Differences in the clinical characteristics and outcomes of COVID-19 patients in the epicenter and peripheral areas of the pandemic from China: a retrospective, large-sample, comparative analysis

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Research article

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Abstract

Background: There is limited information on differences in epidemiology, clinical characteristics and outcomes of the initial outbreak of the coronavirus disease (COVID-19) in Wuhan (the epicenter) and Sichuan (the peripheral area) in the early phase of the COVID-19 pandemic. This study was conducted to investigate the differences in the epidemiological and clinical characteristics of patients with COVID-19 between the epicenter and peripheral areas of pandemic and thereby generate information that would be potentially helpful in formulating clinical practice recommendations to tackle the COVID-19 pandemic.

Methods: The Sichuan & Wuhan Collaboration Research Group for COVID-19 established two retrospective cohorts that separately reflect the epicenter and peripheral area during the early pandemic. The epidemiology, clinical characteristics and outcomes of patients in the two groups were compared. Multivariate regression analyses were used to estimate the adjusted odds ratios (aOR) with regard to the outcomes.

Results: The Wuhan (epicenter) cohort included 710 randomly selected patients, and the peripheral (Sichuan) cohort included 474 consecutive patients. A higher proportion of patients from the periphery had upper airway symptoms, whereas a lower proportion of patients in the epicenter had lower airway symptoms and comorbidities. Patients in the epicenter had a higher risk of death (aOR=7.64), intensive care unit (ICU) admission (aOR=1.66), delayed time from illness onset to hospital and ICU admission (aOR=6.29 and aOR=8.03, respectively), and prolonged duration of viral shedding (aOR=1.64).

Conclusions: The worse outcomes in the epicenter could be explained by the prolonged time from illness onset to hospital and ICU admission. This could potentially have been associated with elevated systemic inflammation secondary to organ dysfunction and prolonged duration of virus shedding independent of age and comorbidities. Thus, early supportive care could achieve better clinical outcomes.

Background

In December 2019, an outbreak of pneumonia of unknown cause was identified in Wuhan, the capital of Hubei province in China. A novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which had not been detected previously in humans, was identified subsequently as the cause by Chinese scientists[1]. The disease was named the coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). The clinical spectrum of COVID-19 appears to be wide, and ranges from self-limited mild upper respiratory tract illness to severe pneumonia necessitating hospitalization or death. The clinical characteristics of some COVID-19 case series in Wuhan, which was the epicenter of the pandemic, have been previously reported in detail. The reports indicated that 26% to 33% of patients required intensive care and 4% to 15% died[2-4].

After the outbreak of COVID-19 in Wuhan, the government of the Sichuan province has implemented strict measures to combat 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 recommended by the National Health Commission of China. All medical resources were allocated by the HCSP to ensure efficient use. An expert panel drawn from multidisciplinary teams was established and comprised 125 physicians who were led by Dr. Wei Min Li and Dr. Zong An Liang (the corresponding authors of this study) since January 15, 2020. This expert panel soon released the emergency prevention and control guidelines for COVID-19 in the medical institutions of the Sichuan province[5]. Furthermore, we funded two additional important expert panels with psychological counseling[6] and traditional Chinese medicine as a complementary and alternative treatment option[7, 8]. Severely or critically ill patients would receive consultations with the expert panel team using the 5G network whenever necessary at 16:30 every day. There were 208 designated hospitals across the Sichuan Province that would be accessible for SARS-CoV-2-suspected or -confirmed individuals in every city. Accordingly, this arrangement resulted in an improved outcome in Sichuan province as one of the peripheral areas of the pandemic, with 2% to 10.1% of patients needing intensive care, and an approximately 1.0% morality rate[9-11] in recently published studies.

The factors underlying the significantly different clinical outcomes between the epicenter and peripheral areas affected by the pandemic remains largely unexplored. Recently, Liang et al.[12] observed the clinical characteristics and outcomes of hospitalized patients with COVID-19 who were treated in Hubei (epicenter) or outside Hubei (non-epicenter). However, as theirs is a multicenter study, the possibility of selection bias for the included patients cannot be ruled out. Furthermore, hospitalized patients in Hubei but not in Wuhan, would not be well representative of the first-generation COVID-19 cases. Considering the rapidly increasing number of cases confirmed SARS-CoV-2 infection worldwide, the existing researches into the differences between the epicenter and peripheral areas of the pandemic in the clinical characteristics and outcomes of COVID-19 patients were insufficient.
Here, we performed a comparative study to analyze the differences in the epidemiological and clinical characteristics of patients with COVID-19 between the epicenter and peripheral areas of pandemic. This study could provide information that would be potentially helpful in formulating clinical practice recommendations to tackle the COVID-19 pandemic worldwide.

