Title: Critical Care for Patients with Severe Covid-19 in Sichuan Province, China——A Provincial Cohort Study

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ABSTRACT

Background

Data regarding critical care for patients with severe Covid-19 are limited. We aimed to describe the clinical course and critical care implemented for this patient population at the provincial level in Sichuan, China.

Methods

In this population-based multicenter cohort study, conducted from January 16 to March 15, 2020, all microbiologically confirmed Covid-19 patients who met the national severe or critical criteria were included and followed-up until discharge, death, or the end of the study.

Results

Out of 539 confirmed Covid-19 patients, 81 severe cases (15.0%) were identified. The median (IQR) age was 50 (39-65) years, 37% were female, and 53.1% had chronic comorbidities. Among the five predefined criteria for severe illness, low PaO_2:FiO_2 ratio (<300 mmHg), low pulse oxygen saturation (≤93%), and dyspnea were the most commonly reported, accounting for 87.7%, 66.7% and 27.2% of the severe cases, respectively. The median period from the onset of symptoms to the first hospitalization was 3 (1-6) days. Seventy-seven patients (95.06%) were admitted to hospitals being able to provide critical care by day 1. By day 28, 53 (65.4%) were discharged, 3 (3.7%) were deceased, and 25 (30.9%) were still hospitalized. Conventional oxygen therapy, administered to 95.1% of the patients, was the most commonly used respiratory support

and met 62.7% of the respiratory support needed, followed by high-flow nasal cannula (19.5%) and noninvasive mechanical ventilation (10%).

Conclusions

Early identification, hospitalization, and provision of critical care to severe Covid-19 patients may improve prognosis. Sufficient conventional oxygen equipment should be prioritized and implemented without delay.

INTRODUCTION

The 2019 novel coronavirus disease (Covid-19) has spread globally since its outbreak in December 2019 and was declared a pandemic by the World Health Organization on March 11. Out of over 200,000 patients affected worldwide, approximately 19% are expected to progress to severe or critical disease, which poses a high mortality rate up to 8.1%.[1,2] However, little data has been published regarding critical care for Covid-19.

Early studies from Wuhan investigated the epidemiological and clinical characteristics of patients affected by Covid-19. The in-hospital mortality rate ranged from 4.9% to 15%.[3-5] A recent single-center study reported a 28-day mortality of 61% among 52 critically ill patients who were admitted to the intensive care unit (ICU) and experienced considerable respiratory compromise.[6] Several studies reported a few severe cases of Covid-19, with one in Zhejiang Province[7], five in Shanxi Province[8], China. No severe cases were reported in Singapore[9]. The clinical characteristics of 173 patients with severe Covid-19, using data from 30 provinces in China, were described by Guan et al.[2] However, the clinical course, critical care, and patient prognosis of severe Covid-19 remain largely unexplored.[10,11] Population-based studies regarding these subjects may provide important data to reduce the mortality rate among patients with severe Covid-19.

Sichuan province located in the south west of China, with a total area of 486 thousand square kilometers and 83 million population.[12] Since the first reported case of Covid-19 on January 16, 2020, a total of 539 cases have been confirmed in Sichuan. Due to the urban-rural disparities in healthcare, provision of critical care for severely ill patients was centralized by dispatching ICU staff and resources to designated hospitals. In this multicenter cohort study (StUdy of 2019 Novel coRonavirus pneumonia Infected critically ill patients in Sichuan provincE, SUNRISE), we aimed to analyze the epidemiology, clinical course and critical care for severe Covid-19 at the provincial level.

METHODS

Setting

To ensure high quality care despite region-based healthcare disparities, the Sichuan Provincial Department of Health (SPDH) dispatched ICU physicians, nurses, respiratory therapists and resources to designated hospitals. A designated hospital was considered eligible for severe Covid-19 patients if it was covered by ICU physicians and provided advanced respiratory support which was defined as the use of high flow nasal cannula (HFNC), non-invasive (NIV), or invasive ventilation (IV). Remote multi-disciplinary consultation was arranged to discuss complex patients daily. The number and severity classification[1] of Covid-19 patients in all designated hospitals were required to be reported daily.

