ORIGINAL ARTICLE
INFECTIOUS DISEASE

Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicentre) and outside Hubei (non-epicentre): a nationwide analysis of China

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This study highlights the necessity of urgent and vigorous support of healthcare resources and increased public awareness during the early stages of an outbreak of COVID-19 or similar diseases https://bit.ly/39OWFf0

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ABSTRACT

Background: During the outbreak of coronavirus disease 2019 (COVID-19), consistent and considerable differences in disease severity and mortality rate of patients treated in Hubei province compared to those in other parts of China have been observed. We sought to compare the clinical characteristics and outcomes of patients being treated inside and outside Hubei province, and explore the factors underlying these differences.

Methods: Collaborating with the National Health Commission, we established a retrospective cohort to study hospitalised COVID-19 cases in China. Clinical characteristics, the rate of severe events and deaths, and the time to critical illness (invasive ventilation or intensive care unit admission or death) were compared between patients within and outside Hubei. The impact of Wuhan-related exposure (a presumed key factor that drove the severe situation in Hubei, as Wuhan is the epicentre as well the administrative centre of Hubei province) and the duration between symptom onset and admission on prognosis were also determined.

Results: At the data cut-off (31 January 2020), 1590 cases from 575 hospitals in 31 provincial administrative regions were collected (core cohort). The overall rate of severe cases and mortality was 16.0% and 3.2%, respectively. Patients in Hubei (predominantly with Wuhan-related exposure, 597 (92.3%) out of 647) were older (mean age 49.7 *versus* 44.9 years), had more cases with comorbidity (32.9% *versus* 19.7%), higher symptomatic burden, abnormal radiologic manifestations and, especially, a longer waiting time between symptom onset and admission (5.7 *versus* 4.5 days) compared with patients outside Hubei. Patients in Hubei (severe event rate 23.0% *versus* 11.1%, death rate 7.3% *versus* 0.3%, HR (95% CI) for critical illness 1.59 (1.05–2.41)) have a poorer prognosis compared with patients outside Hubei after adjusting for age and comorbidity. However, among patients outside Hubei, the duration from symptom onset to hospitalisation (mean 4.4 *versus* 4.7 days) and prognosis (HR (95%) 0.84 (0.40–1.80)) were similar between patients with or without Wuhan-related exposure. In the overall population, the waiting time, but neither treated in Hubei nor Wuhan-related exposure, remained an independent prognostic factor (HR (95%) 1.05 (1.01–1.08)).

Conclusion: There were more severe cases and poorer outcomes for COVID-19 patients treated in Hubei, which might be attributed to the prolonged duration of symptom onset to hospitalisation in the epicentre. Future studies to determine the reason for delaying hospitalisation are warranted.

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Introduction

A rapid outbreak of coronavirus disease 2019 (COVID-19) that arose from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and originating in Wuhan city, Hubei province, China, and has become a global threat [1, 2]. COVID-19 can result in severe illnesses such as acute respiratory distress syndrome, multiorgan dysfunction syndrome and resultant death [1–3]. The World Health Organization declared SARS-CoV-2 a public health emergency of international concern on 30 January 2020. As of 16 February 2020, 58 873 laboratory confirmed cases and 1699 deaths have been documented globally [4].

Considerable differences in disease severity and patient mortality have been documented in Hubei province compared with other parts of China [5]. Most primarily infected patients have been identified and treated in Hubei province, and predominantly have close exposure to Wuhan. This is because Wuhan, the epicentre of COVID-19, is the administrative centre of Hubei province and the majority of the population displaced from Wuhan have temporarily relocated to other areas of Hubei. But contrary to the initial wave of cases, an increasing number of patients have been diagnosed outside Wuhan and/or Hubei province, many of whom did not have close contact with people from Wuhan. These patients were more likely to have been infected by secondary or tertiary transmission of SARS-CoV-2. Other investigators have assumed that the high percentage of patients with Wuhan-related exposure (indicating potentially higher virulence) drove the severe situation in Hubei [6].

Exploring the difference between patients within and outside the highly endemic area, as well as by primary and progeny virus, may help clinicians better appreciate the evolution of SARS-CoV-2, and lead to more efficient allocation of healthcare resources. In addition, the exploration of the driving forces underlying these observations such as virus virulence and temporary shortage of health resources may help inform clinical practice and disease prevention. In this nationwide study, we sought to compare the clinical characteristics and outcomes of patients with COVID-19 between these populations, and explore the factors contributing to these differences.

Methods

Data sources

On behalf of the National Clinical Research Center for Respiratory Disease, and collaborating with the National Health Commission of the People's Republic of China, we have established a retrospective cohort to study the COVID-19 cases throughout China. We obtained medical records and compiled the data from laboratory confirmed hospitalised cases with COVID-19 reported to the China National Health Commission between 21 November 2019 and 31 January 2020. The National Health Commission requested that all hospitals submit clinical records to the database. Hospitals whose clinical records had not been submitted by this deadline were requested again by the National Health Commission. Confirmed cases of COVID-19 were defined as patients who tested positive by high-throughput sequencing or real-time, reverse-transcription PCR assay for nasal and pharyngeal swab specimens. Only laboratory

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confirmed cases were included in our analysis. This study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China).

