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Age-dependent Gender Differences in COVID-19 in Mainland China: Comparative Study

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(See the Editorial Commentary by Yang and Esper on pages 2495–6.)

Background. The ongoing pandemic of novel coronavirus disease 2019 (COVID-19) is challenging the global public health system. Sex differences in infectious diseases are a common but neglected problem.

Methods. We used the national surveillance database of COVID-19 in mainland China to compare gender differences in attack rate (AR), proportion of severe and critical cases (PSCC), and case fatality rate (CFR) in relation to age, affected province, and onset-to-diagnosis interval.

Results. The overall AR was significantly higher in females than in males (63.9 vs 60.5 per 1 million persons; $P < .001$). In contrast, PSCC and CFR were significantly lower among females (16.9% and 4.0%) than among males (19.5% and 7.2%), with odds ratios of 0.87 and 0.57, respectively (both $P < .001$). The female-to-male differences were age dependent, and were significant among people aged 50–69 years for AR and in patients aged 30 years or older for both PSCC and CFR (all $P \leq .001$). The AR, PSCC, and CFR varied greatly from province to province. However, female-to-male differences in AR, PSCC, and CFR were significant in the epicenter, Hubei province, where 82.2% confirmed cases and 97.4% deaths occurred. After adjusting for age, affected province, and onset-to-diagnosis interval, the female-to-male difference in AR, PSCC, and CFR remained significant in multivariate logistic regression analyses.

Conclusions. We elucidate an age-dependent gender dimorphism for COVID-19, in which females have higher susceptibility but lower severity and fatality. Further epidemiological and biological investigations are required to better understand the sex-specific differences for effective interventions.

Keywords. COVID-19; gender differences; age-dependent; attack rate; fatality.

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China, in December 2019 [1], and is leading to a global health crisis. Consideration of the gender differences in infectious diseases in humans is a common but neglected global health problem [2]; there is a great need to investigate this specific question with regard to COVID-19. Global Health 50/50, an independent health equity research organization based at the University College London, compiled sex-disaggregated infection and mortality data available from many affected countries, and implied that male patients were more likely to die than female patients. However, data have so far provided no clear pattern in terms of who is more likely to become infected with SARS-CoV-2 [3]. Furthermore, no data on severity of the disease are available to do the comparative analyses. In mainland China, some reports have mentioned differences in fatality between male and female patients using data only from early reported cases or hospital settings [4–6]. In this study, we used the surveillance data containing all confirmed cases in mainland China as of 28 April 2020 to evaluated gender-specific differences in attack rate (AR), proportion of severe and critical cases, and case fatality in relation to age, affected province, and onset-to-diagnosis interval, in order to provide evidence-based guidance for more effective and equitable interventions and treatments.

METHODS

Case Definition and Data Collection

According to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7), which was updated by National Health Commission and State Administration of Traditional Chinese Medicine on 3 March 2020 (Supplementary Table 1) [7], confirmed cases were patients who had related epidemiological history and clinical manifestations, who met one of the following etiological or serological criteria: SARS-CoV-2 nucleic acid detected by specific real-time reverse transcriptase–polymerase chain reaction assay, viral gene sequence homologous to SARS-CoV-2, specific immunoglobulin (Ig) M and/or IgG detectable in serum, or a 4-fold increase in IgG titer

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in convalescent serum compared with the acute phase. Among the confirmed cases, if patients had mild symptoms but no sign of pneumonia on imaging, they were defined as mild cases. If patients presented fever and respiratory symptoms with radiological findings of pneumonia, they were defined as moderate cases. If adult patients met any of the following criteria, they were defined as severe cases: respiratory distress (≥30 breaths per minute [BPM]), oxygen saturation ≤93% at rest, or arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤300 mm Hg (l mm Hg = 0.133 kPa). The criteria for severe child cases were as following: respiratory distress (≥60 BPM for infants aged <2 months, ≥50 BPM for infants aged 2–12 months, ≥40 BPM for children aged 1–5 years, and respiratory rate ≥30 BPM for children >5 years old); oxygen saturation ≤92% at rest; having labored breathing, cyanosis, or intermittent apnea; showing lethargy and convulsion; or having difficulty of feeding and signs of dehydration. Critical cases were defined if they had respiratory failure requiring mechanical ventilation, shock, or other organ failure that required care in the intensive care unit.

