Incubation Period of Coronavirus Disease 2019: New Implications for Intervention and Control

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Incubation Period of Coronavirus Disease 2019: New Implications for Intervention and Control

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Abstract

Background: The COVID-19 pandemic raging around the world has caused serious disasters to mankind. The incubation period is a key parameter for epidemic control and also an important basis for epidemic prediction, but its distribution law remain unclear.

Methods: The incubation period T was described by the accelerated failure time models, and the principle of interval-censored data processing and estimation methods were used. Statistical analysis were performed on R-4.0.2 software using "coarseDataTools 0.6-5" package to optimize the parameters to be estimated and calculate the confidence interval. The optimization method used when solving the maximum likelihood function is the simplex method. We used bootstrap re-sampling procedures with 1000 iterations to estimate the confidence interval.

Results: Here we analyzed the epidemiological information of 787 confirmed non-Wuhan resident cases, and systematically studied the characteristics of the incubation period of COVID-19 based on the interval-censored data estimation method. Through the statistical analysis of the overall and 7 types of sub-group samples, it was concluded that the incubation period of COVID-19 approximately conformed to the Gamma distribution with a mean value of 7.8 (95%CI: 7.4-8.5) days and a median value of 7.0 (95%CI: 6.7-7.3) days.

Conclusions: The incubation period was positively correlated with age and negatively correlated with disease severity. Female cases presented a slightly higher incubation period than that of males. The incubation period of cases with travel history to Hubei and multiple exposures was shorter. The proportion of infected persons who developed symptoms within 14 days was 91.6%. These results are of great significance to the prevention and control of the COVID-19 pandemic.

Keywords: Coronavirus Disease 2019, COVID-19, Incubation Period, Pandemic, Interval-censored, Intervention and Control

Backgrounds

Incubation period is a key parameter of the epidemiological characteristics of infectious diseases. It is defined as the time interval from the pathogen invading the body to the earliest symptom onset. It is affected by multiple factors such as pathogen characteristics and individual immune performance. Clarifying the distribution of incubation period of infectious diseases is of great significance to determine the quarantine time, develop prevention and control measures, and predict epidemic trends [1]. Comparing with SARS and MERS, of which the infected cases generally become infectious after symptoms onset [2,3], the hiddenness and high contagiousness of COVID-19 make it more necessary to investigate the incubation period distribution rules [4]. What kind of distribution does the incubation period of COVID-19 fit into? How long is it?

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Since the outbreak of COVID-19, many previous studies have focused on the incubation period distribution. Li et al. showed that the mean incubation period was 5.2 days using data from 10 cases confirmed before January 22 by fitting the Log-normal distribution [5], which is the earliest study estimating the incubation period for COVID-19; Zhang et al. obtained the same result as 5.2 days to be the mean incubation period using data from 49 cases without travel history to Hubei; He et al. further found the cases became infectious 2.3 days before symptom onset and the transmissibility peaked 0.7 days before symptom onset [6]. But both of percentile distribution is quite different. To increase the sample size, some studies included the resident cases in Wuhan. Backer et al. found that the mean incubation period was 6.4 days using 88 cases, of which 63 cases were Wuhan residents [7]. Linton et al. divided samples into two groups according to whether including Wuhan residents [8]. Results showed that the incubation period estimate of the group including Wuhan cases was bigger than that of the other group. To analyze the sensitivity of diverse factors affecting the incubation period, some studies subdivided the cases into different clusters according to characteristics such as age structure and infected area. Dai et al. found a longer median incubation period estimate in the elders than in the youngers based on data from 180 cases in Hubei [9]. Tan et al. drew similar conclusions using data from 164 cases in Singapore, and the mean incubation period estimate was 5.5 (95% CI: 5.2-5.9) days [10]. Patrikar et al. estimated the mean incubation period was 6.9 (95%CI: 6.1-7.8) days using data from 268 cases in India [11]. The incubation period determined by the World Health Organization (WHO), the European Centers for Disease Control (ECDC), and Chinese Guidelines for the Diagnosis and Treatment of Novel Coronavirus Pneumonia (eighth edition) ranges from 0-14.0 days, 2.0-14.0 days, and 1.0-14.0 days, respectively.

Those results above vary from each other to some extent, presumably affected by the factors such as sample selection, estimation methods, and data processing methods. However, they played critical roles in the prevention and control of COVID-19 in specific time and space. Although based on only 10 cases data, the earliest estimate found the characteristics of the incubation period and more importantly, direct evidence of the transmission features in incubation period according to time interval. Previous studies on the prediction of global epidemic [12] and the reconstruction of the full transmission dynamic models in Wuhan [4,13] set the incubation period to 5.2 days. Besides, it has played a key role in making targeted quarantine and isolation decisions by analysis of different regions, different ages, and different ways of contact. The epidemiological characteristics of COVID-19 could be known better from larger sample size and more detailed analysis. Based on previous research results, this paper has studied the distribution of COVID-19 incubation period in response to above scientific issues.

