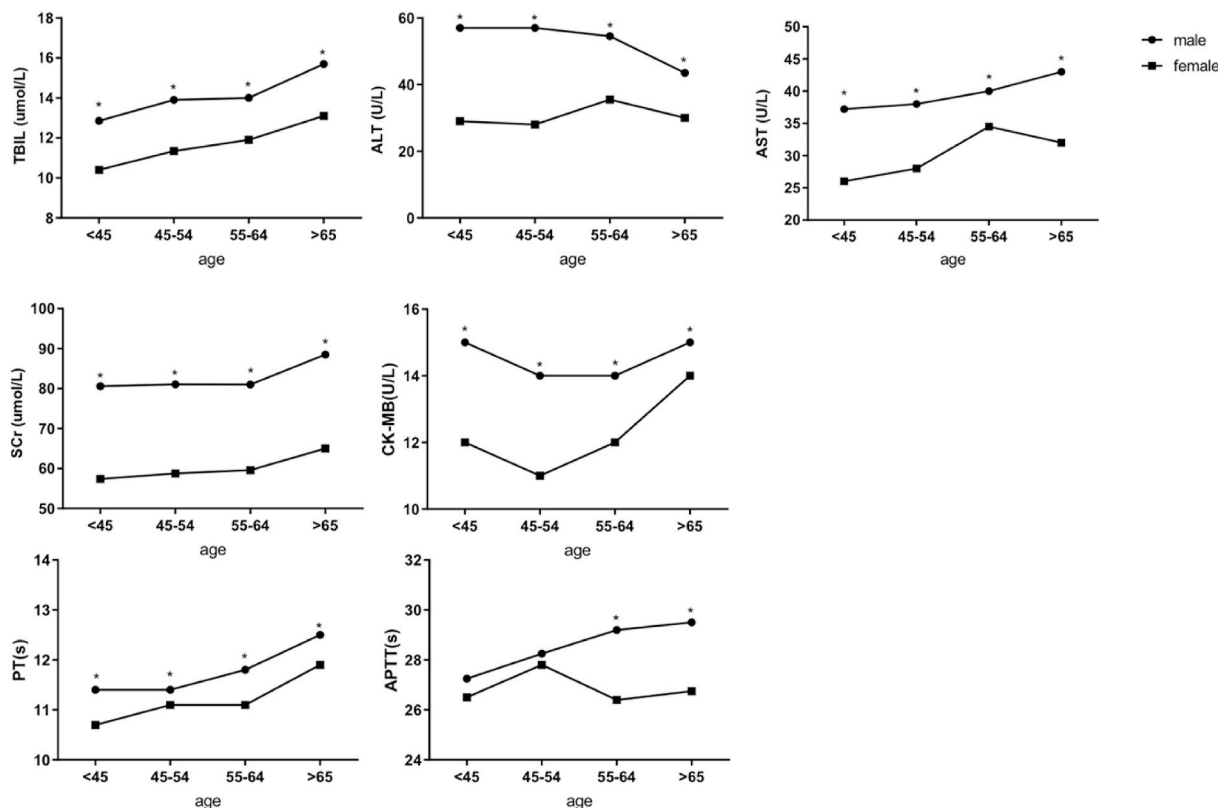Laboratory findings of patients with COVID-19 by gender category.

