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Epidemiological characteristics of patients with severe COVID-19 infection in Wuhan, China: evidence from a retrospective observational study

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Abstract

Background: The new coronavirus (COVID-19) rapidly resulted in a pandemic. We report the characteristics of patients with severe or critical severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Wuhan city, China, and the risk factors related to infection severity and death.

Methods: We extracted the demographic and clinical data of 7283 patients with severe COVID-19 infection from designated Wuhan hospitals as of 25 February 2020. Factors associated with COVID-19 critical illness and mortality were analysed using logistic- and Cox-regression analyses.

Results: We studied 6269 patients with severe COVID-19 illness and 1014 critically ill patients. The median (IQR) age was 64 (53–71) years; 51.2% were male, 38.9% were retirees and 7.4% had self-reported histories of chronic disease. Up to the end of the study, 1180 patients (16.2%) recovered and were discharged, 649 (8.9%) died and the remainder were still receiving treatment. The number of daily confirmed critical cases peaked between 23 January and 1 February 2020. Patients with advanced age [odds ratio (OR), 1.03; 95% confidence intervals (CIs), 1.03–1.04], male sex (OR, 1.57; 95% CI, 1.33–1.86) and pre-existing diabetes (OR, 2.11), hypertension (OR, 2.72), cardiovascular disease (OR, 2.15) or respiratory disease (OR, 3.50) were more likely to be critically ill. Compared with those who recovered and were discharged, patients who died were older [hazard ratio (HR), 1.04; 95% CI, 1.03–1.05], more likely to be male (HR, 1.74; 95% CI, 1.44–2.11) and more likely to have hypertension (HR, 5.58), cardiovascular disease (HR, 1.83) or diabetes (HR, 1.67).

Conclusion: Advanced age, male sex and a history of chronic disease were associated with COVID-19 critical illness and death. Identifying these risk factors could help in the clinical monitoring of susceptible populations.

Key words: COVID-19, pneumonia, clinical characteristics, severity, oxygen therapy, risk factors, Wuhan

Key Messages

- In 7283 patients with severe or critical COVID-19 infection, the ratio of severe to critical illness was 6.18. A total of 1180 patients (16.2%) recovered and were discharged, and 649 (8.9%) died.
- Advanced age, male sex and pre-existing chronic diseases were predictors for critical illness and death.
- Patients with underlying diseases and living in non-central areas in Wuhan had an increased risk of developing critical COVID-19 illness.
- The identification of risk factors for disease severity and death could be helpful in early clinical monitoring of disease progression in susceptible populations.

Introduction

In early December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which results in coronavirus disease 2019 (COVID-19),[1,2] emerged in Wuhan city, China and spread rapidly throughout China, then around the world, leading to a global pandemic. SARS-CoV-2 is the third coronavirus-induced human epidemic in the past 20 years[3–6] and one of the major pathogens that primarily targets the human respiratory system.[7–9] The World Health Organization has characterized the pandemic as an 'international public-health emergency' and defined the global risk level as very high.[10,11]

The outbreak, first reported in Wuhan, spread across the country in just a few months, with the number of infections and deaths rising rapidly. However, under the effective control of the government and the assistance of all sectors, the epidemic prevention and control situation across the country has been well developed. According to official reports, the number of newly diagnosed cases in Wuhan started to decrease on 19 February. By 30 April, China had reported a total of 84 385 confirmed cases; of these, 4643 patients died and 78 845 patients recovered.[12] China has gained valuable experience throughout the epidemic; meanwhile, the global situation is intensifying and still very serious. Therefore, it is necessary and important to analyse and share the available Chinese data and experience.

In the early stages of the epidemic, a great deal of research focused on epidemic curve modelling and prediction, as well as detection methods and virus characteristics.[13–16] Recently, some epidemiological studies on COVID-19 have been reported;[17,18] however, these studies focused mainly on the clinical and radiological characteristics or were simple studies based on public data.[19–23] There is a lack of large-sample studies of patients with severe or critical COVID-19 illness with an extremely high risk of death and details of the risk factors associated with severity have not yet been well described. In this study, we retrospectively analysed the clinical data of severely and critically ill COVID-19 patients in designated hospitals in Wuhan, with the aim of identifying risk factors for both the severity of COVID-19 infection and its related mortality, to provide a basis for research and prevention strategies.

Methods

Data sources

The data for this retrospective observational study were collected from the Chinese infectious-disease-reporting information system. According to national Chinese laws and regulations, as a class B infectious disease, all cases of COVID-19 must be immediately reported through the infectious-disease information system, by local hospitals or municipal Centers for Disease Control and Prevention (CDCs) and aggregated to the infectious-disease-reporting system. We systematically screened the case data of patients with COVID-19 from designated third-level medical hospitals in Wuhan (details are in the Supplementary material, eMethods and Supplementary Table 1, available as Supplementary data at *IJE* online).