Methods

The data were extracted from the official website of the China Health Commission and the supplementary materials of related literature [8,14,15]. Except the resident cases in Wuhan and the overlapping cases in different documents, we collected and organized the cases information according to factors including place onset, age, gender, exposure time window, onset time window, fever symptom time window, travel history to Hubei, route of infection, generation of sub-cases, etc. All cases were divided into 7 sub-groups according to age, gender, travel history to Hubei, initial symptoms, disease severity, exposure time window, generation of sub-cases, route of infection, etc. The 787 cases studied in our study did not contain the residents in Wuhan. The travel time of cases with travel history to Hubei were less than or equal to 7.0 days [16]. The left symptom onset date (SL) should be later than the left exposure date (EL), and the right exposure date (ER) should be earlier than or equal to SL. The time interval between ER and EL should not less than 1.0 day. If the symptom onset date was missing, let SL=ER+1 and the right symptom onset date (SR) would be determined based on the date of admission, diagnosis, and report.

In this paper, the way to describe the incubation period T was the accelerated failure time models, with the basis of the Log-normal distribution, Gamma distribution, Weibull distribution and Erlang distribution [17]. The principle of interval-censored data processing and estimation methods were described in detail elsewhere [18]. Statistical analysis were performed on R-4.0.2 software using "coarseDataTools 0.6-5" package to optimize the parameters to be estimated and calculate the confidence interval. The optimization method used when solving the maximum likelihood function is the simplex method. We used bootstrap re-sampling procedures with 1000 iterations to estimate the confidence interval.

Results

Of the 787 cases (Figure 1), the mean age is 43.6 years. 429 (54.4%) cases, 331 (42.1%) cases, and 27 (3.5%) cases were male, female, and unknown gender, respectively. 151 (19.2%) cases had travel history to Wuhan, while 557 (70.8%) cases did not. There were 321 (40.8%) cases whose initial symptom was fever. 23 (2.9%) cases were related to the emerging infection in Beijing. There were 413 (52.5%) second-generation and above cases and 517 (65.7%) cases whose exposure time interval was less than one day.

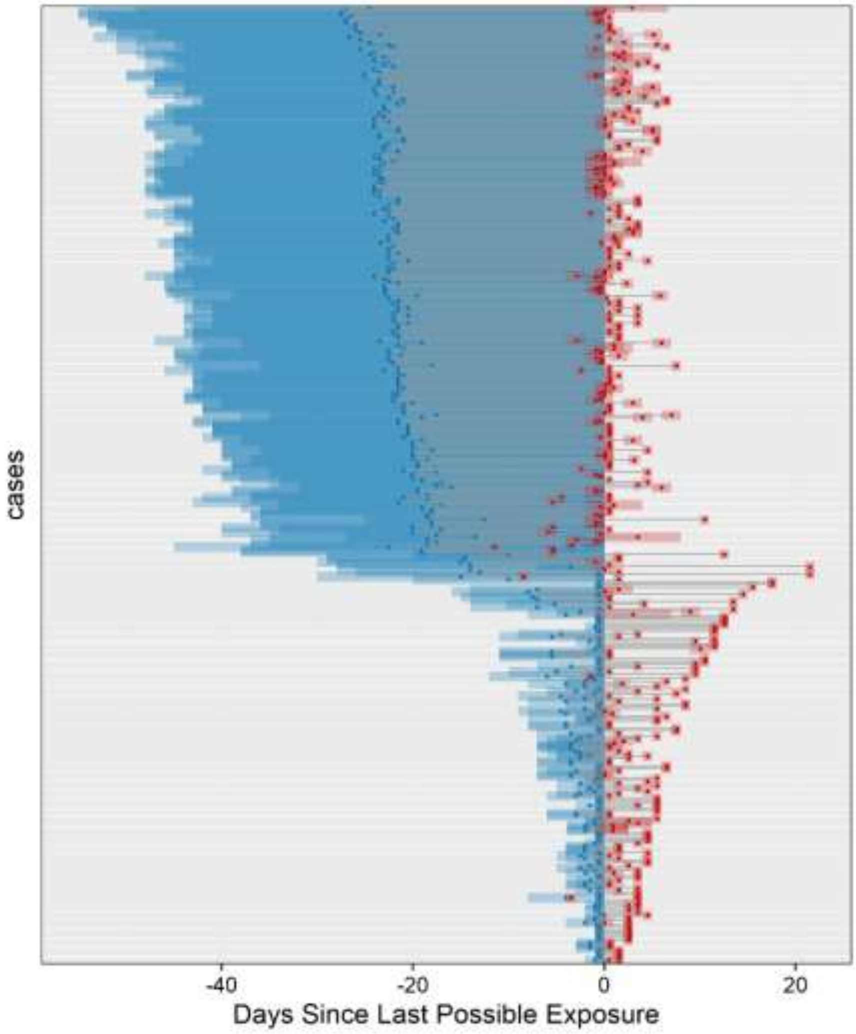

***Fig 1.* SARS-CoV-2 exposure and symptom onset times for 787 confirmed cases**. The red and the blue solid points are the median symptom onset date and median exposure date, respectively. The zero point is ER, and the shaded part is the time interval.

