

The Comparison of Epidemiological Characteristics Between Confirmed and Clinically Diagnosed Cases With COVID-19 in Wuhan, China

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Research

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Abstract

Background: To put COVID-19 patients into hospital timely, the clinical diagnosis had been implemented in Wuhan in the early outbreak. Here we compared the epidemiological characteristics of laboratory-confirmed and clinically diagnosed cases with COVID-19 in Wuhan.

Methods: Demographics, case severity and outcomes of 29886 confirmed cases and 21960 clinically diagnosed cases reported between December 2019 and February 24, 2020, were compared. The risk factors were estimated, and the effective reproduction number of SARS-CoV-2 (R_t) was also calculated.

Results: The interval between symptom onset and diagnosis of confirmed and clinically diagnosed cases reduced gradually as time went by, and the proportion of severe and critical cases as well as case fatality rates of the two groups all decreased over time. The proportion of severe and critical cases (21.5% vs 14.0%, $P < 0.0001$) and case fatality rates (5.2% vs 1.2%, $P < 0.0001$) of confirmed cases were all higher than those of clinically diagnosed cases. Risk factors for death we observed in all two groups were older age, male, severe or critical cases. R_t showed a downward trend after the lockdown of Wuhan, it dropped below 1.0 on February 6 among confirmed cases, and February 8 among clinically diagnosed cases.

Conclusion: Public health responses taken in Wuhan, including clinical diagnosis, have contributed to slow transmission. In cases where testing kits are insufficient, clinical diagnosis is effective, which is helpful to quarantine or treat infected cases as soon as possible, and prevent the epidemic from worsening. To decrease the case fatality rate of COVID-19, it is necessary to strengthen early warning and intervention of severe and critical elderly men.

Introduction

In December 2019, a highly pathogenic coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was recognized in Wuhan, China, and then sustained transmission has been seen throughout and outside China. The World Health Organization named the pneumonia caused by SARS-CoV-2 as Corona Virus Disease 2019 (COVID-19) [1], and announced that new coronary pneumonia has developed into a "pandemic" on 11 March 2020.

Wuhan, the provincial capital of Hubei Province, is the epicenter of the outbreak, Massive measures have been taken by the government to curb the spread of COVID-19 in Wuhan, including the lockdown of Wuhan, which helped in limiting crowd movement to prevent infected cases from spreading to other areas [2].

The viral nucleic acid test (real-time reverse transcriptase–polymerase chain reaction [RT-PCR] assay or genome sequencing) is considered as the diagnostic gold standard of COVID-19 [3, 4] Before February 8, only patients who had positive results on virus nucleic acid tests were regarded as laboratory-confirmed cases across China (To be consistent with the Chinese government's report, the following laboratory-confirmed cases are referred to as confirmed cases). However, due to a large number of patients, insufficient testing kits, and bottlenecks in laboratory testing capacity, the nucleic acid detection failed to meet clinical needs, and patients in Hubei Province couldn't be admitted to the hospital for treatment in time [5]. It's important to admit patients into hospitals as soon as possible since a deferred admission may turn patients critical and lead to

more infections. To raise the hospital admission and improve the efficiency of treatment, the broadened diagnostic criteria were used and the designation 'clinically diagnosed cases' emerged. According to the revised fifth version of the guideline over the diagnosis and treatment of COVID-19 issued on Feb 8, jointly released by the National Health Commission of China and the State Administration of Traditional Chinese Medicine, clinical diagnosis was being used in Hubei Province only [3]. Without laboratory confirmation, clinically diagnosed cases were diagnosed by symptoms, exposures and CT scan only [3, 6]. Thanks to the revision in the diagnostic criteria, the patient admission rate has surged immediately. In the later period, the detection of COVID-19 had been greatly improved, the laboratory diagnostic ability could be met current needs, and the suspected cases in Hubei Province could be rapidly detected. Therefore, the updated guideline known as the sixth edition issued on Feb 19 abolished different epidemic-related standards inside and outside Hubei Province, "clinically diagnosed cases" were no longer listed [4]. In addition, the number of clinically diagnosed cases was revised on Feb 24 [5].

To inform evidence-based decisions, more information relevant to the epidemiology of COVID-19 was urgently needed [7]. There are many studies on the confirmed cases [8–10], but no description of the epidemiology of clinically diagnosed cases has been seen. Here is a generalization and comparison of epidemiological characteristics of confirmed and clinically diagnosed cases with COVID-19 in Wuhan.

Methods

Data sources

This was a retrospective cohort study. All data from December 8, 2019 (date of the first onset) to 24 February 2020, were extracted from China's Infectious Disease Information System. Precise details of data collection are provided elsewhere [11]. After excluding duplicate cases and those who were unable to obtain a unique identifying card, a total of 29886 confirmed cases and 21960 clinically diagnosed cases with COVID-19 in Wuhan were eligible for this study finally.

Variables

COVID-19 was classified into mild type, moderate type, severe type as well as critical type according to disease severity, the detailed classification criteria were shown in **Supplementary Table S1**. The date of onset was defined as the day when the symptom was observed. The proportion of severe and critical cases was defined as $(\text{severe cases} + \text{critical cases}) / (\text{mild cases} + \text{moderate cases} + \text{severe cases} + \text{critical cases})$. Case fatality rates were calculated as the number of deaths divided by the total number of cases. Incidence density was estimated as the number of cases divided by the number of permanent resident population, which obtained from the Wuhan Statistics Bureau. Because there was no permanent resident data for 2019 and 2020, we replaced it with the data for 2018.

Case Definitions

According to the 5th edition of the guideline over the diagnosis and treatment of COVID-19 [3], confirmed cases were patients who had positive results for SARS-CoV-2 virus after conducting RT-PCR assay or high-throughput sequencing of nasal and pharyngeal swab specimens. Clinically diagnosed cases were suspected

cases with lung imaging features consistent with coronavirus pneumonia. Bilateral distribution of patchy shadows and ground glass opacity were typical hallmarks of CT scan for COVID-19 [6].

