

Age-dependent gender differences of COVID-19 in mainland China: comparative study

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Summary

The attack rate of COVID-19 was higher in females than in males. Conversely, proportion of severe and critical cases and fatality were lower among female patients. The gender differences were age-dependent, and useful for effective surveillance and target treatment.

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Abstract

Background. The ongoing pandemic of novel coronavirus disease 2019 (COVID-19) is challenging 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 compared 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 female population than in males (63.9 versus 60.5 per million persons; $P < .001$). By contrast, PSCC and CFR were significantly lower among female patients (16.9% and 4.0%) than among males (19.5% and 7.2%), with ORs of 0.87 and 0.57, respectively (both $P < .001$). The female-to-male differences were age-dependent, which were significant among people aged 50–69 years for AR, and in the patients of 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 the 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.

Introduction

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. Considering the gender differences in infectious diseases of humans are a common but neglected global health problem [2], there is a greatly need to investigate the specific question as regard to COVID-19. Global Health 50/50, an independent health equity research organization based at University College London, compiled sex-disaggregated infection and mortality data available from tens of affected countries, and implied that the male patients were more likely to die than the 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 for them 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 April 28, 2020 to evaluated gender-specific differences in attack rate, 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 & State Administration of Traditional Chinese Medicine on March 3, 2020 (Supplemental Material) [7], confirmed cases were patients who had related epidemiological history and clinical manifestations, with one of the following etiological or serological evidences: SARS-CoV-2 nucleic acid detected by specific real-time RT-PCR assay, viral gene sequence homologous to SARS-CoV-2, specific IgM and/or IgG are detectable in serum, or a 4-fold increase in IgG titer 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, i.e. respiratory distress (≥ 30 breaths per minute, BPM), oxygen saturation $\leq 93\%$ at rest, or arterial partial pressure of oxygen (PaO_2) / fraction of inspired oxygen (FiO_2) ≤ 300 mm Hg (1 mm Hg = 0.133 kPa), they were defined as severe cases. The criteria for severe child cases were as following: respiratory distress (≥ 60 BPM for infants aged below 2 months, ≥ 50 BPM for infants aged 2-12 months, ≥ 40 BPM for children aged 1-5 years, and $\text{RR} \geq 30$ BPM for children above 5 years old), oxygen saturation $\leq 92\%$ at rest, having labored breathing, cyanosis or intermittent apnea, showing lethargy and convulsion, or having difficulty for feeding and signs of dehydration. Critical cases were defined if they had respiratory failure requiring mechanical ventilation, shock, or other organ failure that requires cares in the Intensive Care Unit.

We collected data of 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 April 28, 2020. The surveillance data included the 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 the 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 the information regarding individual persons had been anonymized.

Statistical Analysis

We summarized continuous variables as median (interquartile range [IQR]) or mean (\pm standard deviation [SD]), and categorical variables as frequencies or proportions. The attack rate (AR) of COVID-19 with 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 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 percentage of deaths among confirmed cases.

To estimate the differences between groups, the student's t test for a continuous variable, and the Chi-square test or a Fisher's exact test for a categorical variable were used where appropriate. The administrative divisions including provinces, autonomous regions, and municipalities of China were 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 risk ratio (RR) and its 95% CI by Woolf method. We compared the

PSCCs and CFRs between female and male patients in each age group and affected province, and then estimated odds ratio (OR) and its 95% CI by 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) by including gender as an independent variable and age group, affected province, and onset-to-diagnosis interval as co-variables. A two-sided *P* value less than 0.05 was considered to be significant.

RESULTS

Comparing Characteristics of COVID-19 Cases Between Female and Male

As of April 28, 2020, a total of 82,858 confirmed cases were reported, of which 41,580 (50.2%) were female (Table 1). The median age of the patients was 51 years (IQR 39–63), with a mean (\pm SD) of 51.0 ± 16.7 years. There was no significant difference in age distribution between female and male patients. The number of health care 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 (\pm SD) time 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 million persons (95% CI, 61.7–62.6), which was significantly higher in female population than in males (63.9 versus 60.5 per 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 / 41580, 16.9%) than in males (8045 / 41278, 19.5%) with a female-to-male OR was 0.87 (95% CI, 0.84–0.89; $P < .001$). The overall CFR was 5.6% (4633 / 82858), which was significantly lower among female patients (1681/41580, 4.0%) than among male patients (2952 / 41278, 7.2%), with an OR of 0.57 (95% CI 0.53–0.60; $P < .001$). The PSCC (15.4%) and CFR (2.1%) among

verHCWs 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 males HCWs (19.3% and 4.4%) (both $P < .001$).