We estimated the probability density parameters for all cases by fitting the Log-normal distribution, Gamma distribution, Weibull distribution, and Erlang distribution (Table 1). Gamma distribution obtained the lowest AIC and BIC, indicating that Gamma distribution is the optimal distribution of incubation period for COVID-19. The mean incubation period is 7.8 (7.4~8.5) days. Figure 2 shows the estimated cumulative probability distribution and probability distribution of the incubation period, which fit the Gamma distribution. The incubation period of the 2.5th, 25th, 50th, 75th and 97.5th percentiles are respectively 1.8 (1.7~2.0) days, 4.7 (4.4~4.9) days, 7.0 (6.7~7.3) days, 10.0 (9.7~10.4) days, 17.9 (17.1~18.7) days. According to the distribution of the percentile position confidence interval (Figure 3), 2.5% of infected persons develop symptoms within 1.8d and 97.5% do so within 17.9d of exposure.

Table 1. Parameter estimation of probability density function for different incubation period distribution

Distribution	Parameter type	Parameter estimate（95% CI）	Mean incubation period（days, 95% CI）	AIC	BIC
Log-normal	Logarithmic mean μ	1.90（1.86~1.94）	7.8（7.5~8.2）	3701.45	3710.79
	Standard deviation σ	0.56（0.54~0.59）			
Gamma	Shape parameter α	3.41（3.13~3.73）	7.8（7.4~8.5）	3684.08	3693.42
	Scale parameter β	2.28（2.08~2.49）			
Weibull	Shape parameter k	1.95（1.85~2.04）	7.8（7.7~8.3）	3703.49	3712.82
	Scale parameter λ	8.76（8.46~9.13）			
Erlang	Shape parameter m	3.00（3.00~4.00）	7.7（7.4~8.5）	3689.90	3699.23
	Scale parameter β	2.58（1.93~2.67）			

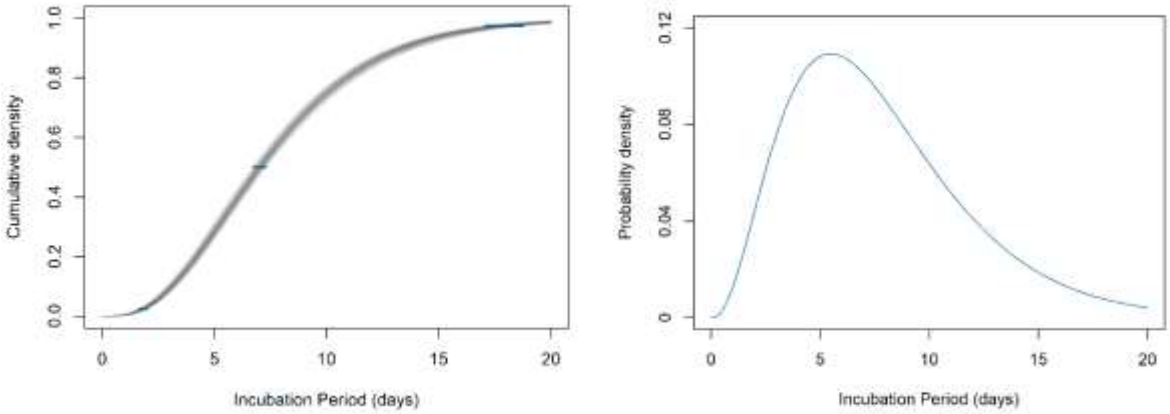

Fig 2. The cumulative density function and probability density function of the estimated Gamma incubation period distribution

We divided all cases into 7 types of subgroups according to the characteristics of age, gender, region, and ways of contact and performed the average incubation period of each subgroup based on the Gamma distribution (Table 2). Figure 3 shows the incubation period of the 2.5th, 25th, 50th, 75th and 97.5th percentile.

