
Distinct clinical characteristics and risk factors for mortality in female COVID-19 inpatients:
a sex-stratified large-scale cohort study in Wuhan, China

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Summary: Females underwent less critical illness and experienced a low mortality rate compared with males. Sex was still a prognostic risk factor even adjusting for age and coexisting diseases, and risk factors associated with mortality varied among male and female populations.

Abstract

Background

As the coronavirus disease 2019 (COVID-19) outbreak accelerates worldwide, it is highly significant to evaluate sex-specific clinical characteristics and outcomes, that may affect public health policies.

Methods

COVID-19 patients admitted to Tongji Hospital between January 18 and March 27, 2020 were evaluated. Clinical features, laboratory data, complications and outcomes were compared between females and males. Risk factors for mortality in the whole population, females and males were determined respectively.

Results

There were 1667 (50.38%) females among the 3309 patients included in this study. The mortality rate was only 5.9% in females but 12.7% in males. Compared with males, more females had no initial symptoms (11.1% vs 8.3%, $p=0.008$). Complications including acute respiratory distress syndrome, acute kidney injury, septic shock, cardiac injury and coagulation disorder were less common in females; critical illness was also significantly less common in females (31.1% vs 39.4%, $p<0.0001$). Significantly fewer female patients received antibiotics treatment ($p=0.001$), antiviral therapy ($p=0.025$) glucocorticoids treatment ($p<0.0001$), mechanical ventilation ($p<0.0001$) and had Intensive Care Unit admission ($p<0.0001$). A lower risk of death was found in females (odds ratio 0.44, 95% confidence interval 0.34-0.58) after adjusting for age and coexisting diseases. Among females,

age, malignancy, chronic kidney disease and days from onset to admission were significant associated with mortality, while chronic kidney disease was not risk factor in males.

Conclusions

Significantly more mild illness and fewer deaths were found in female COVID-19 inpatients and risk factors associated with mortality varied among male and female population.

Key words: SARS-CoV-2; COVID-19; Novel coronavirus; Sex; Risk factors

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Introduction

A novel coronavirus, which is now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a cluster of pneumonia cases in Wuhan, China from December, 2019 [1]. Officially called coronavirus disease 2019 (COVID-19), this virus-related pneumonia quickly spread in China and more than 208 countries around the world, bringing a serious threat to global public health. Up to May 15, 2020, there have been a cumulative 4,307,287 confirmed COVID-19 cases and more than 295,101 patients have been died from the disease, with a mortality rate of 6.85% according to the World Health Organization (WHO) COVID-19 situation dashboard [2].

Recent studies have revealed part of the epidemiology and clinical characteristics of COVID-19 in the general population. Older age, comorbidity, higher lymphocytes count, high level of lactate dehydrogenase, high sensitivity C-reactive protein (Hs-CRP) and d-dimer were found to be risk factors for mortality [3-5], and age, neutrophilia and organ dysfunction help identify population that development to acute respiratory distress syndrome (ARDS) [6,7]. Whether sex differences are associated with mortality and severity of the disease has not been well described.

Given essential distinctions in lifestyle, physical structures and pathophysiology between men and women, there are tremendous differences in many diseases between the sex. In the past outbreaks of coronaviral related illness, namely Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), a correlation between sex and mortality was demonstrated. Males showed much higher risks of disease deterioration and higher mortality compared to females [8,9]. Emerging researches have revealed the same

pattern in COVID-19. A report from the Chinese Center for Disease Control and Prevention (China CDC) and epidemiological studies showed 54%-58% of severe cases and more than 60% of deceased patients were males [10,11]. Nevertheless, the evidence is still insufficient to certify the conclusive effect of sex-specific for disease severity and prognosis due to presence of descriptive statistics and controversial results. Whether females and males had different risk factors for death was unknown.

To compare clinical features and outcomes between female and male COVID-19 inpatients and clearly elucidate the relationship between sex and mortality, a large-scale population was retrospectively evaluated. The risk factors for mortality in female and male groups were further explored separately. The findings highlight the impact of sex on disease features and provide insight into different risk factors for prognosis in females and males.

Methods

Study population

A big-data intelligence database (Yiducould Technology, Beijing, China), which was established based on diagnosed outpatients and inpatients in three branches of Tongji Hospital, was used to retrospectively screen patients for inclusion. Hospitalized patients were included in this comprehensive evaluation of clinical characteristics and outcomes between January 18 and March 27, 2020. All patients were confirmed cases of COVID-19, with clinically confirmed and laboratory-confirmed cases including in the analysis. This study was approved by The Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20200401). Informed consent

was exempted in accordance with the urgent situation and Ethics Committee's rules.

