A Head-To-Head Comparative Study of Covid-19 Patients Between Epicenter and Peripheral Areas of Pandemic From China

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Abstract

Background: There has been little information on difference of epidemiology, clinical characteristics and outcomes between epicenter and peripheral areas of Covid-19 pandemic.

Methods: Based on Sichuan & Wuhan collaboration research group for Covid-19, we established two retrospective cohorts reflecting the epicenter and peripheral area of pandemic. Epidemiology, clinical characteristics and outcomes of patients were compared. Multivariate regression analyses were used to estimate adjusted odds ratios (aOR) to identify clinical variables associated with outcomes.

Results: Upon March 12, 2020, Wuhan cohort consisted of 710 patients using random sampling, and 474 consecutive cases constituted Sichuan cohort. Sichuan cohort had more upper airway symptoms, while Wuhan cohort is elder, has more lower airway symptoms and comorbidities. Wuhan cohort had higher risk of death (aOR=7.64), ICU admission (aOR=1.66), delayed time from illness onset to hospital and ICU admission (aOR=6.29 and aOR=8.03) and prolonged duration of viral shedding (aOR=1.64).

Conclusions: Worse outcomes in the epicenter would be explained by delayed time from illness onset to hospital and ICU admission associated with elevated systemic inflammation reflecting organ dysfunction and prolonged duration of virus shedding except for age and comorbidities. It indicates potentially clinical implications of Covid-19 that early supportive care would achieve better clinical outcome.

Background

In December 2019, an outbreak of pneumonia of unknown cause were identified in Wuhan, the capital of Hubei province in China. A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which had not been detected in humans previously, was identified as the cause later by Chinese scientists[1]. Then the disease was named coronavirus disease 2019 (Covid-19) by world health organization (WHO).

The clinical spectrum of Covid-19 appears to be wide, ranges from self-limited mild upper respiratory tract illness, severe pneumonia requiring hospitalization to death. Clinical characteristics of some case series in Wuhan as the epicenter area of pandemic have been reported in detail previously, which indicated 26–33% of patients required intensive care and 4–15% died[2–4]. However, some other studies from the peripheral area of pandemic found 2—10.1% of patients who needed intensive care, and about 1.0% died[5–7]. Why it results in significantly different clinical outcomes between the epicenter and peripheral areas of pandemic remains largely unexplored. Recently, Liang et al.[8] observed clinical characteristics and outcomes of hospitalized patients with Covid-19 treated in Hubei (epicenter) and outside Hubei (non-epicenter). Although this is a multi-center study, there may be selection bias for their included patients. Furthermore, hospitalized patients in Hubei but not in Wuhan would not be well representative of first-generation cases with Covid-19. Considering the rapidly increasing number of cases confirmed infection with SARS-CoV-2 worldwide, the existed investigations of patients between epicenter and peripheral areas of pandemic were insufficient.

Here, we performed a head-to-head comparative study to analyze epidemiological and clinical characteristics between the epicenter and peripheral areas of pandemic based on all consecutively recruited Covid-19 patients in Sichuan and random sampling patients from two designated hospitals in Wuhan, which would possibly account for these differential clinical outcomes between these two regions.

Methods

Outbreak response from Sichuan as the peripheral area of pandemic

Since the outbreak of Covid-19 in Wuhan as the epicenter of pandemic, the government of Sichuan province has implemented strict measures to struggle against Covid-19. The Health Commission of Sichuan Province (HCSP) focused on traditional public health outbreak response tactics including isolation, quarantine, social distancing, and community containment as indicated by National Health Commission of China. All medical resources were totally allocated by HCSP to maintain efficient use. We established the expert panel from multiple disciplines team consisting of 125 physicians led by Dr. Wei Min Li and Dr. Zong An Liang as the corresponding authors of this study on Jan 15, 2020, and soon released the emergency prevention and control guidelines for Covid-19 in medical institutions of Sichuan province[9]. Furthermore, we also funded two additionally important expert panels with psychological counseling[10] and traditional Chinese medicine as a complementary and alternative medicine[11, 12]. Severe or critically ill patients would have consultations with the expert panel team by using 5G network technique whenever necessary at 16:30 in the afternoon daily. There were 208 designated hospitals across Sichuan province, which were generally distributed in every city that would be available for SARS-CoV-2 suspected or confirmed individuals.
Fever clinics were created to exclusively screen patients with suspected SARS-CoV-2 infection as indicated in the supplementary data.

**Study design and subjects**

This was a retrospective study based on two cohorts led by the Sichuan and Wuhan Collaboration Research Group for Covid-19, China. The Sichuan cohort Sichuan as the peripheral area of pandemic consisted of SARS-CoV-2 confirmed patients consecutively recruited from 41 designated hospitals until March 12, 2020. Based on the exposure history, we further divided the Sichuan cohort into two sub-cohorts with or without Wuhan exposure history. The Wuhan cohort as the epicenter area of pandemic formed using random sampling method from 2 designated hospitals, namely Wuhan Red Cross Hospital and Renmin Hospital of Wuhan University, Wuhan, China. All patients enrolled in this study were diagnosed as Covid-19 according to the interim guidance issued by the National Health Commission of China and WHO[13]. Cases were confirmed with infection of SARS-CoV-2 by a positive result of real-time reverse-transcriptase-polymerase-chain-reaction of nasopharyngeal, pharyngeal, throat-swab or sputum specimens. Some patients had been reported by Wei et al.[14], Xiong et al.[15] and Xiong et al.[16], but their study purposes are significantly different from this study.

**Data collection**

The medical records of patients with Covid-19 were reviewed by the trained research team. Epidemiological, demographic, clinical, laboratory, radiological characteristics, treatment and outcome data were collected with standardised data collection forms (modified case record form for severe acute respiratory infection clinical characterization shared by International Severe Acute Respiratory and Emerging Infection Consortium [ISARIC] from the electronic medical records. The cutoff date was Mar 12, 2020. We collected the exposure history, clinical symptoms and signs, and laboratory findings on admission. Laboratory examinations were performed according to clinical care needs of the patients. Radiological abnormalities were extracted from the documentation. The patients were excluded if the medical records were not available. A team of trained researchers abstracted the data and entered into structured spreadsheet. All data were cross-checked.