Table 2. The mean incubation period for sub-group cases

Characteristics of sub-group cases	Number of cases	Mean（95% CI）/days	Characteristics of sub-group cases	Number of cases	Mean（95% CI）/days
All cases	787	7.8（7.4~8.5）	Severe or critical symptoms	18	5.8（4.0~10.0）
Male	429	7.5（7.1~8.5）	Span of 1-day exposure period	517	8.4（8.0~9.5）
Female	331	8.2（7.7~9.5）	Span of 2-days exposure period	219	6.6 (6.1~7.8)
Age under 18 years	28	7.0（5.6~10.3）	Span of exposure period over 3 days	52	4.9 (3.5-8.3)
Age between 19 and 64 years	626	7.7（7.4~8.6）	Fever at first symptoms	321	7.8（7.3~9.1）
Age over 65 years	73	9.0（7.9~11.5）	No fever at first symptoms	164	7.6 (6.9~9.3)
Travel history to Hubei	151	5.7（4.7~6.8）	First generation of infected	61	6.3 (5.1~9.3)
No Travel history to Hubei	557	7.8（7.4~8.8）	Second generation of infected	349	8.3（7.8~9.5）
Mild or common symptoms	166	8.2（7.5~10.0）	Third generation of infected	64	6.9 (5.9~9.4)