Study Design

This provincial multicenter cohort study (http://www.chictr.org.cn/index.aspx, ChiCTR2000029758) was initiated by investigators in West China Hospital (WCH) in Sichuan Province.[13] The study involved 21 hospitals designated for severely affected patients, of which 18 were directly caring for patients included in the present study. Data were prospectively collected for patients who were still in the hospital after study enrollment, and otherwise retrospectively collected between January 16 and March 15. The study timeline is shown in the supplementary file. The study protocol was approved by the Ethics Committee of the West China Hospital and the participating hospitals. Informed consent was obtained from the patient or the patient's legally authorized representative.

Participants and follow-up

Confirmed Covid-19 patients meeting any of the following criteria were included as severe cases: 1) dyspnea or respiratory frequency ≥30/min; 2) pulse oxygen saturation (SPO_2) ≤93% without oxygen therapy in resting state; 3) PaO_2:FiO_2 ratio <300; 4) lung infiltrates >50% within 24–48 hours; 5) respiratory failure, septic shock, and/or multiple organ dysfunction.[1] The date of enrollment of each patient was considered day 1 (D1). Covid-19 was diagnosed using real time reverse transcription polymerase chain reaction (RT-PCR) of nasal, pharyngeal swab or sputum specimens by the local Centers for Disease Control (CDC). Patients were followed up from D1 to the end of the study.

Patient characteristics were demonstrated according to the outcome by D28, while the main support methods used were analyzed throughout the study period.

Data collection

In the first stage, 13 designated hospitals were included in our study on February 6. In the second stage, another 8 designated hospitals were included on February 12 after obtaining permission from the SPDH to access information regarding daily reported cases of Covid-19. Detailed demographic, epidemiological, clinical and laboratory data were recorded using the electronic data capture and analysis system (EDC) (more details are provided in the supplementary file). Data entry was completed by physicians and nurses who were trained on the use of EDC and were working in the designated hospitals. Data quality was overseen by a team of senior ICU physicians and statisticians.

Definitions

In the special circumstances as stated above, conventional definitions of ICU admission or discharge will not be used because mildly and severely ill patients were treated in the same ward in some cases. We defined D1 as the day when patient met the criteria for severe illness. Patients were categorized into three groups according to clinical outcomes by D28: rapid recovery (RR), prolonged recovery (PR) and no recovery (NR).

1) RR: patient fully meeting the discharge criteria before D28, with normal body

temperature ≥3 days, obvious improvement in respiratory symptoms and pulmonary imaging, and twice-negative nucleic acid tests (sampling interval being at least 24 hours) on respiratory samples; 2) PR: patient partially meeting the discharge criteria on D28 and still requiring hospitalization but without advanced respiratory support; 3) NR: death or the patient still in need of advanced respiratory support on D28.

Statistics

Data management, manipulation, and analysis were conducted by a professional epidemiologist and statistician, from a third Clinical Research Center, who did not participate in data collection. To ensure the high quality of database, all missing data and outliers detected were checked by two clinicians independently in the medical records. Then the verified data were collected and transferred for data completion or correction. No imputation was made for missing data. Data are expressed as median (IQR) for continuous variables and number (%) for categorical variables. For continuous variables, Wilcoxon test was applied to assess the difference between patients in one group and others, Kruskal-Wallis test to assess the overall difference among the RR, PR and NR groups. For categorical variables, $\chi 2$ test or Fisher's exact test were performed according to the distribution of data. Two-sided tests with a significance level of 0.05 were applied. Needs for different respiratory support throughout the study period were assessed using person-day that denoted the use by one person in one day. All the analyses were conducted using R software version 3.6.2

(R Foundation for Statistical Computing). We used the tydyverse[14] package of to manage daily data and plot the daily use of main support and the pheatmap[15] package to plot the heatmap.

RESULTS

Distribution and referral of the severe Covid-19 patients in Sichuan province

Eighty-one patients from 13 cities and 2 minority autonomous prefectures in Sichuan Province met the criteria for severe Covid-19 and were included in the study, accounting for 15.0% (81/539) of the total provincial patient population. Out of 226 planned designated hospitals, 18 (8.0%) participated in the study. All patients were centralized to the designated hospitals, and 77 patients (95.1%) were admitted by D1 (**Figure 1**). The median (IQR) durations from the onset of symptoms to the first hospitalization, RT-PCR confirmation and the diagnosis of severe condition were 3 (1–6), 7 (5-10), and 9 (6–11) days, respectively.