**Study outcomes**

The primary outcomes included death or the use of mechanical ventilation. Secondary outcomes were the rate of ICU admission, time from illness onset to ICU admission and discharge, hospital length of stay, and duration of viral shedding after Covid-19 onset. The shedding of SARS-CoV-2 was defined as two consecutive negative results with qPCR detection at an interval of 24 hours. The criteria for discharge were absence of fever for at least 3 days, substantial improvement in both lungs in chest CT, clinical remission of respiratory symptoms and comorbidities, and shedding of SARS-Cov-2.

**Statistical analysis**

The aim of our study is to report the difference of epidemiological, clinical characteristics and outcomes of Covid-19 patients in peripheral and epicenter areas of pandemic. The detailed statistical analysis was described in supplementary data.

**Results**

**Epidemiological and clinical characteristics at hospital admission**

As of March 12, 2020, there were 538 patients with Covid-19 who consecutively admitted to 41 designated hospitals in Sichuan province, and a total of 1979 cases from the two hospitals in Wuhan were identified. As a result, Sichuan cohort consisted of 474 patients (Figure 1A), when excluded 64 cases with inaccessible medical records. On the other hand, 35.9% (n=710) of all patients from Wuhan using random sampling method formed Wuhan cohort. Epidemiological data indicated illness onset of SARS-CoV-2 infection in Sichuan cohort firstly occurred on Dec. 2019, and the first case admitted to the designated hospital on Jan 16, 2020 (Figure 1B). The daily Wuhan-related exposure cases having illness onset of Covid-19 in Sichuan cohort peaked on Jan 23, 2020, and those without Wuhan-related exposure afterwards peaked on Feb 1, 2020 (Figure 1C and D). In Wuhan cohort, illness onset of the first case was on Dec. 24, 2019, and the first hospitalization happened on Jan 5, 2020 (Figure 2A). The median time from illness onset to hospital in Sichuan cohort was significantly shorter than Wuhan cohort (5.0 [2.0, 9.0] vs. 10.0 [7.0, 15.0] days, *P*<0.001). Sichuan cohort had a less proportion of patients with exposure history than that in Wuhan cohort (64.3% vs. 99.3%, *P*<0.001).

The demographic and clinical characteristics of these patients are shown in Table 1. Patients in Sichuan cohort were younger (44 [32.0 vs. 54.0] vs. 58 [43.0, 67.0] yrs, *P*<0.001), had less females (46.4% vs. 54.1%, *P*<0.010), but had more current smokers (14.5% vs. 5.1%, *P*<0.001). Two patients (0.4%) were health care workers in Sichuan cohort and 13 (1.8%) were recorded in Wuhan cohort (*P*=0.033). The
most common comorbidity in both cohorts was hypertension (23.6%), followed by diabetes (11.9%). Wuhan cohort had more cases with comorbidity (51.2% vs. 43.8%, \( P=0.012 \)) assessed by Charlson comorbidity index [17] (CCI) (2.0 [2.0, 3] vs. 0 [0, 1.0], \( P<0.001 \)). Less patients in Sichuan cohort had a history of coronary heart disease \( (P=0.004) \), liver disease \( (P<0.001) \), stroke \( (P=0.026) \), hypertension \( (P<0.001) \), and malignancy \( (P=0.012) \) compared with Wuhan cohort.

Fever was the most common symptom and presented in 61.8% patients in Sichuan cohort or 65.1% patients in Wuhan cohort, but no significant difference was detected between the two groups. Sichuan cohort had more productive cough than Wuhan cohort \( (P=0.012) \). However, Wuhan cohort seemed to have a higher symptomatic burden of lower respiratory tract, including shortness of breath (25.4% vs. 9.0%, \( P<0.001 \)), chest distress (23.8% vs. 9.0%, \( P<0.001 \)), wheeze (13.9% vs. 4.8%, \( P<0.001 \)), and general symptomatic burden, including fatigue (36.2% vs. 22.3%, \( P<0.001 \)), hemoptysis (3.0% vs. 1.1%, \( P=0.028 \)), altered consciousness (1.8% vs. 0.2%, \( P=0.011 \)) and diarrhoea (12.1% vs. 6.3%, \( P=0.001 \)). On the contrast, Sichuan cohort was more likely to have upper respiratory symptoms, including pharyngalgia (13.9% vs. 7.5%, \( P<0.001 \)), rhinorrhea (5.0% vs. 1.4%, \( P<0.001 \)), nasal obstruction (3.4% vs. 1.1%, \( P=0.007 \)), and headache (10.1% vs. 4.6%, \( P<0.001 \)) (Figure 3A). Different severity distribution was observed between the two cohorts \( (P<0.001) \) assessed by CURB65 and MULBSTA (both \( P<0.001 \)), respectively. More than 75% of patients in both cohorts were of mild or general diseases, but Sichuan cohort had more severe cases (17.0% vs. 8.4%) and Wuhan cohort had more critically ill patients (13.6% vs. 6.3%). Chest CT radiographs in Wuhan cohort were more likely to show bilateral lung involved \( (P=0.012) \) and consolidation \( (P=0.006) \).

**Laboratory findings and treatments**

The comparison of laboratory findings and treatments between two cohorts are shown in Table 2. There was no difference in white blood cell count, lymphocyte count, prothrombin time, albumin, alanine aminotransferase, aspartate aminotransferase, procalcitonin and IL-6 between two cohorts. Sichuan cohort had lower levels of neutrophil count \( (P<0.001) \), platelet count \( (P<0.001) \), D-dimer \( (P<0.001) \), and C-reactive protein \( (P<0.001) \) and higher levels of haemoglobin \( (P=0.015) \), activated partial thromboplastin time \( (P<0.001) \), creatinine \( (P=0.040) \), and creatine kinase \( (P<0.001) \). Almost all patients received antiviral treatment either in Sichuan (93.9%) or Wuhan (92.7%). Less patients in Sichuan cohort received interventions of antibiotics \( (P<0.001) \), corticosteroids \( (P<0.001) \) and supplementary oxygen therapy \( (P<0.001) \).