We collected data on all confirmed COVID-19 cases reported to the China Information System for Diseases Control and Prevention (CISDCP) official reports by the national, provincial, and municipal health commissions as of 28 April 2020. The surveillance data included information on age, sex, occupation, residence location, date of illness onset, date of diagnosis, and disease classification. According to the regulations issued by the central government of mainland China, all confirmed patients should be admitted to either general hospitals or temporary cabin hospitals until recovery from COVID-19 or death. The disease classification was duly updated according to the change in clinical manifestations of each case. As this study constituted public health surveillance rather than research in human beings, ethical approval from institutional review boards was not required. All of the information regarding individual persons had been anonymized.

Statistical Analysis

We summarized continuous variables as medians (interquartile range [IQR]) or means (± SD) and categorical variables as frequencies or proportions. The AR of COVID-19 with its 95% confidence interval (CI) was computed using the population estimate of the National Census obtained from the National Bureau of Statistics of China, and presented as the number of cases per 1 million persons. To evaluate illness severity of COVID-19, we calculated the proportion of severe and critical cases (PSCC) among confirmed cases. The case fatality rate (CFR) was presented as the percentage of deaths among confirmed cases.

To estimate the differences between groups, Student's *t* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables were used where appropriate. The administrative divisions including provinces, autonomous regions, and municipalities of China are all referred to as provinces in the paper for simplicity. We evaluated the association between gender and AR in each age group and affected province, and then estimated the risk ratio and its 95% CI by the Woolf method. We compared the PSCC and CFRs between female and male patients in each age group and affected province, and then estimated odds ratio (ORs) and their 95% CIs by the maximum likelihood method.

The gender difference in either PSCC or CFR was validated by the multivariate logistic regression analysis using SPSS software (version 18.0; IBM Corporation) by including gender as an independent variable and age group, affected province, and onset-to-diagnosis interval as covariables. A 2-sided *P* value less than .05 was considered significant.

RESULTS

Comparing Characteristics of COVID-19 Cases Between Females and Males

As of 28 April 2020, a total of 82 858 confirmed case were reported, of whom 41 580 (50.2%) were female (Table 1). The median age of the patients was 51 years (IQR, 39–63 years), with a mean (±SD) of 51.0 ± 16.7 years. There was no significant difference in age distribution between female and male patients. The number of healthcare workers (HCWs) was 3402, accounting for 4.1% (95% CI, 4.0–4.2%) of total cases. The female cases (1956) among HCWs outnumbered males (1446; female, 57.5%; male, 42.5%; *P* < .001). The mean (±SD) time

Table 1. Comparison of Characteristics of COVID-19 Cases Between Females and Males in Mainland China

	Total	Females	Males	*P*
No. of cases	82 858	41 580	41 278	
Median (IQR) age, years	51 (39–63)	52 (40–63)	51 (38–64)	
Mean ± SD age, years	51.0 ± 16.7	51.4 ± 16.3	50.5 ± 17.2	<.001
Healthcare workers, n (%)	3402 (4.1)	1956 (4.7)	1446 (3.5)	<.001
Onset-to-diagnosis (mean ± SD), days	9.5 ± 7.4	9.3 ± 7.2	9.7 ± 7.5	<.001
AR (95% CI) per million persons; n/N	62.2 (61.7–62.6); 82 858/1 332 810 869	63.9 (63.3–64.5); 41 580/650 481 765	60.5 (59.9–61.1); 41 278/682 329 104	<.001
PSCC, % (95% CI); n/N	18.2 (17.9–18.4); 15 062/82 858	16.9 (16.5–17.2); 7017/41 580	19.5 (19.1–19.9); 8045/41 278	<.001
CFR, % (95% CI); n/N	5.6 (3.8–4.1); 4633/82 858	4.0 (3.9–4.2); 1681/41 580	7.2 (6.9–7.4); 2952/41 278	<.001

Abbreviations: AR, attack rate; CFR, case fatality rate; CI, confidence interval; COVID-19, novel coronavirus disease 2019; IQR, interquartile range; PSCC, proportion of severe and critical cases.