Statistical analysis

All data were recorded and sorted in Excel. Continuous variables were described using median and interquartile range (IQR) values when the data didn't obey normal distribution. Categorical variables were described by frequency, rates and percentages. The epidemic curve was built; besides, maps of Wuhan at county-level were drawn to depict the numbers of new cases each day. Demographics, case severity and outcomes between confirmed cases and clinically diagnosed cases were compared using Chi square tests or Kolmogorov-Smirnov Z tests. Univariable and multivariable logistic-regression analysis was performed to ascertain the effects of age, sex, occupation, date of onset, days from onset to diagnosis, district of residence, level of hospital on the likelihood of severity or death. Because there was collinearity between variable 'date of onset' and 'days from onset to diagnosis', the logistic-regression model didn't include variable 'days from onset to diagnosis'. Odds ratios (OR) and its 95% confidence intervals were calculated, corresponding forest-plot was drawn. The effective reproduction number (R_t), which is an indicator to measure the transmission of infectious diseases, is defined as the mean number of secondary cases generated by a typical primary case at time t in a population. When R_t is less than 1, the epidemic of infectious diseases will be gradually controlled; when R_t is greater than 1, infectious diseases will continue to spread, suggesting that prevention and control measures need to be optimized or strengthened. We applied the method developed by Anne Cori [12] to estimate R_t and its 95% credible interval via a weekly sliding average. Referring to previous epidemiological surveys of Wuhan in the early stage of the outbreak, the parameters of serial interval distribution (gamma distribution, mean = 7.5 days, SD = 3.4 days) were cited. SPSS version 26.0 and R version 4.0 were used for statistical analyses and ArcGIS version 10.7 was used for cartography.

Results

Baseline epidemiological characteristics

As of 24 February 2020, a total of 29886 confirmed cases and 21960 clinically diagnosed cases with COVID-19 were included in this study, the epidemiological curves were accomplished to compare the number of confirmed cases and clinically diagnosed cases (Fig. 1). The time evolution of the elderly (patients aged above 60 years), children (patients aged under 18 years), healthcare workers, severe and critical cases, death cases and the total cases were consistent (**Supplementary Fig. S1**). The baseline characteristics of cases were shown in Table 1. The sex ratio of confirmed cases and clinically diagnosed cases were 1.01 (15059/14827) and 0.86 (10165/111795), respectively. The epidemiological curves of males and females were similar (**Supplementary Fig. S2**). The median age of confirmed cases was 56.0 years (IQR, 43.0–66.0); meanwhile, the median age of clinically diagnosed cases was 54.0 (40.0–65.0) years. The age distribution of different genders was similar (**Supplementary Fig. S3**). Retirees account for the largest proportion of patient's occupations (33.5% of confirmed cases and 27.8% of clinically diagnosed cases), and healthcare workers accounted for 4.0% of confirmed cases and 5.5% of clinically diagnosed cases, respectively. The median intervals between onset and diagnosis of confirmed cases and clinically diagnosed cases were 9.0 (5.0–13.0) and 11.0 (5.0–18.0) days, respectively. As time goes on, the interval between onset and diagnosis had

decreased significantly (**Supplementary Fig. S4**). The city centres have more diagnosed cases than suburbs. But Hannan district had the highest density of clinically diagnosed cases (Fig. 2 **and Supplementary Table S2**). Tertiary hospitals admit more patients than primary and secondary hospitals. Due to the large sample size, the difference in epidemiological indicators between confirmed and clinically diagnosed cases is significant ($P < 0.0001$)

Table 1

Baseline Epidemiological Characteristics of Confirmed Cases and Clinically Diagnosed Cases in Wuhan

Baseline Characteristics	No. Confirmed Cases (%)	No. Clinically Diagnosed Cases (%)	χ^2/Z	<i>P</i>
Total	29886	21960		
Age, median (IQR *), years	57.0(44.0–67.0)	54.0(41.0–65.0)	9.005	< 0.001
Age group, years			423.542	< 0.001
0~	186(0.6)	220(1.0)		
10~	226(0.8)	173(0.8)		
20~	1371(4.6)	1412(6.4)		
30~	3720(12.4)	3280(14.9)		
40~	4435(14.8)	3736(17.0)		
50~	6347(21.2)	4851(22.1)		
60~	7678(25.7)	5007(22.8)		
70~	3979(13.3)	2285(10.4)		
80~	1671(5.6)	839(3.8)		
≥90	217(0.7)	121(0.6)		
Missing	56(0.2)	36(0.2)		
Sex			85.155	< 0.001
Male	15059(50.4)	10165(46.3)		
Female	14827(49.6)	11795(53.7)		
Occupation			521.949	< 0.001
Child and student	439(1.5)	482(2.2)		
Cadre	1489(5.0)	1119(5.1)		
Freelancer	203(0.7)	194(0.9)		
Physical labor	712(2.4)	641(2.9)		
Public service staff	1816(6.1)	1477(6.7)		
Housework or unemployed	5684(19.0)	5401(24.6)		

Note. *IQR = interquartile range.

Baseline Characteristics	No. Confirmed Cases (%)	No. Clinically Diagnosed Cases (%)	χ^2/Z	<i>P</i>
Retirees	10012(33.5)	6114(27.8)		
Farmer or pastoral worker	1390(4.7)	1002(4.6)		
Healthcare worker	1188(4.0)	1211(5.5)		
Missing	6953(23.3)	4319(19.7)		
Case severity			5342.046	< 0.001
Mild	18192(60.9)	11326(51.6)		
Moderate	4148(13.9)	7446(33.9)		
Severe	5278(17.7)	2749(12.5)		
Critical	823(2.8)	315(1.4)		
Missing	1445(4.8)	124(0.6)		
Death or not			616.585	< 0.001
Not	28322(94.8)	21703(98.8)		
Yes	1564(5.2)	257(1.2)		
Date of onset			1052.209	< 0.001
Before Dec 31, 2019	135(0.5)	92(0.4)		
Jan 1–10, 2020	591(2.0)	388(1.8)		
Jan 11–20, 2020	2921(9.8)	1981(9.0)		
Jan 21–31, 2020	13502(45.2)	7741(35.3)		
Feb 1–10, 2020	9600(32.1)	8583(39.1)		
Feb 11–20, 2020	2758(9.2)	3172(14.4)		
Feb 21–24, 2020	355(1.2)	---		
Missing	24(0.1)	3(0.0)		
Days from onset to diagnosis, median (IQR)	9.0 (5.0–13.0)	11.0 (5.0–18.0)	19.560	< 0.001
District of residence			163.400	< 0.001
City centre	23768(79.5)	17003(77.4)		

Note. *IQR = interquartile range.

Baseline Characteristics	No. Confirmed Cases (%)	No. Clinically Diagnosed Cases (%)	χ^2/Z	<i>P</i>
Suburb	5577(18.7)	4755(21.7)		
Outside Wuhan	339(1.1)	173(0.8)		
Missing	202(0.7)	29(0.1)		
Level of hospital			1069.631	< 0.001
Tertiary hospital	21622(72.3)	18598(84.7)		
Primary and secondary hospital	8166(27.3)	3362(15.3)		
Missing	98(0.3)	--		
Note. *IQR = interquartile range.				