Epidemiology and clinical characteristics of the severe Covid-19 patients on D1

The median age (IQR) of the patients was 50 (39-65) years and 37.0% were female. Of these patients, 37 (45.7%) had travel history to Wuhan, 19 (23.5%) were part of family clusters and 19 (23.5%) had no known contact history. Chronic comorbidities were observed among 43 (53.1%) patients, in which diabetes, hypertension and chronic

pulmonary diseases were the most common, accounting for 22.2%, 18.5% and 13.6%, respectively. Forty-one patients (50.6 %) were with an BMI ≥24 kg/m^2 (**Table 1**).

Only 42 (51.9%) patients had fever on D1 although 69 (85.2%) had a history of fever. Among the five predefined criteria for severe illness, PaO_2:FiO_2 ratio, SPO_2, and dyspnea criteria were the most commonly reported, accounting for 87.7%, 66.7% and 27.2%, respectively. All chest images of the patients (80 with CT scan and 1 with chest X-ray) showed bilateral lesions, but only 4 (4.9%) were diagnosed using the imaging criterion. Seventy-six patients (93.8%) were administrated by respiratory support, including 51 (67.9%) by conventional oxygen therapy (COT) through nasal catheter or mask, 13 (16.1%) by NIV, and 8 (9.9%) by HFNC. No patient was intubated or needed ECMO. Six patients developed acute kidney injury (AKI)[16] and 5 met the criteria for septic shock[17] (**Table 1**).

Patient follow-up and clinical outcomes

All patients were followed up and reached the predefined endpoints. Among 81 patients, 53 (65.4%) were regarded as RR and admitted before D28. Eighteen (22.2%) patients were regarded as PR, including 13 still in need of conventional oxygen therapy and 5 awaiting negative results of RT-PCR on D28. Ten patients (12.3%) were in the NR group, including 3 deaths and 7 still in need of advanced respiratory support on D28. Patients in the NR group tended to be older ($p<0.001$), had higher Apache II[18] ($p=0.01$)

and SOFA scores[19] (p<0.001), were more likely to have comorbidities (p=0.02) including AKI (p=0.004) than the other groups. C-reaction protein (p=0.02) was higher while lymphocyte (p=0.03) and platelet (p=0.005) were lower in the NR group (**Table 1**). Among the 3 deceased, one was a 64-year-old female with scleroderma, pulmonary fibrosis and diabetes, one was an 80-year-old female with hypertension and coronary heart disease. Both patients developed severe respiratory failure and died of multi-organ dysfunction. The third patient was a 73-year-old male with hypertension and end-stage renal disease and died from circulatory failure. By March 15, among those who were still hospitalized on D28, 15 were discharged, 9 patients were still hospitalized, and an 81-year-old male died of end-stage chronic pulmonary disease on D45.

Respiratory support

Daily respiratory support given to each patient from D1 to D28 were shown in **Figure 2**. Of the 81 patients diagnosed severe, 79 (97.5%) used COT, 31 (38.3%) used HFNC, 22 (27.2%) used NIV, 10 (12.3%) used IV, and 1 (1.2%) used ECMO (**Table 2**). Thirty-four patients (42% of 81) used only COT among which 79.4% discharged before D28. In the 25 patients who started with COT and needed escalation to advanced respiratory support methods, 12 (48.0%) were discharged by D28.

Among patients who were discharged within 28 days, the median duration (IQR) of hospitalization was 18 (14–24) days. Only COT, HFNC, and NIV were used as

respiratory support, for a median duration of 10 (5–14), 0 (0–4), and 0 (0–0) days, respectively. As for PR patients, COT, HFNC, NIV, and IV were used for 18 (7–24), 0 (0–7), 0 (0–3), and 0 (0–3) days, respectively. Concerning about the NR patients, the median duration for COT, HFNC, NIV and IV were 3 (1–10), 2.5 (0–11), 0 (0–3), and 2 (0–16) days, respectively. ECMO was used for one day by one patient.