from illness onset to diagnosis was 9.5 ± 7.4 days. The onset-to-diagnosis interval was significantly longer among female cases than among male cases. The overall AR was 62.2 per 1 million persons (95% CI, 61.7–62.6), which was significantly higher in females than in males (63.9 vs 60.5 per 1 million persons; $P < .001$). Among the confirmed cases, 12 366 (14.9%) were severe and 2696 (3.3%) were critical, with an overall PSCC of 18.2%. The PSCC was significantly lower in females (7017/41 580; 16.9%) than in males (8045/41 278; 19.5%) with a female-to-male OR of .87 (95% CI, .84–.89; $P < .001$). The overall CFR was 5.6% (4633/82 858), which was significantly lower among female patients (1681/41 580; 4.0%) than among male patients (2952/41 278; 7.2%), with an OR of .57 (95% CI, .53–.60; $P < .001$). The PSCC (15.4%) and CFR (2.1%) among HCWs were significantly lower than other cases (18.3% and 5.7%; $P < .001$). Similarly, PSCC and CFR were significantly lower in female (13.8% and 1.1%) than male (19.3% and 4.4%) HCWs (both $P < .001$).

Gender Differences in COVID-19 by Age

The overall AR of COVID-19 was significantly increased with age (χ^2 for trend test, $P < .001$), with persons over 60 years having a 9.9 times higher rate than those under 30 years of age (153.8 vs 15.5 per 1 million persons; $P < .001$). The ARs were significantly lower among female than among male individuals aged 10–39 years. Attack rates became significantly higher in the female population aged 50–69 years (Figure 1A; Supplementary Table 2).

The older the patients, the more severe their illness. The PSCC continuously increased with age (χ^2 for trend test, $P < .001$). The PSCC was lower in female than male cases in all age groups except for those aged 20–29 years. The female-to-male ORs were significantly higher in the age groups older than 30 years (all $P < .001$) (Figure 1B, Supplementary Table 3). The CFR sharply increased with age (χ^2 for trend test, $P < .001$). Similar to PSCC, CFRs were lower among female patients in all age groups, and the gender differences in CFR were significant in the patients age 30 years or older (all $P < .001$) (Figure 1C, Supplementary Table 4).

Gender Differences in COVID-19 by Affected Province

COVID-19 affected 1726 (60.4%) counties in all 31 provinces of mainland China, with over 82.2% cases reported in Hubei province, which was the epicenter. In addition to Hubei province, another 10 provinces had more than 500 cases, whereas there were fewer than 100 cases in 7 provinces. Only 1 patient was identified in Tibet. The AR in Hubei province was up to 1190.3 (95% CI, 1181.3–1199.2) per 1 million persons. Among the other 10 most severely affected provinces, ARs ranged from 7.0 (95% CI, 6.4–7.6) per 1 million persons in Sichuan province to 23.3 (95% CI, 22.0–24.6) per 1 million persons in Zhejiang province. The AR was significantly higher among females (1247.1 per 1 million persons) than among males (1136.5 per 1 million persons) in Hubei province ($P < .001$), although there was no significant difference in ARs between the female and male populations in the other provinces as a whole. The gender difference in AR varied from province to province, and the ARs were significantly lower among females in Henan, Shandong, and Jiangsu provinces (Figure 2A, Supplementary Table 5).

The PSCC was lower among female than among male cases in all provinces except for Shandong province. The female-to-male differences in PSCC were statistically significant in Hubei, Zhejiang, Guangdong, Hunan, and Jiangxi provinces (Figure 2B, Supplementary Table 6). Of all deaths, 97.4% occurred in Hubei province, where a significant female-to-male difference in CFR was observed (OR, .55; 95% CI, .52–.58; $P < .001$) (Figure 2C, Supplementary Table 7). The CFR of female patients was comparable to that of male patients in the rest of China (OR, 1.2; 95% CI, .8–1.6; $P = .37$).