Data collection

The demographic characteristics, recent comorbidities, clinical signs at onset, clinical period, laboratory findings, radiologic assessments and disease outcomes were electronic extracted from the database. All the results were captured, if a single patient had more than one test for laboratory index, positive or abnormal results were defined as one anomalous measurement. All data was organized by two clinicians (JC and BL), and any disagreements were resolved by KL.

Definition

According to the Guidance for Corona Virus Disease 2020 (7th edition) by the National Health Commission of China, disease severity was classified as mild, moderate, severe, or critical. ARDS was defined according to the Berlin definition [12]. Acute kidney injury was defined according to the KDIGO clinical practice guidelines [13]. Cardiac injury was defined as the serum level of cardiac biomarkers e.g. hypersensitive cardiac troponin I (Hs-cTn I) was above the 99th percentile upper baseline limit or new abnormal changes in electrocardiography [14]. Heart failure was defined as the level of amino-terminal pro-brain natriuretic peptide (NT pro-BNP) exceeding the normal range [15]. Acute liver injury was identified as total bilirubin increase by $51.3 \mu\text{mol/L}$ and alanine aminotransferase increase to five times the upper reference limit or alkaline phosphatase increase to twice the upper reference limit. Coagulopathy was identified as extension of prothrombin time (PT) or activated partial thromboplastin time (APTT) by 3seconds or 5seconds respectively [11].

Statistical Analysis

Continuous variables are demonstrated as medians and interquartile ranges (IQRs), and categorical variables are presented as counts and percentages. Differences in continuous variables were tested with Student's t test for normally distributed ones, or the Mann-Whitney U test when variables showed a non-normal distribution. Significant differences in categorical variables were assessed using the Chi-square test or Fisher's exact test when appropriate.

To explore the risk factors for mortality, univariable and multivariable logistic regression models were conducted, and variables will import into multivariable logistic regression if their p value < 0.2 in univariable analysis. Age was classified as young age (≤ 45 years) and older age (> 45 years). Days from onset to clinics or on admission were classified according to their medians. Forest plots were used to display logistic regression analysis results.

All statistical analyses were performed using SPSS (Version 25.0. Armonk, NY: IBM Corp). No imputation was made for missing data. Two-sided p values < 0.05 were classified as statistically significant. Data visualization was performed by R software, version 3.6.2 (R Foundation for Statistical Computing).

Results

Demographics and baseline characteristics

A total of 3309 patients with confirmed COVID-19 were included, of whom 1667 (50.38%) were females. The preexisting rate of diabetes was 12.4% in females, which was significantly lower than that in males (15.7%). Other comorbidities, including hypertension,

cardiovascular disease, cerebrovascular disease, malignancy and chronic kidney disease were not significantly different between the male and female groups. Specific cancer types were also comparable between female and male patients (Supplementary Table 1). The most common primary symptoms were fever (68.8%) and cough (56.5%), followed by sputum production (41.7%) and dyspnea (31.7%) in the overall population. There were 185 (11.1%) women who had no initial symptoms, which was significantly more than the 137 (8.3%) cases in male group. Cough (58.2%), sputum production (43.6%) and nausea (6.9%) were more common in females on admission, but a significantly higher proportion of males presented with fever (73.6%). Regarding computed tomography (CT) examination results, males were more prone to have interstitial abnormalities in pulmonary manifestations (3.2% vs 1.5%). Laboratory confirmed COVID-19 cases accounted for 95.8% in the whole population and were comparable between females and males (95.7% vs 95.9%). Among female patients, the median interval time from signs or symptom onset to seeking outpatient care was 5 (IQR 1-9) days, the days from onset to admission was 12 (IQR 7-20), and the period from onset to discharge or death was 37 (IQR 27-48). Significant differences were observed between male and female group. Duration of clinical course were summarized in Supplementary Table 2 detailly. On admission, there were 22.5% of female patients and 25% of male patients who developed severe or critical disease, with no statistical significance ($p=0.094$).