**Clinical outcomes**

Clinical outcomes are summarized in Table 2. The case fatality rate in Sichuan cohort was obviously lower than that in Wuhan cohort (0.6% vs. 8.3%, \( P<0.001 \)). However, it had no significant difference in the proportion of patients receiving non-invasive mechanical ventilation or invasive mechanical ventilation between two cohorts (5.7% vs. 5.9%, \( P=0.872 \) and 1.7% vs. 1.4%, \( P=0.701 \)). For the secondary outcomes, the proportion of patients who admitted to ICU in Sichuan cohort was significantly decreased than that in Wuhan cohort (6.3% vs. 13.6%, \( P<0.001 \)). Time from illness onset to ICU admission and time from illness onset to discharge in Sichuan cohort were evidently shorter than Wuhan cohort (7.0 [4.0, 10.5] vs. 11.5 [8.8, 24.3] days, \( P<0.001 \) and 23.0 [18.0, 31.0] vs. 28.0 [18.0, 38.0] days, \( P<0.001 \)). The hospital length of stay in Sichuan cohort was much longer than that in Wuhan cohort (17.0 [12.0, 24.0] vs. 14.0 [9.0, 24.0] days, \( P<0.001 \)). In addition, the Wuhan cohort had significantly prolonged duration of SARS-CoV-2 shedding compared with Sichuan cohort (19.0 [13.0, 28.0] vs. 14.0 [10.0, 19.0] days, \( P<0.001 \)).

**Logistic regression analyses**

The multivariable logistic regression models were used to explore the difference of clinical outcomes between Sichuan and Wuhan cohorts (Table 3). As a result, Wuhan cohort had higher risk of death \( (aOR=7.64, 95\%CI=[2.31, 25.27], P=0.001) \), ICU admission \( (aOR=1.66, 95\%CI=[1.05, 2.63], P=0.031) \), delayed time from illness onset to hospital \( (aOR=6.29, 95\%CI=[4.70, 8.40], P<0.001) \) and ICU \( (aOR=8.03, 95\%CI=[1.74, 37.06], P<0.001) \) admissions, prolonged duration of viral shedding after Covid-19 onset \( (aOR=1.64, 95\%CI=[1.15, 2.33], P=0.006) \), a decreased hospital stay \( (aOR=0.41, 95\%CI=[0.32, 0.53], P<0.001) \) after adjusting for age, sex, smoking status and CCI. It had no difference in time from illness onset to discharge \( (aOR=0.99, 95\%CI=[0.77, 1.28], P=0.968) \) after adjusting for these confounders. When we additionally adjusted for time from illness onset to hospital, it hardly changed the risk of the Wuhan cohort, but, intriguingly, Sichuan cohort had a low risk for extended time from illness onset to discharge \( (aOR=0.46, 95\%CI=[0.34, 0.63], P<0.001) \).

Within all of Covid-19 patients from the two cohorts, we further constructed multivariable logistic regression models to detect the risk factors at admission for death, ICU admission, mechanical ventilation and duration viral shedding after Covid-19 onset (Table 4). After adjusting for cohort sites, sex, age, smoking status and CCI, we found that white blood cells \( (>10\times10^9/L) \), neutrophils \( (>6.3\times10^9/L) \), lymphocytes \( (>1.0\times10^9/L) \), haemoglobin \( (<90\ g/L) \), D-dimer \( (>0.5\ mg/L) \), creatine kinase \( (>185\ IU/L) \), hyper-sensitive troponin I \( (>0.04\ ng/mL) \), alanine aminotransferase \( (>50\ IU/L) \), aspartate aminotransferase \( (>40\ IU/L) \), procalcitonin \( (>0.5\ ng/mL) \) and delayed hospital
admission was associated with death, ICU admission and mechanical ventilation. In addition, we found time from illness onset to hospital admission was associated with prolonged duration of virus shedding (adjusted $\beta=0.11$, 95% CI=[0.03, 0.24], $P=0.009$).

Subgroup analyses between Sichuan sub-cohorts with vs. without Wuhan-related exposure

As a result, it found almost no difference in clinical characteristics and outcomes between two sub-cohorts with and without Wuhan-related exposure in Sichuan (Figure 1; Tables S1, S2 and S3). The detailed information was provided in Supplementary Data.

Sichuan sub-cohort with Wuhan-related exposure vs. Wuhan cohort

It showed differential clinical characteristics and outcomes between Sichuan sub-cohort with Wuhan-related exposure and Wuhan cohort that were similar to the findings found between Sichuan and Wuhan cohorts. The results were described in details in Supplementary Data (Tables S4, S5 and S6).

Discussion

To the best of our knowledge, there has been little information on difference of epidemiology, clinical characteristics and outcomes of patients with Covid-19 between epicenter (Wuhan) and peripheral areas of pandemic using comparative study design with a large sample size. This comparative study found some important information as follows. First, the outbreak and transmission of Covid-19 within the region of Sichuan as the peripheral epidemic area has well been of containment within no more than two months using traditional public health outbreak response tactics. Second, Sichuan cohort is characterized by more upper airway symptoms, while Wuhan cohort is elder, has more lower airway symptoms and comorbidities, and has elevated pivotal systemic inflammation reflecting organ dysfunction, and worse clinical outcomes independent of sex, age, smoking and comorbidities. Third, the subgroup analysis indicates that, within Sichuan cohort, the Wuhan-related exposure patients have similar clinical features and outcomes to those with non-Wuhan-related exposure. Fourth, the Wuhan-related exposure patients in Sichuan cohort have improved clinical outcomes in comparison with Wuhan cohort, although these two groups of patients have similar Wuhan-related exposure history.

