Risk of severe coronavirus disease in imported and secondary cases in Zhejiang province, China

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ABSTRACT

Background To our knowledge, no previous studies have focused on determining whether the virulence and case fatality rate of the severe acute respiratory coronavirus 2 (SARS-CoV-2) decreases as the virus continues to spread. Hence, our aim was to retrospectively explore the differences in the risk of severe or critical COVID-19 among imported, secondary and tertiary cases in Zhejiang, China.

Methods We categorized COVID-19 cases reported by hospitals in Zhejiang as first-, second- and third-generation cases. Univariate and multivariate logistic regression analyses were performed to compare disease severity and case generation.

Results Of 1187 COVID-19 cases, 227 (19.1%, 95% CI: 16.9–21.4) manifested severe or critical illness. The adjusted risk difference for severe or critical illness was lower for second- (odds ratio (OR) = 0.84, 95% confidence interval (CI): 0.52–1.36) and third-generation (OR = 0.55, 95% CI: 0.37–0.83) cases than for first-generation cases. Compared with hospitalized patients, cases identified at centralized isolation locations (OR = 0.62, 95% CI: 0.40–0.97) and those identified through active search or gateway screening (OR = 0.28, 95% CI: 0.08–1.04) were at a lower risk of severe or critical illness.

Conclusions Second- and third-generation cases of COVID-19 have a lower risk of developing severe or critical illness than first-generation cases.

Keywords community-acquired infections, coronavirus disease, COVID-19, odds ratio, risk assessment

Introduction

Cases of coronavirus disease (COVID-19) were first identified in Wuhan, China, in December 2019.¹⁻³ Within a month, each Chinese province reported over 80 000 COVID-19 cases⁴ and thousands of Chinese citizens died by 16 April 2020.⁵ According to the World Health Organization, >7 million cases were confirmed, resulting in at least 400 000 deaths worldwide by 11 June 2020.⁶

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19 and is characterized by high transmissibility, with an estimated basic reproduction number (R₀) between 1.4 and 4.8.⁷⁻¹⁰ The virus has a high virulence, a severe disease incidence rate of 7.0–17.7%, and a fatality rate of 0.3% in China.¹¹ Although some experts speculate that both the virulence and case fatality rate will gradually decrease due to interactions between the virus and the host, there is no evidence to support this theory yet.

Zhejiang province is one of the leading Chinese provinces with respect to the number of COVID-19 cases. It is estimated that in the period from COVID-19 emergence to the Spring Festival (mid to late January 2020), >200 000 people returned to Zhejiang from Wuhan. In this study, we explored the virulence of SARS-CoV-2 over time by comparing the incidence rate of severe COVID-19 in imported, second-generation and third-generation cases.
Methods

COVID-19 cases were diagnosed using criteria from the seventh edition of The Guideline for the Diagnosis and Treatment of Pneumonia of Novel Coronavirus Infection, provided by the National Health Commission of the People's Republic of China. Using these guidelines, the clinical manifestations of COVID-19 were categorized as mild, severe and critical.

Mild cases were defined as patients with mild or no pneumonia, while severe cases were characterized by dyspnoea, a respiratory rate of ≥30 breaths per minute, blood oxygen saturation of ≤93% and a PaO$_2$/FiO$_2$ ratio of ≤300 mmHg (1 mmHg = 0.133 kPa). Additionally, critical cases had to meet one of the following criteria: respiratory failure and mechanical ventilation, shock or multiple organ failure requiring ICU monitoring and treatment.

Since the first case was reported on 21 January 2020 in Zhejiang province, several more cases, considered first-generation cases in Zhejiang, were imported from Wuhan and continued to spread the virus to hundreds of people via community transmission. Cases infected with the virus by travelers from Wuhan were considered second- and third-generation cases. Thus, in this study, cases were classified into three groups: first-generation cases imported from Hubei Province, second-generation cases infected by imported cases and third-generation cases infected via community transmission that had not originated from the first-generation cases. We identified COVID-19 cases in Zhejiang province in the following settings: hospital fever clinics, central isolation points, home quarantine and active searching or screening at gateways. A uniform questionnaire was used to collect patient demographic information, exposure history from 2 weeks before symptom onset (including dates, frequency and patterns of exposures to patients with respiratory symptoms and farmers’ markets, and patient living environment), clinical symptoms, date of illness onset, clinic visits and outcomes.

Statistical analysis

We compared the distributions of the demographic variables (sex, age and occupation), level of hospital visited (county, municipal or provincial level), case generation (first, second, third), case identification mode and severity (mild, severe, critical) using one-way analysis of variance (ANOVA) for quantitative variables and Fisher’s exact test for qualitative variables.