Data extraction and processing

A team of experienced respiratory clinicians reviewed and extracted the data, including recent exposure history, clinical symptoms and signs, comorbidities and laboratory findings on admission. Data were entered into a computerised database and cross-checked. In the surveillance cohort, we included all patients in the daily report with only the location and patient's clinical status (severity, live and discharge status). In the core cohort, baseline, examination and treatment information was available and collected. The recent exposure history, clinical symptoms and signs, and laboratory findings upon admission were extracted from electronic medical records. Radiologic assessments, including chest radiograph or computed tomography (CT), were performed based on the documentation/description in medical charts or combined with, if imaging films were available, a review by our medical staff. Major disagreement between two reviewers was resolved by consultation with the third reviewer. We defined the severity of COVID-19 (severe *versus* non-severe) based on the American Thoracic Society guidelines for community-acquired pneumonia given its extensive acceptance [7].

Patients with Wuhan-related exposure were defined as patients who lived in or recently travelled to Wuhan or had recent close contact with people from Wuhan, confirmed by China Centers for Disease Control and Prevention (CDC) according to the self-report by patients and survey by the local CDC staff. We compared the differences in clinical characteristics and treatments. In terms of prognosis, the primary end-point was critical illness including admission to the intensive care unit, invasive ventilation or death. We adopted this end-point because admission to the intensive care unit ICU, invasive ventilation and death are serious outcomes of COVID-19 that have been adopted in a previous study to assess the severity of other serious infectious diseases, such as the avian influenza H7N9 virus [8]. Secondary end-points consisted of mortality rate, and the time from symptom onset to the critical illness and each of its components (including invasive ventilation or intensive care unit admission or death). We specifically examined the duration from symptom onset to admission.

Due to the great confounding impact of age and comorbidity on the prognosis of COVID-19, we sought to evaluate the prognostic effect of each candidate variable based on adjustment for age and comorbidity (including COPD, diabetes mellitus, hypertension, coronary heart disease, cerebrovascular disease, viral hepatitis type B, malignant tumour, chronic kidney disease and immunodeficiency). Therefore, we pre-planned several Cox regression analyses to evaluate the prognostic impact of: 1) Hubei location alone; 2) Wuhan-related exposure alone; and 3) Wuhan-related exposure in patients outside Hubei. In addition, we planned to test a hypothesis that the time from symptom onset to hospitalisation might underly the difference in prognosis between the location and contact history. Thus, we included Hubei location, Wuhan-related exposure, time from symptom onset to hospitalisation, age and comorbidity in a Cox model.

Statistical analysis

Continuous variables were expressed as the mean±SD or median (interquartile range (IQR)) as appropriate. Categorical variables were summarised as the counts and percentages in each category. Wilcoxon rank-sum tests were applied to continuous variables. Chi-squared tests and Fisher's exact tests were used for categorical variables as appropriate. The risk of reaching the critical illness and the potential risk factors were analysed using proportional hazard Cox regression models when proportional hazard assumption was not violated. We tested the proportional hazard assumption by modelling the log-log of survival curve using each variable included as strata, if the curve did not cross all time-points the proportional hazard assumption was considered not violated. The hazard ratios and 95% confidence interval were reported. To visualise the probability of reaching critical illness of different categories, we presented the hazard function curves estimated by Cox regression model which adjusted for all included confounders. The significance of the difference between the curves were obtained from the Cox regression model. Significance level was set at p-value <0.05. All analyses were conducted with SPSS software (version 23.0; SPSS, Chicago, IL, USA).

Results

Nationwide Epidemiology Surveillance of COVID-19

Up to 31 January 2020, a total of 11791 patients with laboratory-confirmed COVID-19 had been identified in China. The flowchart of cohort establishment is shown in figure S1. Of these, 7153 (60.7%) patients were identified in Hubei province. The severe cases accounted for 15.9% of the whole cohort, and 19.2% and 11.0% within and outside Hubei province, respectively. The overall mortality was 2.20% throughout China (3.48% in Hubei province, 0.22% outside Hubei province) (figure 1). The latest data has shown a similar trend as of 15 February 2020 (figures S1 and S2).

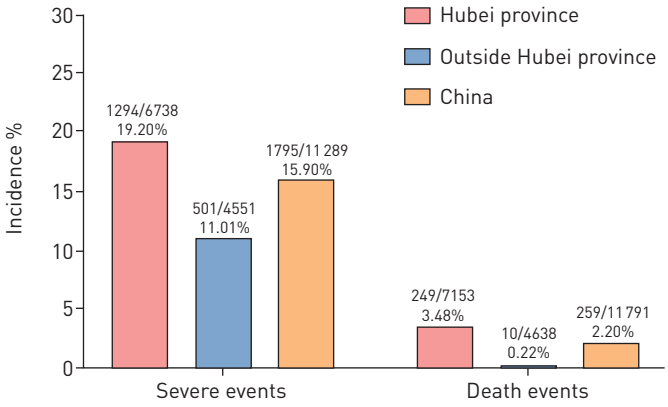

FIGURE 1 Incidence of severe cases and deaths in China, in the Hubei province and outside Hubei as of 31 January 2020. The severe events and death were reported by different statistical sources which presented a slight difference in total number. Data are presented as n/N, unless otherwise stated.