Complications and treatment

During the course of disease, with the exception of heart failure, enormous significant differences in organic damage had developed among female and male (Table 2). Acute kidney

injury was more common in females (13.3%) than in males (10.9%). Compared to males, most complications were significantly rarer in female patient. Specifically, the observed complications in males included septic shock (54.8%), ARDS (46.8%) , cardiac injury (32.8%), coagulation disorder (21.5%) and acute liver injury (4.6%), of which the corresponding incidence in females were all significantly lower. Since coexisting diseases were comparable between males and females as shown in Table 1, we speculate that the significant difference in complications between the two groups is due to acute t organ injury caused by the novel coronavirus.

As summarized in Table 2, significantly more male patients require antibiotic treatment (67%), antiviral treatment (44.5%) and systemic glucocorticoid treatment (41.2%), whereas the proportion was 61.5%, 40.6% and 31.9% in female population. 78% of the whole population needed oxygen treatment. Significantly fewer female patients (11.1%) than male patients (18.6%) received mechanical ventilation, including noninvasive mechanical ventilation (Female vs Male: 6.6% vs 11.0%) and invasive mechanical ventilation (Female vs Male: 4.7% vs 7.8%). Only 41 (2.5%) females needed extracorporeal membrane pulmonary oxygenation, while the number reached 57 (3.5%) in males, although there was no significant difference ($p=0.083$). Compared with 39.4% critical illness in male patients, a significantly lower percentage of female patients (31.1%) had critical type COVID-19. As date of data extraction, accumulative 464 (27.8%) females and 572 (34.8%) males had been admitted to Intensive Care Unit (ICU), and the difference was significant. Overall, the clinical outcomes in female group was also significantly different from that in the males, with discharge rates of 92.8% and 85.7% for females and males, respectively. The mortality rate

was significantly lower in female than in males (5.9% vs 12.7%).

Laboratory findings

In addition, the laboratory findings were summarized in Table 3, most of which had significant differences. Females had lower leucocytes count ($6.74 \times 10^9/L$, IQR 5.43-9.02) and fewer neutrophils ($4.46 \times 10^9/L$, IQR 3.24-6.67). The results of serum biochemical tests also indicated great differences. Women had significantly lower levels of creatine kinase (57 U/L, IQR 39.25-86), Hs-cTn I (6.5 pg/ml, IQR 3.4-16.35), serum creatinine (62 $\mu\text{mol/L}$, IQR 55-72), blood urea (5 $\mu\text{mol/L}$, IQR 4-6), alanine aminotransferase (24 U/L, IQR 16-42), alkaline phosphatase (73 U/L, IQR 59-90) and total bilirubin (10 mmol/L, IQR 7.4-14.1). In the coagulation profile, the PT and APTT were 13.8 (IQR 13.3-14.5) seconds and 39.1 (IQR 36.4-42.9) seconds in the female group, while males showed significant extensions to 14.2 (IQR 13.6-15.1) seconds and 41.5 (IQR 38-46.8) seconds respectively. In addition, substantial indicators of infection and inflammatory reaction were remarkably elevated in males compared with females during the hospital stay. The median levels of cytokines IL-2R (466 vs 620 pg/ml), IL-6 (6.2 vs 14.72 pg/ml), and IL-8 (13.35 vs 16.8 pg/ml) were significantly lower in females than in males, and lower levels of serum infection indicators including procalcitonin (0.06 vs 0.09 ng/ml) and Hs-CRP (9.6 vs 35.8 mg/L) were also detected in female patients.

Risk factors for prognosis

In the univariable analysis (Table 4), sex, age, hypertension, cardiovascular disease, cerebrovascular disease, malignancy, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and days from onset to admission were associated with mortality. In the

multivariable logistic regression analysis, a significantly low risk of death was found in female patients (OR, 0.44; 95% CI, 0.34-0.58). Apart from sex, age (≤ 45 years vs >45 years), malignancy, chronic kidney disease, and interval from symptom onset to admission were also proven as risk factors for death in whole population. In regard to specific cancer types, patients with gastrointestinal cancer were found to have relatively poor prognosis (OR, 3.16; 95% CI, 1.11-9.02; Supplementary Table 3).