Severity of illness

The proportion of severe and critical types in confirmed cases (6101/28441, 21.5%) was higher than that in clinically diagnosed cases (3064/21836, 14.0%). As given in **Supplementary Table S3**, the epidemiological characteristics of COVID-19 varied by the classification of severity. The median ages of the severe and critical cases were higher than mild and moderate cases, and the proportion of severe and critical cases increased with age (**Supplementary Fig. S5**). The proportion of critical cases in males was higher than that in females (53.6% vs 43.7% in confirmed cases, and 60.6% vs 36.4% in clinically diagnosed cases). The residential with the highest proportion of severe and critical cases was Jiang'an district (31.9%) in confirmed cases, while Dongxihu district (22.8%) had the highest proportion of severe and critical clinically diagnosed cases (**Supplementary Fig. S6**). The proportion of severe and critical cases in confirmed and clinically diagnosed cases all decreased over time (Fig. 3). Univariable and multivariable logistic-regression model showed that age greater than 60 years, males, special occupations (such as housework or unemployed, retirees, and healthcare worker) were risk factors of severe and critical disease status for both confirmed cases and clinically diagnosed cases. A later date of onset is associated with a milder disease state for them. Besides, area of residence and level of hospital were associated with the disease state of clinically diagnosed cases, but no association found for confirmed cases (Fig. 4a and **Supplementary Table S4**).

Analysis of Deaths

The case fatality rates of confirmed cases and clinically diagnosed cases with COVID-19 were 5.2% and 1.5%, respectively (Table 2). The median age of deaths was much higher than those who didn't die both in confirmed cases (70 vs 56 years) and clinically diagnosed cases (70 vs 54 years) (**Supplementary Fig. S5**). The sex ratio of death cases was significantly higher than non-death cases (1.91 vs 0.98 in confirmed cases, and 2.21 vs 0.85 in clinically diagnosed cases). The case fatality rates of critical cases and severe cases were higher than those of mild and moderate cases, respectively. The dead who lived in Hannan district accounted for the highest proportion for those of confirmed cases, while the case fatality rate of Dongxihu district was

the highest in clinically diagnosed cases (**Supplementary Fig. S6**). The percentage of deaths decreased over time in the early stage of the outbreak in terms of onset date (Fig. 3). Univariable and multivariable logistic-regression was developed to predict the risk factors of death from COVID-19. Age greater than 60 years, males, and more serious case severity were found to be related to an increased risk of death. Date of onset was associated with a better chance of survival for confirmed cases, with no association found for clinically diagnosed cases (Fig. 4b **and Supplementary Table S5**).

Table 2
Epidemiological Characteristics of Death Cases and Cases not Dead in Wuhan

Characteristics	Confirmed Cases			Clinically Diagnosed Cases			P
	Death (%)	Not Dead (%)	Case Fatality Rate (%)	Death (%)	Not Dead (%)	Case Fatality Rate (%)	
Total	1564	28322	5.2	257	21703	1.2	< 0.001
Age, median (IQR ^a), years	70.0(63.0–79.0)	56.0(53.0–66.0)	—	70.0(62.0–78.0)	54.0(40.0–65.0)	—	—
Age group, years							
0~	0(0.0)	186(0.7)	0.0	0(0.0)	220(1.0)	0.0	—
10~	1(0.1)	225(0.8)	0.4	1(0.4)	172(0.8)	0.6	1.000
20~	6(0.4)	1365(4.8)	0.4	1(0.4)	1411(6.5)	0.1	0.120
30~	20(1.3)	3700(13.1)	0.5	3(1.2)	3277(15.1)	0.1	0.001
40~	49(3.1)	4386(15.5)	1.1	9(3.5)	3727(17.2)	0.2	< 0.001
50~	175(11.2)	6172(21.8)	2.8	34(13.2)	4817(22.2)	0.7	< 0.001
60~	455(29.1)	7223(25.5)	5.9	77(30.0)	4930(22.7)	1.5	< 0.001
70~	473(30.2)	3506(12.4)	11.9	80(31.1)	2205(10.2)	3.5	< 0.001
80~	300(19.2)	1371(4.8)	18.0	45(17.5)	794(3.7)	5.4	< 0.001
≥90	52(3.3)	165(0.6)	24.0	6(2.3)	115(0.5)	5.0	< 0.001
Missing	33(2.1)	23(0.1)	58.9	1(0.4)	35(0.2)	2.8	< 0.001
Sex							
Male	1026(65.6)	14033(49.5)	6.8	177(68.9)	9988(46.0)	1.7	< 0.001
Female	538(34.4)	14289(50.5)	3.6	80(31.1)	11715(54.0)	0.7	< 0.001
Occupation							

^a IQR = interquartile range.

Characteristics	Confirmed Cases			Clinically Diagnosed Cases			P
	Death (%)	Not Dead (%)	Case Fatality Rate (%)	Death (%)	Not Dead (%)	Case Fatality Rate (%)	
Child and student	2(0.1)	437(1.5)	0.5	0(0.0)	482(2.2)	0.0	0.227
Cadre	31(2.0)	1458(5.1)	2.1	4(1.6)	1115(5.1)	0.4	< 0.001
Freelancer	6(0.4)	197(0.7)	3.0	1(0.4)	193(0.9)	0.5	0.143
Physical labor	19(1.2)	693(2.4)	2.7	4(1.6)	637(2.9)	0.6	0.004
Public service staff	23(1.5)	1793(6.3)	1.3	2(0.8)	1475(6.8)	0.1	< 0.001
Housework or unemployed	267(17.1)	5417(19.1)	4.7	57(22.2)	5344(24.6)	1.1	< 0.001
Retirees	753(48.1)	9259(32.7)	7.5	104(40.5)	6010(27.7)	1.7	< 0.001
Farmer or pastoral worker	51(3.3)	1339(4.7)	3.7	15(5.8)	987(4.5)	1.5	0.001
Healthcare worker	12(0.8)	1176(4.2)	1.0	2(0.8)	1209(5.6)	0.2	0.007
Missing	400(25.6)	6553(23.1)	5.8	68(26.5)	4251(19.6)	1.6	< 0.001
Case severity							
Mild	603(38.6)	17589(62.1)	3.3	79(30.7)	11247(51.8)	0.7	< 0.001
Moderate	69(4.4)	4079(14.4)	1.7	31(12.1)	7415(34.2)	0.4	< 0.001
Severe	477(30.5)	4801(17.0)	9.0	73(28.4)	2676(12.3)	2.7	< 0.001
Critical	210(13.4)	613(2.2)	25.5	39(15.2)	276(1.3)	12.4	< 0.001
Missing	205(13.1)	1240(4.4)	14.2	35(13.6)	89(0.4)	28.2	< 0.001
Date of onset							
Before Dec 31, 2019	29(1.9)	106(0.4)	21.5	4(1.6)	88(0.4)	4.3	< 0.001

^a IQR = interquartile range.