**Methods**

**Study design and subjects**

This was a retrospective study based on two cohorts evaluated by the Sichuan and Wuhan Collaboration Research Group for COVID-19, China. The Sichuan cohort, as the group of patients from the peripheral area of the pandemic, consisted of SARS-CoV-2-confirmed patients who were 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, drawn from the epicenter area of the pandemic, was formed using a computer-generated simple random sampling method that was applied to enroll subjects from two designated hospitals, namely the Wuhan Red Cross Hospital and Renmin Hospital of Wuhan University, Wuhan, China. All patients enrolled in this study were diagnosed with COVID-19 according to the interim guidance issued by the National Health Commission of China and the WHO[13]. SARS-CoV-2 infection was confirmed by a positive result on a real-time reverse-transcriptase-polymerase-chain-reaction of nasopharyngeal, pharyngeal, throat-swab or sputum specimens. Some of these patients were included in studies reported by Wei et al.[14], Xiong et al.[15] and Xiong et al.[16]; however, their study purposes are significantly different from that of this study.

**Data collection**

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

**Study outcomes**

The primary outcomes included death or mechanical ventilation involving admission to the intensive care unit (ICU) for mechanical ventilation or ward, if ventilation was not performed in the ICU due to overwhelming numbers of COVID-19 patients. The secondary outcomes were the rate of ICU admission, time from illness onset to ICU admission and discharge, hospital 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 24-h intervals. The criteria for discharge were absence of fever for at least 3 days, substantial improvement in both lungs on chest computed tomography (CT), clinical remission of respiratory symptoms and comorbidities, and shedding of SARS-CoV-2.

**Statistical analysis**

Continuous variables were compared using the Student’s t test or Mann-Whitney U test; categorical variables were compared by the chi-square test or Fisher’s exact test as appropriate. Logistic or linear regression was performed to identify clinical variables that were associated with outcomes. The detailed statistical analysis is described in the supplementary data.

**Results**

**Epidemiological and clinical characteristics at hospitalization**

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

The demographic and clinical characteristics of these patients are shown in Table 1 and S1. Patients in the Sichuan cohort were younger (44 [32.0, 54.0] vs. 58 [43.0, 67.0] yrs, \( P<0.001 \)), there were fewer females (46.4% vs. 54.1%, \( P=0.010 \)), and included a higher number of current smokers (14.5% vs. 5.1%, \( P<0.001 \)). Two patients (0.4%) in the Sichuan cohort and 13 (1.8%) in the Wuhan cohort were healthcare workers (\( P=0.033 \)). The commonest comorbidity in both cohorts was hypertension (23.6%), followed by diabetes (11.9%). The Wuhan cohort had more cases with comorbidity (51.2% vs. 43.8%, \( P=0.012 \)) as assessed by the Charlson Comorbidity Index[17] (CCI) (2.0 [2.0, 3] vs. 0 [0, 1.0], \( P<0.001 \)). Fewer patients in the 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 (\( P<0.001 \)) than those in the Wuhan cohort.

Fever was the commonest symptom and was present in 61.8% of patients in the Sichuan cohort or 65.1% of patients in the Wuhan cohort, but no significant difference was detected between the two groups. The Sichuan cohort had a higher incidence of productive cough than the Wuhan cohort (\( P=0.012 \)). However, the Wuhan cohort seemed to have a higher symptomatic burden with regard to the 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 diarrhea (12.1% vs. 6.3%, \( P<0.001 \)). In contrast, the 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 distributions were observed between the two cohorts (\( P<0.001 \)), as assessed by CURB-65 and MuLBSTA (both \( P<0.001 \)). More than 75% of patients in both cohorts had mild or general disease, although the Sichuan cohort had a higher proportion of severe cases (17.0% vs. 8.4%) and the Wuhan cohort had more critically ill patients (13.6% vs. 6.3%). Chest CT radiographs in the Wuhan cohort were more likely to show bilateral lung involvement (\( P=0.012 \)) and consolidation (\( P=0.006 \)).