In addition, the sex-specific risk factors for mortality of COVID-19 inpatients were analyzed since they had significantly different outcomes. In the female group, age (>45 years), malignancy, chronic kidney disease, COPD and days from onset to admission were associated with mortality in the univariable model, and age (>45 years), malignancy, chronic kidney disease and days from onset to admission (≤ 12 days) were identified as risk factors in the multivariable logistic regression models (Supplementary Table 4 and Figure 1A). Among male patients, age (>45 years), hypertension, cardiovascular disease, malignancy, days from onset to admission (≤ 12 days) were related to death in the univariable logistic regression analysis (Supplementary Table 2), and the multivariable models showed that age (>45 years), hypertension, malignancy and days from onset to admission (≤ 12 days) were factors that significantly influenced prognosis (Supplementary Table 5 and Figure 1B).

Discussion

It is of great significance to clearly evaluate the impact of sex in clinical features and outcomes of COVID-19, of which may affect the health policy decision-making by global health institutions or governments, such as in assignment of front-line workers for medical

and social assistance in fight against COVID-19. Sound public-health policies will potentially remarkably decrease current high prevalence of infection and mortality rate in COVID-19-related staff. Call on as public health specialist, great efforts should be paid to research in this area [16,17].

The remarkable difference in clinical features and severity of disease between male and female COVID-19 patients was addressed in this study. More women were found to have no initial symptoms at the onset of infection and develop fewer complications, such as ARDS, acute kidney injury, septic shock, cardiac injury and coagulation disorder. Females had a lower mortality rate, even after adjusting for other confounding factors. In addition, we investigated the prognostic factors for females and males separately. Age, malignancy, chronic kidney disease and days from onset to admission were risk factors for the female group, while age, hypertension, malignancy and days from onset to admission were risk factors for males.

In terms of clinical presentation, more male patients suffered from organ damage and needed ICU admission, drug treatment and mechanical ventilation therapy. Interestingly, a preprint meta-analysis concluded that days from symptom onset to admission was related to death rates, with an approximately 1.27% increase for every day of delay [18], whereas in our study, the onset to admission time was significantly longer in women than in men, which might due to the fact that most females had mild or general illness and did not need urgent medical care.

Although sex differences seem to affect the prognosis of COVID-19, the exact mechanism of different outcomes between women and men is still unclear. Recently published studies

involved laboratory test results may provide some insight into the underlying reasons. First, estrogen may protect females from seriously poor outcomes during coronavirus infection and women's immune systems are more specific to fight against SARS-CoV-2 [19,20]. As shown in our results, the serum levels of IL-2R, IL-6 and IL-8 were significantly lower in women than in males, which indicated that the extreme immune attacks called the cytokine storms were less common in women. Second, in the analysis of preexisting diseases, we found that the proportion of patients with diabetes was significantly higher in males than in females. As we know, patients with diabetes are vulnerable to complicated infections [21,22], which may be the reason why we found infection-related indicators, such as Hs-CRP and procalcitonin, to be remarkably elevated in men. Additionally, angiotensin-converting enzyme 2 (ACE2) is the receptor-binding domain for SARS-CoV-2 [23], thus, the expression pattern of ACE2 in different organs and individuals might account for the susceptibility, severity and outcome of SARS-CoV-2 infectious pneumonia [24,25]. A recent Single-cell RNA expression analysis demonstrated higher expression of ACE2 in male lungs, which may account for the high rate of severe disease and mortality in males [26]. Unfortunately, tissue samples of all COVID-19 patients were unavailable to detect differences expression of ACE2 between males and females, so revealing molecular differences would be a key direction in the future.

According to the multivariable analysis, we found that sex, age (>45 years), malignancy, chronic kidney disease, and the interval from symptom onset to admission were risk factors for death in the whole population. A previous meta-analysis including eight studies also addressed that most severe disease among COVID-19 patients was accompanied with higher proportions of cardiovascular disease, hypertension, respiratory disease [27], and older age

and cancer patients had higher mortality [4,28]. In contrast to previous research, we found that sex was independently related to risk of mortality among hospitalized COVID-19 patients, and the result was still reliable after adjustment for age and pre-existing illness. Our data indicated that males faced more than twice the risk of death from COVID-19.

To our knowledge, the findings of this study concluded from cohort study with the largest sample-size for the comparison of clinical distinction between male and female hospitalized patients with COVID-19. Additionally, this is the first study to evaluate the risk factors for COVID-19 mortality in females and males separately. In the present study, cancer patients, females with chronic kidney disease and male with hypertension were identified high risks of death from COVID-19, which displayed preexisting comorbidities associated with mortality rates might vary in different populations.