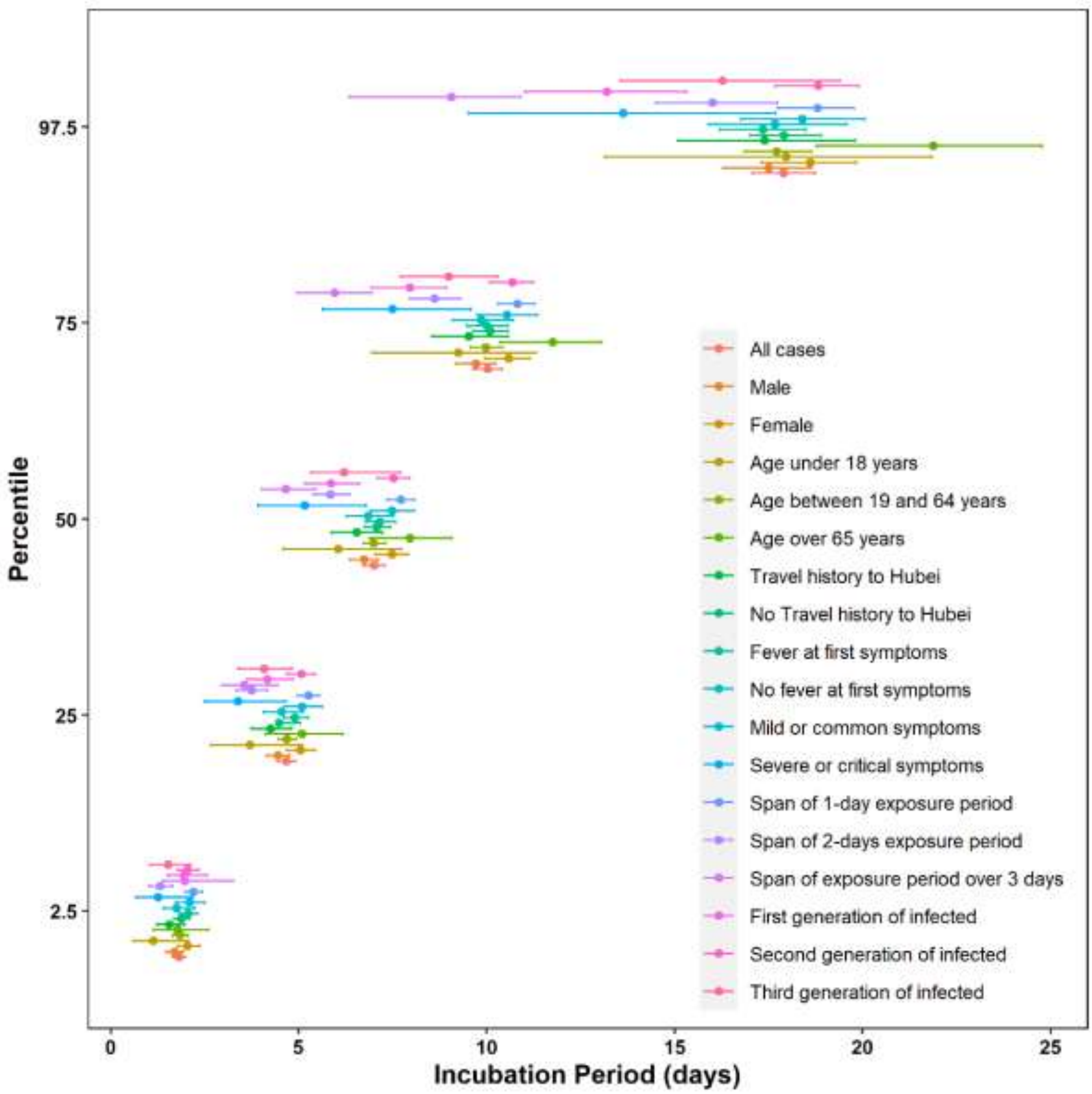

Fig 3. Percentile distribution of incubation period for sub-group cases

Discussion

It is concluded that the Gamma distribution fits best, based on interval-censored data processing estimation method, 787 case data be concerned, and the rest in turn were Erlang distribution, Log-normal distribution, and Weibull distribution, which reflected the distribution characteristics of the incubation period of COVID-19. We came to this conclusion by the model diagnosis and verification method which were supported by AIC criterion or BIC criterion. However, the difference between these four distributions is not big, indicating that the result estimation is relatively robust. Some studies researched the best fit distribution result for different sample data situations, as the weighted Akaike Information Criterion by Linton et al.[8], the log-likelihood function value by Du et al.[19], the leave-one-out information criterion by Backer et al.[20], which were related to the representativeness of the sample data and the different evaluation index criteria. When evaluating the performance of the distribution with the same number of parameters, the log-likelihood function and the AIC criterion are essentially equivalent. The mean and median of the incubation period are 7.8 (7.4~8.5) days and 7.0 (6.7~7.3) days, respectively, based on the Gamma distribution, which is longer than the earlier studies and is similar to Qin et al. (mean 8.3d) and Ma et al. (mean 7.0d). Qin et al. [21] found that nearly 109 cases have symptoms onset 14 days after infection, and mentioned some other evidence of longer incubation period. For example, 1 case was diagnosed 20 days after leaving Wuhan, reported on February 11 in Yibin City, while Guan et al. also found 2 cases with an incubation period of 24.0 days [22], Bai et al. found a case with an incubation period of 19.0 days [23], even longer. The incubation period for new cases on December 14 in Chaoyang District, Beijing, was also more than 14 days.

Older infected persons have a longer incubation period, and the difference between people of all ages is about 1.0 day. It is analyzed that the length of the incubation period depends on the sensitivity of the human immune system [9], while the elderly are exposed to various pathogens for a long time so that the immune T cells are highly differentiated into effector T cells and memory T cells. Memory T cells has a relatively high proportion, which will lose the expression of co-stimulatory molecules, thereby delaying the immune system to transmit defense messages [24], so the clinical symptoms appear later. Among cases over 65 years old, symptoms of 2.5% infected persons emerges after 21.8 days, which indicates that older close contacts should be quarantined and isolated for a longer period of time. Of note, the longer incubation period of older cases does not mean that this group can effectively resist the virus during the asymptomatic period. On the contrary, if the immune system of the infected person has not been activated during this period, the virus will replicate in large numbers, significantly increasing the viral load of infected persons, which is the reason for the high proportion of severe or critically ill elderly patients.

Women have a longer incubation period than men, about 0.7 days, for that women have stronger antiviral immunity than men. The Wuhan University People's Hospital team has also analyzed and emphasized the particularity of women in COVID-19. To some extent, individual antiviral immunity can affect the development of the disease, like asymptomatic infection, mild, common symptoms, severe or critical illness, etc. The incubation period of mild or common symptom cases is longer than that of severe cases. Having analyzed cases with mild or common symptoms and those with severe or higher conditions, the result showed that the mean incubation period was 8.2 (7.5~10.0) days and 5.8 (4.0~10.0) days, and the median was 7.5(6.9~8.1) days, 5.2(3.9~6.8) days, and the 97.5th percentile difference is close to 5 days. These asymptomatic or mild but infectious infections make epidemic prevention and control more difficult.

The incubation period is related to the amount of incoming virus. The greater the viral load in the body, the shorter the incubation period. The subgroup of cases without a travel or residence history in Hubei has a longer incubation period and a more scattered distribution while the ones with a travel history in Hubei is equivalent to the overall estimate. Such difference is due to the infectious doses [25]. Cases without travel history in Hubei only have short exposure to infection but those with travel history in Wuhan were exposed to the source of infection repeatedly during their stay. This feature is also reflected in the contrast of two subgroups of clustered and non-clustered epidemic case infections. The latter group has a slightly larger mean and each percentile value of incubation period than clustered cases. Similarly, short-term exposure to infection and long-term, multiple exposures will cause different infection doses. Given the analysis of cases with an exposure interval of 1, 2, or 3 days or more, cases with an exposure time of 1 day has the longest incubation period, as well, the difference between each subgroup of cases is about 2 days. More exposure causes a greater amount of virus infections, which leads to a more severe inflammatory response, then, clinical symptoms are likely to appear earlier [26].

The incubation period of fever as the initial symptom is larger than the estimated incubation period value of the overall data, and there are differences between each percentile. This is because the infected persons usually have a clearer memory of fever symptoms, but the recall of other symptoms is prone to bias. Circumstances, it is possible that the time of symptom onset may be earlier. Among the cases of different progenies, the mean incubation period of the second-generation sub-cases is the largest, followed by the first-generation sub-cases, and the third-or-more-generation sub-cases are the smallest. This conclusion does not support the assumption that the pathogenicity decreases with the increase of generation. We infer that this phenomenon is related to the evolution of the COVID-19. Early studies have shown that the COVID-19 has evolved into two sub-types, L and S, and that the L-type virus has a stronger transmission ability, a faster replication in the human body, and a more powerful pathogenic virulence [27] .