Characteristics	Confirmed Cases			Clinically Diagnosed Cases			P
	Death (%)	Not Dead (%)	Case Fatality Rate (%)	Death (%)	Not Dead (%)	Case Fatality Rate (%)	
Jan 1–10, 2020	132(8.4)	459(1.6)	22.3	9(3.5)	379(1.7)	2.3	< 0.001
Jan 11–20, 2020	392(25.1)	2529(8.9)	13.4	30(11.7)	1951(9.0)	1.5	< 0.001
Jan 21–31, 2020	769(49.2)	12733(45.0)	5.7	95(37.0)	7646(35.2)	1.2	< 0.001
Feb 1–10, 2020	215(13.7)	9385(33.1)	2.2	84(32.7)	8499(39.2)	1.0	< 0.001
Feb 11–20, 2020	26(1.7)	2732(9.6)	0.9	32(12.5)	3140(14.5)	1.0	0.796
Feb 21–24, 2020	0(0.0)	355(1.3)	0.0	0(0.0)	0(0.0)	---	---
Missing	1(0.1)	23(0.1)	4.2	3(1.2)	---	0.0	---
Days from onset to diagnosis, median (IQR)	10.0(7.0–14.0)	9.0(4.0–13.0)	---	8.0(3.0–15.0)	11.0(5.0–18.0)	---	---
District of residence							
City centre	1208(77.2)	22560(79.6)	5.1	169(65.8)	16834(77.6)	1.0	< 0.001
Suburb	227(14.5)	5350(18.9)	4.1	58(22.6)	4697(21.6)	1.2	< 0.001
Outside Wuhan	33(2.1)	306(1.1)	9.7	1(0.4)	172(0.8)	0.6	< 0.001
Missing	96(6.1)	106(0.4)	47.5	29(11.3)	---	---	---
Level of hospital							
Tertiary hospital	1254(80.2)	20368(71.9)	5.8	205(79.8)	18393(84.7)	1.1	< 0.001
Primary / secondary hospital	310(19.8)	7856(27.8)	3.8	52(20.2)	3310(15.3)	1.5	< 0.001
Missing	---	98(0.3)	---	---	---	---	---
^a IQR = interquartile range.							

Rt of confirmed and clinically diagnosed cases

For confirmed (or clinically diagnosed) cases, R_t fluctuated above 2.0 before January 30, reached a peak of 3.64 (3.54) on January 23 (January 22), and further declined after Wuhan city lockdown, finally decreased to below 1.0 after February 6 (February 8). The trend of R_t was shown in Fig. 5.

Discussion

Wuhan has borne the brunt during the epidemic. To put patients into hospital and under treatment timely, the clinically diagnosed cases had been identified from February 8 to February 18. Besides, the number of clinically diagnosed cases was revised on February 24 [5]. After performing the clinical diagnosis, it's encouraging that the number of new cases had been trending downward, R_t had decreased to below 1, indicating the explosive growth of new infections was effectively contained in Wuhan.

This study showed that people of all ages were susceptible to the virus, but the vast majority of patients were middle-aged and old people. The median age of confirmed cases was marginally above that of clinically diagnosed cases (56 vs 54 years), and the elderly accounts for a higher proportion in confirmed cases (41.0% vs 36.6%). The occupational distributions of confirmed cases and clinically diagnosed cases were similar, but the sex ratios of them were slightly different (1.01 vs 0.86). The epidemic peak of clinical diagnosis cases was later than that of confirmed cases, which may be because that the patients with early-onset received the nucleic acid diagnosis preferentially, while the patients with late-onset couldn't receive RT-PCR or genome sequencing of SARS-COV-2 virus in time when the detection kits were insufficient. At this time, it is necessary to carry out a clinical diagnosis for these patients who have already developed symptoms but can't be confirmed by the laboratory, since the condition will worsen if they cannot be isolated or admitted promptly. The median (IQR) interval between onset and diagnosis of confirmed cases was 9(5–13) days, which were slightly shorter than that of clinically diagnosed cases [11(5–17) days]. Reagents were insufficient in the early stage of the outbreak, which caused them to take too long from onset to diagnosis. The interval between onset and diagnosis had seen a continuous decrease as time went by, meaning the implementation of clinical diagnosis effectively shortened the duration before diagnosis in the early stage of the outbreak.

There are 13 districts in Wuhan: Jiang'an, Jianghan, Qiaokou, Hanyang, Wuchang, Qingshan, Hongshan, Dongxihu, Hannan, Caidian, Jiangxia, Huangpi and Xinzhou, the first seven of which are city centres. The city centres have a large number of permanent residents and floating population, which is prone to the spread of the virus. Besides, the city centres have abundant and concentrated medical resources, for example, there are more tertiary hospitals (**Supplementary Fig. S7**), which make it easier for the infected people there to be diagnosed than suburbanites. The geographical distribution further indicated the obvious regional diversity of confirmed cases and clinically diagnosed cases. Jianghan district virtually had the highest density of confirmed cases. The Huanan Seafood Wholesale Market, which is regarded as the epidemic focus of this virus, is located here. At the end of December 2019, the National Health Commission of China reported a cluster of patients with pneumonia in Wuhan, part of which was exposure to Huanan Seafood Wholesale Market illegally selling wildlife [13]. Jiang'an district, Qiaokou district and Hanyang district, which were all

hardest-hit regions, were geographically close to Jiangnan district. Hannan district had the highest density of clinically diagnosed cases, followed by Jiangnan district. Hannan district is located in the suburb of Wuhan, where medical resources are relatively scarce. Although it was difficult to confirm COVID-19 promptly in the early stage of the outbreak, many patients in Hannan district had benefited from clinical diagnosis and received timely treatment. Besides, the high density of clinically diagnosed cases in Hannan district may owe to its least permanent resident population.

The proportion of severe and critical types in confirmed cases was different from that in clinically diagnosed cases (21.5% vs 14.0%, $P < 0.05$), one of the reasons may be that the proportions of the elderly and males were higher in confirmed cases. Logistic-regression result suggested that age was closely related to the proportion of severe and critical cases, which was consistent with early reports [9, 11, 14]. Because older people tend to have serious underlying illnesses, the older the age is, the more severe the disease is. The later the date of onset, the milder the disease state. In addition to the improved treatment effect, it may also be related to the shorter intervals between onset and diagnosis in the later stage of the outbreak. The median intervals between onset and diagnosis of severe and critical patients were significantly longer than those of mild patients. Some severe patients with critical illness who progressed to acute respiratory distress syndrome (ARDS) after mild symptoms for 7–8 days had been observed [15], implying the early recognition of infected cases is extremely important and mild patients should also receive early treatment to avoid becoming critically ill [16]. Our data showed that the proportion of severe and critical cases has a continuous decrease as time went by, meaning the growth of severe and critical cases was in check in Wuhan. It should be noted that clinically diagnosed cases lived in suburbs had more critical disease compared with those lived in city centres. We speculated that was because health resources were relatively deficient in suburbs. For example, Dongxihu district, one of suburbs in Wuhan, had the highest incidence density of severe and critical clinically diagnosed cases. In regions with insufficient medical resources, clinical diagnosis is an important supplement to conventional diagnostic methods.