Patient characteristics in the core cohort

In the core cohort, we collected 1590 cases from 575 hospitals in 31 provincial administrative regions (a full list can be found in the supplementary material) upon data cut-off on 31 January 2020. Our dataset covered 13.4% (1590 out of 11791) of all cases being reported and covered 91.2% of regions (31 out of 34) that had confirmed cases (figure 2). Overall, mean age was 48.9 years; 904 (57.3%) patients were male and 399 (25.1%) had coexisting conditions, including hypertension (n=269, 16.9%), diabetes (n=130, 8.2%) and cardiovascular disease (n=59, 3.7%). Fever (88.0%), dry cough (70.2%), fatigue (42.8%), productive cough (36.0%) and shortness of breath (20.8%) were the most common symptoms. Most patients (71.1%) had abnormal chest CT manifestations. The overall rate of severe cases and mortality was 16.0% and 3.2%, respectively. Details are summarised in table 1.

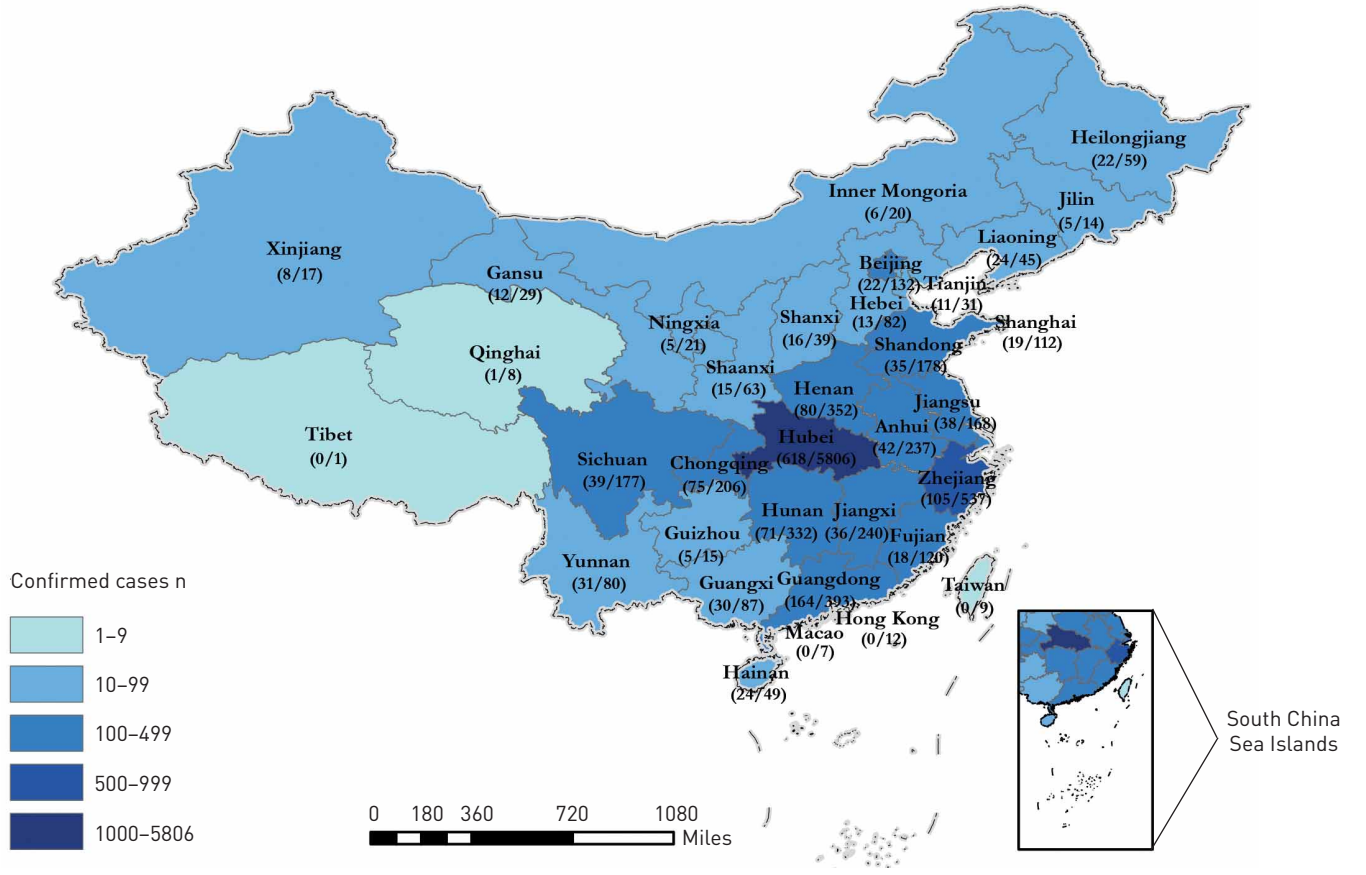

FIGURE 2 The official statistics of all documented laboratory confirmed cases throughout China according to the National Health Commission (as of 31 January 2020). Data are presented as n/N, where n is the number of patients being included in the final data analysis for each province/autonomous region/provincial municipalities, while N is the number of laboratory confirmed cases for each province/autonomous region/provincial municipalities as reported by the National Health Commission.