Our team was among those who participated in obtaining the original uncleared data from the designated hospitals during the epidemic; cleaning, shortening and analysing the original data; sending the data to the CDC and the infectious-disease-reporting information system; and working with CDC staff in ensuring the quality of the data. We were given official approvals for monitoring the data of registered patients with severe and critical COVID-19 illness in Wuhan until 25 February 2020 (i.e. the final date of follow-up in this study). All identifiable personal information was deleted for privacy protection. After excluding duplicate cases, a total of 7283 patients were diagnosed as being severely or critically ill, forming the sample for this study. A flowchart of the study population is presented in Supplementary Figure 1, available as Supplementary data at *IJE* online. The study design and data analysis were approved by the Ethics Committee of the Medical Department of Wuhan University.

Case definitions

All the patients included in this study were diagnosed with severe or critical COVID-19 illness after laboratory confirmation, according to the diagnostic criteria of the new coronavirus infection pneumonia diagnosis and treatment plan (trial fifth version).[24] The diagnostic criteria were as follows:

- Severe illness: Patients with dyspnoea or a respiratory rate $\geq$30 breaths/min (in resting state, refers to oxygen saturation $\leq$93%) and/or arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) $\leq$300 mmHg (1 mmHg = 0.133 kPa).
- Critical illness: Patients who meet any of the following criteria: the occurrence of respiratory failure requiring mechanical ventilation, shock and/or other organ failures that require admission to the intensive care unit.

Variables

We collected hospital-admission data on patient demographics and self-reported history of chronic diseases. Clinical characteristics included the classification of severity (severe or critical illness); date of onset, divided into four periods based on the key time points of China Chunyun (Spring Festival travel season) (December 2019 to 9 January 2020), Wuhan city lockdown (10–22 January 2020), centralized quarantines (23 January to 1 February 2020) and treatment strategies (2–25 February 2020); symptoms from onset to hospital admission (e.g. fever, cough); and clinical oxygen-therapy methods. Time-related indicators included duration from the onset of symptoms to the first day of hospitalization, duration from the onset of symptoms to clinical confirmation and duration from the onset of symptoms to the endpoint (death, recovered and discharged, or end of study on 25 February 2020).

Statistical analysis

The Kolmogorov–Smirnov test was used to test the distribution of the patients' characteristics. Results of descriptive analyses are presented as medians and interquartile ranges (IQRs) for continuous variables and as counts and percentages in each category for categorical variables. The Kruskal–Wallis test was used to test the differences in normally and non-normally distributed continuous data and the chi-squared test was used to examine the difference in proportions of categorical variables between different groups. The geographical distributions of the newly confirmed COVID-19 cases throughout the four date-of-onset periods are presented using ArcGIS software version 10.6 (Environmental Systems Research Institute Inc). To explore the risk factors associated with severity of COVID-19 (critical illness) and the risk of mortality among severely and critically ill patients until 25 February 2020, univariate and multivariate logistic-regression and Cox proportional-hazards-regression models were used to estimate the odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariate model included age (continuous variable), sex (male or female), location (central Wuhan area or suburbs), occupation (retirees, medical workers or others), dichotomous self-reported co-morbidities (yes or no), number of presenting symptoms (continuous variable) and the three later date-of-onset periods in reference to the December 2019 to 9 January 2020 period. The interactions between occupation categories with the presence of any co-morbidities towards the risk of developing critical COVID-19 illness and death were also investigated by adding cross-product terms of these variables to the regression models. All analyses were performed using SPSS, version 22.0 (SPSS Inc).

Results

Characteristics of patients with severe or critical COVID-19 illness

Table 1 shows the general characteristics of the study population. Of the 7283 patients with COVID-19, 86.1%

Table 1. Baseline characteristics of severe or critically ill COVID-19 patients in Wuhan, China