The Gender Differences of COVID-19 by Age

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

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

The Gender Differences of COVID-19 by Affected Province

COVID-19 affected 1,726 (60.4%) counties in all 31 provinces of mainland China, with over 82.2% cases reported in Hubei province, where was the epicenter. Besides Hubei province, other 10 provinces had more than 500 cases, while there were fewer than 100 case in seven provinces. Only one patient was identified in Tibet. The AR in Hubei province was up to 1190.3 (95% CI, 1181.3–1199.2) per million persons. Among the other 10 most severely affected provinces, ARs ranged from 7.0 (95% CI, 6.4–7.6) per million persons in Sichuan province to 23.3 (95% CI, 22.0–24.6) per million persons in Zhejiang province. The AR was

significantly higher among female population (1247.1 per million persons) than among males (1136.5 per million persons) in Hubei province ($P < .001$). While there was no significant difference in AR between female and male populations in the rest of 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 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). 97.4% of all dead cases occurred in Hubei province, where significant female-to-male difference in CFR was observed, with an OR of 0.55 (95% CI 0.52–0.58; $P < .001$) (Figure 2C, Supplementary Table 7). The CFR of female patients was comparable to that of male patients in rest of China (OR = 1.2; 95% CI 0.8–1.6; $P = .37$).

The Gender Differences of 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 in the univariate analyses. Considering both PSCC and CFR were increased with age group and onset-to-diagnosis interval we included them as continuous co-variables, while affected province as categorical co-variables in the models. We revealed that female-to-male OR for PSCC remained significant after adjusting for those possible confounding variables, with an adjusted OR of 0.80 (95% CI 0.77–0.83). The older age and longer onset-to-diagnosis interval was also identified as risk predictor for severity of illness (both $P < .001$) (Table 2). Similarly, the adjusted female-to-male OR of CFR was 0.53 with a 95% CI of 0.49–0.57 ($P < .001$). In the finale model for CFR, the OR for age was 1.10 (95% CI 1.10–

1.11) with each 10-year increase ($P < .001$), and OR for onset-to-diagnosis interval was 1.01 (95% CI 1.01–1.02) for each day longer ($P < .001$) (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 for creating 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 of mainland China. The age-dependent gender differences in incidence, severity and fatality of COVID-19 imply that more intensive 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 attentions should be provided to male patients especially those over 30 years of age for enhanced clinical managements. Furthermore, our findings on gender differences have also provided evidences for addressing the health needs of men and women equally, so as to help policy maker 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 look at the AR by taking sex constitution into consideration. As a result, the female tendency is significant especially in Hubei province, where 82.2% cases occurred. The gender difference in AR in mainland China is age-dependent, with the peak in individuals aged 50-69 years. This is disparate 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 ration of nearly 2:1 [12]. These

findings in the two early affected countries imply that women are in general more likely infected by SARS-CoV-2, especially in some specific age groups. The infection of SARS-CoV-2 is primarily through 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 for more susceptible to SARS-CoV-2 infection in comparison to males. Further investigations 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 the Shincheonji religious community [12]. Lockdown of city and closure of schools to control COVID-19 transmission in China might have increased risk of SARS-CoV-2 infection in women, who have provided cares in families and communities. As seen in outbreak of Ebola virus disease in west African during 2014 to 2016, women were more likely to be infected, given their predominant roles as caregivers within families and as front-line health-care workers [15]. The higher COVID-19 morbidity in female than male population might also come from more likely seeing a doctor after symptom onset. An example is that 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]. Systematically investigations are required to understand whether observed age-dependent gender difference in AR is 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 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 fatality 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 the female patients have higher level of IgG antibody against SARS-CoV-2 compared with male patients [24], provides direct evidence for sex differences in immune responses. Further investigations on the association between stronger immune response and less severity in female are warranted. Sex-differences in ACE2 might also play a role in this process, because ACE2 can protect against lung damage through its anti-inflammatory function [12]. Therefore, the higher ACE2 levels among women are supposed to protect them from more severe disease [12].