**Laboratory findings and treatments**

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

**Clinical outcomes**

The clinical outcomes are summarized in Table 2. The case fatality rate in the Sichuan cohort was obviously lower than that in the Wuhan cohort (0.6% vs. 8.3%, \( P<0.001 \)). However, there was no significant difference in the proportion of patients receiving noninvasive mechanical ventilation or invasive mechanical ventilation between the two cohorts (5.7% vs. 5.9%, \( P=0.872 \) and 1.7% vs. 1.4%, \( P=0.701 \)).

With regard to the secondary outcomes, the proportion of patients who were admitted to the ICU in the Sichuan cohort was significantly lower than that in the Wuhan cohort (6.3% vs. 13.6%, \( P<0.001 \)). The time from illness onset to ICU admission and time from illness onset to discharge in the Sichuan cohort were evidently shorter than that in the 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 stay in the Sichuan cohort was much longer than that in the 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 a significantly prolonged duration of SARS-CoV-2 shedding than that in the Sichuan cohort (19.0 [13.0, 28.0] vs. 14.0 [10.0, 19.0] days, \( P<0.001 \)).

**Logistic regression analyses**

Multivariable logistic regression models were used to explore the differences in clinical outcomes between the Sichuan and Wuhan cohorts (Table 3). The results showed that the Wuhan cohort had higher risk of death (\( \text{aOR}=7.64, 95\% \text{CI}=[2.31, 25.27], P=0.001 \)), ICU admission (\( \text{aOR}=1.66, 95\% \text{CI}=[1.05, 2.63], P=0.031 \)), delayed time from illness onset to hospital (\( \text{aOR}=6.29, 95\% \text{CI}=[4.70, 8.40], P<0.001 \)) and ICU admission (\( \text{aOR}=8.03, 95\% \text{CI}=[1.74, 37.06], P=0.001 \)) admissions, prolonged duration of viral shedding after COVID-19 onset (\( \text{aOR}=1.64, 95\% \text{CI}=[1.15, 2.33], P=0.006 \)), a decreased hospital stay (\( \text{aOR}=0.41, 95\% \text{CI}=[0.32, 0.53], P<0.001 \)) after adjusting for age, sex,
smoking status and the CCI. There was 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 hospitalization, the risk of the Wuhan cohort was nearly unchanged; however, the Sichuan cohort had a lower risk for extended time from illness onset to discharge (aOR=0.46, 95% CI= [0.34, 0.63], P<0.001).

In the overall study population of COVID-19 patients from the two cohorts, we constructed multivariable logistic regression models to detect the risk factors at admission for death, ICU admission, mechanical ventilation and duration of viral shedding after COVID-19 onset (Table 4). After adjusting for the cohort sites, sex, age, smoking status and the CCI, we found that white blood cells (>10×10^9/L), neutrophils (>6.3×10^9/L), lymphocytes (>1.0×10^9/L), hemoglobin (<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 hospitalization were associated with death, ICU admission and mechanical ventilation. In addition, we found that time from illness onset to hospitalization was associated with prolonged duration of virus shedding (adjusted β=0.11, 95% CI= [0.03, 0.24], P=0.009).

We analyzed the relationship between the delay in hospitalization and elevated systemic inflammation and features of organ dysfunction. The time from illness onset to hospitalization was positively correlated with systemic inflammatory cells such as white blood cells (r=0.086, P=0.004), neutrophils (r=0.089, P=0.003), eosinophils (r=0.116, P<0.001), platelets (r=0.212, P<0.001), and inflammatory biomarkers, such as D-dimer (r=0.101, P=0.004), procalcitonin (r=−0.093, P=0.019), features of organ dysfunction, such as hemoglobin (r=−0.155, P<0.001), BUN (r=0.10, P=0.002), creatine (r=−0.094, P=0.003), albumin (r=−0.263, P<0.001), and APTT (r=−0.247, P<0.001) (Table 5). After adjusting for age, the correlations of delay in hospitalization with BUN and D-dimer did not achieve statistical significance, which indicated that the delay in hospitalization was independent of age. We further analyzed the relationship between the delay in hospitalization and ICU admission with elevated systemic inflammation after adjusting for age, sex, smoking, and steroid use. In general, the relationship between the delay in hospitalization and elevated systemic inflammation did not change, which implied that these relationships were independent of age, sex, smoking, and steroid use.