To describe the needs for respiratory support throughout the study period, we also analyzed the usage of respiratory support along with the daily number of newly diagnosed patients with Covid-19 disease in Sichuan, newly diagnosed severe cases, and patients with severe disease hospitalized (**Figure 3**). In total, all forms of respiratory support were used 1579 person-day, of which COT took up 62.7 % (990 person-day), HFNC 19.3% (305 person-day), NIV 9.4% (149 person-day), IV 8.5% (134 person-day), and ECMO 0.06% (1 person-day).

The peak needs of respiratory support, which lasted for 20 days and paralleled with hospitalization needs for severely ill patients, had a significant lag of 9 days behind the peak of newly diagnosed patients in Sichuan. During the most demanding days for respiratory support measures, 47 patients with severe disease needed access. Of these demands, 55.3% were COT, 21.3% were HFNC, 12.8% were NIV, and 10.6% were IV.

Other support measures and medical treatment

Some patients needed life-saving measures such as renal replacement (5 patients, 6.2%), vasopressors (5, 6.2%), and blood transfusion (6, 7.4%). Other support methods included the prone position, partial parenteral nutrition therapy, analgesics and sedatives, used by 16 (19.8%), 17 (21.0%), and 13 (16.1%) patients, respectively (**Table 2**).

Various drug treatments were given despite the absence of effective evidence-based antiviral and immunomodulates. Antiviral agents lopinavir/ritnonavir and abidol were used in 71 (87.7%) and 25 (30.9%) patients, respectively. Regarding immunomodulates, nebulized recombinant human interferon α2b, corticosteroid and thymosin α were used by 57 (70.4%), 44 (54.3%) and 33 (40.7%) patients, respectively. Antibiotics were used for prevention in 58 (71.6%) patients.

DISCUSSION

To our knowledge, it is the first time that the clinical course and critical care of severe Covid-19 patient was demonstrated in detail from the first day when recognized as severe illness to 28-day outcome. Among all the Covid-19 patients Sichuan, only 0.56% (3/539) deceased; even among the severe Covid-19 patients, the rate was 3.7% (3/81), lower than the mortality rates reported elsewhere worldwide[1-6]. Some features of the severe Covid-19 patients were observed in our study: the median duration from the onset of symptoms to hospitalization and D1 was 3 (1–6) and 9 (6–11) days,

respectively. Seventy-seven (95.06%) patients were admitted to the designated hospitals with ability to provide critical care by D1. Low PaO_2:FO_2 ratio was observed among 87.8% of the patients, the highest among the five severity criteria. Conventional oxygen therapy was the most commonly used respiratory support method given to 95.1% of the patients and met 62.7% of all the respiratory support needed.

Limited data has been reported regarding the importance of PaO_2:FiO_2 ratio in the identification of severe Covid-19. Results in our study suggested that PaO_2:FiO_2 ratio was a sensitive indicator for early identification of severe Covid-19. On D1 87.8% of the patients in our study had an PaO_2:FiO_2 ratio lower than 300 mmHg, while the SPO_2 was 96 (93-97) %, and 72.8% without symptoms of dyspnea. With the early identification of the severe illness, 93.8% patients were receiving various respiratory support from or before D1, with a median PaO_2:FO_2 ratio of 204 mmHg. In the previous studies,[4,6] the median PaO_2:FO_2 ratio on ICU admission reported were much lower (103.8 and 136 mmHg), while many of the studies didn't report the data.[1-3,5,20]

It is reasonable to hypothesis that hypoxemia may participate in the inflammation and multiple organ injury[21] if the hypoxic compensatory period was ignored or not timely treated due to limited oxygen support equipment when confronting a surge of patient flow.[22,23] Therefore, we comprehensively analyzed the respiratory support used during the study period. If severely ill patients can be recognized earlier, basic oxygen therapy

and close monitoring may suffice, as in the 42% of the patients in our study. This scenario is quite different from that in Wuhan, where more than 80% of patients needed advanced respiratory support.[4,6] Advanced respiratory support equipment is life-saving but a large availability of conventional oxygen therapy is also necessary. Prioritizing and providing basic care for severe Covid-19 patients should be considered by healthcare providers in early stage.