We estimated the risk of symptoms after the quarantine and isolation period of different lengths to determine the appropriate length of quarantine. With reference to the risk standard assumed in previous studies, the 1% probability of infection after exposure is a high-risk group, followed by 0.1% medium risk, and 0.01% low risk. Then, we use the accelerated failure model based on Gamma distribution by the Bootstrap method to repeat 10,000 samplings, get the sampling results of different levels of risk infection groups after 7d, 14d, 21d, 28d and other different isolation and quarantine periods without symptoms (should have symptoms but have not yet appeared) (the 99th percentile value in brackets), as shown in Table 3. It is assumed that all infected persons have symptoms, eliminating the interference of asymptomatic infected persons. It is clear that for the high-risk infection group, symptoms of 8.4 out of 10,000 infected persons will not appear after 14 days of quarantine, and 50.1 people will be missed if the quarantine be reduced to 7 days. This conclusion could give a support to the 14-day quarantine measures to some extent. Moreover, given an analysis in combination with the subgroup results, we hold that it is necessary to focus more on the elderly, and the population with short exposure time window, whose incubation period of these characteristics is longer.

Table 3. Estimated values of asymptomatic infections after different isolation time for the different risk level

isolation time	low risk（0.01%）	middle risk（0.1%）	high risk（1%）	Confirmed（100%）
7.0d	0.5（0.5）	5.0（5.3）	50.1（53.3）	5014.0（5325.9）
14.0d	**0.1（0.1）**	**0.8（1.0）**	**8.4（10.1）**	**837.1（1014.3）**
21.0d	0.0（0.0）	0.1（0.1）	0.9（1.3）	90.5（134.6）
28.0d	**0.0（0.0）**	**0.0（0.0）**	**0.1（0.1）**	**8.0（14.4）**

Limitations

The limitations of this study mainly come from three aspects: Firstly, the sample size of these 787 cases collected is above the average level, although it can meet the basic needs of incubation period estimation, more effective samples need to be added up in follow-up research. Secondly, although 9 subgroups were divided according to age, gender, travel history in Hubei, whether the initial symptoms were fever, severity of illness, exposure interval, generation of cases, ways of infection, etc., cases of some subgroup is far from enough, and factors affecting the incubation period have not been involved. Thirdly, as previous studies, the data comes from publically available epidemiological survey and supplementary materials in journal literature, while there will be some bias when they recall the exposure time and onset time on cases themselves.

Conclusions

This work analyzes 787 cases based on the interval censored data processing method. The study found that the optimal distribution of the incubation period of COVID-19 basically fits the Gamma distribution, the mean and median incubation period are 7.7 (7.4~8.5) days and 7.0 (6.7~7.3) days, the length of the incubation period is positively correlated with age, negatively correlated with the severity of symptoms. The incubation period of female cases is a bit higher than that of males. Cases with a history of travel to Hubei and multiple exposures have a shorter incubation period. Symptoms of 91.6% of infected persons appeared within 14 days, indicating that the 14-days quarantine measures are reasonable. Particularly, it is possible for any infected person to develop symptoms after 14 days. If we extend the isolation and quarantine period of close contacts to increase the intensity of prevention and control measures, the relationship between prevention and control costs and infection risk needs to be balanced.

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Author contributions

J.L. and S.H. were involved in study design; J.L., C.D., Z.T., J.X., X.X., X.H., Z.W., C.L. and S.H. performed research; J.L., C.D. and S.H. interpreted and analyzed the data; J.L., C.D., C.L. and S.H. were involved in article writing and reviewed the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The data sets used and/or analyzed during the current present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Academic Ethics Committee of XiangYa School of Public Health approved of our study and an acknowledgement of consent was appended within the survey for every participant. Informed consent was obtained from all subjects in the study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

No competing interests to disclose.

