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

Wen-hua Liang1,2, Wei-jie Guan1,2, Cai-chen Li1,2, Yi-min Li2,2, Heng-rui Liang1,2, Yi Zhao1,2, Xiao-qing Liu3, Ling Sang1,2, Ru-chong Chen4, Chun-li Tang1, Tao Wang3, Wei Wang3, Qi-hua He1, Zi-sheng Chen1, Sook-San Wong1, Mark Zanin5, Jun Fu Li1, Li-min Ou1, Bo Cheng1, Shan Xiong1, Zhan-hong Xie6, Zheng-yi Ni7, Yu Hu4, Lei Liu7, Hong Shan8, Chun-liang Lei9, Yi-xiang Peng10, Li Wei10, Yong Liu11, Peng Peng11, Jian-ming Wang12, Jing-yang Liu12, Hong Shan9, Chun-liang Cheng12, Peng Ye12, Shi-yue Li10,11, Jiu-qing Zhang12, Nian-shan Zhong1,2, and Jian-xing He1,2

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.

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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 years 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 days 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 1,699 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
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 11 791 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).
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.
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 |
| 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) | 48 (18.8) | 351 (26.3) | 0.012 |
| Former/current | 111 (7.0) | 50 (7.7) | 61 (6.5) | 2 (0.8) | 28 (2.1) | 0.210 |
| Comorbidities | 0.395 | 0.023 |
| Any | 1517 (95.4) | 621 (96) | 896 (95.0) | 237 (92.6) | 1280 (96.0) | 0.023 |
| COPD | 1351/1536 (88.0) | 552/623 (88.6) | 799/913 (87.5) | 213/243 (87.7) | 1138/1293 (88.0) | 0.914 |
| Tonsil swelling | 513/1426 (36.0) | 234/582 (40.2) | 279/842 (33.1) | 0.007 | 94/218 (43.1) | 419/1260 (34.7) | 0.021 |
| Fatigue | 584/1365 (42.8) | 255/549 (46.4) | 329/816 (40.3) | 0.026 | 85/209 (40.7) | 499/1171 (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 |
| Symptoms | 0.026 | 0.017 |
| 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 |
| Signs | 163/1333 (12.2) | 77/547 (14.1) | 66/786 (10.9) | 0.090 | 35/191 (18.3) | 128/1142 (11.2) | 0.008 |
| Abnormal chest images | 0.343 | 0.134 |
| Abnormal chest images | 21/1286 (1.6) | 7/525 (1.3) | 14/761 (1.8) | 0.655 | 1/180 (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 | 2/1735 (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 |
| Final illness | 20/1421 (1.4) | 16/595 (2.7) | 4/826 (0.5) | 0.001 | 1/199 (0.5) | 19/1122 (1.6) | 0.342 |

Data are mean±s, 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 1.05–2.39; p=0.018) and those with Wuhan exposure history (HR 1.34, 95%CI 0.70–2.57; p=0.385) 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
| Characteristics                              | Wuhan-related exposure | p-value   |
|---------------------------------------------|------------------------|-----------|
|                                             | No                     | Yes       |           |
| Subjects n                                  | 206                    | 737       | 0.717     |
| Age years                                  | 44.2±14.8              | 44.7±15.6 | 0.690     |
| Sex                                         |                        |           |           |
| 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     |
| Chills                                      | 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 means±s, 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.
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 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.](https://doi.org/10.1183/13993003.00562-2020)
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.

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.
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) | 0.725    |
| 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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