Gender Differences in COVID-19 by Multivariate Analyses

We conducted a multivariate logistic regression to validate the gender differences in PSCC and CFR by adjusting for age, affected province, and onset-to-diagnosis interval, which were significant in the univariate analyses. Considering both PSCC and CFR were increased with age group and onset-to-diagnosis interval, we included them as continuous covariables, with affected province as a categorical covariable in the models. We found that the female-to-male OR for PSCC remained significant after adjusting for those possible confounding variables, with an adjusted OR of .80 (95% CI, .77–.83). Older age and longer onset-to-diagnosis interval were also identified as risk factors for severity of illness (both $P < .001$) (Table 2). Similarly, the adjusted female-to-male OR of CFR was .53 with a 95% CI of .49–.57 ($P < .001$). In the final model for CFR, the OR for age was 1.10 (95% CI, 1.10–1.11) with each 10-year increase ($P < .001$) and the OR for onset-to-diagnosis interval was 1.01 (95% CI, 1.01–1.02) for each additional day ($P < .001$) (Table 2).

DISCUSSION

As the world responds to the unprecedented pandemic of COVID-19, it is critical to recognize the populations at high risk for SARS-CoV-2 infection and disease severity to create effective surveillance and target interventions. Because gender is a determinant of health [8], understanding the extent to which outbreaks affect women and men differently is a fundamental step to evaluating the primary and secondary effects of a health emergency on individuals and communities [9]. We did comparative analyses using the national surveillance data containing all confirmed COVID-19 cases in mainland China. The age-dependent gender differences in incidence, severity, and fatality of COVID-19 imply that more intensive