Next, severe and critical cases were combined into one category with the aim to divide the clinical outcomes into mild and severe. Univariate and multivariable logistic regression analyses were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) were used as measures of associations between the clinical outcome and the above variables. All analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). A $P$-value of < 0.05 was considered statistically significant.

Results

A total of 1187 COVID-19 cases were confirmed, including 960 mild (80.9%, 95% CI: 78.6–83.1) and 227 severe or critical (19.1%, 95% CI: 16.9–21.4) cases. The first Zhejiang COVID-19 case, documented on 8 January 2020, was a traveler returning from Wuhan, Hubei province. The number of cases peaked on 27 January 2020, and the number of new cases decreased to ≤10 cases/day after 8 February 2020. The distribution of the onset dates for severe or critical COVID-19 cases resembled the distribution of the onset dates of the mild cases. The interval between symptom onset and progression to severe or critical disease ranged from 24 h to 24 days, with a median of 9 days (Fig. 1).

Compared with mild COVID-19 cases, severe or critical cases were more likely to be male and older. Moreover, there were statistically significant differences in occupation between mild, severe and critical cases ($P < 0.05$). However, there were no observed differences in other factors, including onset-to-diagnosis interval, hospital level, case generation and detection mode among mild, severe and critical cases (Table 1).

Further, to examine the association between the related factors and clinical outcomes, we combined severe and critical cases into one group and conducted a binary logistic regression analysis. Univariate analysis showed that age, sex, occupation, hospital level and the case identification setting were significantly associated with the clinical outcomes of COVID-19 (Table 2).

The results of the multivariate analysis are shown in Table 2, indicating that older age could increase the risk of severe COVID-19 ($OR = 1.07$, 95% CI: 1.05–1.08). Compared with female cases, male cases showed a significantly higher risk of severe disease ($OR = 2.52$, 95% CI: 1.80–3.54).

Patients treated at municipal hospitals were at higher risk of severe disease than those treated at county hospitals, although the difference was not statistically significant ($OR = 1.39$, 95% CI: 0.98–1.97). The risk of severe disease was significantly lower for third-generation cases ($OR = 0.55$, 95% CI: 0.37–0.83) than for first-generation cases. Moreover, the risk of severe disease was significantly lower for patients identified at centralized isolation locations ($OR = 0.62$, 95% CI: 0.40–0.97) and those identified through active search or gateway screening ($OR = 0.28$, 95% CI: 0.08–1.04) than for the majority of patients identified in hospital fever clinics.
Discussion

Main findings of this study

Our study found that the incidence of severe illness was significantly higher among men and the elderly. The average age of patients in critical condition was over 60 years, which is consistent with previously published results. Due to underlying diseases, decreased cardiopulmonary function, and reduced immune capacity, the elderly were more likely to develop critical or severe disease. Both univariate and multivariate analyses showed that the risk of severe COVID-19 was significantly higher in men than in women, possibly due to the fact that men tend to have more health problems, such as high blood pressure, cardiovascular disease, diabetes, and chronic lung disease. If infected with SARS-CoV-2, patients with these conditions are at an increased risk of complications and accelerated disease progression. In contrast, women generate more robust immune responses and are less susceptible to a variety of infectious agents. Moreover, we found that female cases produce higher levels of interferons (important components of the immune system) in response to severe acute respiratory syndrome coronavirus 2 infection than do male cases.

Our univariate analysis showed no significant association between the three generations of COVID-19 cases and disease severity, which is similar to the findings of previously published studies. Multivariate analysis performed after adjusting for potential confounders showed that second- and third-generation cases were at lower risk of severe or critical disease. This finding is consistent with the virulence progression observed for other viruses, where the severity gradually decreases while the transmissibility increases as the virus evolves in new host species. One study indicated that SARS-CoV-2 may have mutated in February and March 2020, thus reducing its virulence. Alternatively, the decrease in the percentage of patients suffering from the severe or critical disease may relate to the rapid increase in the knowledge on SARS-CoV-2 and COVID-19. Also, improved experience of health care workers’ in treating patients would actually reduce the severity of the disease.

What is already known on this topic

Among all COVID-19 cases reported in Zhejiang province, severe or critical cases accounted for approximately 19%, which is similar to the prevalence (18%) observed in Wuhan and significantly higher than the prevalence (14.6%) observed in China overall. In Zhejiang, 38% of the COVID-19 cases were imported from Wuhan, 16% were infected by imported cases and 46% were local cases. While Zhejiang province was the first affected province, the disease developed most rapidly in Hubei Province.