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. Lack of such information has prohibited us from further investigating their possible impacts on gender differences. Second, we did comparative analyses using the surveillance data, which did not include the information on

the clinical managements. Unfortunately, we could not compare any treatments given that 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 among female and male patients. Third, missed diagnosis is avoidable due to lack of health facilities and /or laboratory capacity in the early stage of the outbreak. This situation certainly have led to under-estimates of COVID-19 burdens, 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, the females might be more prone to get the disease, but less likely for a poor or fatal outcome. The age-dependent gender dimorphism in COVID-19 might contribute to various factors, and deserves further investigations on immune responses and other biological mechanisms for sex differences. Policies and public health efforts have rarely addressed the gendered impacts of disease outbreaks [25]. Our gender analyses using the data from the first outbreak country have not only got insight into the gender differences, but also provided evidences for target treatment, more precise prevention and more efficient surveillance of COVID-19 in China as well as in other affected countries.

Contributors

JQ, XJL and YLL designed the study, performed the main data analysis, and wrote the paper.

JQ, LZ, RZY and XJL managed the data and did the statistical analysis.

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Conflicts of interest

We declare that we have no conflicts of interest.

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Figure legend

Figure 1. The gender differences in incidence, severity and fatality of COVID-19 by age group. (A) The attack rate. (B) The proportion of severe and critical cases. (C) The case fatality rate. COVID-19, novel coronavirus disease 2019.

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

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2 **Table 1. Comparison of Characteristics of COVID-19 Cases between Female and Male Individuals in Mainland China**

	Total	Female	Male	<i>P</i> value
No. of cases	82858	41580	41278	-
Median age (IQR), year	51 (39–63)	52 (40–63)	51 (38–64)	-
Mean age (\pm SD), year	51.0 \pm 16.7	51.4 \pm 16.3	50.5 \pm 17.2	< .001
Health care workers, No.(%)	3402 (4.1)	1956 (4.7)	1446 (3.5)	< .001
Onset-to-diagnosis (mean \pm SD), day	9.5 \pm 7.4	9.3 \pm 7.2	9.7 \pm 7.5	< .001
AR (95% CI) per million persons; n / N	62.2 (61.7–62.6); 82858 / 1332810869	63.9 (63.3–64.5); 41580 / 650481765	60.5 (59.9–61.1); 41278 / 682329104	< .001
PSCC (%) (95% CI); n / N	18.2 (17.9–18.4); 15062 / 82858	16.9 (16.5–17.2); 7017 / 41580	19.5 (19.1–19.9); 8045 / 41278	< .001
CFR (%) (95% CI); n / N	5.6 (3.8–4.1); 4633 / 82858	4.0 (3.9–4.2); 1681 / 41580	7.2 (6.9–7.4); 2952 / 41278	< .001

3 Abbreviations: IQR, interquartile range; SD, standard deviation; AR, attack rate; PSCC, proportion of severe and critical cases; CFR, case fatality

4 rate; CI, confidence interval; n, numerators; N, denominators.

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

Variables	Proportion of severe and critical cases			Case fatality rate		
	Adjusted OR	95% CI	<i>P</i> value	Adjusted OR	95% CI	<i>P</i> value
Gender						
Male	Ref			Ref		
Female	0.80	0.77-0.83	<0.0001	0.53	0.49–0.57	< .001
Age-group (10-year)	1.042	1.041-1.044	<0.0001	1.10	1.10–1.11	< .001
Onset-to-diagnosis (day)	1.03	1.03- 1.04	<0.0001	1.01	1.01–1.02	< .001
Province						
Hubei	Ref			Ref		
Guangdong	0.72	0.59- 0.88	0.001	0.23	0.11-0.5	< .001
Henan	1.26	1.08-1.47	0.004	0.62	0.39-0.98	0.04
Zhejiang	1.12	0.95-1.32	0.19	0.03	0-0.2	< .001
Hunan	1.10	0.92- 1.32	0.31	0.14	0.05-0.37	< .001
Anhui	1.13	0.94- 1.36	0.21	0.26	0.11-0.57	0.001
Jiangxi	1.00	0.82- 1.22	0.99	0.04	0.01-0.3	0.002
Shandong	0.65	0.50- 0.84	0.001	0.36	0.15-0.78	0.02
Jiangsu	0.54	0.41- 0.72	<0.0001	-	-	-
Chongqing	1.27	1.01- 1.59	0.04	0.34	0.15-0.76	0.01
Sichuan	1.42	1.12- 1.80	0.004	0.23	0.07-0.73	0.01
Others	1.37	1.25- 1.51	<0.0001	0.47	0.36-0.63	< .001

OR= odds ratio. CI= confidence interval. Others indicate all other affected provinces of mainland China.