	All patients (n = 1190)	Males (n = 635)	Females (n = 555)	P value
Laboratory findings, Mean (95%CI)				
Leucocytes (10^9/L)	8.0 (7.7,8.4)	8.7 (8.2,9.2)	7.3 (6.7,8.0)	<0.001
Neutrophils (10^9/L)	6.9 (6.4,7.4)	7.8 (7.0,8.7)	5.8 (5.2,6.4)	<0.001
Lymphocytes (10^9/L)	1.5 (1.3,1.7)	1.4 (1.2,1.6)	1.7 (1.3,2.1)	0.124
Platelets (10^9/L)	199 (194,205)	192 (185,200)	207 (200,215)	0.005
CD4 (/uL)	456 (409,502)	420 (365,474)	513 (430,596)	0.052
CD8 (/uL)	265 (240,291)	269 (237,301)	260 (217,303)	0.742
CD4/CD8	2.0 (1.7,2.4)	1.8 (1.6,1.9)	2.4 (1.6,3.3)	0.049
PT (s)	13.3 (12.6,14.1)	13.5 (12.6,14.3)	13.1 (11.8,14.4)	0.612
APTT (s)	29.3 (28.8,29.9)	30.6 (29.7,31.5)	27.9 (27.2,28.5)	<0.001
TT (s)	19.6 (19.2,20.1)	19.8 (19.1,20.4)	19.5 (18.9,20.1)	0.546
D-dimer (ug/mL)	7.5 (5.3,9.7)	8.5 (5.5,11.5)	6.4 (3.1,9.7)	0.374
TBIL (umol/L)	16.3 (15.4,17.1)	17.7 (16.6,18.7)	14.6 (13.4,15.9)	<0.001
ALT (U/L)	62 (55,68)	76 (68,84)	46 (36,55)	<0.001
AST (U/L)	56 (47,64)	61 (51,70)	50 (35,66)	0.242
BUN (mmol/L)	7.9 (6.6,9.1)	8.7 (6.9,10.5)	6.9 (5.2,8.6)	0.146
SCr (umol/L)	89.1 (84.3,94.0)	100.5 (94.3106.8)	76.2 (68.8,83.7)	<0.001
CK-MB (U/L)	24.3 (14.5,34.2)	30.1 (12.1,48.1)	17.7 (13.5,22.0)	<0.001
hsCRP (mg/L)	57.6 (53.3,61.9)	67.6 (61.2,73.9)	46.2 (40.5,51.9)	<0.001
PCT (ng/mL)	0.7 (0.4,1.0)	0.7 (0.3,1.1)	0.6 (0.1,1.1)	0.008
SAA (mg/L)	170.6 (157.4183.9)	184.4 (174.5194.3)	155.1 (129.3180.9)	0.030
Serum ferritin (ng/mL)	619.2 (553.9684.5)	792.2 (682.8901.7)	405.3 (358.8451.9)	<0.001
IL-6 (pg/mL)	309.1 (275.6342.7)	414.7 (360.2469.2)	189.4 (156.6222.3)	<0.001

Abbreviation: prothrombin time, PT; Activated-partial thromboplastin time, APTT; thrombin time, TT; total bilirubin, TBIL; alanine-aminotransferase, ALT; aspartate-aminotransferase, AST; blood urea nitrogen, BUN; serum creatinine, SCr; creatine kinase isoenzyme, CKMB; hyper-sensitive C-reactive protein, hsCRP; procalcitonin, PCT; serum amyloid protein A, SAA; interleukin, IL; mechanical ventilation, MV; extracorporeal membrane oxygenation, ECMO.

4. Discussion

With the intensification of the adverse impact of COVID-19 pandemic to the world, lots of studies on biological and clinical characteristics of the disease have been published. Official Chinese statistics showed that the male-to-female ratio was 1.06:1 in China and the fatality rate for males was 2.8% versus 1.7% for females [3]. Given the sex differences in case fatality rate, the clinical characteristics of the disease need to be stratified by sex.

In our study, male patients showed significantly increased incidence of acute kidney injury, acute cardiac injury and DIC, as well as higher inhospital mortality. Angiotensin-converting enzyme 2 (ACE2), the main binding site for the entry of SARS-CoV-2 into host cells, is predominantly expressed in heart, kidney, and testis [11–13]. This may explain the vulnerability of cardiovascular system and kidney to SARS-CoV-2 infection. However, after stratification by age group, significant gender differences in organ failure and mortality were observed only in patients older than 65 years. Interestingly, males of all ages showed higher levels of organ and coagulation function parameters than that in age-matched female patients. Biological sex, age, as well as

Fig. 1. Comparison of organ and coagulation function parameters in patients with COVID-19 by sex and age group.
*P < 0.05 for males *vs.* age-matched females. Abbreviation: total bilirubin, TBIL; alanine-aminotransferase, ALT; aspartate-aminotransferase, AST; serum creatinine, SCr; creatine kinase isoenzyme, CK-MB; prothrombin time, PT; Activated-partial thromboplastin time, APTT.

Table 3
Clinical outcomes of patients with COVID-19 by gender category.