The case fatality rate of confirmed cases was considerably higher than that of clinically diagnosed patients (5.2% vs 1.5%, $P < 0.05$), of which the result consistent with the above severe rate. There has been no available wonder drug for COVID-19, so the fatality rate of severe patients is still remarkable. The outcomes of COVID-19 cases in our study were followed up to February 24, but the true ratio may not be known until the epidemic is over [17]. According to the National Health Commission of China, a total of 50333 cases were confirmed with COVID-19 in Wuhan and 3869 died as of 30 April 2020, the case fatality rate was 7.7%. It speculates that many patients died later. Approximately 9.4% of elderly patients with COVID-19 were dying in confirmed cases group. The elderly should be regarded as the key population for epidemic prevention and control. The immune function and organ reserve capacity of the elderly are receded, and most of the elderly suffer from serious coexisting illnesses [18]. Infectious diseases, especially acute infection will bring adverse prognosis and death risk to the elderly. The case fatality rate of males was higher than that of females, the same sex-based difference was observed in severe acute respiratory syndrome coronavirus (SARS) infection, it may be because X chromosome and estrogen protect females from lethal infection [19, 20]; besides, numerous evidences indicted ACE2, which used by SARS-CoV-2 to enter into the host cells [21, 22], generally has a higher expression in males than in females; moreover, females and males vary in their susceptibility and response to

viral infections, the number and activity of innate immune cells, and immune responses are higher in females than in males [23].

The transmission dynamics of COVID-19 are similar in confirmed and clinically diagnosed cases. R_t declined rapidly from the peak of 3.64 (and 3.54) for confirmed (and clinically diagnosed) cases after the lockdown of Wuhan city, and further decreased to below 1 after clinical diagnosis. It proves that rapid public health responses including the Wuhan lockdown and the implementation of clinical diagnosis, have successfully contained the spread of SARS-CoV-2 and mitigated the development of the epidemic.

Our study has several limitations. Firstly, there were a few missing values that might slightly affect the result. Secondly, patient's outcomes were followed up to February 24, when many patients had not been discharged, so the ultimate case fatality rate couldn't be calculated. Thirdly, data reliability of the interval between onset and diagnosis depended on the patients, which might have caused some recall bias. Finally, we once again reiterated that the results were based on the data of Wuhan which was the worst-hit region in China, so it should be prudent to extrapolate those data to areas with less epidemic.

In summary, the epidemic in Wuhan had been declining which should primarily be attributed to the swift and rigorous measures China took, especially the implementation of clinical diagnosis. The demographics of confirmed and clinically diagnosed cases were similar, and the geographical distributions of severity and fatality were complementary. In cases where medical resources are insufficient to cover the viral nucleic acid test of all COVID-19 cases, clinical diagnosis is effective and necessary. Clinical diagnosis is helpful to shorten the interval between onset and diagnosis, quarantine or treat patients as soon as possible, and improve the cure rate. To decrease the case fatality rate of COVID-19, it is necessary to carry out key monitoring, prevention and control of the elderly men, and strengthen early warning and intervention of severe and critical cases.

List Of Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: Corona Virus Disease 2019; RT-PCR: real-time reverse transcriptase–polymerase chain reaction; IQR: interquartile range; OR: odds ratio; R_t : effective reproduction number; SARS: severe acute respiratory syndrome coronavirus.

Declarations

Ethics approval and consent to participate

Data collection, which determined by the National Health Commission of the People's Republic of China, was exempt from institutional review board approval because it was part of an outbreak investigation. Study design and data analysis have been reviewed and approved by the Medical Ethical Committees of Wuhan University (WHU2020-2020YF0031).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the National Health Commission of the People's Republic of China, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the National Health Commission of the People's Republic of China.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CY supervised the study. CY, FS and HW designed the study. CY, FS, HW and JB collected and organized the data. FS, HW and RL analyzed the data. FS, FW, SM, XL, YY, QH and JC interpreted the results. FS wrote the first draft. All authors contributed to the final draft.