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

There was almost no difference in clinical characteristics and outcomes between the two sub-cohorts with and without Wuhan-related exposure in Sichuan. Detailed information is provided in Supplementary Data (Tables S2, S3 and S4).

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

The differences in the clinical characteristics and outcomes between the Sichuan sub-cohort with Wuhan-related exposure and Wuhan cohort were similar to the differences between the Sichuan and Wuhan cohorts. The results are described in detail in the Supplementary Data (Tables S5, S6 and S7).

**Discussion**

To the best of our knowledge, there exists a paucity in information obtained from a comparative large-sample study on the differences in epidemiology, clinical characteristics and outcomes of patients with COVID-19 between the epicenter (Wuhan) and the peripheral areas of pandemic. This comparative study provides important insights. First, the outbreak and transmission of COVID-19 within the region of Sichuan as the peripheral epidemic area has been well contained within two months through the use of traditional public health outbreak response tactics. Second, the Sichuan cohort is characterized by a higher incidence of upper airway symptoms, whereas the Wuhan cohort was older, had fewer lower airway symptoms and comorbidities, and had elevated pivotal systemic inflammation indicative of organ dysfunction as well as worse clinical outcomes independent of sex, age, smoking and comorbidities. Third, the subgroup analysis indicated that, within the Sichuan cohort, the patients with Wuhan-related exposure had similar clinical features and outcomes to those with non-Wuhan-related exposure. Fourth, the Wuhan-related exposure patients in the Sichuan cohort had improved clinical outcomes than those in the Wuhan cohort, although these two groups of patients had a similar Wuhan-related exposure history.

As indicated in recently published studies[12], the COVID-19 patients in Wuhan, at the epicenter area of the epidemic, were older, had more co-existing conditions assessed by the CCI, had extended time from illness onset to hospitalization, and included more severely ill patients. However, the Sichuan cohort, as the peripheral area, had some characteristics features. First, there were fewer healthcare workers in the Sichuan cohort than in the Wuhan cohort, which could be at least partially explained by the insufficient implementation of precautions and the overwhelmed health system during the earlier stage of this outbreak in Wuhan. Second, intriguingly, there was a higher incidence of upper airway symptoms, rather than high incidence of lower airway symptoms in the Wuhan cohort at the epicenter epidemic, which was similar to the findings from exported cases in Singapore[18]. Accordingly, the exported patients from the epicenter were usually diagnosed
with a "common cold" at the beginning of the COVID-19 outbreak. The different populations, the airway proliferation location, or the evolution of SARS-CoV-2 possibly could account for these differential symptoms[18-21]. Third, within the consecutively recruited cases in the Sichuan cohort as a well-defined population, the subgroup analyses indicated a higher proportion of males and older patients among the non-Wuhan-related exposure patients, which supported the theory of the propensity for SARS-CoV-2 infection in males and elders[9, 22, 23]. Recent studies from the USA and Italy have reported that a greater proportion of elderly and male COVID-19 patients would experience more critical illness[24, 25].

Until now no antiviral treatment for COVID-19 has proven effective, and supportive care is the mainstay of treatment is. Compared with the Wuhan cohort, the use of antibiotics (i.e. cephalosporin and quinolones) and glucocorticoids in the Sichuan cohort decreased by 26.4% and 16.1%, respectively. These results could possibly be explained as follows. First, as indicated earlier, the expert panel drawn from the multidisciplinary team established by HCSP together developed and adjusted the treatment plan for severely or critically ill patients according to the interim guidance from the National Health Commission of China and the WHO across the 208 designated hospitals in Sichuan by using the 5G network every day. Accordingly, the use of systemic corticosteroids was strictly managed and they were not routinely administered for the treatment of COVID-19 patients. Second, the COVID-19 patients in the Wuhan cohort would actually be more severe or critically ill, which was supported by the increased use of supplemental oxygen in cases of acute hypoxia. In addition, prone-position ventilation, physical rehabilitation and a variety of traditional Chinese medicines were used more often in Sichuan under the guidance of the expert panel; however, this aspect needs to be investigated further in randomized controlled trials[7, 8].