Characteristics[a]		Total ($n = 7283$)	Classification of severity		P
			Severe illness ($n = 6269$)	Critical illness ($n = 1014$)	
Age, years	Median (IQR)	64 (53–71)	63 (52–70)	67 (57–75)	<0.0001
Age groups, years	<40	715 (9.8)	668 (10.7)	47 (4.6)	<0.0001
	40–59	2098 (28.8)	1863 (29.7)	235 (23.2)	
	60–79	3803 (52.2)	3228 (51.5)	575 (56.7)	
	≥80	665 (9.1)	509 (8.1)	156 (15.4)	
Sex	Male	3732 (51.2)	3101 (49.5)	631 (62.2)	<0.0001
	Female	3551 (48.8)	3168 (50.5)	383 (37.8)	
Source	From outpatient and emergency direct admission	2828 (38.8)	2439 (38.9)	389 (38.4)	<0.0001
	From community/isolation point admission	1109 (15.2)	1031 (16.4)	78 (7.7)	
	Transferred from another hospital	2445 (33.6)	2033 (32.4)	412 (40.6)	
	Transferred from an unknown route	728 (10)	624 (10)	104 (10.3)	
	Missing	173 (2.4)	142 (2.3)	31 (3.1)	
Location	Central area in Wuhan	5552 (76.2)	4816 (76.8)	736 (72.6)	<0.0001
	Suburban area in Wuhan	836 (11.5)	685 (10.9)	151 (14.9)	
	Out of city	80 (1.1)	58 (0.9)	22 (2.2)	
	Missing	815 (11.2)	710 (11.3)	105 (10.4)	
Occupations	Children and students	11 (0.2)	9 (0.1)	2 (0.2)	0.0003
	Cadres	269 (3.7)	246 (3.9)	23 (2.3)	
	Individuals and freelancers	26 (0.4)	25 (0.4)	1 (0.1)	
	Labourers	92 (1.3)	84 (1.3)	8 (0.8)	
	Public servants	299 (4.1)	266 (4.2)	33 (3.3)	
	Houseworkers and unemployed	1231 (16.9)	1046 (16.7)	185 (18.2)	
	Retirees	2830 (38.9)	2387 (38.1)	443 (43.7)	
	Farmers and migrant workers	128 (1.8)	103 (1.6)	25 (2.5)	
	Medical workers	163 (2.2)	146 (2.3)	17 (1.7)	
	Missing	2234 (30.7)	1957 (31.2)	277 (27.3)	
Co-morbidities	Diabetes	126 (1.7)	69 (1.1)	57 (5.6)	<0.0001
	Hypertension	300 (4.1)	172 (2.7)	128 (12.6)	<0.0001
	Cardiovascular disease	161 (2.2)	87 (1.4)	74 (7.3)	<0.0001
	Respiratory disease	50 (0.7)	23 (0.4)	27 (2.7)	<0.0001
	Any	538 (7.4)	315 (5)	223 (22)	<0.0001
Date of onset	Dec 2019–9 Jan 2020	156 (2.1)	118 (1.9)	38 (3.7)	<0.0001
	10–22 Jan 2020	1417 (19.5)	1169 (18.6)	248 (24.5)	
	23 Jan–1 Feb 2020	3560 (48.9)	3111 (49.6)	449 (44.3)	
	2–25 Feb 2020	2113 (29)	1847 (29.5)	266 (26.2)	
	Missing	37 (0.5)	24 (0.4)	13 (1.3)	
Symptoms at admission	Fever	5466 (75.1)	4672 (74.5)	794 (78.3)	0.0099
	Diarrhoea	663 (9.1)	579 (9.2)	84 (8.3)	0.3283
	Fatigue	1616 (22.2)	1343 (21.4)	273 (26.9)	0.0001
	Cough	3721 (51.1)	3193 (50.9)	528 (52.1)	0.5013
	Chest stuffiness	1323 (18.2)	1118 (17.8)	205 (20.2)	0.0678
	Nasal obstruction	68 (0.9)	59 (0.9)	9 (0.9)	0.8693
	Runny nose	79 (1.1)	64 (1)	15 (1.5)	0.1911
	Dyspnoea	1077 (14.8)	852 (13.6)	225 (22.2)	<0.0001
Number of symptoms at admission	0	105 (1.4)	81 (1.3)	24 (2.4)	<0.0001
	1	2810 (38.6)	2529 (40.3)	281 (27.7)	
	2	2300 (31.6)	1946 (31)	354 (34.9)	
	3	1331 (18.3)	1103 (17.6)	228 (22.5)	
	4	493 (6.8)	405 (6.5)	88 (8.7)	
	≥5	244 (3.4)	205 (3.3)	39 (3.8)	

(Continued)