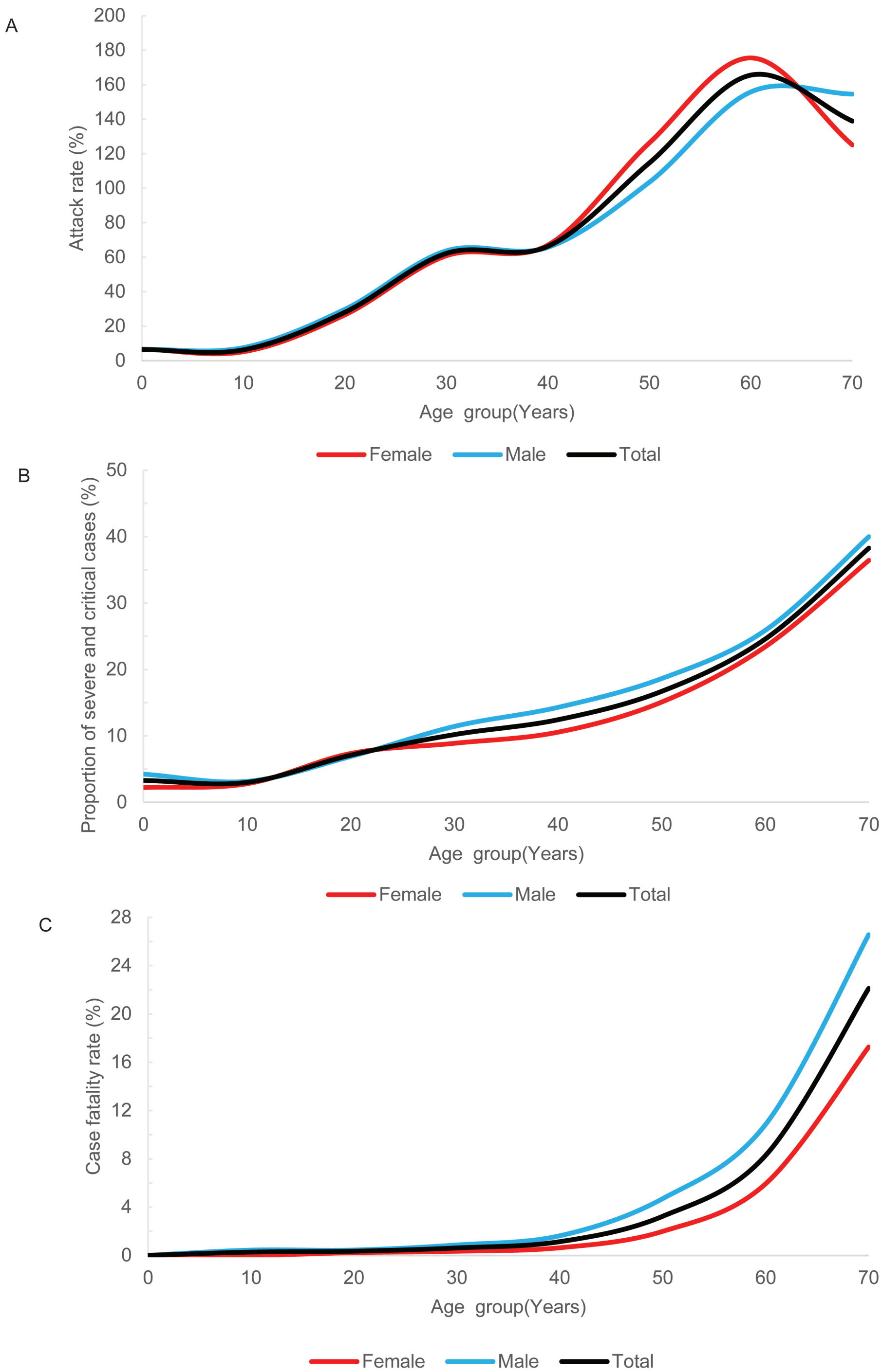

Figure 1. Gender differences in incidence, severity, and fatality of COVID-19 by age group. *A*, Attack rate. *B*, Proportion of severe and critical cases. *C*, Case fatality rate. Abbreviation: COVID-19, novel coronavirus disease 2019.

public health surveillance and preventions should focus on women older than 50 years, especially in the epicenter to control the transmission more efficiently. On the other hand, more attention should be paid to male patients, especially those over 30 years of age, for enhanced clinical management. Furthermore, our findings on gender differences have also provided evidence for addressing the health needs of men and women equally, so as to help policymakers and societies prevent future human tragedies [10, 11].

At first glance, COVID-19 seems to occur equally among women and men. Because there are more men than women in the general population of mainland China, we looked at the AR by taking sex into consideration. As a result, the females have a significantly higher AR especially in Hubei province where