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Figures

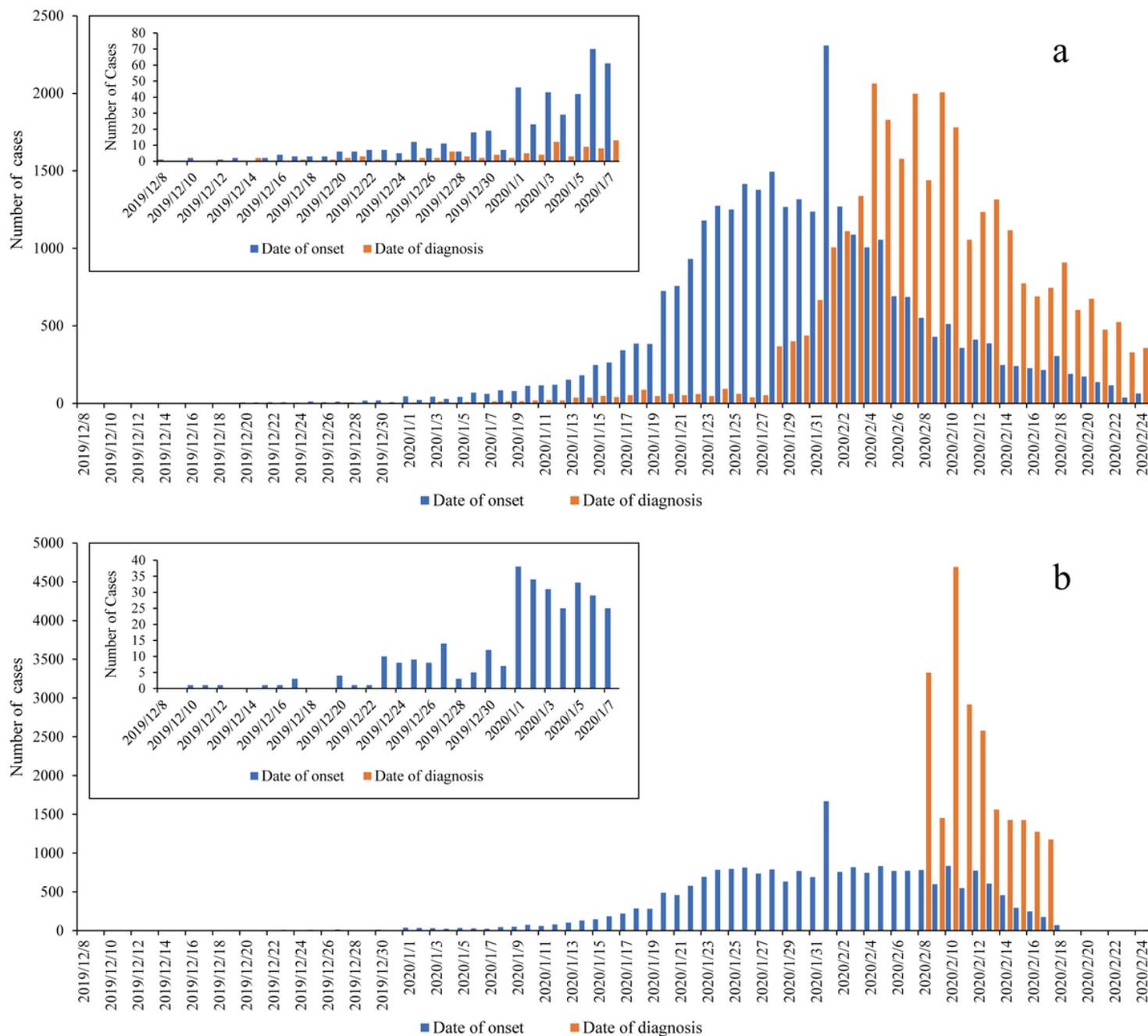


Figure 1

The epidemiological curves of (a) confirmed cases and (b) clinically diagnosed cases with COVID-19 in Wuhan from December 8, 2019, to February 24, 2020

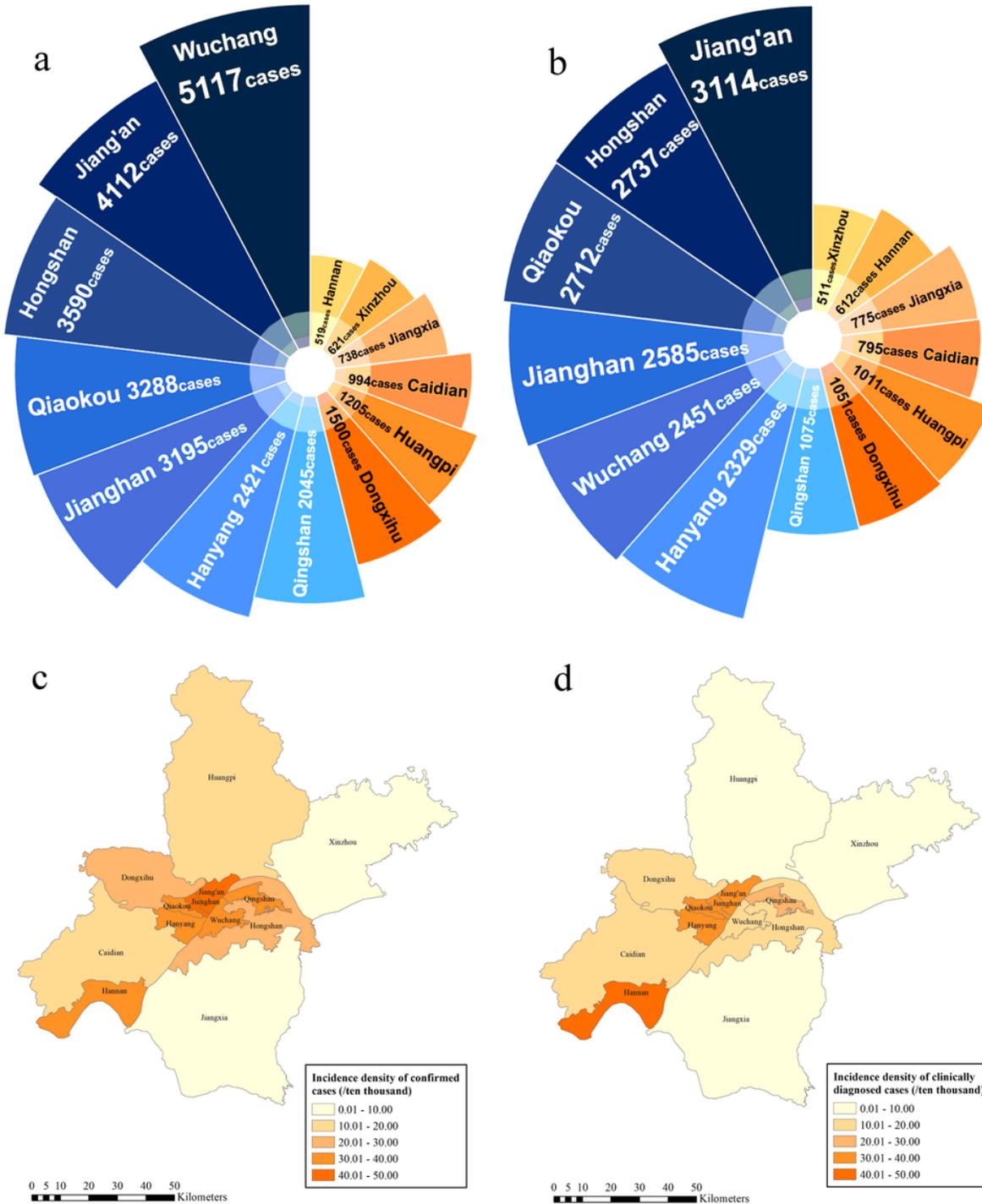


Figure 2

The cumulative numbers and incidence density of confirmed and clinically diagnosed cases with COVID-19 in 13 districts of Wuhan from December 8, 2019, to February 24, 2020. (a) rose diagram of cumulative confirmed cases, (b) rose diagram of cumulative clinically diagnosed cases. The 7 districts with blue series belong to the city centres, and the 6 districts with orange series belong to the suburbs in Wuhan. (c) map of incidence density of confirmed cases, (d) map of incidence density of clinically diagnosed cases. Note: The