Table 1. Continued

Characteristics[a]		Total ($n = 7283$)	Classification of severity		*P*
			Severe illness ($n = 6269$)	Critical illness ($n = 1014$)	
Initial oxygen therapy	Untreated	1172 (16.1)	1102 (17.6)	70 (6.9)	<0.0001
	Nasal catheter	4743 (65.1)	4360 (69.5)	383 (37.8)	
	Mask oxygen inhalation	293 (4)	178 (2.8)	115 (11.3)	
	High-flow oxygen therapy	680 (9.3)	459 (7.3)	221 (21.8)	
	Non-invasive ventilation	188 (2.6)	29 (0.5)	159 (15.7)	
	Invasive ventilation	58 (0.8)	2 (0.03)	56 (5.5)	
	Without record	149 (2)	139 (2.2)	10 (0.99)	
Highest oxygen therapy	Untreated	632 (8.7)	616 (9.8)	16 (1.6)	<0.0001
	Nasal catheter	3599 (49.4)	3455 (55.1)	144 (14.2)	
	Mask oxygen inhalation	420 (5.8)	340 (5.4)	80 (7.9)	
	High-flow oxygen therapy	853 (11.7)	677 (10.8)	176 (17.4)	
	Non-invasive ventilation	467 (6.4)	202 (3.2)	265 (26.1)	
	Invasive ventilation	283 (3.9)	66 (1.1)	217 (21.4)	
	Without record	1029 (14.1)	913 (14.6)	116 (11.4)	
Final oxygen therapy	Untreated	720 (9.9)	698 (11.1)	22 (2.2)	<0.0001
	Nasal catheter	1099 (15.1)	1046 (16.7)	53 (5.2)	
	Mask oxygen inhalation	113 (1.6)	85 (1.4)	28 (2.8)	
	High-flow oxygen therapy	229 (3.1)	132 (2.1)	97 (9.6)	
	Non-invasive ventilation	265 (3.6)	102 (1.6)	163 (16.1)	
	Invasive ventilation	208 (2.9)	44 (0.7)	164 (16.2)	
	Without record	4649 (63.8)	4162 (66.4)	487 (48)	
Clinical outcome	Recovered	1180 (16.2)	1150 (18.3)	30 (3.0)	<0.0001
	Continuing treatment	5088 (69.9)	4581 (73.1)	507 (50.0)	
	Transferred[b]	366 (5)	303 (4.8)	63 (6.2)	
	Death	649 (8.9)	235 (3.7)	414 (40.8)	
Duration from	Symptom onset to clinical confirmation, median (IQR)	11 (7–15.3)	11 (7–16)	10 (7–15)	0.0993
	Symptom onset to endpoint, median (IQR)	21 (16–27)	22 (17–27)	19 (14–25)	<0.0001
	Clinical confirmation to endpoint, median (IQR)	10 (6–14)	11 (7–15)	7 (4–12)	<0.0001
	Symptom onset to first hospitalization, median (IQR)	10 (5–14)	10 (6–14)	8 (4–13)	<0.0001

COVID-19, coronavirus disease 2019; IQR, interquartile range.

[a]Figures are numbers (percentages) unless otherwise specified.

[b]Transferred: by the final follow-up date, patients were transferred to other medical departments or hospitals.

were diagnosed with severe illness and 13.9% with critical illness. The median age was 64 years and 51.2% were men. Among all patients, 76.2% lived in the central area in Wuhan, 38.90% were retirees and 2.2% were medical workers. There were 7.4% of patients who self-reported histories of chronic medical disease: 4.1% had pre-existing hypertension and 2.2% had cardiovascular disease. The prevalence of these chronic diseases was higher among critically ill patients than among severely ill patients. When comparing the presenting symptoms at hospital admission, critically ill patients were more likely to have fever and dyspnoea than severely ill patients.

Time and geographic characteristics

As shown in Figure 1, the incidence of severe and critical COVID-19 illness peaked between 23 January and 1 February 2020, with nearly 50% of all cases being confirmed in this period. Severe cases accounted for a higher proportion than critically ill cases at this stage; later on, the number of confirmed severe cases decreased. The median duration from onset of symptoms to the endpoint was 22 days in severely ill patients and 19 days in critically ill patients (Table 1).

The outbreak began in the central area in Wuhan and gradually spread to suburban and rural areas across the four time periods, with the same trend seen for severely and critically ill patients (Figure 2). The geographical difference of confirmed cases was quite large, with the highest incidence in the central districts.

Treatment by oxygen therapy

Table 1 shows that 81.9% of patients received initial oxygen therapy, mainly via a nasal catheter (65.1%). The prevalence of initial oxygen therapy by any method was higher in