As indicated in just published studies[8], the Covid-19 patients in Wuhan as the epicenter area of epidemic had elder age, more co-existing conditions assessed by Charlson comorbidity index, extended time from illness onset to hospital admission and severe patients in this study, but Sichuan cohort as the peripheral area had some featured characteristics as follows. Firstly, less health care workers in Sichuan cohort were infected than Wuhan cohort, which would be at least explained by insufficient precautions and overwhelmed health system at an earlier stage of this outbreak in Wuhan. Second, intriguingly, we found Sichuan cohort had more upper-airway symptoms rather than lower airway symptoms featured in Wuhan cohort in the epicenter epidemic, which was similarly found in exported cases in Singapore[18]. Accordingly, the exported patients from epicenter usually esteemed to have “common cold” at the beginning of Covid-19 outbreak. Different population, proliferation location of airway or evolution of SARS-CoV-2 would account for these differential symptoms[18–21]. Third, within the consecutively recruited cases in Sichuan cohort as a well-defined population, our subgroup analyses indicated more males and elder age in non-Wuhan-related exposure patients, which supported the propensity of SARS-CoV-2 infection in males and elders[5, 22, 23]. Recently reported studies from USA and Italy supported that the greater proportion of elder and male Covid-19 patients would result in more critical illness[24, 25].

Until no antiviral treatment for Covid-19 has been proven to be effective, and the mainstay of treatment is supportive care. Compared with the Wuhan cohort, use of antibiotics (i.e. cephalosporin and quinolones) and glucocorticoids in Sichuan cohort, fell by 26.4% and 16.1%, respectively. These results could be possibly explained as following. Firstly, as indicated above, the expert panel from multiple disciplines team established by HCSP together developed and adjusted treatment plan for severe or critically ill patients according to interim guidance from National Health Commission of China and WHO across the 208 designated hospitals in Sichuan via 5G network technique every day. Accordingly, systemic corticosteroids were strictly managed and not routinely given for treatment of Covid-19 patients. Second, the Covid-19 patients in Wuhan cohort would actually be more severe or critically ill, who were supported by increased use of oxygen support if acute hypoxia occurred. In addition, prone position ventilation, physical rehabilitation and a variety of traditional Chinese medicine was used more in Sichuan under the guidance of expert panel, although it needed to be further investigated in randomized controlled trials[11, 12].

In terms of clinical outcomes, there were several important findings indicated by this study. Epidemic outbreak provided an opportunity to gain important information, some of which was associated with a limited window of opportunity. Our study showed that it had a delay from illness onset to hospital admission in Wuhan cohort, which might be an important risk factor for progression of Covid-19. Our multivariate regression analysis proved that the time from illness onset to hospital admission was significantly associated with mortality.

Page 6/19
and ICU admission, which suggested some important implications about the pathogenesis of SARS-CoV-2 and may provide a unique window of opportunity for intervention\[11\]. Liang et al\[8\] recently found the Wuhan-related exposure patients have worse clinical outcomes compared with non-Wuhan-related exposure cases, which, they think, would be explained by attenuated disease due to onward transmission of Covid-19. Actually, it is paradoxical in Liang et al’s study\[8\] because relationship of Wuhan-related exposure with the prognosis disappears after adjusting for confounders. Our study firstly found that Covid-19 patients in the Wuhan cohort had worse clinical outcomes including case fatality rate, ICU admission and duration of virus shedding independent of sex, age, smoking, comorbidities and even time from illness onset to hospital admission. Severity of Covid-19 and shortage of medical resources would partly account for these worse outcomes. For example, at an earlier stage of outbreak, some patients would not achieve enough oxygen support because of insufficient oxygen pressure.

Duration of infectious virus replication is an important factor in assessing the risk of transmission and guiding decisions regarding isolation of patients, but the duration of SARS-CoV-2 RNA detection has not been well explored. Our study found the Wuhan cohort in epicenter area had the prolonged virus shedding that may contribute to severity of disease and clinical course\[26, 27\]. Further, it firstly found duration of virus shedding was independently associated with age and time from illness onset to hospital admission. Our findings were supported by other studies. Liu et al\[28\] found that viral load of severe cases was higher than that of mild cases who had an early viral shedding. Wolfel et al\[29\] found that virus shedding in upper airway where is the location of mild Covid-19, was very high during the first week of symptoms, but shedding of viral RNA from sputum derived from lower airway where is the region of general to critical illness of Covid-19, outlasted the end of symptoms. Although Xu et al\[30\] found elder cases had a prolonged virial shedding, the correlation of age with duration of viral shedding disappeared after adjusting for confounders, which might be partly explained by small sample size.

Although this head-to-head comparative study provides informative findings on difference of epidemiology, clinical characteristics and outcomes of patients with Covid-19 between epicenter (Wuhan) and peripheral (Sichuan) areas of pandemic with a large sample size, there are several limitations that need to be addressed. First, due to the retrospective study design, data generation was clinically driven and not all laboratory data were available in all patients. Accordingly, the missing data on patients may have biased the findings. Second, Sichuan cohort representing peripheral area of Covid-19 pandemic was incomplete, although consecutive patients accounting for 88.1% of total cases with Covid-19 were recruited from 41 designated hospitals across Sichuan. Third, we did not analyze genetic diversity of virus strains and evolutionary history, which may well explain these biological differences between epicenter and peripheral areas of pandemic.

**Conclusions**

This head-to-head comparative study found that there have significant differences of epidemiology, clinical characteristics and outcomes of patients with Covid-19 between epicenter and peripheral areas of pandemic. Worse outcomes in the epicenter of pandemic would be partly explained by overwhelmed health resources, delayed time from illness onset to hospital admission associated with elevated systemic inflammation reflecting organ dysfunction and prolonged duration of virus shedding except for sex, age, smoking and comorbidities. It indicates potential implications of clinical relevance in intervention of Covid-19 that urgent or early supportive care would achieve improved clinical outcomes including mortality, although no proven effective therapies for this virus currently exist. However, no differences of epidemiology, clinical characteristics and outcomes between the first generation and secondary generation patients in the peripheral area of pandemic were found. Biological differences accounting for the differences between the Wuhan-related exposure patients in Sichuan cohort and Wuhan cohort need to be further investigated.

**List Of Abbreviations**

aOR: adjusted odds ratio  
CCI: Charlson comorbidity index  
CI: confidence interval  
Covid-19: coronavirus disease 2019  
HCSP: The Health Commission of Sichuan Province  
ISARIC: International Severe Acute Respiratory and Emerging Infection Consortium  
OR: odds ratio
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

WHO: world health organization

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Biological and Medical Ethics Committee of West China Hospital (No. 2020-304 and 2020-126) and the Ethic Committee of Renmin Hospital of Wuhan University (No. WDRY2020-K068). Written informed consent from each participant was waived for design of a retrospective study.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Author's contributions**

GW, FML, DL, NX, JFL, ZAL, WML had roles in the study design, data analysis, data interpretation, and writing of the manuscript. YW, HC, PWT, TF, LT, HY, LW, MF, ZN, BW, ZFS, XLW, XT, MX, HJW, XYL, BL, CJ, JX, JS had roles in the collection, processing, cleaning, and interpretation of data. All authors read and approved the final manuscript.