Resources and timing are of critical importance to critical care for severe Covid-19 patients. All the severe Covid-19 patients were centralized to the 18 designated hospitals covering with ICU staff and advanced organ support methods, allowing all patients to receive critical care, albeit at a lower quality than usual.[24] While in other study, only 19.1% of the severe cases were treated in the ICU.[2] In addition, the median duration from symptom onset to admission for critical care in our study was 9 days, while data from Wuhan were 9.5-12 days.[4,6,20] The time lag of provision of critical care may have significant impact on patient prognosis. Regarding the duration from symptom onset to hospital visit time, there's obvious difference between studies from Wuhan and outside Wuhan where the mortality rate was much lower than Wuhan. The reported median hospitalization duration was 5-11 days in Wuhan,[3,4,20] while 2-4.5 days in Zhejiang province,[7] Beijing[10] and our study. In the 41 cases study from Wuhan[3], a significant difference was observed for this duration between ICU and non-ICU patients (8 vs. 1 day, p=0.002). In our study, because most of our patients were admitted

to hospital early, the duration was similar in the RR, PR and NR group (median: 3, 4, and 4.5 days, respectively). Studies with larger sample size including patients from different cities may further clarify the association between admission timing and patient outcomes.

Our study has the following limitations. First, a small part of the data was collected retrospectively, leading to potential incompleteness and inaccuracy for some variables. We mitigated this limitation by designating a team of researchers to verify and complete the data. Second, our study was mainly descriptive due to the small sample size; however, this limitation did not detract from our main objective in a relatively well-controlled clinical environment. Third, the findings reported in our study might not be generalizable to populations with completely different impact of the pandemic and government strategies.

Covid-19 patients with severe illness should be early identified and closely monitored in a critical care setting. Sufficient conventional oxygen equipment should be well prepared and implemented as first-line treatment without delay to patients with risk of hypoxia.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study design, conduction, data collection, writing, examination and approval of the final manuscript.

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Yan Kang, Xuelian Liao, Zhen Li, Bo Wang and Xiaodong Jin wrote the manuscript and had primary responsibility for final content.

CONFLICTS OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Table 1. Clinical Characteristics of the severe Covid-19 patients, according to outcome by D28

Characteristics	Total (N=81)	Rapid Recovery (N=53)	No Recovery (N=10)	Pronged Recovery (N=18)
Epidemiological and general characteristics				
Age				
Median (IQR) — yr	50.0 (39.0-65.0)	49.0 (39.0-63.0)	76.0 (64.0-80.0)	48.0 (37.0-60.0)
Distribution — no. (%)				
<45	28 (34.6)	20 (37.7)	6 (60.0)	8 (44.4)
45-65	30 (37.0)	21 (39.6)	3 (30.0)	6 (33.4)
≥65	23 (28.4)	12 (22.6)	1 (10.0)	4 (22.2)
Female sex — no. (%)	30 (37.0)	19 (35.9)	6 (60.0)	5 (27.8)

Current smokers — no. (%)	3 (3.7)	1 (1.9)	1 (10.0)	1 (5.6)
BMI				
Median (IQR) — kg/m^2	24.0 (21.5-27.3)	24.5 (22.3-27.7)	25.2 (21.1-27.3)	23.2 (20.0-25.2)
Distribution — no. (%) [a]				
<18.5	8 (9.9)	5 (9.4)	1 (10.0)	2 (11.1)
18.5-23.9	32 (39.5)	19 (35.9)	3 (30.0)	10 (55.5)
24-27.9	26 (32.1)	18 (34.0)	5 (50.0)	3 (16.7)
≥28.0	15 (18.5)	11 (20.8)	1 (10.0)	3 (16.7)
Exposure to source of transmission				
Yes — no. (%)	62 (76.5)	42 (79.3)	6 (60.0)	14 (77.8)
Family cluster	19 (23.5)	15 (28.3)	1 (10.0)	3 (16.7)
Living in or having travelled to Wuhan	37 (45.7)	26 (49.1)	3 (30.0)	8 (44.4)