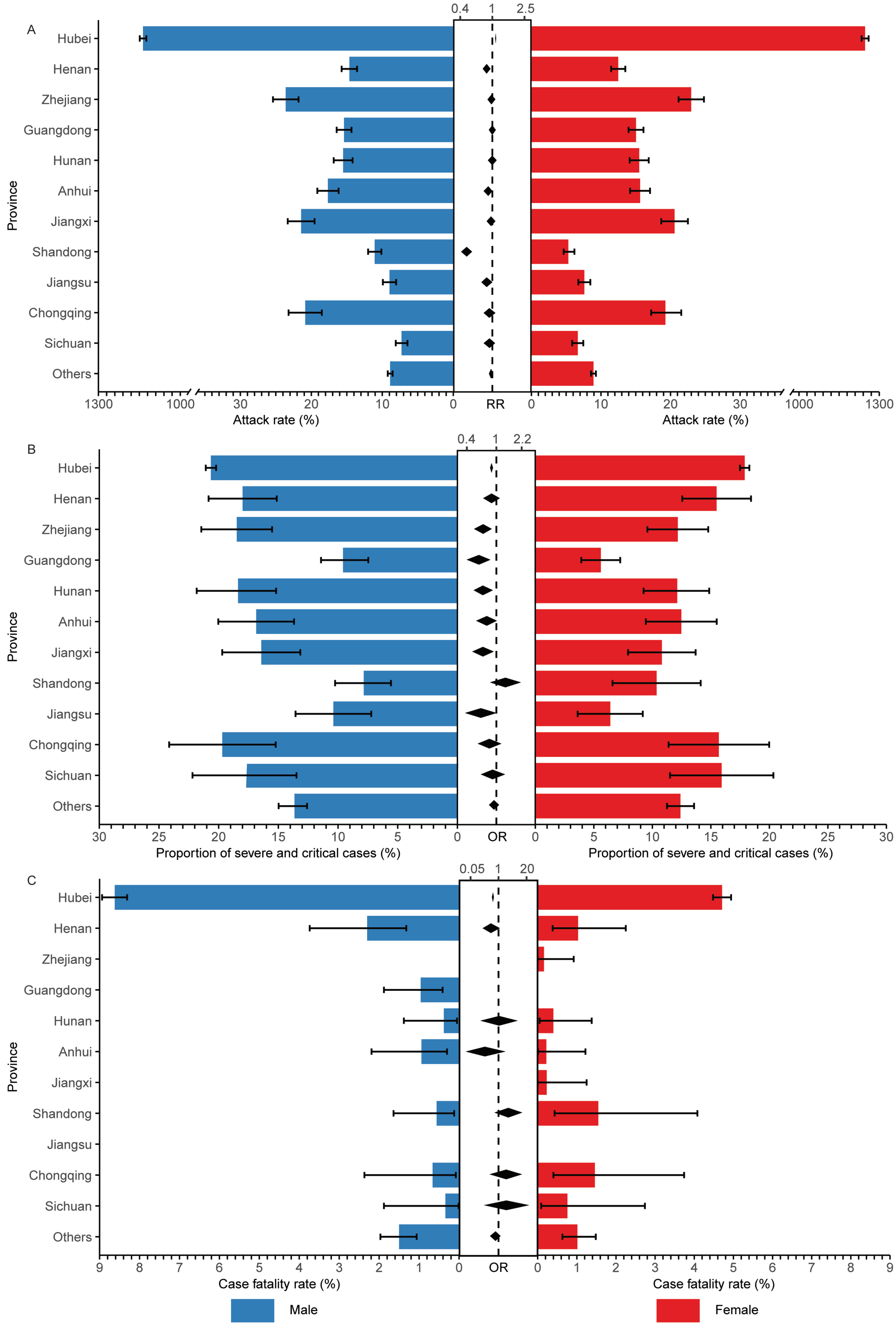

Figure 2. Gender differences in incidence, severity, and fatality of COVID-19 by province. The estimated attack rates (*A*), proportions of severe and critical cases (*B*), and case fatality rates (*C*) of severely affected provinces and other provinces. Abbreviation: COVID-19, novel coronavirus disease 2019.

82.2% of cases occurred. The gender difference in AR in mainland China is age dependent, with the peak in individuals aged 50–69 years. This differs from that in the Republic of Korea, where the highest rate is among people aged 20–39 years, with a much greater female-to-male ratio of nearly 2:1 [12]. These findings in the 2 early affected countries imply that women are,

Table 2. Gender Differences in the Proportion of Severe and Critical Cases of COVID-19 in Mainland China After Adjusting for Possible Confounders

	Proportion of Severe and Critical Cases			Case Fatality Rate		
Variables	Adjusted OR	95% CI	*P*	Adjusted OR	95% CI	*P*
Gender						
Male	Ref			Ref		
Female	0.80	.77–.83	<.0001	.53	.49–.57	<.001
Age group (10-year)	1.042	1.041–1.044	<.0001	1.10	1.10–1.11	<.001
Onset-to-diagnosis (days)	1.03	1.03–1.04	<.0001	1.01	1.01–1.02	<.001
Province						
Hubei	Ref			Ref		
Guangdong	0.72	.59–.88	.001	.23	.11–.5	<.001
Henan	1.26	1.08–1.47	.004	.62	.39–.98	.04
Zhejiang	1.12	.95–1.32	.19	.03	0–.2	<.001
Hunan	1.10	.92–1.32	.31	.14	.05–.37	<.001
Anhui	1.13	.94–1.36	.21	.26	.11–.57	.001
Jiangxi	1.00	.82–1.22	.99	.04	.01–.3	.002
Shandong	0.65	.50–.84	.001	.36	.15–.78	.02
Jiangsu	0.54	.41–.72	<.0001	…	…	
Chongqing	1.27	1.01–1.59	.04	.34	.15–.76	.01
Sichuan	1.42	1.12–1.80	.004	.23	.07–.73	.01
Others[a]	1.37	1.25–1.51	<.0001	.47	.36–.63	<.001

Abbreviations: CI, confidence interval; COVID-19, novel coronavirus disease 2019; OR, odds ratio; Ref, reference.
[a]"Others" indicates all other affected provinces of mainland China.

in general, more likely to be infected by SARS-CoV-2, especially in some specific age groups. The infection of SARS-CoV-2 occurs primarily through the angiotensin-converting enzyme 2 (ACE2) receptor, which serves as a gateway for the virus's entry into tissues [13]. The ACE2 gene is located on the X chromosome; therefore, female individuals should have higher ACE2 levels [14], which might be the reason they are more susceptible to SARS-CoV-2 infection in comparison to males. Further investigation into ACE2 enzyme activity in correlation with sex is required to verify the hypothesis.