In terms of clinical outcomes, several important findings were identified in this study. An epidemic outbreak provided an opportunity to obtain important information, some of which were associated with a limited window of opportunity. This study showed that there was a delay from illness onset to hospitalization in the Wuhan cohort, which might be an important risk factor for the progression of COVID-19. Multivariate regression analysis showed that the time from illness onset to hospitalization was significantly associated with mortality and ICU admission, which suggested some important implications with regard to the pathogenesis of SARS-CoV-2 and may provide insights into a unique window of opportunity for intervention[7]. Liang et al.[12] recently found that Wuhan-related exposure patients have worse clinical outcomes compared with the non-Wuhan-related exposure cases; they attributed the attenuated disease to the onward transmission of SARS-CoV-2. In fact, this is paradoxical to the findings reported from Liang et al.’s study[12] because the relationship between Wuhan-related exposure and prognosis disappeared 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 hospitalization. The severity of COVID-19 and the shortage of medical resources would partly account for these worse outcomes. For example, during an earlier stage of the outbreak, some patients would not have received sufficient oxygen support because of insufficient oxygen pressure.

The duration of infectious virus replication is an important factor in assessing the risk of transmission and for guiding decisions on the isolation of patients; however, the duration of SARS-CoV-2 RNA detection has not been well explored. Our study found that the Wuhan cohort in the epicenter area had the prolonged virus shedding, which may contribute to the disease severity and clinical course[26, 27]. Furthermore, we found for the first time that the duration of virus shedding was independently associated with age and time from illness onset to hospitalization. Our findings are supported by those of other studies. Liu et al.[28] found that the viral load in severe cases was higher than that of mild cases, which had early viral shedding. Wolfel et al.[29] found that virus shedding in the upper airway, which is the location of mild COVID-19, was very high during the first week of symptoms, whereas shedding of viral RNA from sputum derived from the lower airway, which is the region of general to critical illness in COVID-19, outlasts the disappearance of symptoms. Xu et al.[30] found that elderly patients had prolonged viral shedding, but the correlation of age with the duration of viral shedding disappeared after adjusting for confounders, although this might be partly attributed to the small sample size.

As the pandemic evolves, mutations and natural selection of SARS-CoV-2 inevitably occur, although this virus a lower mutation rate than that of other RNA viruses[31]. The China National Center for Bioinformation aligned 77,801 genome sequences of SARS-CoV-2 that were detected globally and identified a total of 15,018 mutations[32]. Studies have shown that mutations play an important role in the virulence and infectivity of SARS-CoV-2, although no significant association was found between mutations and outcomes pertaining to hospitalization or death[33-35]. Thus, it is unclear whether the different clinical outcomes of patients with COVID-19 between the epicenter and peripheral areas affected by the pandemic are due to mutations in SARS-CoV-2.

This large-sample comparative study provides informative insights into the differences in epidemiology, clinical characteristics and outcomes of patients with COVID-19 between the epicenter (Wuhan) and peripheral (Sichuan) areas of the pandemic. However, 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 for all patients. Accordingly, the missing data for some patients may have biased the findings. Second, the
Sichuan cohort, which represented the peripheral area of the COVID-19 pandemic, was incomplete although consecutive patients accounting for 88.1% of total cases with COVID-19 were recruited from 41 designated hospitals in Sichuan. Third, we did not analyze the genetic diversity of virus strains and the evolutionary history, which may well explain these biological differences between the epicenter and peripheral areas affected by the pandemic.

Conclusions

This comparative study found that there were significant differences in the epidemiology, clinical characteristics, and outcomes of patients with COVID-19 between the epicenter and peripheral areas affected by the pandemic. The worse outcomes in the epicenter could be partly explained by the overwhelming of health systems and the delayed time from illness onset to hospitalization that was associated with elevated systemic inflammation could indicate organ dysfunction and prolonged duration of virus shedding, independent of sex, age, smoking and comorbidities. This indicates potential implications that are of clinical relevance in interventions for COVID-19, wherein urgent or early supportive care would achieve improved clinical outcomes, including a lower mortality rate, although no proven effective therapies for this virus currently exist. However, no differences were found in the epidemiology, clinical characteristics, and outcomes between the first generation and secondary generation of patients in the peripheral area of pandemic. Biological differences accounting for the differences between the Wuhan-related exposure patients in the 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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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 (%) | 837 (90.5) | 369 (96.3) | 468 (86.3) |
| 0-1 | 68 (7.4) | 12 (3.1) | 56 (10.3) |
| 2 | 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) |