Patients treated inside and outside Hubei

As shown in table 1, 40.7% of the patients from the core dataset were hospitalised in Hubei province (647 out of 1590). Most patients (597 (92.3%) out of 647) in Hubei province had Wuhan-related exposure. Patients in Hubei province were older (mean age 55.1 *versus* 44.6 years) and had more cases with

TABLE 1 Clinical characteristics and outcomes of patients with COVID-19 stratified by Hubei hospitalisation and Wuhan-related exposure

Characteristics	Total	In Hubei		p-value	Wuhan-related exposure		p-value
		Yes	No		No	Yes	
Subjects n	1590	647	943		256	1334	
Age years	48.9±16.3	55.1±15.4	44.6±15.5	<0.001	44.9±14.6	49.7±16.5	<0.001
Sex				0.756			0.782
Male	904/1578 (57.3)	369/638 (57.8)	535/940 (56.9)		148/254 (58.3)	756/1324 (57.1)	
Female	674/1578 (42.7)	269/638 (42.2)	405/940 (43.1)		106/254 (41.7)	568/1324 (42.9)	
Smoking status				0.367			0.505
Never/unknown	1479 (93.0)	597 (92.3)	882 (93.5)		241 (94.1)	1238 (92.8)	
Former/current	111 (7.0)	50 (7.7)	61 (6.5)		15 (5.9)	96 (7.2)	
Comorbidities							
Any	399 (25.1)	213 (32.9)	186 (19.7)	<0.001	48 (18.8)	351 (26.3)	0.012
COPD	24 (1.5)	14 (2.2)	10 (1.1)	0.094	2 (0.8)	22 (1.6)	0.408
Diabetes	130 (8.2)	79 (12.2)	51 (5.4)	<0.001	12 (4.7)	118 (8.8)	0.025
Hypertension	269 (16.9)	156 (24.1)	113 (12.0)	<0.001	27 (10.5)	242 (18.1)	0.003
Cardiovascular disease	59 (3.7)	38 (5.9)	21 (2.2)	<0.001	7 (2.7)	52 (3.9)	0.471
Cerebrovascular disease	30 (1.9)	24 (3.7)	6 (0.6)	<0.001	2 (0.8)	28 (2.1)	0.210
Hepatitis B infection	28 (1.8)	9 (1.4)	19 (2.0)	0.439	6 (2.3)	22 (1.6)	0.436
Malignancy	18 (1.1)	12 (1.9)	6 (0.6)	0.030	0 (0)	18 (1.3)	0.097
Chronic kidney disease	21 (1.3)	16 (2.5)	5 (0.5)	0.001	3 (1.2)	18 (1.3)	1.000
Immunodeficiency	3 (0.2)	2 (0.3)	1 (0.1)	0.570	0 (0)	3 (0.2)	1.000
Symptoms							
Any	1517 (95.4)	621 (96)	896 (95.0)	0.395	237 (92.6)	1280 (96.0)	0.023
Fever	1351/1536 (88.0)	552/623 (88.6)	799/913 (87.5)	0.576	213/243 (87.7)	1138/1293 (88.0)	0.914
Conjunctival congestion	10/1345 (0.7)	3/554 (0.5)	7/791 (0.9)	0.538	3/192 (1.6)	7/1153 (0.6)	0.161
Nasal congestion	73/1299 (5.6)	24/535 (4.5)	49/764 (6.4)	0.144	11/185 (5.9)	62/1114 (5.6)	0.863
Headache	205/1328 (15.4)	94/540 (17.4)	111/788 (14.1)	0.105	30/191 (15.7)	175/1137 (15.4)	0.914
Dry cough	1052/1498 (70.2)	450/617 (72.9)	602/881 (68.3)	0.058	167/233 (71.7)	885/1265 (70.0)	0.640
Pharyngalgia	194/1317 (14.7)	60/530 (11.3)	134/787 (17.0)	0.004	31/194 (16.0)	163/1123 (14.5)	0.584
Productive cough	513/1424 (36.0)	234/582 (40.2)	279/842 (33.1)	0.007	94/218 (43.1)	419/1206 (34.7)	0.021
Fatigue	584/1365 (42.8)	255/549 (46.4)	329/816 (40.3)	0.026	85/209 (40.7)	499/1156 (43.2)	0.544
Haemoptysis	16/1315(1.2)	12/533 (2.3)	4/782 (0.5)	0.008	2/189 (1.1)	14/1126 (1.2)	1.000
Shortness of breath	331 (20.8)	235 (36.3)	96 (10.2)	<0.001	40 (15.6)	291 (21.8)	<0.029
Nausea/vomiting	80/1371 (5.8)	46/568 (8.1)	34/803 (4.2)	0.003	12/200 (6.0)	68/1171 (5.8)	0.871
Diarrhoea	57/1359 (4.2)	28/559 (5.0)	29/800 (3.6)	0.218	9/195 (4.6)	48/1164 (4.1)	0.701
Myalgia/arthralgia	234/1338 (17.5)	112/551 (20.3)	122/787 (15.5)	0.024	32/195 (16.4)	202/1143 (17.7)	0.760
Chill	163/1333 (12.2)	77/547 (14.1)	86/786 (10.9)	0.090	35/191 (18.3)	128/1142 (11.2)	0.008
Signs							
Throat congestion	21/1286 (1.6)	7/525 (1.3)	14/761 (1.8)	0.655	1/181 (0.6)	20/1105 (1.8)	0.343
Tonsil swelling	31/1376 (2.3)	16/589 (2.7)	15/787 (1.9)	0.360	4/184 (2.2)	27/1192 (2.3)	1.000
Lymphadenectasis	2/1375 (0.1)	2/588 (0.3)	0/787 (0)	0.183	0/189 (0)	2/1186 (0.2)	1.000
Rash	3/1378 (0.2)	2/583 (0.3)	1/795 (0.1)	0.577	0/191 (0)	3/1187 (0.3)	1.000
Unconsciousness	20/1421 (1.4)	16/595 (2.7)	4/826 (0.5)	0.001	1/199 (0.5)	19/1222 (1.6)	0.342
Abnormal chest images							
Radiograph	243 (15.3)	117 (18.1)	126 (13.4)	0.011	27 (10.5)	216 (16.2)	0.023
Computed tomography	1130 (71.1)	483 (74.7)	647 (68.6)	0.010	171 (66.8)	959 (71.9)	0.114
Outcomes							
Critical illness	131 (8.24)	95 (14.7)	36 (3.8)	<0.001	10 (3.9)	121 (9.1)	0.004
ICU admission	99 (6.23)	68 (10.5)	31 (3.3)	<0.001	7 (2.7)	92 (6.9)	0.010
Invasive ventilation	50 (3.14)	39 (6.0)	11 (1.2)	<0.001	4 (1.6)	46 (3.4)	0.168
Death	50 (3.14)	47 (7.3)	3 (0.3)	<0.001	2 (0.8)	48 (3.6)	0.017