	All patients (n = 1190)	Males (n = 635)	Females (n = 555)	P value
Outcomes				
ARDS-n (%)	228 (19.2)	133 (20.9)	95 (17.1)	0.094
AKI-n (%)	51 (4.3)	35 (5.5)	16 (2.9)	0.026
AHI-n (%)	115 (9.7)	71 (11.2)	44 (7.9)	0.058
ACI-n (%)	82 (6.9)	58 (9.1)	24 (4.3)	0.001
DIC-n (%)	19 (1.7)	15 (2.5)	4 (0.7)	0.024
Shock-n (%)	69 (5.8)	41 (6.5)	28 (5.1)	0.299
Duration of MV, Median (IQR)-days	5 (2,8)	5 (2,8)	5 (2,10)	0.919
Duration of in-hospital stay, Median (IQR)-days	11 (7,14)	11 (8,15)	10 (7,14)	0.002
In-hospital mortality-n (%)	157 (13.2)	100 (15.7)	57 (10.3)	0.005

Abbreviation: acute respiratory distress syndrome, ARDS; acute kidney injury, AKI; acute hepatic injury, AHI; acute cardiac injury, ACI; disseminated intravascular coagulation, DIC.

gender-associated lifestyle behaviors and comorbidities might contribute to the disparity between men and women in COVID-19 outcomes.

Unhealthy lifestyle behaviors like smoking and drinking are prevalent in males. Alcohol and pathogenic constituents of tobacco smoke including nitric oxide, carbon monoxide and phenolic free radicals has proved proinflammatory [14–16]. What's more, active smoking has been shown to raise ACE2 receptor expression in the lungs, which increases SARS-CoV-2 attachment and entry into alveolar epithelial cells [17,18].

Comorbidities that are associated with fatal COVID-19 cases in the study, include diabetes, hypertension, heart disease, stock and chronic obstructive pulmonary disease (Supplementary Table 1). Among these comorbidities, hypertension occurs more frequently in male patients. Obesity, hypertension and diabetes in the context of metabolic syndrome is considered to provide a permissive inflammatory environment that intensifies a rapid development of cytokine storm which is associated with COVID-19 severity [19,20].

Previous studies confirmed that estrogen have a protective effect on vascular endothelial cells [21–23]. Endothelial dysfunction may contribute to acute kidney injury and acute cardiac injury in critically ill patients [24,25]. However, in patients with COVID-19, mechanisms behind the gender differences might not only due to the levels of endogenous hormones, given that laboratory findings in postmenopausal elderly female patients were still superior to their male peers.

Robust immune systems in females might play another positive role in the gender disparity. Firstly, the bi-allelic expressions of several immune regulatory genes which located on the X chromosome (e.g. TLR7, TLR8, FOXP3, CXCR3 and CD40L) contribute to stronger immune response against viruses in women [26–28]. Secondly, a comparison of adaptive immune responses between males and females demonstrates that females generally have higher levels of CD4/CD8 ratio [29]. The sex-based differences in CD4/CD8 ratio also exist in our patients with COVID-19. In addition, several antiviral genes expressed by cytotoxic T cells carry estrogen receptor elements in their promoter and contribute to stronger cytotoxic response in females [30,31]. Thus, females exhibit robust innate and adaptive immune responses to viral infections.

In spite of the marked sex differences in organ function and mortality in the univariate analysis, we found no relation between sex and hospital deaths in multivariable analysis, which showed that SOFA score, lymphocytopenia, thrombocytopenia and elevated D-dimer were all
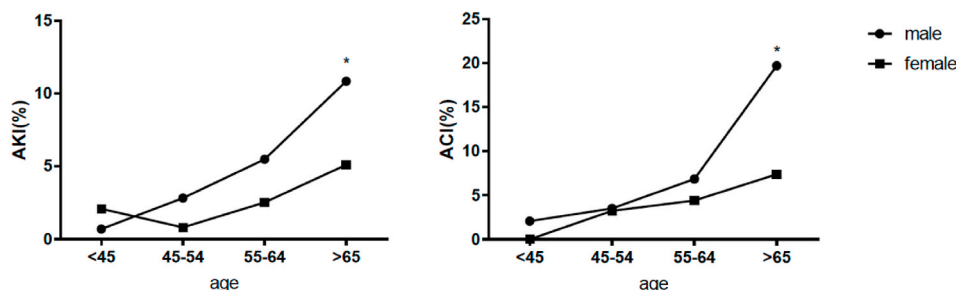
Fig. 2. Comparison of acute kidney injury (AKI) and acute cardiac injury (ACI) in patients with COVID-19 by sex and age group.
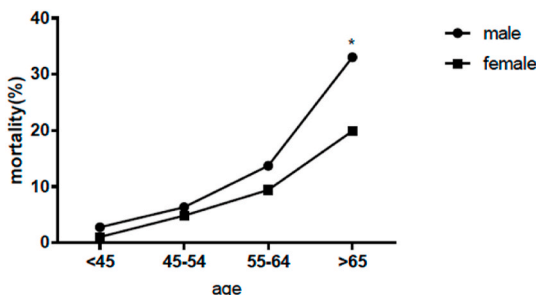*P < 0.05 for males *vs.* age-matched females.