In terms of virulence, the rates in Zhejiang were similar to those observed in Wuhan. The case fatality rate in Zhejiang province was $<1/1000$ (only one death), which was much lower than the average fatality rate of 5.5% in China and the global case fatality rate of 6.9% as of 8 May 2020. Moreover, Zhejiang was one of the first provinces in China to effectively contain the epidemic. The high incidence of severe disease in Zhejiang province likely relates to the high virulence of the virus.

In China, COVID-19 cases are usually treated in designated hospitals with advanced medical equipment, experienced medical staff and sufficient drug reserves. Additionally,
Table 1 Characteristics of mild, severe and critical coronavirus disease (COVID-19) cases in Zhejiang province, China, from 5 January to 19 February 2020, (n = 1187)

| Characteristic                        | Mild cases |          | Severe cases |          | Critical cases |          | Chi-square or F value | P-value |
|---------------------------------------|------------|----------|--------------|----------|----------------|----------|-----------------------|---------|
| n                                     | 44.6 ± 14.6|          | 53.1 ± 13.5  |          | 63.8 ± 16.7  |          | 62.521                | <0.001  |
| Duration of onset to confirmation     | 6.5 ± 4.2  |          | 7.3 ± 4.0    |          | 6.5 ± 3.5     |          | 2.405                 | 0.091   |
| Sex                                   |            |          |              |          |                |          | 20.663                | <0.001  |
| Male                                  | 457        | 47.6     | 112          | 63.6     | 34             | 66.7     | 52.119                | <0.001  |
| Female                                | 503        | 52.4     | 64           | 36.4     | 17             | 33.3     |                       |         |
| Age (years, x ± s)                    |            |          |              |          |                |          |                       |         |
| Duration of onset to confirmation (days, x ± s) | 6.5 ± 4.2  |          | 7.3 ± 4.0    |          | 6.5 ± 3.5     |          |                       |         |
| Sex                                   |            |          |              |          |                |          |                       |         |
| Male                                  | 457        | 47.6     | 112          | 63.6     | 34             | 66.7     | 52.119                | <0.001  |
| Female                                | 503        | 52.4     | 64           | 36.4     | 17             | 33.3     |                       |         |
| Hospital                              |            |          |              |          |                |          |                       |         |
| County-level                          | 321        | 33.4     | 71           | 40.3     | 21             | 41.2     | 4.130                 | 0.129   |
| Municipal or provincial               | 639        | 66.6     | 105          | 59.7     | 30             | 58.8     |                       |         |
| Type of cases                         |            |          |              |          |                |          |                       |         |
| Imported from Hubei (first generation)| 378        | 39.4     | 80           | 45.5     | 19             | 37.3     | 3.018                 | 0.560   |
| Infected by the first generation (second generation) | 156         | 16.3     | 29           | 16.5     | 8              | 15.7     |                       |         |
| Infected by the second generation (third generation) | 426         | 44.4     | 67           | 38.1     | 24             | 47.1     |                       |         |
| Case identification setting           |            |          |              |          |                |          |                       |         |
| Fever clinics of hospitals            | 487        | 50.7     | 108          | 61.4     | 31             | 60.8     | 10.571                | 0.090   |
| Centralized isolation points          | 249        | 25.9     | 31           | 17.6     | 9              | 17.6     |                       |         |
| Home quarantine                       | 196        | 20.4     | 35           | 19.9     | 10             | 19.6     |                       |         |
| Active searching or screening at gateways | 28       | 2.9      | 2            | 1.1      | 1              | 2.0      |                       |         |

hospitals have implemented standard precautions and structured the facilities to prevent nosocomial infections. The county-level hospitals promptly transfer severe COVID-19 cases to municipal or provincial hospitals for treatment. We believe that this reduces the risk of development of severe or critical illness; congruently, our results showed higher rates of severe and critical cases at municipal or provincial hospitals.

What this study adds
Our epidemic curve reflects the stringent measures (searching for all potentially infected persons, limiting public gatherings, extensive and effective testing, research and development of drugs and vaccines, sufficient material preparation, rigorous contact tracing, quarantine, isolation, mask-wearing, hygiene and reduction in regular economic activity) implemented by the Zhejiang provincial government as a level-one response starting on 23 January 2020. In Zhejiang, ~2 weeks passed from the initiation of the response before the epidemic was controlled. Containing the source of new infections and managing close contacts of confirmed cases were critical measures that allowed officials to gain control of the outbreak. Patients were directly escorted by the government to designated hospitals oriented toward infection containment, evidence-based treatment, and efficient use of medical resources.