Data are mean±SD, n (%) or n/N (%) where N is the total number of patients with available data, unless otherwise stated. P-values were calculated by Chi-squared test, Fisher's exact test, or Mann–Whitney U-test. ICU: intensive care unit.

comorbidity (32.9% *versus* 19.7%). Patients in Hubei province had a higher symptomatic burden including fatigue (46.4% *versus* 40.3%), productive cough (40.2% *versus* 33.1%), shortness of breath (36.3% *versus* 10.2%), myalgia or arthralgia (20.3% *versus* 15.5%), nausea or vomiting (8.1% *versus* 4.2%), haemoptysis (2.3% *versus* 0.5%) and unconsciousness (2.7% *versus* 0.5%), but not pharyngalgia (11.3% *versus* 17.0%) compared to non-Hubei patients. Moreover, patients in Hubei province were more likely to have abnormal chest radiograph (18.1% *versus* 13.4%) and CT (74.7% *versus* 68.6%) manifestations. Patients in Hubei province also had a longer duration from symptom onset to hospitalisation (5.7 *versus* 4.5 days) compared with patients outside Hubei province.

Patients with versus *without Wuhan-related exposure*

The majority of patients (1334 (83.9%) out of 1590) in this dataset had Wuhan exposure history: 18.1% lived in Wuhan, 36.7% recently travelled to Wuhan, and 45.1% had recent contact with people from Wuhan. Compared with those that had no exposure to Wuhan, Wuhan-exposed patients were significantly older (mean age 49.7 *versus* 44.9 years) and had more cases with comorbidity (26.3% *versus* 18.8%, p=0.012), including hypertension (18.1% *versus* 10.5%), diabetes (8.8% *versus* 4.7%), malignancy (1.3% *versus* 0%), fever (88.0% *versus* 87.7%), fatigue (43.2% *versus* 40.7%) and shortness of breath (21.8% *versus* 15.6%). Furthermore, abnormal manifestation in chest radiograph (16.2% *versus* 10.5%) and CT (71.9% *versus* 66.8%) were more commonly seen in patients with Wuhan-related exposure than their counterparts. Table 1 summarises detailed information.

Patient with versus *without Wuhan-related exposure outside Hubei*

Of the 943 patients outside Hubei province, 737 (78.2%) reported Wuhan-related exposure. There were no differences in patient's clinical characteristics, signs, comorbidities, the rate of abnormal chest images and most symptoms between patients with and without Wuhan-related exposure. However, Wuhan-related patients reported less productive cough (30.5% *versus* 43.8%) and shortness of breath (8.7% *versus* 15.5%) than their counterparts (table 2). The duration from symptom onset to hospitalisation was similar between patients with and without Wuhan-related exposure (mean 4.4 *versus* 4.7 years) treated outside Hubei province.

Prognostic analyses

As shown in figure 3, both patients treated in Hubei province (23.0% *versus* 11.1%, p<0.001) and those with Wuhan-related exposure (16.9% *versus* 11.3%, p=0.026) had more severe or fatal cases compared to their counterparts. Similarly, Hubei patients (7.3% *versus* 0.3%, p<0.001) and patients with Wuhan-related exposure (3.6% *versus* 0.8%, p=0.017) had a higher mortality rate. After adjusting for age and comorbidity, the Cox regression model without proportional hazard assumption violation revealed that patients in Hubei province (HR 1.59, 95%CI 1.05–2.41; p=0.027) (figure 4a) and those with Wuhan exposure history (HR 1.34, 95%CI 0.70–2.57; p=0.385) (figure 4b) were more likely to reach critical illness (tables S1–S3).