Fig. 3. Comparison of in-hospital mortality in patients with COVID-19 by sex and age group.
*P < 0.05 for males *vs.* age-matched females.

Table 4
Multivariate Analysis of Risk Factors associated with in-hospital Mortality in patients with COVID-19.

Variables	Cox regression model HR 95% CI P value		
Age (<45yr as reference)			
45~54 yr	0.950	0.777, 1.161	0.615
55~64 yr	0.888	0.726, 1.085	0.246
>65 yr	1.034	0.834, 1.282	0.760
Male sex	1.020	0.889, 1.171	0.779
Comorbidity	0.994	0.854, 1.157	0.936
SOFA	1.057	1.028, 1.087	<0.001
Lymphocytopenia	1.249	1.054, 1.479	0.010
Thrombocytopenia	1.600	1.142, 2.247	0.006
Elevated D-dimer	1.156	1.065, 1.255	<0.001
Glucocorticoid	0.618	0.521, 0.735	<0.001
Antiviral drugs	0.747	0.648, 0.862	<0.001

Abbreviation: sequential organ failure assessment, SOFA.

independent prognostic factors. We conclude that the sex underlying mechanisms are not strong enough to significantly alter such a complex and multifactorial endpoint inhospital mortality. Clinical outcomes are not only related to patients' conditions and disease severity, but also closely related to treatment including respiratory support, glucocorticoid and antiviral therapy. In the study, more males were treated with glucocorticoid due to severe disease. COX proportional regression analysis showed that glucocorticoid therapy reduced the inhospital mortality. Although glucocorticoid therapy of COVID-19 remains controversial and might impact the inhospital mortality, but given comparing men *vs.* women, the main aim of this study, the bias may be minimized.

4.1. Limitations

This study had some limitations. Firstly, although our research was based on a large population, this was a retrospective single-center study with all patients enrolled from Wuhan Infectious Disease Hospital at the early stages of COVID-19 outbreak. The interpretation of our findings might be limited by the sample size. In addition, in the early stages of COVID-19 outbreak, the disease treatment including respiratory support, glucocorticoid and antiviral therapy mainly relied on clinical judgment and experience of the doctors due to lack of evidence-based guidelines, which might impact the inhospital mortality. However, comparing men *vs.* women, the main aim of this study, the bias may be minimized. Secondly, not all laboratory tests were performed on all patients, which might introduce some biases albeit the use of multiple analytical strategies to increase the robustness of our estimates. Thirdly, we did not have data on menopausal status of female patients, although no significant relationship was identified when we searched the interaction based on the average age of menopause. Finally, there was no long-term follow-up.

5. Conclusion

In summary, male sex was associated with a worse prognosis of COVID-19, but it seems not to be an independent prognostic factor.

CRediT authorship contribution statement

Jiao Liu: drafted the manuscript. **Lidi Zhang:** drafted the manuscript. **Yizhu Chen:** collected the clinical data. **Zhixiong Wu:** collected the clinical data. **Xuan Dong:** collected the clinical data. **Jean-Louis Teboul:** drafted the manuscript. **Sheng Zhang:** did statistical analysis. **Xiaofei Ye:** did statistical analysis. **Yongan Liu:** summarized all the collected data. **Tao Wang:** summarized all the collected data. **Hangxiang Du:** summarized all the collected data. **Wenzhe Li:** summarized all the collected data. **Dechang Chen:** revised the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106159.

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