Figure 1

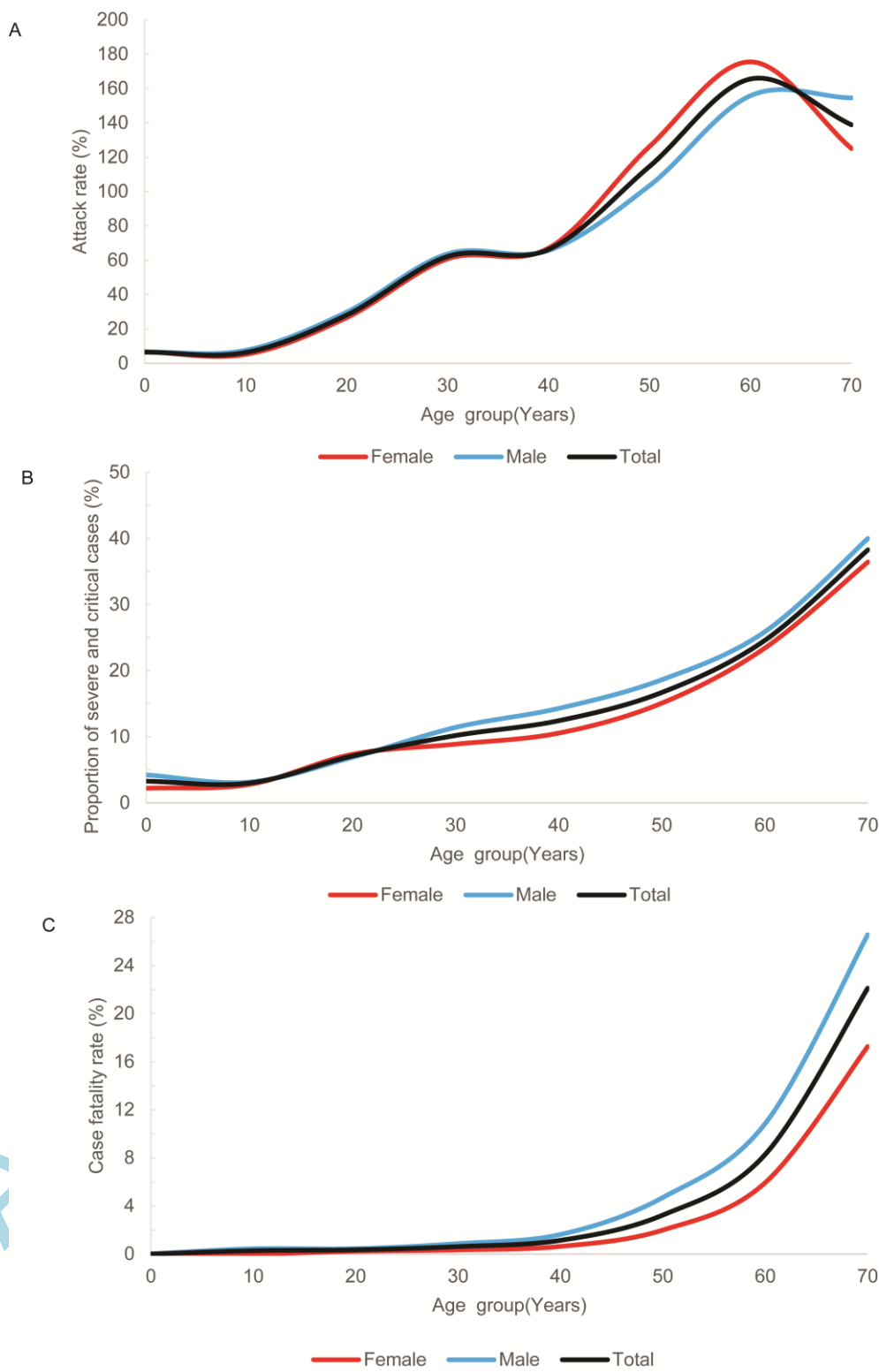


Figure 2