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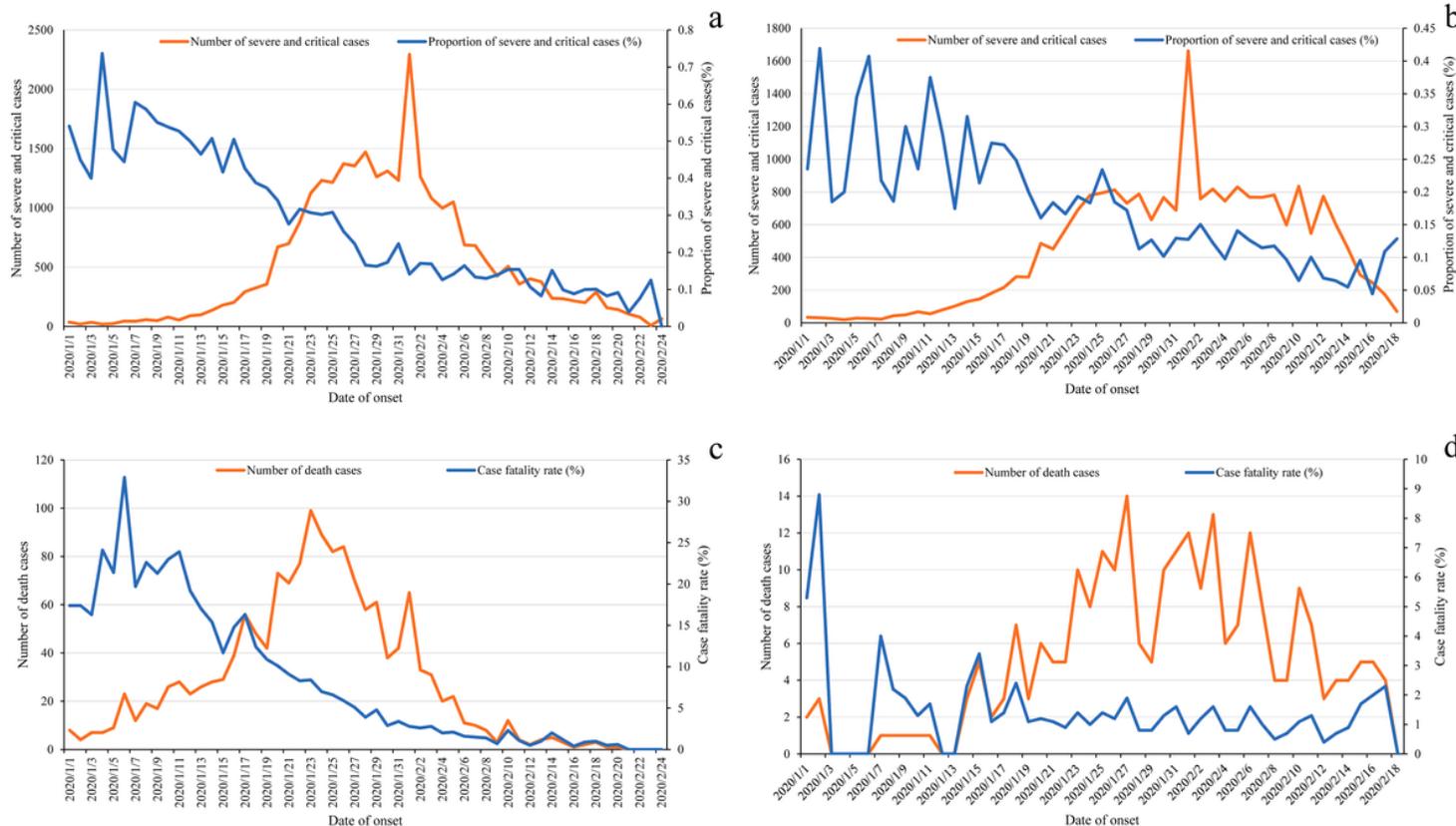
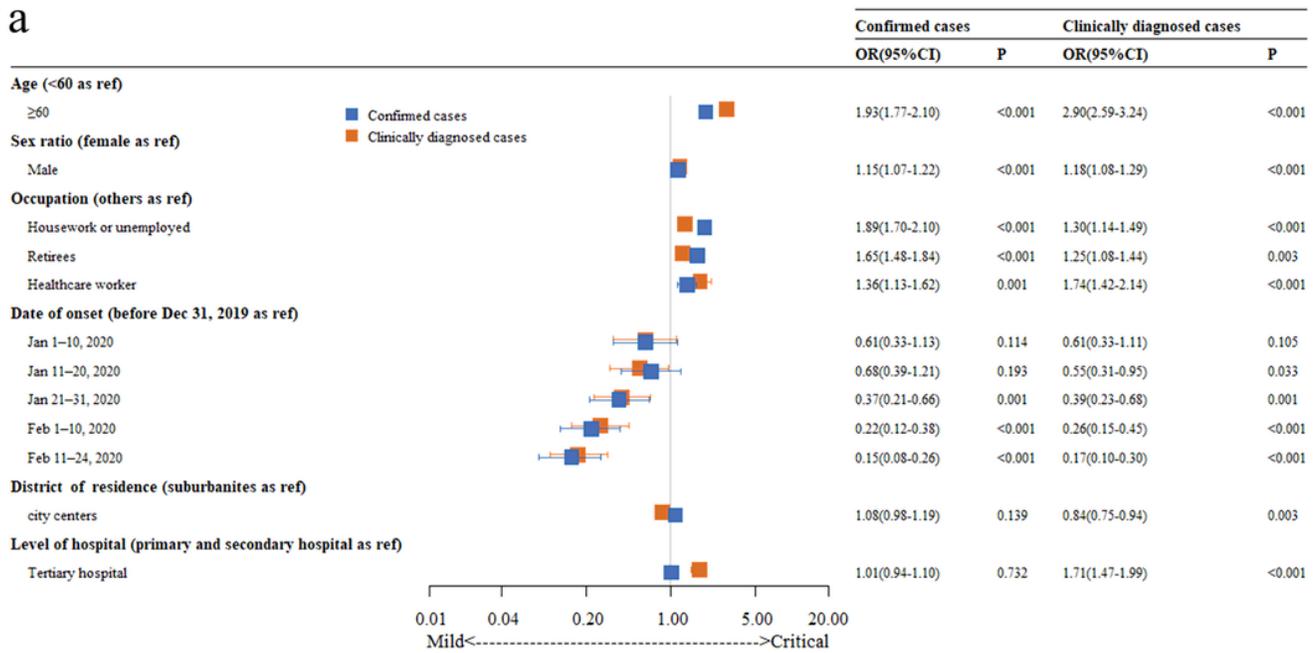


Figure 3

The time trend of proportion of severe and critical cases and case fatality rate with onset date. (a) Proportion of severe and critical cases in confirmed cases, (b) Proportion of severe and critical cases in clinically diagnosed cases, (c) case fatality rate of confirmed cases, (d) case fatality rate of clinically diagnosed cases.