We further subdivided patients with Wuhan-related exposure according to the location of hospitals. Patients with Wuhan exposure history who underwent treatment outside Hubei province had a better prognosis compared with those treated in Hubei (HR (95% CI) 0.57 (0.36–0.91), p=0.018) (figure 4c), and yielded similar outcomes compared with patients with no Wuhan exposure history (HR (95% CI) 0.84 (0.40–1.80), p=0.653) (figure 4c and d). Most importantly, after being included in the Cox regression model, the duration from symptom onset to hospitalisation, but not Hubei or Wuhan-related exposure, remained an independent factor of the prognosis among the general population (HR (95% CI) 1.05 (1.01–1.08), p=0.005) (table 3).

Discussion

Although the pandemic has lessened in China and the results reported here focus on the early stage of the outbreak, an increasing number of patients have been diagnosed outside China and some other areas have become new epicentres, such as Lombardia, Italy and Madrid, Spain. Summarising the experience from China and providing in-depth understanding of the situation in the previous epicentre can help to improve the strategy in the current epicentres. For the situation outside the epicentre Hubei, two studies presented characteristics and outcomes among patients outside Hubei in Shenzhen and Zhejiang; however, the sample size is small and, therefore, comparison to Hubei patients cannot be performed [9]. To our knowledge this is the first nationwide study in China investigating the differences in the clinical characteristics and prognosis of patients with COVID-19 between both those within and outside Hubei province, and those with and without Wuhan-related exposure. We believe that our core cohort could partially represent the overall situation as of 31 January 2020, taking into account the patient number (13.4% of all cases) and the broad coverage (covering almost all major provinces/cities/autonomous

TABLE 2 Clinical characteristics and outcomes of patients with COVID-19 with or without Wuhan-related exposure outside Hubei

Characteristics	Wuhan-related exposure		p-value
	No	Yes	
Subjects n	206	737	
Age years	44.2±14.8	44.7±15.6	0.717
Sex			0.690
Male	119/204 (58.3)	416/736 (56.5)	
Female	85/204 (41.7)	320/736 (43.5)	
Smoking status			
Never/unknown	196 (95.1)	686 (93.1)	0.338
Former/current	10 (4.9)	51 (6.9)	
Comorbidities			
Any	46 (22.3)	140 (19.0)	0.322
COPD	2 (1.0)	8 (1.1)	1.000
Diabetes	11 (5.3)	40 (5.4)	1.000
Hypertension	25 (12.1)	88 (11.9)	0.904
Cardiovascular disease	7 (3.4)	14 (1.9)	0.190
Cerebrovascular disease	2 (1.0)	4 (0.5)	0.617
Hepatitis B infection	6 (2.9)	13 (1.8)	0.275
Malignancy	0 (0)	6 (0.8)	0.349
Chronic kidney disease	2 (1.0)	3 (0.4)	0.301
Immunodeficiency	0 (0)	1 (0.1)	1.000
Disease severity			
Non-severe	197 (95.6)	710 (96.3)	0.681
Severe	9 (4.4)	27 (3.7)	
Symptoms			
Any	188 (91.3)	708 (96.1)	0.010
Fever	168/194 (86.6)	631/719 (87.8)	0.713
Conjunctival congestion	2/148 (1.4)	5/643 (0.8)	0.621
Nasal congestion	7/140 (5.0)	42/624 (6.7)	0.568
Headache	21/145 (14.5)	90/643 (14.0)	0.895
Dry cough	134/184 (72.8)	468/697 (67.1)	0.154
Pharyngalgia	25/145 (17.2)	109/642 (17.0)	0.903
Productive cough	74/169 (43.8)	205/673 (30.5)	0.001
Fatigue	68/162 (42.0)	261/654 (39.9)	0.655
Haemoptysis	2/143 (1.4)	2/639 (0.3)	0.155
Shortness of breath	32 (15.5)	64 (8.7)	0.006
Nausea/vomiting	10/153 (6.5)	24/650 (3.7)	0.121
Diarrhoea	8/148 (5.4)	21/652 (3.2)	0.221
Myalgia/arthralgia	21/148 (14.2)	101/639 (15.8)	0.706
Chill	23/146 (15.8)	63/640 (9.8)	0.055
Signs			
Throat congestion	1/135 (0.7)	13/626 (2.1)	0.484
Tonsil swelling	4/140 (2.9)	11/647 (1.7)	0.321
Lymphadenectasis	0/141 (0)	0/646 (0)	
Rash	0/142 (0)	1/653 (0.2)	1.000
Unconsciousness	1/152 (0.7)	3/674 (0.4)	0.557
Abnormal chest images			
Radiograph	22 (10.7)	104 (14.1)	0.246
Computed tomography	136 (66.0)	511 (69.3)	0.396
Outcomes			
Critical illness	9 (4.4)	27 (3.7)	0.681
ICU admission	7 (3.4)	24 (3.3)	1.000
Invasive ventilation	4 (1.9)	7 (0.9)	0.269
Death	1 (0.5)	2 (0.3)	0.523

Data are mean±SD, n (%) or n/N (%) where N is the total number of patients with available data, unless otherwise stated. P-values were calculated by the Chi-squared, Fisher's exact test, or Mann–Whitney U-test. ICU: intensive care unit.