**Laboratory findings**

| Parameter | Sichuan | Wuhan | Wuhan | p-value |
|-----------|---------|-------|-------|---------|
| White blood cell count, ×10^3 /L | 5.45(4.22,7.07) | 5.37(4.18,5.37) | 5.58(4.22,7.28) | 0.088 |
| Neutrophil count, ×10^3 /L | 3.45(2.50,4.99) | 3.45(2.53,4.73) | 3.45(2.47,5.26) | <0.001 |
| Lymphocyte count, ×10^3 /L | 1.18(0.83,1.63) | 1.18(0.81,1.60) | 1.18(0.84,1.64) | 0.157 |
| Eosinophil count, ×10^3 /L | 0.30(0.00,1.30) | 0.20(0.01,0.80) | 0.50(0.0,1.7) | <0.001 |
| Haemoglobin, g/L | 131.00(119.00,144.00) | 137.00(126.00,151.00) | 127.00(117.00,137.00) | 0.015 |
| Platelet count, ×10^3 /L | 197.00(148.00,262.50) | 175.00(137.00,230.50) | 215.00(165.00,281.00) | <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) | <0.001 |
| Prothrombin time, s | 12.20(11.50,13.00) | 12.60(11.70,13.30) | 12.00(11.33,12.70) | 0.115 |
| D-dimer, mg/L | 0.56(0.29,1.59) | 0.50(0.22,1.17) | 0.63(0.33,1.79) | 0.001 |
| Albumin, g/L | 39.70(35.50,43.30) | 43.00(39.60,45.70) | 37.70(34.00,40.80) | 0.128 |
| Creatinine, µmol/L | 63.00(51.00,76.15) | 65.20(53.00,77.33) | 62.00(50.70,75.00) | 0.040 |
| Creatine kinase, U/L | 62.70(41.00,106.25) | 71.00(50.00,122.00) | 56.00(34.40,99.00) | <0.001 |
| Alanine aminotransferase, U/L | 23.55(16.00,39.05) | 24.00(16.00,39.90) | 23.00(15.48,39.00) | 0.665 |
| Aspartate aminotransferase, U/L | 25.00(19.67,35.73) | 25.60(20.00,35.00) | 25.00(19.00,36.00) | 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) | <0.001 |
| Procalcitonin, ng/mL | 0.05(0.04,0.12) | 0.06(0.04,0.17) | 0.05(0.03,0.11) | 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) | <0.001 |