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Figures

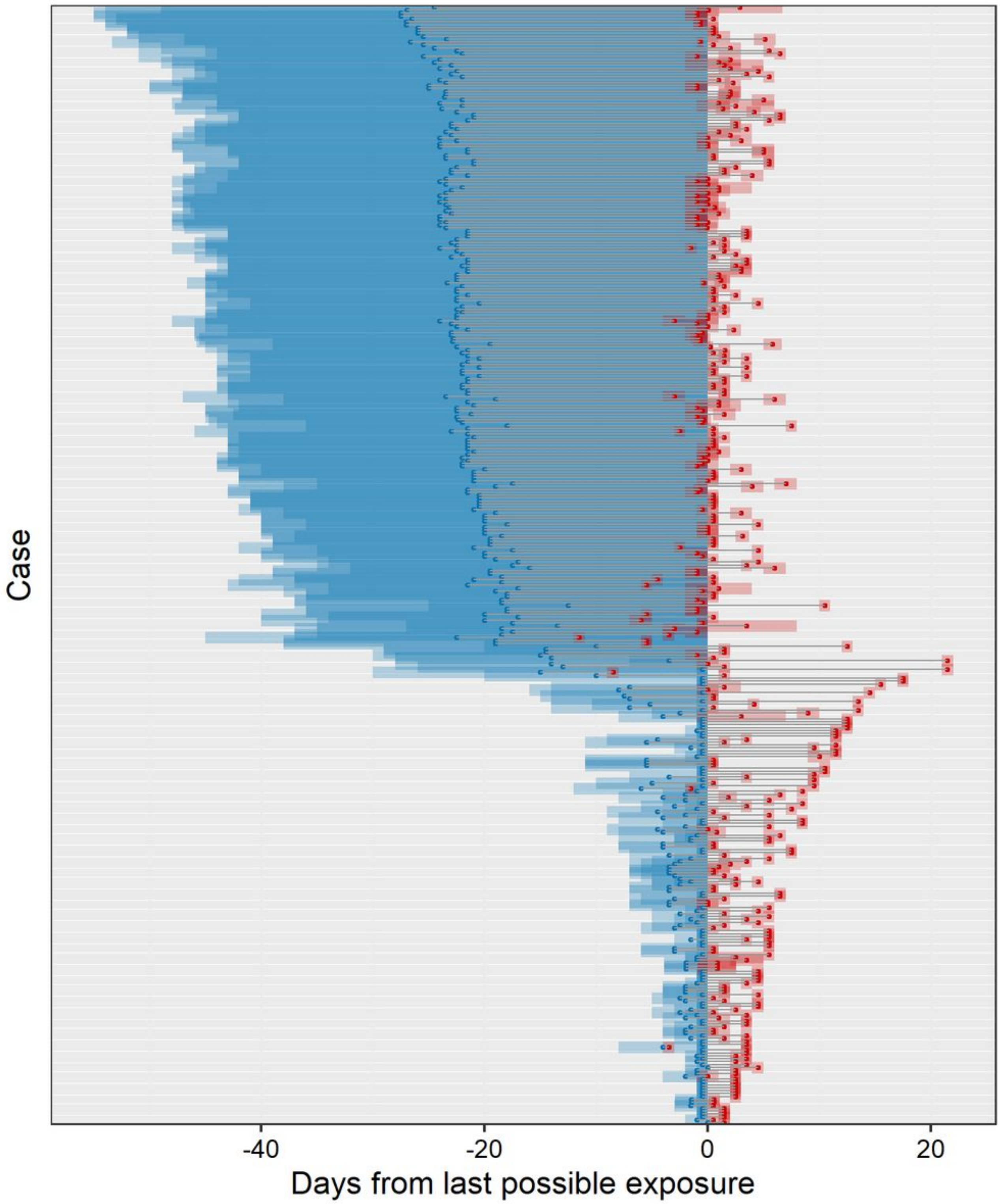

Figure 1

SARS-CoV-2 exposure and symptom onset times for 787 confirmed cases. The red and the blue solid points are the median symptom onset date and median exposure date, respectively. The zero point is ER, and the shaded part is the time interval.