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Tables

Table 1. Demographics and clinical characteristics of patients in Sichuan and Wuhan cohorts
| Variable                              | Total     | Sichuan cohort | Wuhan cohort | Statistics | P value |
|--------------------------------------|-----------|----------------|--------------|------------|---------|
| n                                    | 1184      | 474            | 710          |            |         |
| Female, n (%)                        | 604 (51.0)| 220 (46.4)     | 384 (54.1)   | 6.693      | 0.010   |
| Age, years                           | 50.50(37.00, 64.00) | 44.00(32.00, 54.00) | 58.00(43.00, 67.00) | 12.054     | <0.001  |
| <18                                  | 18 (1.5)  | 16 (3.4)       | 2 (0.3)      | 87.521     | <0.001  |
| 18~64                                | 870 (73.9)| 403 (85.2)     | 467 (66.2)   |            |         |
| ≥65                                  | 290 (24.6)| 54 (11.4)      | 236 (33.5)   |            |         |
| Exposure history, n (%)              |           |                |              | 527.493    | <0.001  |
| Travel in Wuhan                      | 141 (11.9)| 128 (27.0)     | 13 (1.8)     |            |         |
| Residents in Wuhan                   | 869 (73.4)| 177 (37.3)     | 692 (97.5)   |            |         |
| No exposure history                  | 174 (14.7)| 169 (35.7)     | 5 (0.7)      |            |         |
| Health care workers, n (%)           | 15 (1.3)  | 2 (0.4)        | 13 (1.8)     | 4.532      | 0.033   |
| Smoking, n (%)                       |           |                |              | 26.843     | <0.001  |
| Current smoker                       | 96 (9.3)  | 67 (14.5)      | 29 (5.1)     |            |         |
| Ever smoker                          | 42 (4.1)  | 18 (3.9)       | 24 (4.2)     |            |         |
| No smoker                            | 892 (86.6)| 376 (81.6)     | 516 (90.7)   |            |         |
| Any comorbidity                      | 574 (48.2)| 208 (43.8)     | 366 (51.2)   | 6.258      | 0.012   |
| Asthma, n (%)                        | 9 (0.8)   | 5 (1.1)        | 4 (0.6)      | 0.925      | 0.336   |
| Coronary heart disease, n (%)        | 84 (7.1)  | 21 (4.4)       | 63 (8.8)     | 8.384      | 0.004   |
| Chronic obstructive pulmonary disease, n (%)| 24 (2.0) | 9 (1.9)       | 15 (2.1)     | 0.060      | 0.807   |
| Chronic lung disease, n (%)          | 35 (2.9)  | 15 (3.2)       | 20 (2.8)     | 0.130      | 0.718   |
| Chronic kidney disease, n (%)        | 24 (2.0)  | 12 (2.5)       | 12 (1.7)     | 1.039      | 0.308   |
| Liver disease, n (%)                 | 90 (7.6)  | 56 (11.7)      | 34 (4.7)     | 25.018     | <0.001  |
| Nervous system disorder, n (%)       | 9 (0.8)   | 4 (0.8)        | 5 (0.7)      | 0.078      | 0.781   |
| Cancer, n (%)                        | 29 (2.4)  | 5 (1.1)        | 24 (3.4)     | 6.372      | 0.012   |
| Diabetes, n (%)                      | 142 (11.9)| 48 (10.1)      | 94 (13.1)    | 2.530      | 0.282   |
| Immune disease, n (%)                | 19 (1.6)  | 7 (1.5)        | 12 (1.7)     | 0.076      | 0.783   |
| Dementia, n (%)                      | 8 (0.7)   | 2 (0.4)        | 6 (0.8)      | 0.747      | 0.387   |
| Malnutrition, n (%)                  | 3 (0.3)   | 2 (0.4)        | 1 (0.1)      | 0.897      | 0.343   |
| Hematological system diseases, n (%) | 7 (0.6)   | 4 (0.8)        | 3 (0.4)      | 0.871      | 0.351   |
| Stroke, n (%)                        | 23 (1.9)  | 4 (0.8)        | 19 (2.7)     | 4.962      | 0.026   |
| Hypertension, n (%)                  | 281 (23.6)| 76 (16.0)      | 205 (28.7)   | 25.405     | <0.001  |
| Charlson Comorbidity Index (CCI)     | 1.0 (0-2.0)| 0 (0-1.0)    | 2 (2.0-3.0)  | -9.190     | <0.001  |
| Disease severity status, n (%)       |           |                |              | 97.524     | <0.001  |
| Mild                                 | 194 (16.3)| 28 (5.9)       | 166 (23.3)   |            |         |
| General                              | 725 (61.1)| 337 (70.8)     | 388 (54.6)   |            |         |
| Severe                               | 141 (11.9)| 81 (17.0)      | 60 (8.4)     |            |         |
| Critical       | 127 (10.7) | 30 (6.3) | 97 (13.6) |
|----------------|------------|----------|-----------|
| Curb-65 score, n (%) |            |          |           |
| 0-1            | 837 (90.5) | 369 (96.3) | 468 (86.3) | 26.430 | <0.001 |
| 2              | 68 (7.4)   | 12 (3.1) | 56 (10.3) |
| 3–5            | 20 (2.2)   | 2 (0.5)  | 18 (3.3)  |
| MuLBSTA score  | 7.00(5.00,9.00) | 5.00(5.00,9.00) | 7.00(5.00,9.00) | 3.96 | <0.001 |