There are some limitations in our study. First, our medical center is one of the COVID-19 treatment-specific hospitals for severe or critical cases, thus, a low proportion of mild and general cases were included in our study. Next, some laboratory test (NT pro-BNP, Hs-cTn I and so on) were not presented in some of the patients, which may have resulted in bias of laboratory findings. Finally, since there are no internationally recognized guidelines for the treatment of COVID-19, impact of treatment on prognosis was not evaluated. Future prospective randomized controlled trials focused on the dynamic changes in laboratory tests and the impact of treatment are needed.

Conclusion

This large-scale retrospective cohort study determined differences in clinical features,

complications, severity of disease and outcomes between female and male COVID-19 patients. Females underwent less severe and critical illness and resulted in a low mortality rate compared with males. In addition to sex, older age (>45 years), comorbid chronic kidney disease and malignancies were independent risk factors for poor prognosis. It is worth noticing that many female patients have no initial symptoms at onset, thus, close contacts of female COVID-19 patients should be strict monitored. As the COVID-19 outbreak accelerates around the world, our findings may provide vital information to help develop public health policies to battle against this coronavirus-related disease.

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Authors' Contributions: KL, JA, GangChen and DM contributed equally to the manuscript as corresponding authors, and they are the guarantors. They contributed into the conception the research and revised the manuscript critically for important intellectual content. JC and HB contributed equally to the design of the study, analysis and interpretation of the data and drafting the manuscript. JL, GeChen and QL participated in the data collection, analysis of data and preparation of the manuscript. JY, PW and JW participated in data analyses, manuscript preparation and revision. All authors gave final approval for the version to be published. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgments: We thank all the participants and their families involved in this study, as well as the many doctors, nurses, and civilians working together to fight against COVID-19. The data used to support the findings of this study are available from the corresponding author upon request.

Funding: This work was supported by the National Key Research and Development Program (2019YFC1005200, 2019YFC1005202) of the National Science and technology Department of China; the Hubei Province Health and Family Planning Scientific Research Project (WJ2019M127) and National Clinical Research Center of Gynecology and Obstetrics (2015BAI13B05). The funder had no role in designing research, in data acquisition, analysis or interpreting data and writing manuscript. The corresponding authors have full access to all data and are responsible for decision-making about submission for publication.

Conflict of Interest: None reported.

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Table 1: Comparison of Clinical Characteristics Between male and female COVID-19

patients

Characteristics	Total(n=3309)	Females(n=1667)	Males(n=1642)	p value ^a
Age, years	62(49-69)	61(51-69)	62(48-70)	0.582
Comorbidity				
Hypertension	988(29.9%)	481(28.9%)	507(30.9%)	0.204
Diabetes	464(14%)	206(12.4%)	258(15.7%)	0.005
Cardiovascular disease	242(7.3%)	116(7%)	126(7.7%)	0.205
Cerebrovascular disease	130(3.9%)	47(2.8%)	83(5.1%)	0.209
Malignancy	93(2.8%)	43(2.6%)	50(3%)	0.207
Chronic kidney disease	57(1.7%)	29(1.7%)	28(1.7%)	0.208
COPD	42(1.3%)	8(0.5%)	34(2.1%)	0.206
Symptoms on admission				
Fever	2275(68.8%)	1067(64.0%)	1208(73.6%)	< 0.0001
Cough	1868(56.5%)	971(58.2%)	897(54.6%)	0.036
Sputum production	1381(41.7%)	727(43.6%)	654(39.8%)	0.027
Dyspnea	1049(31.7%)	527(31.6%)	522(31.8%)	0.913
Diarrhea	620(18.8%)	323(19.4%)	297(18.1%)	0.342
Fatigue	490(14.8%)	255(15.3%)	235(14.3%)	0.421
Chest tightness	462(14.0%)	241(14.5%)	221(13.5%)	0.408
Chills	295(8.9%)	135(8.1%)	160(9.7%)	0.097
Myalgia	237(7.2%)	125(7.5%)	112(6.8%)	0.450

Nausea	188(5.7%)	115(6.9%)	73(4.4%)	0.002
Asymptomatic	322(9.7%)	185(11.1%)	137(8.3%)	0.008
CT features				
Patchy shadow	2275(78.5%)	1186(78.8%)	1089(78.3%)	0.762
Ground-glass opacity	1582(54.6%)	833(55.3%)	749(53.8%)	0.428
Interstitial abnormalities	66(2.3%)	22(1.5%)	44(3.2%)	0.002
Confirmed cases				0.799
Positive SARS-CoV-2	3169(95.8%)	1595(95.7%)	1574(95.9%)	
laboratory tests				
Radiographic diagnosis	140(4.2%)	72(4.3%)	68(4.1%)	
Disease Severity on admission				0.094
Mild/general	2524(76.3%)	1292(77.5%)	1232(75%)	
Severe/Critical	785(23.7%)	375(22.5%)	410(25%)	

The results are presented as median (IQR) for continuous variables and number (%) for categorical variables.