a



b

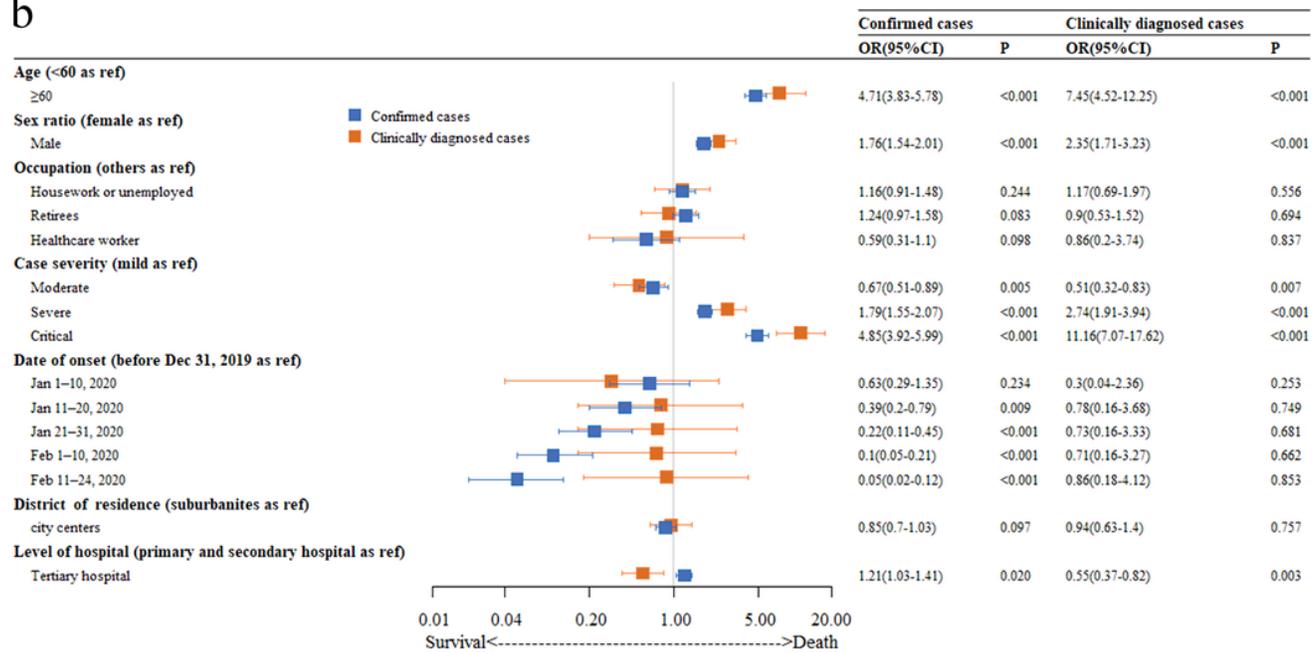


Figure 4

Risk factors of (a) severity and (b) death from multivariable logistic-regression analysis. The 95% confidence intervals of the odds ratios and p-value of logistic-regression analysis are shown.

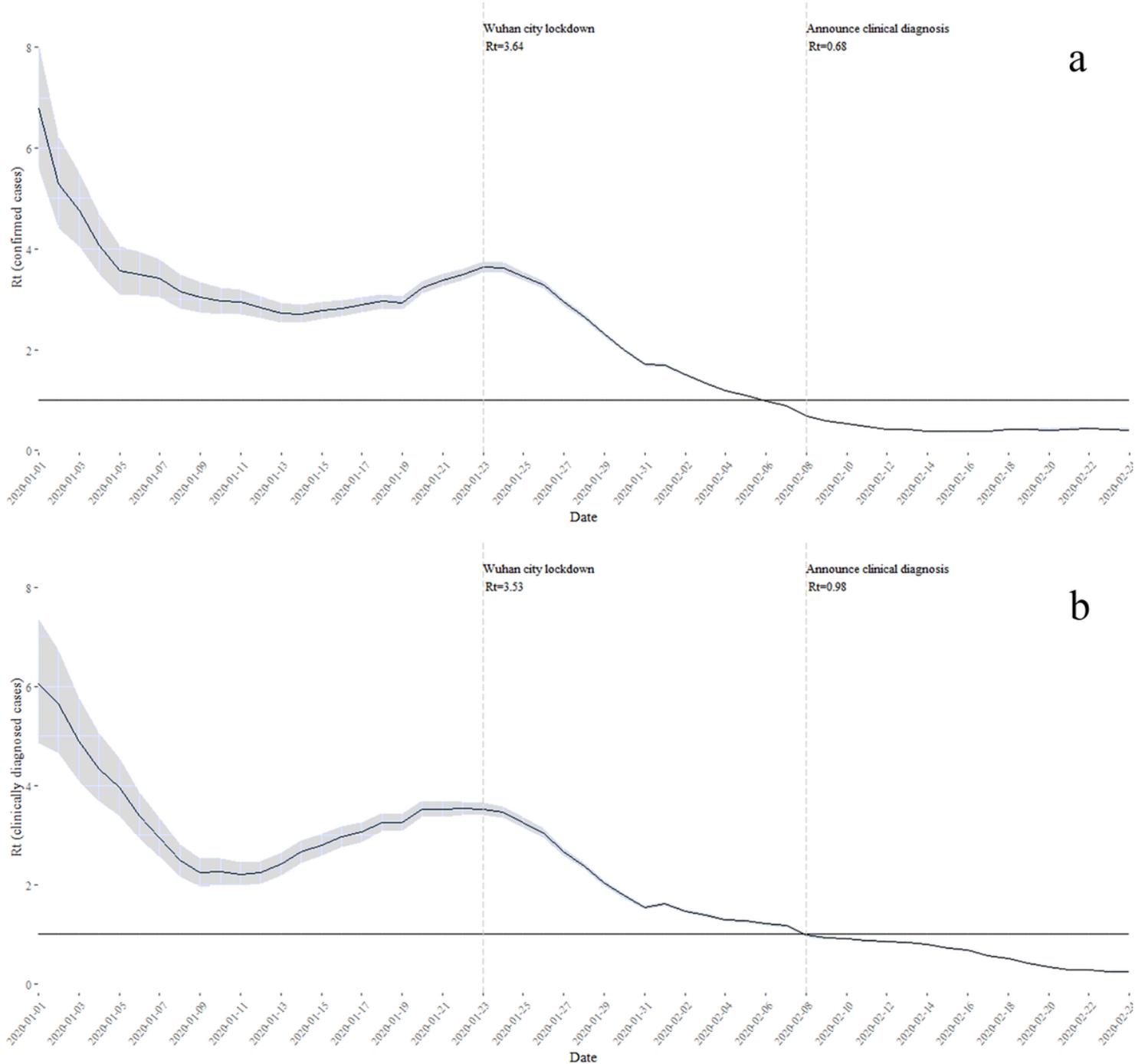


Figure 5

Estimated Rt of (a) confirmed cases and (b) clinically diagnosed cases with COVID-19 in Wuhan, China. The 95% confidence intervals are presented as blue shading. The black horizontal line indicates $R_t = 1$, below which suggests that the outbreak is gradually controlled.

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