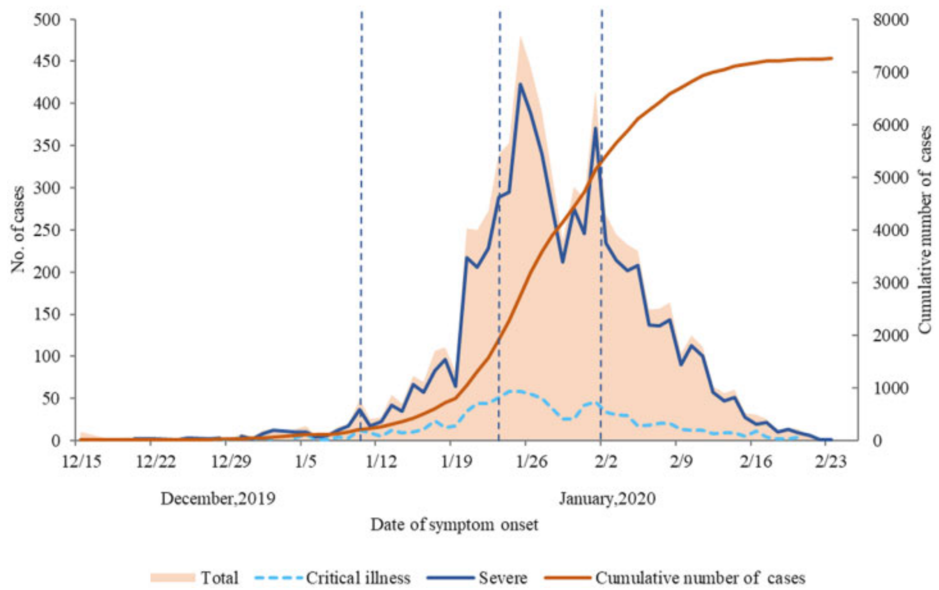

Figure 1. Daily and cumulative numbers of severe-diagnosed COVID-19 cases by symptom-onset date.

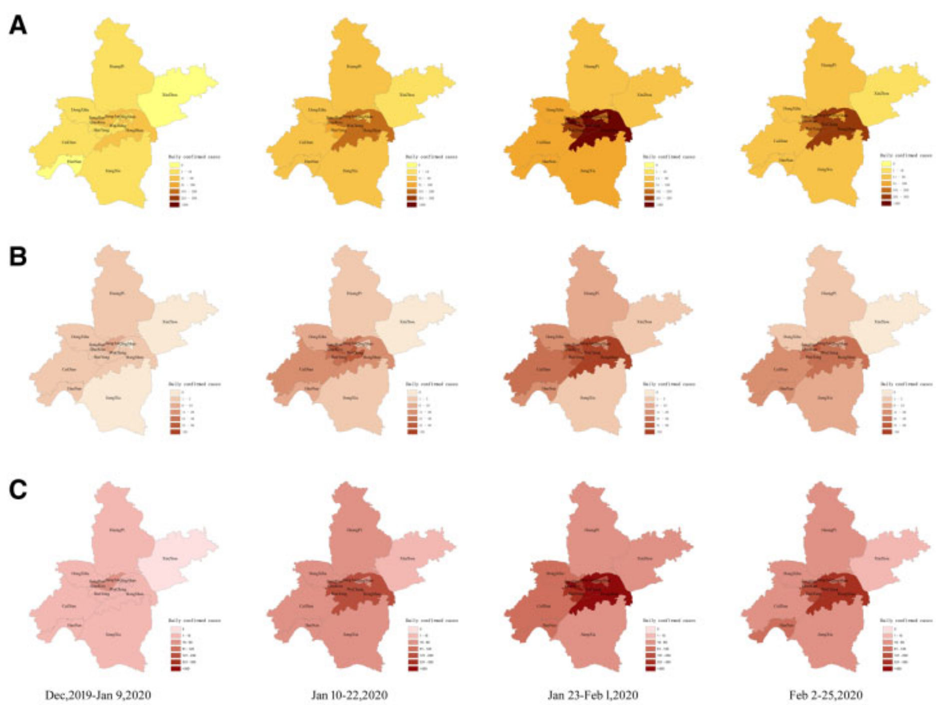

Figure 2. The geographic distribution of daily rates of COVID-19 cases (A: severe, B: critical illness, C: total) across the four periods in Wuhan, China.

critically ill patients than in severely ill patients, except for nasal-catheter inhalation. During treatment, the most commonly used forms of oxygen therapy for patients were nasal-catheter oxygen therapy and high-flow oxygen therapy.

Clinical outcomes

Until the end of the study on 25 February 2020, of the 7283 severely and critically ill COVID-19 patients, 8.9% of the patients died, 16.2% recovered and were discharged, 5% were transferred to other medical departments or hospitals and the remaining 69.9% were continuing to receive treatment. The distribution of these clinical outcomes varied according to the patients' characteristics (Supplementary Table 2, available as Supplementary data at *IJE* online).