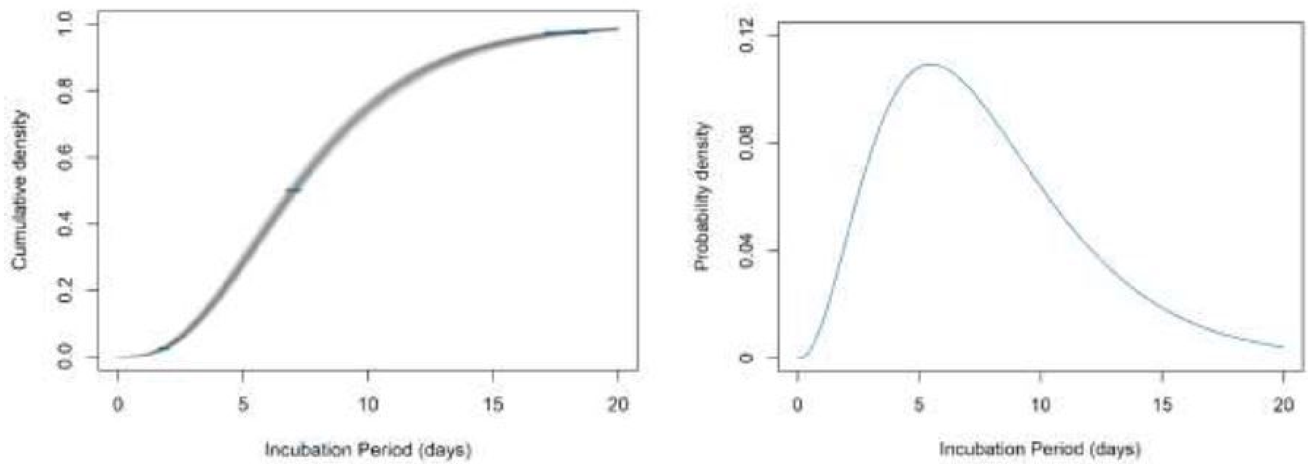

Figure 2

The cumulative density function and probability density function of the estimated Gamma incubation period distribution

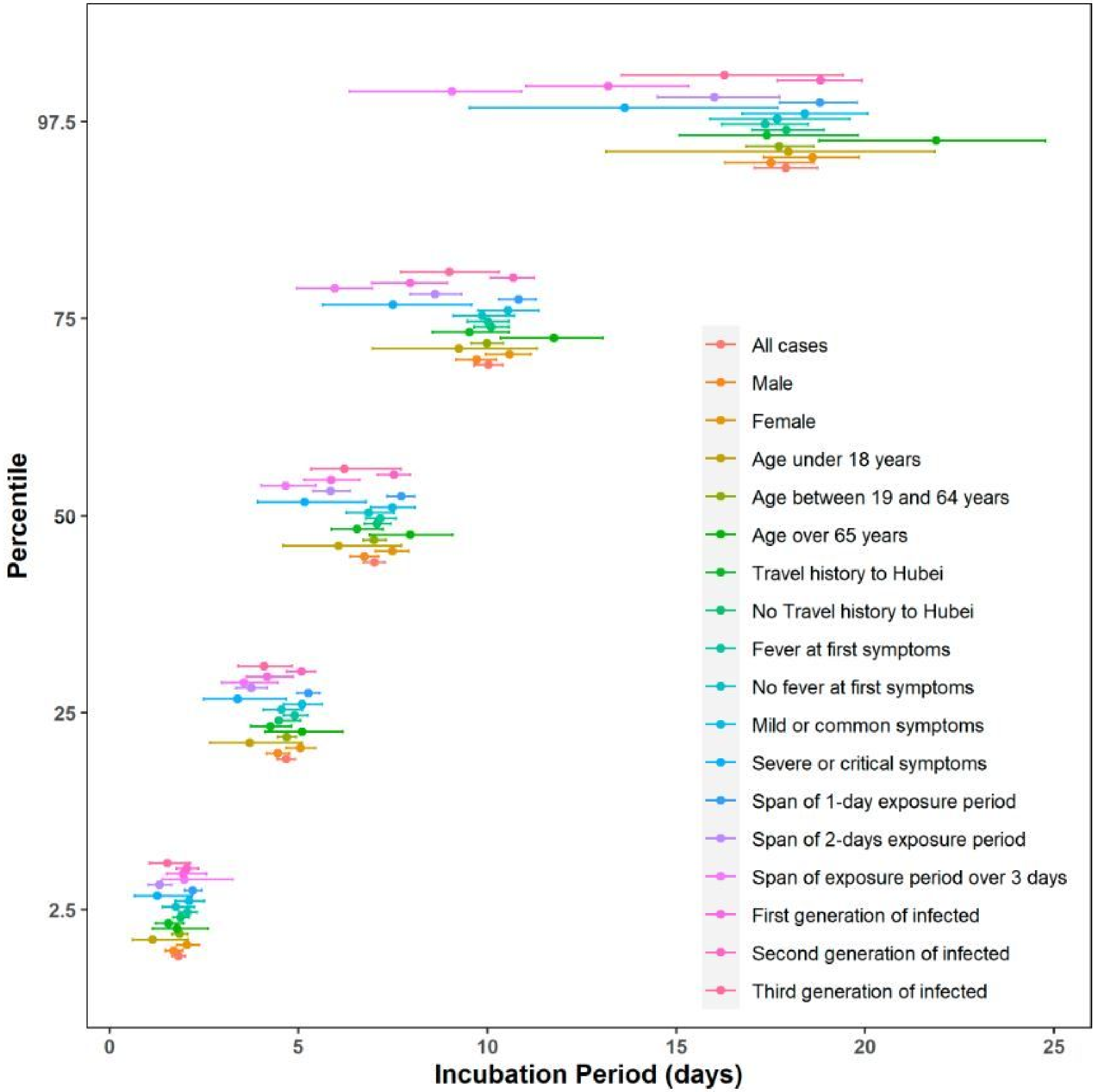

Figure 3

Percentile distribution of incubation period for sub-group cases