| Laboratory findings |          |          |           |
|---------------------|----------|----------|-----------|
| White blood cell count, ×10⁹ /L | 5.45(4.22,7.07) | 5.37(4.18,5.37) | 5.58(4.22,7.28) | 1.570 | 0.088 |
| Neutrophil count, ×10⁹ /L | 3.45(2.50,4.99) | 3.45(2.53,4.73) | 3.45(2.47,5.26) | 2.723 | <0.001 |
| Lymphocyte count, ×10⁹ /L | 1.18(0.83,1.63) | 1.18(0.81,1.60) | 1.18(0.84,1.64) | 1.074 | 0.157 |
| Eosinophil count, ×10⁹ /L | 0.30(0.00,1.30) | 0.20(0.01,0.80) | 0.50(0.0,1.7) | 5.751 | <0.001 |
| Haemoglobin, g/L | 131.00(119.00,144.00) | 137.00(126.00,151.00) | 127.00(117.00,137.00) | 8.049 | 0.015 |
| Platelet count, ×10⁹ /L | 197.00(148.00,262.50) | 175.00(137.00,230.50) | 215.00(165.00,281.00) | 7.909 | <0.001 |
| Activated partial thromboplastin time, s | 28.50(25.90,32.20) | 30.90(27.70,34.90) | 27.40(25.20,29.90) | 10.129 | <0.001 |
| Prothrombin time, s | 12.20(11.50,13.00) | 12.60(11.70,13.30) | 12.00(11.33,12.70) | 2.052 | 0.115 |
| D-dimer, mg/L | 0.56(0.29,1.59) | 0.50(0.22,1.17) | 0.63(0.33,1.79) | 3.194 | 0.001 |
| Albumin, g/L | 39.70(35.50,43.30) | 43.00(39.60,45.70) | 37.70(34.00,40.80) | 11.556 | 0.128 |
| Creatinine, µmol/L | 63.00(51.00,76.15) | 65.20(53.00,77.33) | 62.00(50.70,75.00) | 2.051 | 0.040 |
| Creatine kinase, U/L | 62.70(41.00,106.25) | 71.00(50.00,122.00) | 56.00(34.40,99.00) | 5.181 | <0.001 |
| Alanine aminotransferase, U/L | 23.55(16.00,39.05) | 24.00(16.00,39.90) | 23.00(15.48,39.00) | 0.433 | 0.665 |
| Aspartate aminotransferase, U/L | 25.00(19.67,35.73) | 25.60(20.00,35.00) | 25.00(19.00,36.00) | 0.459 | 0.647 |
| C-reactive protein, mg/L | 19.95(6.80,53.92) | 10.16(2.67,24.72) | 28.45(8.70,65.20) | 6.066 | <0.001 |
| Procalcitonin, ng/mL | 0.05(0.04,0.12) | 0.06(0.04,0.17) | 0.05(0.03,0.11) | 2.06 | 0.039 |
| Hypersensitive troponin I, pg/mL | 0.01(0.01,0.01) | 0.01(0.01,0.01) | 0.02(0.01,0.05) | 3.615 | <0.001 |

| Chest CT |          |          |           |
|----------|----------|----------|-----------|
| Bilateral lungs involved, n (%) | 741 (93.1) | 328 (90.6) | 413 (95.2) | 6.363 | 0.012 |
| Consolidation, n (%) | 180 (19.6) | 73 (16.0) | 107 (23.2) | 7.533 | 0.006 |
| Ground-glass opacity, n (%) | 666 (71.3) | 328 (71.6) | 338 (71.0) | 0.042 | 0.837 |
| Linear opacity, n (%) | 257 (27.8) | 112 (24.5) | 145 (31.2) | 5.200 | 0.023 |
| Pleural effusion, n (%) | 49 (5.4) | 19 (4.2) | 30 (6.6) | 2.559 | 0.110 |