Risk factors for the severity of COVID-19 infection

In Table 2, older age, male sex and having pre-existing chronic disease were associated with more severe infection

Table 2. Logistic-regression analysis of risk factors associated with severity of COVID-19 infection (critical illness) in 7283 patients with COVID-19 in Wuhan

Variables	Number (%) of critical illness cases	Univariable logistic regression[a]		Multivariable logistic regression[b]	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years	1014 (13.9)	1.02 (1.02,1.03)	<0.0001	1.03 (1.03,1.04)	<0.0001
Sex					
Female	631 (16.9)	1 (ref)		1 (ref)	
Male	383 (10.8)	1.68 (1.47,1.93)	<0.0001	1.57 (1.33,1.86)	<0.0001
Location					
Central area in Wuhan	736 (13.3)	1 (ref)		1 (ref)	
Other areas[c]	173 (18.9)	1.52 (1.27,1.83)	<0.0001	1.62 (1.30,2.04)	<0.0001
Occupation					
Medical workers	17 (10.4)	0.75 (0.45,1.23)	0.271	1.25 (0.73,2.13)	0.423
Retirees	443 (15.7)	1.19 (1.01,1.40)	0.034	0.82 (0.68,1.00)	0.045
Others	277 (13.5)	1 (ref)		1 (ref)	
Diabetes					
Yes	57 (45.2)	5.35 (3.74,7.65)	<0.0001	2.11 (1.32,3.38)	0.002
No	957 (13.4)	1 (ref)		1 (ref)	
Hypertension					
Yes	128 (42.7)	5.12 (4.03,6.51)	<0.0001	2.72 (1.97,3.76)	<0.0001
No	886 (12.7)	1 (ref)		1 (ref)	
Cardiovascular disease					
Yes	74 (46.0)	5.59 (4.07,7.68)	<0.0001	2.15 (1.38,3.33)	0.001
No	940 (13.2)	1 (ref)		1 (ref)	
Respiratory disease					
Yes	27 (54.0)	7.43 (4.24,13.01)	<0.0001	3.50 (1.67,7.34)	0.001
No	987 (13.6)	1 (ref)		1 (ref)	
Number of symptoms at admission	1014 (13.9)	1.19 (1.12,1.26)	<0.0001	1.19 (1.11,1.28)	<0.0001
Date of onset*					
Dec 2019–9 Jan 2020	38 (24.4)	1 (ref)		1 (ref)	
10–22 Jan 2020	248 (17.5)	0.66 (0.45,0.97)	<0.0001	0.59 (0.34,1.00)	0.051
23 Jan–1 Feb 2020	449 (12.6)	0.45 (0.31,0.66)	<0.0001	0.40 (0.24,0.68)	0.001
2–25 Feb 2020	266 (13.8)	0.45 (0.30,0.66)	<0.0001	0.39 (0.23,0.66)	<0.0001

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval.

*P trend = 0.00003 < 0.001.

[a]The model included one variable at a time.

[b]The model included all variables in the table.

[c]Other areas: suburban area in Wuhan and out of city.

(critical COVID-19 illness); the multivariate ORs (95% CIs) were 1.03 (1.03–1.04) for 1-year increment of age and 1.57 (1.33–1.86) in male patients. The likelihood of developing critical illness increased with an increasing number of presenting symptoms of COVID-19 infection at hospital admission (OR, 1.19 per one-symptom increment). The risk of critical illness tended to decrease across the four time periods; thus, patients with symptomatic onset in the early stage of the epidemic were more likely to develop critical illness. In terms of occupation, retirees showed a higher risk in the univariate model (OR, 1.19; 95% CI, 1.01–1.40); however, after multivariate adjustment for demographic and clinical data, the OR was of an inverse trend (OR, 0.82; 95% CI, 0.68–1.00). Supplementary Table 3, available as Supplementary data at *IJE* online, shows that there was no interaction between pre-existing chronic disease and retirement towards the risk of developing critical COVID-19 illness.

Risk factors for COVID-19 death

Older age, male sex and pre-existing hypertension, cardiovascular disease and diabetes were associated with increased risk of mortality in COVID-19 patients; the multivariate HRs (95% CIs) were 1.04 (1.03–1.05), 1.74 (1.44–2.11), 5.58 (4.30–7.26), 1.83 (1.33–2.51) and 1.67 (1.22–2.30), respectively (Table 3). As a large proportion of patients were still receiving treatment, with no definite outcome of being discharged alive or death by the end of our study on 25 February 2020, in a sensitivity analysis,

Table 3. Cox-regression analysis of risk factors associated with death in 7283 patients with COVID-19 in Wuhan until 25 February 2020