^a The difference in characteristics between females and females were tested by Chi-square test (categorical variables).

COPD=Chronic obstructive pulmonary disease. CT=Computed tomography.

Table 2: Comparison of complications, treatment and clinical outcomes between female and male COVID-19 patients

Clinical features	Total (n=3309)	Females (n=1667)	Males (n=1642)	p value^a
Complication				
Septic shock	1582(47.8%)	682(40.9%)	900(54.8%)	<0.0001
Acute respiratory distress syndrome	1325(40.0%)	557(33.4%)	768(46.8%)	<0.0001
Cardiac injury	1038(31.4%)	411(24.7%)	627(38.2%)	<0.0001
Heart failure	629(19.0%)	321(19.3%)	308(18.8%)	0.715
Coagulation disorder	620(18.7%)	208(12.5%)	412(25.1%)	<0.0001
Acute kidney injury	401(12.1%)	222(13.3%)	179(10.9%)	0.033
Acute liver injury	89(2.7%)	13(0.8%)	76(4.6%)	<0.0001
Drug treatment				
Antibiotic treatments	2127(64.28%)	1100(61.6%)	1027(67%)	0.001
Antiviral treatments	1407(42.52%)	677(40.6%)	730(44.5%)	0.025
Systemic glucocorticoids	1209(36.53%)	532(31.9%)	677(41.2%)	<0.0001
Supporting therapy				
Oxygen treatment	2580(78%)	1310(78.6%)	1270(77.3%)	0.390
Mechanical ventilation	490(14.8%)	185(11.1%)	305(18.6%)	<0.0001
Noninvasive Mechanical ventilation	290(8.8%)	110(6.6%)	180(11.0)	<0.0001
Invasive Mechanical ventilation	206(6.2%)	78(4.7%)	128(7.8%)	<0.0001
ECMO	98(3.0%)	41(2.5%)	57(3.5%)	0.086

ICU admission	1036(31.3%)	464(27.8%)	572(34.8%)	<0.0001
Disease Severity status				<0.0001
Mild/general	670(20.2%)	336(20.5%)	334(20%)	
Severe	1471(44.5%)	659(40.1%)	812(48.7%)	
Critical	1168(35.3%)	647(39.4%)	521(31.1%)	
Outcomes				<0.0001
Discharge	2943(89.2%)	1547(92.8%)	1407(85.7%)	
Hospitalization	48(1.5%)	21(1.3%)	27(1.6%)	
Death	307(9.3%)	99(5.9%)	208(12.7%)	

The results are presented as median (IQR) for continuous variables and number (%) for categorical variables.

^a The difference in characteristics between females and females were tested by Chi-square test for categorical variables.

ECMO=Extracorporeal Membrane Oxygenation. ICU=Intensive Care Unit.

Table 3: Comparison of laboratory findings between female and male COVID-19 patients