Table 2. Treatments and outcomes of the patients in Sichuan and Wuhan cohorts
| Variable                                      | Total | Sichuan cohort | Wuhan cohort | Statistics | P value |
|-----------------------------------------------|-------|---------------|--------------|------------|---------|
| Treatments                                    |       |               |              |            |         |
| Antiviral treatment, n (%)                    | 1110 (93.8) | 448 (94.7) | 662 (93.2) | 1.067 | 0.302   |
| Antibiotics, n (%)                            | 698 (59.0) | 204 (43.0) | 494 (69.6) | 82.734 | <0.001 |
| Penicillins, n (%)                            | 49 (4.1) | 30 (6.3) | 19 (2.7) | 9.561 | 0.002   |
| Cephalosporins, n (%)                         | 233 (19.7) | 78 (16.5) | 155 (21.8) | 5.196 | 0.023   |
| β-lactam antibiotic, n (%)                    | 52 (4.4) | 17 (3.6) | 35 (4.9) | 1.221 | 0.269   |
| Aminoglycosides, n (%)                        | 6 (0.5) | 1 (0.2) | 5 (0.7) | 1.372 | 0.242   |
| Macrolides, n (%)                             | 28 (2.4) | 10 (2.1) | 18 (2.5) | 0.223 | 0.637   |
| Lincomycin, n (%)                             | 3 (0.3) | 1 (0.2) | 2 (0.3) | 0.056 | 0.813   |
| Quinolones, n (%)                             | 507 (42.8) | 151 (31.9) | 356 (50.1) | 38.810 | <0.001 |
| Antifungal treatment, n (%)                   | 35 (3.0) | 15 (3.2) | 20 (2.8) | 0.120 | 0.729   |
| Corticosteroids, n (%)                        | 272 (23.0) | 63 (13.3) | 209 (29.4) | 41.872 | <0.001 |
| Tranquilizing drug, n (%)                     | 52 (4.4) | 26 (5.5) | 26 (3.7) | 2.032 | 0.154   |
| Intravenous immunoglobulin, n (%)             | 9 (0.8) | 3 (0.6) | 6 (0.8) | 0.170 | 0.680   |
| Inotropic agents, n (%)                       | 46 (3.9) | 8 (1.7) | 38 (5.3) | 10.232 | 0.001   |
| Muscle relaxant, n (%)                        | 16 (1.4) | 11 (2.3) | 5 (0.7) | 5.367 | 0.021   |
| Oxygen therapy, n (%)                         | 791 (66.9) | 273 (57.7) | 518 (731) | 30.175 | <0.001 |
| Prone position ventilation, n (%)             | 30 (2.5) | 22 (4.6) | 8 (1.1) | 14.217 | <0.001 |
| Tracheotomy, n (%)                            | 8 (0.7) | 4 (0.8) | 4 (0.6) | 0.720* |         |
| Renal replacement, n (%)                      | 9 (0.8) | 5 (1.1) | 4 (0.6) | 0.497* |         |
| Blood transfusion, n (%)                      | 165 (14.0) | 30 (6.3) | 135 (19.1) | 38.587 | <0.001 |
| Nutrition support, n (%)                      | 131 (11.1) | 52 (11.0) | 79 (11.2) | 0.014 | 0.906   |
| TCM treatments, n (%)                         | 912 (77.0) | 418 (88.2) | 494 (69.6) | 55.620 | <0.001 |
| Physiotherapy, n (%)                          | 29 (2.4) | 24 (5.1) | 5 (0.7) | 22.605 | <0.001 |
| Outcomes                                      |       |               |              |            |         |
| ICU admission, n (%)                          | 127 (10.7) | 30 (6.3) | 97 (13.7) | 15.961 | <0.001 |
| Non-invasive mechanical ventilation, n (%)    | 69 (5.8) | 27 (5.7) | 42 (5.9) | 0.025 | 0.875   |
| Invasive mechanical ventilation, n (%)        | 18 (1.5) | 8 (1.7) | 10 (1.4) | 0.148 | 0.700   |
| ECMO, n (%)                                   | 3 (0.3) | 1 (0.2) | 2 (0.3) | 1.000* |         |
| Death                                         | 62 (5.2) | 3 (0.6) | 59 (8.3) | 33.758 | <0.001 |
| Time from illness onset to admission, days    | 8.00(4.00,13.00) | 5.00(2.00,9.00) | 10.00(7.00,15.00) | 13.626 | <0.001 |
| Hospital length of stay, days                 | 16.00 (9.00,24.00) | 17.00 (12.00,24.00) | 14.00 (9.00, 24.00) | -2.726 | <0.001 |
| Time from illness onset to ICU admission, days| 9.00(6.00,17.00) | 7.00(4.00,10.50) | 11.50(8.75,24.25) | 3.192* | <0.001 |
| Time from hospital admission to ICU admission, days| 3.00(0.00,9.00) | 4.00(0.00,9.00) | 3.00(0.00,10.50) | 0.415 | 0.678   |
| Outcomes                              | Unadjusted                          | Adjusted#                          |
|--------------------------------------|-------------------------------------|------------------------------------|
|                                      | OR  | 95%CI     | P       | OR  | 95%CI     | P       |
| ICU admission                        | 2.347  | 1.531-3.597  | <0.001  | 1.659  | 1.047-2.627  | 0.031  |
| Non-invasive mechanical ventilation  | 1.044  | 0.635-1.718  | 0.865  | 0.651  | 0.376-1.127  | 0.125  |
| Invasive mechanical ventilation      | 0.835  | 0.327-2.132  | 0.705  | 0.381  | 0.138-1.054  | 0.063  |
| Tracheotomy                          | 0.668  | 0.166-2.681  | 0.569  | 0.225  | 0.050-1.015  | 0.052  |
| Death                                | 14.286  | 4.444-45.455  | <0.001  | 7.643  | 2.311-25.274  | 0.001  |
| Time from illness onset to admission (>5 days) | 6.849  | 5.208-9.009  | <0.001  | 6.289  | 4.695-8.403  | <0.001  |
| Hospital length of stay (>17 days)   | 0.481  | 0.380-0.609  | <0.001  | 0.411  | 0.316-0.533  | <0.001  |
| Time from illness onset to ICU admission (>7 days) | 6.364  | 1.836-22.061  | 0.027  | 8.030  | 1.740-37.057  | <0.001  |
| Time from illness onset to discharge (>23 days) | 1.180  | 0.935-1.489  | 0.163  | 0.995  | 0.772-1.281  | 0.968  |
| Time from illness onset to death (>10 days) | 4.706  | 0.399-55.447  | 0.218  | 4.731  | 0.314-71.265  | 0.261  |
| Time from hospital admission to ICU admission (>4 days) | 0.857  | 0.243-3.024  | 0.811  | 0.665  | 0.122-3.620  | 0.637  |
| Time from hospital admission to death (>10 days) | 0.426  | 0.035-5.161  | 0.502  | 0.155  | 0.007-3.694  | 0.249  |
| Duration of viral shedding (>13 days) | 1.881  | 1.363-2.597  | <0.001  | 1.640  | 1.153-2.333  | 0.006  |

# Adjusted for gender, age, smoking and Charlson Comorbidity Index.

*Fisher's exact test.

ECMO, extracorporeal membrane oxygenation; TCM, traditional Chinese medicine.

Table 3. Risk of adverse outcomes in Wuhan cohort when taking Sichuan cohort as reference