In addition to the biological factors, age-related social and behavioral factors might have contributed to the age-dependent gender difference in COVID-19 morbidity. Lack of adherence to social distancing and self-quarantine recommendations initiated by Korean health authorities is supposed to be the risk factor for the higher infection rates among the young adults and teenagers as well as in the Shincheonji religious community [12]. Lockdown of city and closure of schools to control COVID-19 transmission in China might have increased the risk of SARS-CoV-2 infection in women, who provide care in families and communities. As seen in the outbreak of Ebola virus disease in West Africa during 2014–2016, women were more likely to be infected, given their predominant roles as caregivers within families and as frontline HCWs [15]. The higher COVID-19 morbidity in females than in males might also be due to females being more likely to see a doctor after symptom onset. For example, the incidence rate of Zika virus disease for persons seeking care was higher among women than among men during the 2007 outbreak in Micronesia [16]. Systematic investigations are required to understand whether observed age-dependent gender differences in AR are due to differences in infection rates, development of disease, seeking medical care, or reporting bias.

Our analyses revealed that both PSCC and CFR were lower among female patients than among male patients in nearly all provinces and all age groups. These findings are consistent with the results of previous reports based on hospital data in China and in other affected countries [5, 12, 17, 18]. The reasons for the gender difference in the severity and fatality of COVID-19 might be attributed to underlying comorbidity and higher-risk behaviors such as smoking [3, 4, 19]. The higher female proportion of HCWs might have some contribution to the gender difference in PSCC and CFR, because HCWs tend to have less severe illness as observed in our study and in the United States [20].

Female individuals generally have stronger innate and adaptive immune responses than males, because the X chromosome contains more copy numbers of immune-related genes [21], which might lead to more prompt clearance of SARS-CoV-2 in women, and subsequently decrease the severity and mortality of the disease. In addition, sex-dependent production of steroid hormones may contribute to gender-specific disease outcomes after virus infections [22, 23]. A recent observation that female patients had higher level of IgG antibody against SARS-CoV-2 compared with male patients [24] provides direct evidence for sex differences in immune responses. Further investigation on the association between stronger immune response and less severity in females is warranted. Sex differences in ACE2 might also play a role in pathogenesis, because ACE2 can protect against lung damage through its anti-inflammatory function

[13]. Therefore, the higher ACE2 levels among women are supposed to protect them from more severe disease [14].

The study had some limitations. First, we used the database of CISDCP, in which the individual characteristics relevant to gender, such as socioeconomic status, comorbidity, and immunological condition, were not recorded. The lack of such information prohibited us from further investigating their possible impacts on gender differences. Second, we performed comparative analyses using the surveillance data, which did not include information on clinical management. Unfortunately, we could not compare any treatments given that this may confound the results regarding PSCC and CFR between female and male patients. In fact, treatments in different hospitals and areas varied, and even in the same hospital the treatments might be different between female and male patients. Third, missed diagnosis is avoidable due to the lack of health facilities and/or laboratory capacity in the early stage of the outbreak. This situation certainly may have led to underestimates of COVID-19 burden, and might cause bias in some specific groups.

In conclusion, this report raises awareness about the age-based gender differences in incidence, severity, and fatality of COVID-19. Interestingly, females might be more prone to get the disease but are less likely to have a poor or fatal outcome. The age-dependent gender dimorphism in COVID-19 might contribute to various factors, and deserves further investigation on immune response and other biological mechanisms related to sex differences. Policies and public health efforts have rarely addressed the gender impacts of disease outbreaks [25]. Our gender analyses using the data from the first outbreak country have not only provided insight into the gender differences but also provided evidence for targeted treatment, more precise prevention, and more efficient surveillance of COVID-19 in China as well as in other affected countries.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. Q., X.-J. L., and Y.-L. L. designed the study, performed the main data analysis, and wrote the paper. J. Q., L. Z., R.-Z. Y., and X.-J. L. managed the data and did the statistical analysis.

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