Laboratory findings	Total	Female	Male	p value ^a
WBC, *10 ⁹ /L	7.18(5.63-9.85)	6.74(5.43-9.02)	7.67(5.91-10.98)	<0.0001
Neutrophils, *10 ⁹ /L	4.80(3.39-4.67)	4.46(3.24-6.67)	5.20(3.59-8.93)	<0.0001
Lymphocytes, *10 ⁹ /L	1.70(1.31-2.13)	1.73(1.37-2.13)	1.67(1.26-2.12)	0.128
NT pro-BNP, pg/ml	138(49-517.5)	129(53-402)	152(46-758)	0.059
Creatine Kinase, U/L	67(44-115.5)	57(39.25-86)	82(52-156)	<0.0001
Hs-cTn I, pg/ml	7.1(3.6-19.85)	6.5(3.4-16.35)	7.7(3.8-26.3)	<0.0001
Serum creatinine, µmol/L	74(61-90)	62(55-72)	86(75-100)	<0.0001
Blood Urea, µmol/L	5.4(4.3-7.2)	5(4-6)	5.8(4.6-8.4)	<0.0001
ALT, U/L	32(19-56)	24(16-42)	41(25-70)	<0.0001
AST, U/L	29(21-46)	25(19-39)	34(23-53)	0.196
Alkaline phosphatase, U/L	75(61-95)	73(59-90)	76(64-102)	<0.0001
Total bilirubin, mmol/L	11.2(8.3-16.1)	10(7.4-14.1)	12.5(9.4-17.8)	<0.0001
D-dimer, µg/mL	0.87(0.36-2.39)	0.75(0.34-2.03)	0.99(0.38-2.81)	<0.0001
Prothrombin time, sec	14(13.4-14.8)	13.8(13.3-14.5)	14.2(13.6-15.1)	<0.0001
APTT, sec	40.2(37.1-44.7)	39.1(36.4-42.9)	41.5(38-46.8)	<0.0001
Procalcitonin, ng/mL	0.07(0.05-0.17)	0.06(0.04-0.10)	0.09(0.06-0.24)	<0.0001
Hs-CRP, mg/L	19(2.4-75.4)	9.6(1.65-49.85)	35.8(4.4-100.98)	<0.0001
Interleukin-6, pg/ml	9.23(3.54-37.42)	6.2(3.03-22.77)	14.72(4.48-56.32)	<0.0001
Interleukin-8, pg/ml	14.8(8.9-30.1)	13.35(8.6-24.18)	16.8(9.5-36.2)	<0.0001
Interleukin-10, pg/ml	9.3(6.5-16.5)	8.9(6.3-16.2)	9.5(6.6-16.8)	0.618

Interleukin-1 β , pg/ml	9.7(6.6-17.6)	9.55(6.6-15.4)	9.85(6.7-21.28)	0.608
Interleukin-2R, pg/ml	539(339-860)	466(299-724)	620(401-987)	<0.0001

The results are presented as median (IQR) for continuous variables.

^a The difference in characteristics between females and males were tested by t-test or Mann-Whitney U test.

WBC=White blood cell. RBC=Red blood cell. NT pro-BNP = amino-terminal pro-brain natriuretic peptide.

Hs-cTnI=Hypersensitive cardiac troponin I. ALT=Alanine aminotransferase. AST= Aspartate aminotransferase.

ATPP=activated partial thromboplastin time. Hs-CRP=High sensitivity C-reactive protein.

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Table 4: Univariate and Multivariate logistic regression analysis of factors associated with mortality in hospitalized COVID-19 patients

Factors	Univariate		Multivariate	
	OR (95%CI)	p value ^a	OR (95%CI)	p value ^b
Sex Female (vs Male)	0.44(0.34-0.56)	<0.0001	0.44(0.34-0.58)	<0.0001
Age, years (vs ≤45 years)	8.37(4.43-15.81)	<0.0001	9.08(4.44-18.59)	<0.0001
Comorbidity (vs not present)				
Hypertension	1.53(1.20-1.95)	0.001	1.14(0.87-1.50)	0.336
Diabetes	0.97(0.70-1.36)	0.870	NA	NA
Cardiovascular disease	1.94(1.34-2.80)	<0.0001	1.41(0.94-2.13)	0.096
Cerebrovascular disease	1.72(1.04-2.84)	0.034	1.25(0.73-2.13)	0.416
Malignancy	3.65(2.23-5.83)	<0.0001	3.17(1.84-5.46)	<0.0001
Chronic kidney disease	2.67(1.40-5.11)	0.003	2.85(1.42-5.73)	<0.0001
COPD	2.72(1.29-5.73)	0.009	1.72(0.80-3.71)	0.169
Days from onset to clinics (vs ≤5d)	0.94(0.72-1.21)	0.610	NA	0.169
Days from onset to admission (vs ≤12d)	0.61(0.47-0.78)	<0.0001	0.61(0.47-0.78)	<0.0001

^a Tested by univariable logistic regression models.

^b Tested by multivariable logistic regression models, variables will import into multivariable logistic regression if their p value <0.2 in univariable analysis.

COPD=Chronic Obstructive Pulmonary Disease. NA=Not available for Not included in the multivariable analysis.

Figure legend

Figure 1 Forest plot of multivariate logistic regression analysis of factors associated with mortality in COVID-19 inpatients. (A) Females, (B)Males.