Table 4. Regression analysis of risk factors for death, ICU admission and mechanical ventilation in all patients from Sichuan and Wuhan cohorts*
| Variables                                      | Death                                                                 | ICU admission                          | Non-invasive mechanical ventilation | Invasive mechanical ventilation |
|-----------------------------------------------|------------------------------------------------------------------------|----------------------------------------|-------------------------------------|---------------------------------|
|                                               | aOR  | 95% CI     | P   | aOR  | 95% CI    | P   | aOR  | 95% CI    | P   | aOR  | 95% CI    | P   |
| White blood cell count, $\times 10^9$/L       |      |            |     |      |            |     |      |            |     |      |            |     |
| <4                                            | 0.77 | 0.31-1.89  | 0.563 | 0.72 | 0.41-1.27 | 0.261 | 0.50 | 0.21-1.21 | 0.123 | 0.87 | 0.23-3.23 | 0.829 |
| 4~10                                          | -    | -          | -   | -    | -          | -   | -    | -          | -   | -    | -          | -   |
| >10                                           | 8.74 | 4.10-18.63 | <0.001 | 3.35 | 1.86-6.02 | <0.001 | 5.00 | 2.51-9.80 | <0.001 | 0.74 | 0.09-6.09 | 0.777 |
| Neutrophil count, $\times 10^9$/L             |      |            |     |      |            |     |      |            |     |      |            |     |
| <1.8                                          | 0.87 | 0.19-3.91  | 0.851 | 1.50 | 0.73-3.08 | 0.270 | 1.41 | 0.48-4.19 | 0.533 | 1.25 | 0.15-10.21 | 0.839 |
| 1.8~6.3                                       | -    | -          | -   | -    | -          | -   | -    | -          | -   | -    | -          | -   |
| >6.3                                          | 7.93 | 4.13-15.24 | <0.001 | 4.79 | 3.02-7.59 | <0.001 | 6.49 | 3.63-11.59 | <0.001 | 1.59 | 0.48-5.33 | 0.451 |
| Lymphocyte count, <1.0×10^9/L                 | 0.09 | 0.04-0.21  | <0.001 | 0.36 | 0.24-0.55 | <0.001 | 0.21 | 0.11-0.39 | <0.001 | 0.14 | 0.03-0.66 | 0.013 |
| Haemoglobin, <90 g/L                          | 7.35 | 2.63-20.53 | <0.001 | 2.64 | 1.07-6.52 | 0.035 | 2.98 | 0.98-9.07 | 0.055 | 3.42 | 0.54-21.74 | 0.193 |
| Platelet count, <100×10^9/L                  | 2.35 | 0.83-6.69  | 0.109 | 0.51 | 0.17-1.51 | 0.223 | 0.41 | 0.09-1.79 | 0.234 | 0.61 | 0.07-5.22 | 0.649 |
| D-dimer, $\geq 0.5$mg/L                      | 5.69 | 1.97-16.47 | 0.001 | 2.72 | 1.59-4.68 | <0.001 | 3.39 | 1.58-7.25 | 0.002 | 3.86 | 0.79-18.86 | 0.095 |
| Creatinine, $>133$μmol/L                     | 5.45 | 1.87-15.94 | 0.002 | 2.33 | 0.89-6.06 | 0.084 | 1.19 | 0.31-4.52 | 0.800 | 0.74 | 0.08-6.71 | 0.790 |
| Creatine kinase, $>1850$/U                   | 10.23 | 4.41-23.73 | <0.001 | 3.17 | 1.72-5.82 | <0.001 | 4.23 | 2.09-8.55 | <0.001 | 2.33 | 0.63-8.54 | 0.204 |
| Hypersensitive troponin I, $>0.04$ pg/ml      | 13.33 | 5.06-35.12 | <0.001 | 3.89 | 1.60-9.48 | 0.003 | 2.60 | 0.76-8.84 | 0.128 | 10.24 | 0.82-127.94 | 0.071 |
| Alanine aminotransferase, $>50$ U/L           | 2.63 | 1.22-5.69  | 0.014 | 1.70 | 1.01-2.85 | 0.045 | 1.74 | 0.89-3.41 | 0.103 | 1.28 | 0.33-4.94 | 0.719 |
| Aspartate aminotransferase, $>40$ U/L         | 7.11 | 3.60-14.06 | <0.001 | 2.36 | 1.48-3.77 | <0.001 | 2.73 | 1.51-4.96 | 0.001 | 2.21 | 0.67-7.27 | 0.193 |
| CRP, $\geq 10$ mg/L                          | -    | -          | -   | 2.18 | 1.22-3.88 | 0.008 | 9.97 | 2.32-42.91 | 0.002 | -    | -          | -   |
| Procalcitonin, $\geq 0.5$ ng/mL               | 23.87 | 7.62-74.75 | <0.001 | 1.72 | 0.73-4.08 | 0.217 | 1.01 | 0.31-3.25 | 0.991 | 4.26 | 0.88-20.71 | 0.072 |
| Chest CT                                      |      |            |     |      |            |     |      |            |     |      |            |     |
| Bilateral lungs involved                     | 0.37 | 0.04-3.17  | 0.363 | 1.41 | 0.42-4.75 | 0.577 | 1.31 | 0.30-5.69 | 0.723 | 0.31 | 0.03-2.91 | 0.307 |
| Consolidation                                | 0.84 | 0.23-3.10  | 0.794 | 1.09 | 0.63-1.89 | 0.771 | 1.53 | 0.78-2.99 | 0.214 | 1.04 | 0.21-5.02 | 0.965 |
| Ground-glass opacity                         | 7.33 | 0.94-57.28 | 0.057 | 0.83 | 0.51-1.34 | 0.437 | 1.11 | 0.58-2.15 | 0.749 | 4.11 | 0.50-33.46 | 0.187 |
| Linear opacity | 0.54 | 0.17-1.73 | 0.299 | 0.40 | 0.22-0.72 | 0.002 | 0.47 | 0.22-1.00 | 0.005 | 1.69 | 0.48-5.98 | 0.413 |
| Pleural effusion | 2.57 | 0.63-10.43 | 0.186 | 4.87 | 2.49-9.55 | <0.001 | 6.92 | 3.26-14.70 | <0.001 | 5.18 | 1.19-22.58 | 0.029 |
| Time from illness onset to admission (>5 days) | 2.40 | 1.00-5.78 | 0.049 | 1.42 | 0.60-3.37 | 0.424 | 1.62 | 0.96-3.03 | 0.133 | 1.34 | 0.44-4.09 | 0.609 |

* Adjusted for study region, gender, age, smoking, and Charlson Comorbidity Index.

**Figures**

(A) Distribution of patients with Covid-19 in Sichuan cohort (Map was generated by QGIS version 3.8.3); (B) Time of illness onset and hospital admission of patients in Sichuan cohort; (C) Time of illness onset of patients with or without Wuhan-related exposure in Sichuan cohort; (D) Time of hospital admission of patient with or without Wuhan-related exposure in Sichuan cohort. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.
Figure 2

(A) Time of illness onset and hospital admission of patients in Wuhan cohort; (B) The ratio of the number of patients without Wuhan-related exposure to cases with Wuhan exposure in Sichuan cohort.
Figure 3

(A) Symptomatic burden of patients with Covid-19 between Sichuan cohort and Wuhan cohort; Kaplan-Meier survival curve for time from illness onset to hospital admission (B), to ICU admission (C) and to discharge (D) of patients with Covid-19 between Sichuan and Wuhan cohorts.

Supplementary Files

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