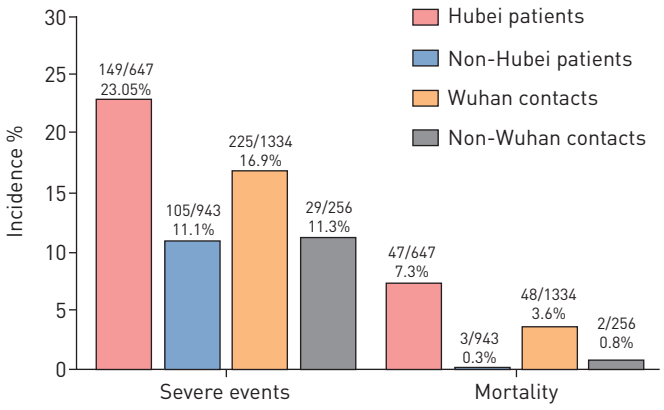

FIGURE 3 Incidence of severe cases and deaths, in Hubei patients, in non-Hubei patients, in Wuhan contacts and in non-Wuhan contacts. Data are presented as n/N, unless otherwise stated.

regions). Moreover, this dataset showed consistent epidemiological characteristics with the surveillance dataset, indicating that it represented the real-world conditions.

Compared with those with contact history with people from Wuhan or living in Hubei province, patients without Wuhan-related exposure or living outside Hubei were younger, had fewer comorbidities, less abnormal chest radiographic manifestations and slightly lower symptom burden. These findings suggested a potentially augmented infectivity in the general population beyond fragile individuals (*i.e.* the elderly). This is in agreement with the median reproduction number (R_0), which has increased from 2.0 in early studies to 3.8 in more recent studies [10, 11]. In addition, viral genome sequencing of cases from Hubei province and other regions/countries has also lent support to the continuous revolution in the viral functional regions that facilitates its transmission among the human population (self-adaptation) [12]. However, we should be cautious about the bias resulting from the undiagnosed cases in the early phase of transmission when most people were not aware of this disease.

It has been believed that the onward transmission of a virus might result in attenuated disease [13, 14]. Our results showed fewer severe events and a lower mortality rate among patients outside of Hubei province and patients that had no history of Wuhan-related exposure. However, these results might have been biased by the temporary shortage of health resources, such as the limited hospital performance and detection capacity, that resulted from the sudden outbreak of COVID-19 in Hubei. After the surge of cases in January 2020, hospitals in Hubei province were heavily overloaded and managed an overwhelming increase in the number of patients. These shortages could have led to a delay in the diagnosis and treatment of patients, which further contributed to the worsening of overall status upon admission and an increased risk of death.

In this study, we have included the duration from symptom onset to admission to evaluate the impact of the healthcare capacity on the difference between Hubei and other regions in China. Significantly longer waiting time was observed among patients in Hubei province, whereas patients with or without Wuhan-related exposure shared similar waiting time outside Hubei province. Importantly, we have found that the prolonged waiting time, rather than the geographic location or the Wuhan-related exposure history, predicted the clinical prognosis of COVID-19. We speculated that some patients from Wuhan travelled to other cities outside of Hubei province seeking more timely treatment. These patients reported a similar waiting time and medical care records, which translated into a similar prognosis with the local residents. Consistently, the incidence of severe cases and mortality continuously decreased (figure S1) since clinicians, nurses and medical instruments were been dispatched to Hubei province. However, timely screening of candidates with suspected symptoms or contact with confirmed cases might help promptly initiate medical care, thus preventing further spreading of the disease.

There are some limitations of this study. First, although we made every effort to collect data from all patients, some hospitals did not answer our request. Thus, although the dataset had a broad coverage of all patients and regions, the non-responsive bias cannot be fully excluded. Secondly, as the date of symptom onset is self-report based, bias from patient recall might exist. Thirdly, we cannot evaluate the exact healthcare capacity of each hospital but used a duration from symptom onset to admission as an indirect measure. Fourthly, only a small proportion of patients had Wuhan exposure history, which may give a non-balanced result with some possible bias. Finally, some other factors that may have impact on the prognosis, *e.g.* secondary infection, which cannot be evaluated in this study. In addition, a significant proportion of people infected by SARS-CoV-2 are asymptomatic and were not included in this study of hospitalised patients, the situation in the general infected population requires further studies.