Other scenarios [b]	6 (7.4)	1 (1.9)	2 (20.0)	3 (16.7)
Symptoms				
Fever (≥37.5°C)	39 (48.2)	25 (47.2)	5 (50.0)	9 (50.0)
Non-productive cough	40 (49.4)	29 (54.7)	3 (30.0)	8 (44.4)
Productive cough	38 (46.9)	24 (45.3)	3 (30.0)	11 (61.1)
Fatigue	30 (37.0)	20 (37.7)	2 (20.0)	8 (44.4)
Dyspnea	25 (30.9)	17 (32.1)	3 (30)	5 (27.8)
Other symptoms [c]	37 (45.7)	27 (50.9)	2 (20.0)	8 (44.4)
Coexisting disorders				
Yes — no. (%)	43 (53.1)	23 (43.4)	10 (100.0)	10 (55.6)
Diabetes	18 (22.2)	8 (15.1)	3 (30.0)	7 (38.9)
Hypertension	15 (18.5)	9 (17.0)	4 (40.0)	2 (11.1)

Chronic pulmonary disease	11 (13.6)	5 (9.4)	3 (30.0)	3 (16.7)
Cardiovascular or cerebrovascular disease	5 (6.2)	2 (3.8)	3 (30.0)	0 (0.0)
Congestive heart failure	4 (4.9)	2 (3.8)	1 (10.0)	1 (5.6)
Moderate to severe renal disease	3 (3.7)	1 (1.9)	2 (20.0)	0 (0.0)
AIDS, metastatic malignancy, or moderate to severe hepatic disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other coexisting disorder	34 (42.0)	18 (34.0)	9 (90.0)	7 (38.9)
Clinical features on D1				
Median SOFA score (IQR)	3.0 (3.0-5.0)	3.0 (3.0-4.0)	7.0 (5.0-8.0)	3.0 (2.0-4.0)
Median Apache II score (IQR)	10.0 (6.0-13.0)	10.0 (6.0-12.0)	15.0 (11.0-17.0)	7.0 (2.0-10.0)
Vital signs				

Median systolic blood pressure (IQR) — mmHg	123.0 (114.0-137.0)	123.0 (113.0-137.0)	136.0 (121.0-158.0)	121.5 (118.0-130.0)
Median diastolic blood pressure (IQR) — mmHg	74.0 (68.0-80.0)	75.0 (68.0-84.0)	78.5 (73.0-80.0)	71.5 (67.0-78.0)
Median heart rate (IQR) — beats/min	88.0 (81.0-97.0)	88.0 (81.0-97.0)	87.0 (80.0-104.0)	88.0 (83.0-95.0)
Median respiratory rate (IQR) —breaths/min	22 (20-25)	22 (20-25)	22 (20-26)	21 (20-24)
Median pulse oxygen saturation (IQR) — %	96.0 (93.0-97.0)	96.0 (93.0-97.0)	96.0 (89.0-97.0)	96.5 (95.0-97.0)
Laboratory findings				
White blood cell count				
Median (IQR) — 10^9/liter	6.2 (4.5-7.8)	6.3 (4.9-8.2)	6.7 (4.9-7.4)	5.9 (3.9-9.5)
Distribution — no. (%)				
<4.0	17 (21.0)	10 (18.9)	2 (20.0)	5 (27.8)

>10.0	11 (13.6)	7 (13.2)	0 (0.0)	4 (22.2)
Neutrophil count				
Median (IQR) — 10^9/liter	5.0 (3.1-6.6)	4.6 (3.1-6.6)	5.4 (4.5-5.7)	4.2 (3.1-8.4)
Lymphocyte count				
Median (IQR) — 10^9/liter	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.4 (0.3-1.1)	0.8 (0.6-1.1)
Distribution — no. (%)				
<1.5	69 (85.2)	45 (84.9)	9 (90.0)	15 (83.3)
Platelet count				
Median (IQR) — 10^9/liter	166.0 (136.0-217.0)	178.0 (139.0-237.0)	124.0 (111.0-147.0)	169.5 (150.0-202.0)
Distribution — no. (%)				
<150	31 (38.2)	19 (35.9)	8 (80.0)	4 (22.2)
Total bilirubin				