Variables	Number (%) of deaths	Univariate[a]		Multivariate[b]	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age	649 (8.9)	1.05 (1.04,1.06)	<0.0001	1.04 (1.03,1.05)	<0.0001
Sex					
Female	435 (11.7)	1 (ref)		1 (ref)	
Male	214 (6.0)	1.98 (1.68,2.33)	<0.0001	1.74 (1.44,2.11)	<0.0001
Location					
Central area in Wuhan	503 (9.1)	1 (ref)		1 (ref)	
Other areas[c]	104 (11.3)	1.25 (1.01,1.55)	0.040	1.23 (0.96,1.58)	0.108
Occupation					
Medical workers	6 (3.7)	0.40 (0.18,0.91)	0.028	0.89 (0.39,2.00)	0.760
Retirees	311 (11.0)	1.27 (1.05,1.53)	0.011	0.82 (0.67,0.99)	0.041
Others	177 (8.6)	1 (ref)		1 (ref)	
Diabetes					
Yes	73 (57.9)	9.60 (7.50,12.27)	<0.0001	1.67 (1.22,2.30)	0.002
No	576 (8.0)	1 (ref)		1 (ref)	
Hypertension					
Yes	174 (58.0)	11.86 (9.40,14.14)	<0.0001	5.58 (4.30,7.26)	<0.0001
No	475 (6.8)	1 (ref)		1 (ref)	
Cardiovascular disease					
Yes	96 (59.6)	10.42 (8.36,12.98)	<0.0001	1.83 (1.33,2.51)	<0.0001
No	553 (7.8)	1 (ref)		1 (ref)	
Respiratory disease					
Yes	32 (64.0)	9.40 (6.59,13.42)	<0.0001	1.32 (0.83,2.07)	0.238
No	617 (8.5)	1 (ref)		1 (ref)	
Number of symptoms at admission	649 (8.9)	649 (35.5)	<0.0001	1.07 (0.99,1.16)	0.090
Date of onset					
Dec 2019–9 Jan 2020	24 (15.4)	1 (ref)		1 (ref)	
10–22 Jan 2020	174 (12.3)	1.46 (0.89,2.39)	0.134	1.40 (0.73,2.68)	0.314
23 Jan–1 Feb 2020	326 (9.2)	1.52 (0.92,2.50)	0.099	1.73 (0.90,3.33)	0.098
2–25 Feb 2020	117 (5.5)	1.77 (1.05,2.98)	0.033	1.93 (0.98,3.81)	0.058

COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval.
[a]The model included one variable at a time.
[b]The model included all variables in the table.
[c]Other areas: suburban area in Wuhan and out of city.

we restricted the Cox-regression analysis of COVID-19 death to those with a definite outcome by the study end. Accordingly, we analysed the risk of death in 1829 patients (1180 recovered and discharged and 649 deaths, excluding patients still under treatment or transferred to other facilities with no knowledge of their survival or death status). Similar results were obtained in this sensitivity analysis (Supplementary Table 4, available as Supplementary data at *IJE* online). There were no associations between occupation and risk of death after adjustment for socio-demographic and clinical factors. There was an interaction between pre-existing chronic disease and retirement towards the risk of death in COVID-19 patients (OR, 0.72; 95% CI, 0.55–0.94).

Discussion

We report on 7283 severely and critically ill patients with confirmed SARS-CoV-2 infection during the epidemic in Wuhan, China. Critical illness accounted for 13.9% of the cases. Death occurred in 8.9% of patients, of whom 63.8% were critically ill at the time of hospital admission. Older age, male sex and having pre-existing chronic disease were associated with the incidence of critical illness and a higher risk of death. The number of initial symptoms was a risk factor for those presenting with critical illness and those who died.

Advanced age has been previously reported as an independent predictor of mortality in SARS, MERS and COVID-19.[25–27] Some epidemiological observations have shown that all age groups were susceptible to COVID-19 infection and that older men with chronic diseases were more severely affected.[28,29] Among the confirmed severely and critically ill patients in our study, the prevalence of chronic diseases in men (8.68%) was higher than that in women (6.03%). The proportion of critical illness and the risk of death were higher in men than in women, which is consistent with the findings of previous studies from China suggesting a higher death rate among men compared with women.[30,31] The exact mechanism for the augmented risk profile in men compared with women is still unclear; however, studies have suggested that the higher level of angiotensin-converting enzyme-2 (ACE2) in men might interact with viruses, rendering them more capable of infecting healthy cells.[32] In addition, men generally have more risky behaviours than women, such as their higher smoking rate, which makes them vulnerable to the risk of mortality. Our univariate analyses showed that the retired population tended to have a higher risk of developing critical illness and a high risk of mortality that vanished after adjusting for socio-demographic and clinical factors. The higher risk of more severe illness and mortality among retirees was more likely attributed to factors such as their advanced age and pre-existing chronic diseases. Controlling for such factors turned the association and interaction to null in retirees.