This study suggests that the risk of severe or critical disease was significantly reduced for cases detected at centralized isolation locations and those found through active search and checkpoint screening. Moreover, it shows that proactive detection of newly infected persons can reduce the infection-
Table 2 Univariate and multivariate analyses of potential risk factors for severe COVID-19 cases in Zhejiang province, China, from 5 January to 19 February 2020, (n = 1187)

| Variables                                      | Univariate analysis | Multivariate analysis |
|------------------------------------------------|---------------------|-----------------------|
|                                                | OR 95% CI           | P-value               |
|                                                |                    | Adjusted OR<sup>a</sup> 95% CI | P-value |
| Age (years, x ± s)                             | 1.05 1.04–1.06     | <0.001                |
| Duration of onset to confirmation (days, x ± s) | 1.03 1.00–1.07     | 0.065                 |
| Male                                           | 1.98 1.47–2.68     | <0.001                |
| Job                                            | Ref.               |                        |
| Business services                              | 1.58 1.04–2.41     | 0.032                 |
| Farmers                                        | 1.36 0.86–2.19     | 0.185                 |
| Housework and unemployment                     | 2.12 1.21–3.69     | 0.008                 |
| Workers<sup>b</sup>                            | 3.94 2.26–6.85     | <0.001                |
| Retirees                                       | 0.65 0.27–1.60     | 0.348                 |
| Cadre staff                                    | 0.35 0.11–1.18     | 0.090                 |
| Teachers and students                          | 0.97 0.55–1.71     | 0.922                 |
| Others                                         | Ref.               |                        |
| Hospital                                       | 1.36 1.01–1.83     | 0.044                 |
| County-level                                   | 1.39 0.98–1.97     | 0.065                 |
| Municipal or provincial                       | Ref.               |                        |
| Type of cases                                  | 0.91 0.59–1.38     | 0.644                 |
| Introduced from Hubei (first generation)       | 0.84 0.52–1.36     | 0.487                 |
| Infected by the first generation               | 0.82 0.59–1.12     | 0.207                 |
| Infected by the second generation (second generation) | 0.55 0.37–0.83 | 0.004                 |
| Case identification setting                    | Ref.               |                        |
| Fever clinics of hospitals                     | 0.56 0.38–0.83     | 0.003                 |
| Centralized isolation points                   | 0.80 0.55–1.17     | 0.255                 |
| Home quarantine                                | 0.38 0.11–1.25     | 0.111                 |
| Active searching or screening at gateways      | 0.40 0.28–0.62     | 0.08–1.04             |

<sup>a</sup>Adjusted for age, duration of onset to confirmation, sex, job, hospital, type of cases, case identification setting.

<sup>b</sup>Workers refer to laborers and staff members of enterprises and public institutions in China.

to-treatment interval and improve outcomes through prompt intervention and evidence-based treatment.

**Limitations of this study**

This study has some limitations. First, more research is needed in larger populations. The study sample size could potentially limit the relevance of the evidence. As the region is ethnically homogenous, we were limited in the ability to determine whether heterogeneous populations might have different outcomes. Therefore, as the study was conducted in Zhejiang province, the results may not be applicable to other geographic areas or populations. Second, individual differences and environmental factors may have affected the clinical severity of COVID-19; therefore, future studies should consider other variables and seek to address the limitations of this study. Therefore, further research with more statistical power and characterization of the epidemiology of COVID-19 in different populations is needed.

**Conclusions**

In conclusion, the risk of COVID-19 progression to severe or critical illness may decline as COVID-19 continues to spread as the number of second- and third-generation cases increases. Moreover, identification of patients at centralized isolation locations and through active search or gateway
screening can shorten the interval between the onset of illness and consultation with a medical professional, potentially reducing the risk of developing severe illness. Our results suggest that a focus on identifying potentially infected people and their close contacts may improve the likelihood of timely case detection and reduce the spread of COVID-19. Simultaneously, while health monitoring and public education should be strengthened, COVID-19 symptoms should be promptly reported to local medical and health institutions to ensure early intervention and to reduce the incidence of severe disease.

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**Conflicts of Interest**

None.

**Ethical Approval**

As this study was part of the response to a public health emergency, it was exempted from the requirement for ethical approval and informed consent by the Ethics Committee at the Zhejiang Provincial Centre for Disease Control and Prevention.

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