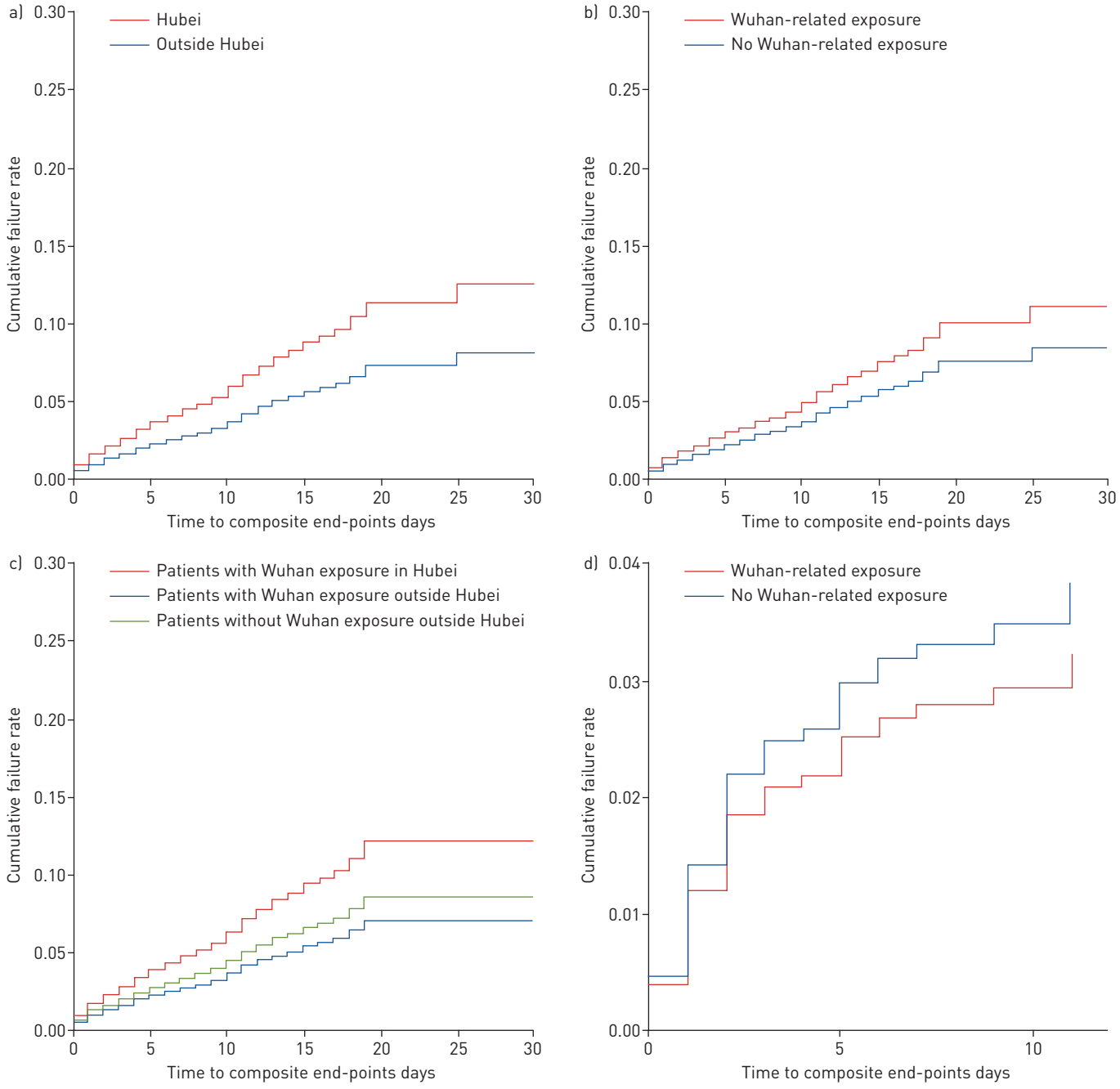

FIGURE 4 a) The time-dependent risk of reaching critical illness between patients inside and outside the Hubei province. b) The time-dependent risk of reaching critical illness between patients with and without Wuhan-related exposure. c) The time-dependent risk of reaching critical illness among patients in the Hubei province who had Wuhan-related exposure, patients outside the Hubei province who had Wuhan-related exposure, and patients outside the Hubei province who did not have a Wuhan-related exposure. d) The time-dependent risk of reaching critical illness between patients treated outside Hubei with and without Wuhan-related exposure.

Our findings indicate that the temporary shortage in healthcare capacity in the outbreak epicentre, rather than the transmission history, has resulted in the large number of severe cases or deaths in Hubei province. These results have expanded our understanding of patients infected by secondary or tertiary transmission which will account for the majority of patients that are infected worldwide, and provided timely and important implications for basic research and establishing public health policy. Adequate management of healthcare resources as well as the public's response is important to mitigate the impact of the outbreak. This study highlights the necessity of urgent and vigorous support of healthcare resources and increased public awareness during the early stages of an outbreak of COVID-19 or similar diseases.

TABLE 3 Hazard ratios estimated by multivariate proportional hazard Cox model

Variables	HR (95% CI)	p-value
Age continuous	1.036 (1.021–1.052)	<0.001
Any comorbidity yes *versus* no	2.132 (1.393–3.261)	<0.001
Wuhan-related exposure yes *versus* no	1.13 (0.556–2.296)	0.735
Hubei location yes *versus* no	1.333 (0.86–2.065)	0.198
Time from symptom onset to hospitalisation continuous	1.045 (1.013–1.078)	0.005

Comorbidity included COPD, diabetes mellitus, hypertension, coronary heart disease, cerebrovascular disease, viral hepatitis type B, malignant tumour, chronic kidney disease and immunodeficiency.

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