**Chest CT**

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

**Table 2. Treatments and outcomes of the patients in Sichuan and Wuhan cohorts**
| Variable                                               | Total | Sichuan cohort | Wuhan cohort | Statistics | P value |
|--------------------------------------------------------|-------|----------------|--------------|------------|---------|
| n                                                      | 1184  | 474            | 710          |            |         |
| Treatments                                             |       |                |              |            |         |
| Antiviral treatment, n (%)                             | 1110  | 448 (94.7)     | 662 (93.2)   | 1.067      | 0.302   |
| Antibiotics, n (%)                                     | 698   | 204 (43.0)     | 494 (69.6)   | 82.734     | <0.001  |
| Penicillins, n (%)                                     | 49    | 30 (6.3)       | 19 (2.7)     | 9.561      | 0.002   |
| Cephalosporins, n (%)                                  | 233   | 78 (16.5)      | 155 (21.8)   | 5.196      | 0.023   |
| β-lactam antibiotic, n (%)                            | 52    | 17 (3.6)       | 35 (4.9)     | 1.221      | 0.269   |
| Aminoglycosides, n (%)                                 | 6     | 1 (0.2)        | 5 (0.7)      | 1.372      | 0.242   |
| Macrolides, n (%)                                      | 28    | 10 (2.1)       | 18 (2.5)     | 0.223      | 0.637   |
| Lincomycin, n (%)                                      | 3     | 1 (0.2)        | 2 (0.3)      | 0.056      | 0.813   |
| Quinolones, n (%)                                      | 507   | 151 (31.9)     | 356 (50.1)   | 38.810     | <0.001  |
| Antifungal treatment, n (%)                            | 35    | 15 (3.2)       | 20 (2.8)     | 0.120      | 0.729   |
| Corticosteroids, n (%)                                 | 272   | 63 (13.3)      | 209 (29.4)   | 41.872     | <0.001  |
| Tranquilizing drug, n (%)                              | 52    | 26 (5.5)       | 26 (3.7)     | 2.032      | 0.154   |
| Intravenous immunoglobulin, n (%)                      | 9     | 3 (0.6)        | 6 (0.8)      | 0.170      | 0.680   |
| Inotropic agents, n (%)                                | 46    | 8 (1.7)        | 38 (5.3)     | 10.232     | 0.001   |
| Muscle relaxant, n (%)                                 | 16    | 11 (2.3)       | 5 (0.7)      | 5.367      | 0.021   |
| Oxygen therapy, n (%)                                  | 791   | 273 (57.7)     | 518 (731)    | 30.175     | <0.001  |
| Prone position ventilation, n (%)                      | 30    | 22 (4.6)       | 8 (1.1)      | 14.217     | <0.001  |
| Tracheotomy, n (%)                                     | 8     | 4 (0.8)        | 4 (0.6)      | 0.720*     |         |
| Renal replacement, n (%)                               | 9     | 5 (1.1)        | 4 (0.6)      | 0.497*     |         |
| Blood transfusion, n (%)                               | 165   | 30 (6.3)       | 135 (19.1)   | 38.587     | <0.001  |
| Nutrition support, n (%)                               | 131   | 52 (11.0)      | 79 (11.2)    | 0.014      | 0.906   |
| TCM treatments, n (%)                                  | 912   | 418 (88.2)     | 494 (69.6)   | 55.620     | <0.001  |
| Physiotherapy, n (%)                                   | 29    | 24 (5.1)       | 5 (0.7)      | 22.605     | <0.001  |
| Outcomes                                               |       |                |              |            |         |
| ICU admission, n (%)                                   | 127   | 30 (6.3)       | 97 (13.7)    | 15.961     | <0.001  |
| Non-invasive mechanical ventilation, n (%)             | 69    | 27 (5.7)       | 42 (5.9)     | 0.025      | 0.875   |
| Invasive mechanical ventilation, n (%)                 | 18    | 8 (1.7)        | 10 (1.4)     | 0.148      | 0.700   |
| ECMO, n (%)                                            | 3     | 1 (0.2)        | 2 (0.3)      | 1.005      | <0.001  |
| Death                                                  | 62    | 3 (0.6)        | 59 (8.3)     | 33.758     | <0.001  |
| Time from illness onset to admission, days             | 8.00  | 5.00 (2.00,9.00) | 10.00 (7.00,15.00) | 13.626 | <0.001 |
| Hospital length of stay, days                         | 16.00 | 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  | 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  | 4.00 (0.00,9.00) | 3.00 (0.00,10.50) | 0.415 | 0.678  |
Time from illness onset to discharge, days  
26.00(18.00,35.00) 23.00(18.00,31.00) 28.00(18.00,38.00) 5.693 <0.001  
Time from illness onset to death, days  
16.50(13.00,21.75) 13.00(11, -) 17.00(13.00,23.50) 1.240a 0.235  
Time from hospital admission to death, days  
5.00(3.00,7.00) 10.00(6.00,-) 4.00(3.00,7.00) 1.427 0.153  
Duration of viral shedding, days  
14.00(9.00;22.00) 13.00(8.00,18.00) 17.00(11.00,27.00) 6.665 <0.001  
* 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

| 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.

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 | 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             |
| $<4$                              | 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 | 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            |
| $<1.8$                            | -                           | -                           | -                                   | -                               |
| $1.8-6.3$                         | -                           | -                           | -                                   | -                               |
| $>6.3$                            | 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            | 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, $<100\times 10^5$/L | 0.109 0.51 0.233            | 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          | 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         | 2.33 0.89-6.06 0.084        | 0.89-6.06 0.084             | 1.19 0.31-4.52 0.800                | 0.74 0.08-6.71 0.790             |
| Creatine kinase, $>185$ U/L       | 3.77 2.85 9.48              | 2.85 9.48 0.003             | 2.60 0.76-8.84 0.128                | 0.128 0.82-127.94 0.071          |
| Hypersensitive troponin I, $>0.04$ pg/ml | 3.89 1.60-9.48 0.003        | 1.60-9.48 0.003             | 2.60 0.76-8.84 0.128                | 0.128 0.82-127.94 0.071          |
| Alanine aminotransferase, $>50$ U/L | 1.70 1.01-2.85 0.045        | 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 | 1.36 1.48-3.77 $<0.001$    | 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               | 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             |
| Procalcitonin, $\geq 0.5$ ng/mL   | 2.87 7.62-74.75 $<0.001$   | 7.62-74.75 $<0.001$        | 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 | 0.86-3.03 | 0.133 | 1.34 | 0.44-4.09 | 0.609 |

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