In our study, 44% of the patients who died reported a history of at least one pre-existing chronic disease (hypertension, cardiovascular diseases or diabetes). Those co-morbidities were associated with critical illness and a higher risk of mortality in COVID-19 patients. SARS-CoV-2 is an enveloped RNA virus; it can enter the cell through the ACE2. Studies have shown that the overexpression of ACE2 in highly differentiated airway epithelial cells is the basis of SARS-CoV susceptibility. ACE2 plays an important role in normal physiological activities, to control blood pressure and cardiovascular risk. When hypertensive patients are infected by the novel coronavirus, the blood-pressure-regulation process becomes more complicated and difficult to control, and the risk of cardiovascular, renal and other systemic adverse events in COVID-19 patients will be higher.[27,33,34] Our study confirmed that not only in general COVID-19 patients, but also in severely and critically ill patients, the role of pre-existing hypertension and cardiovascular disease remains important in regard to death after COVID-19 infection. Patients with diabetes are more likely to have serious complications from the new coronavirus because their high blood-glucose level promotes viral growth, impairs the patient's immune function and their ability to resist infection, and paves the way for secondary bacterial and viral co-infections. In addition, in the event of diabetes complications, the risk of multiple organ failure and death is greatly increased. One study indicated that mortality and multi-organ damage were significantly higher in COVID-19 patients with type 2 diabetes than in non-diabetic patients (HR, 1.5).[35] Knowledge of these risk factors can guide clinicians to conduct appropriate medical management of patients with COVID-19 and co-morbid cardiovascular disease, and indicate the group of patients in whom the progression of symptoms should be vigorously monitored and controlled.[36]

Moreover, our research has also found that the proportion of critically ill patients was higher among those living in suburban areas than among those living in the central areas of Wuhan, and the risk of critical pneumonia infection among residents in suburban areas was also higher than that in central areas. We consider this phenomenon to be related to the distribution of medical resources. More medical resources were concentrated in the central area of Wuhan, whereas accessibility to and the availability of medical services for residents in the suburbs were lower.

Over the four periods of the epidemic, the risk of developing critical infection tended to decline. The incidence of severe or critical illness peaked between 23 January and 1 February 2020, followed by a decline. This was largely attributed to the timely initiatives of the Chinese government and the Wuhan authorities.[29] For example, Wuhan had been closed since 23 January. On 11 February, all the residential communities in Wuhan were closed and managed, and the scope was extended to Hubei Province on 16 February. From 24 January, Hubei Province launched a Level 1 emergency response to a public-health emergency. Thanks to the improved diagnostic techniques, increased national attention and hospital treatment capacity over time, patients in the later stages of the epidemic were diagnosed and treated earlier. Under the leadership of the national organization, since 24 January, medical teams have been set up in provinces across the country to go to Wuhan and >35 000 medical staff supported Wuhan, which greatly relieved the pressure of medical care in Wuhan. All these initiatives contributed to the reduced risk of developing critical COVID-19 illness over time.

This study has several limitations. The observational-study design precludes causal inference. However, under such public-health emergencies, there is really no way to carry out a more comprehensive study. Moreover, the follow-up time was relatively short and, by the end of the study period, the clinical outcome of more than half of the study's patients was not yet clear. The data on pre-existing chronic diseases were based on self-report and we could not verify their validity. Also, there was a lack and incompleteness of information on other epidemiological variables, such as body mass index and history of cancer and dyslipidaemia, and clinical characteristics. However, access to such information about a nationwide epidemic is strictly regulated by higher authorities. Currently, we are seeking official approvals to obtain updated and more comprehensive data for further research.

In summary, rigorous and timely epidemiological measures are essential to help control the rapid spread of COVID-19 infection. This study sheds light on the risk factors for both the severity of COVID-19 and its related mortality, suggesting that age, sex and pre-existing chronic diseases are independent predictors of more severe disease (critical illness) and a higher risk of death. Patients with underlying diseases living in non-central areas of Wuhan, where limited resources were available, had an increased risk of developing critical COVID-19 illness. The identification of risk factors for COVID-19 severity and mortality in this study could be helpful for early clinical monitoring of disease progression in susceptible populations.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

F.W., J.C., J.B., Z.Z. and C.Y. collected the data. F.W., J.C., Y.Y. and C.Y. performed statistical analyses and F.W. drafted the manuscript. F.W., J.C., J.D., E.S.E., K.L., S.M., F.S., H.W. and C.Y. revised the final manuscript. C.Y. acts as the guarantor for the paper. All authors have read and agree to publish the final manuscript.

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Conflict of interest

None declared.

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