Median (IQR) — umol/liter	11.7 (6.9-18.4)	12.6 (9.0-17.5)	7.9 (3.5-19.5)	10.8 (6.2-19.7)
Creatine				
Median (IQR) — mg/liter	67.8 (55.3-80.0)	62.1 (53.8-78.9)	80.0 (69.0-464.0)	73.2 (59.9-84.0)
Distribution — no. (%)				
>133	5 (6.2)	2 (3.8)	3 (30)	0 (0.0)
Median C-reactive protein (IQR) —mg/liter[c]	40.6 (18.7-69.3)	39.4 (24.0-71.6)	99.5 (43.0-129.0)	33.0 9.92-44.6)
Median PaO2 (IQR) — mmHg	69.2 (59.0-85.0)	69.8 (58.8-84.3)	71.6 (54.6-92.6)	66.7 (60.0-104.1)
Median FiO2 (IQR) — mmHg	33.0 (29.0-41.0)	33.0 (29.0-41.0)	33.0 (29.0-57.0)	33.0 (29.0-37.0)
Median D-Dimer (IQR) — mg/liter[c]	0.78 (0.35-1.28)	0.74 (0.35-1.24)	1.34 (0.81-5.59)	0.62 (0.16-1.10)
Bilateral lung infiltrates — no. (%)	81 (100.0)	52 (98.1)	10 (100.0)	19 (100.0)
Criteria for the diagnosis of severe illness				

Dyspnea or respiratory frequency ≥30 — no. (%)	22 (27.2)	16 (30.2)	2 (20.0)	4 (22.2)
Pulse oxygen saturation (SPO_2) ≤93% — no. (%)	54 (66.7)	34 (64.2)	6 (60.0)	14 (77.8)
PaO2:FiO2				
Median (IQR) — mmHg	204.0 (156.8-266.5)	204.0 (156.8-252.0)	183.6 (115.8-255.2)	224.8 (173.6-331.4)
Distribution — no. (%)				
150-299	55 (67.9)	43 (81.1)	4 (40.0)	8 (44.4)
<150	16 (19.8)	9 (17.0)	4 (40.0)	3 (16.7)
Lung infiltrates >50% within 24 to 48 hours	3 (3.7)	2 (3.8)	1 (10.0)	0 (0.0)
Respiratory failure, septic shock, and/or MOF — no. (%) [d]	17 (21.0)	7 (13.2)	5 (50.0)	5 (27.8)

Main organ dysfunction				
Acute respiratory distress syndrome— no. (%)	30 (37.7)	20 (37.7)	4 (40.0)	6 (33.3)
Acute kidney injury — no. (%)	6 (7.4)	3 (5.7)	3 (30.0)	0 (0.0)
Septic shock — no. (%)	1 (1.2)	0 (0.0)	1 (10.0)	0 (0.0)
Main organ support				
No use — no. (%)	5 (6.2)	3 (5.7)	1 (10.0)	1 (5.6)
Conventional oxygen therapy through nasal catheter — no. (%)	51 (63.0)	34 (64.2)	7 (70.0)	10 (55.6)
Conventional oxygen therapy through mask — no. (%)	4 (4.9)	3 (5.7)	0 (0.0)	1 (5.6)
High flow nasal cannula — no. (%)	8 (9.9)	5 (9.4)	0 (0.0)	3 (16.7)

Non-invasive ventilation — no. (%)	13 (16.0)	8 (15.1)	2 (20.0)	3 (16.7)
Invasive ventilation or ECMO — no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal-replacement therapy — no. (%)	5 (6.2)	0 (0.0)	5 (50.0)	0 (0.0)
Vasopressors	1 (1.2)	0 (0.0)	1 (10.0)	0 (0.0)

[a.] BMI was classified into 4 groups according to the criteria for Chinese population: underweight (<18.5 kg/m2), normal (18.5-23.9 kg/m2), overweight (24-27.9 kg/m2), and obese (≥18 kg/m2).

[b.] Other scenarios included having visited a designated hospital for Covid-19 patients or being in another city with confirmed Covid-19 cases during the past 14 days.

[c.] Other symptoms included muscle soreness, loss of appetite, diarrhea, abdominal pain, headache, dizziness, nausea, vomiting.

[d.] Data were missing for the measurement of C-reactive protein in 12 patients (14.8) and D-Dimer in 4 patients (4.9%).

Table 2. Treatment for severe Covid-19 throughout the study period, according to outcome by D28

Treatment	**Total**	**Rapid Recovery (N=53)**	**No Recovery (N=10)**	**Pronged Recovery (N=18)**
	(N=81)	(N=53)	(N=10)	(N=18)
Respiratory Support— no. (%)				
Conventional oxygen therapy through nasal catheter	78 (96.3)	52 (98.1)	8 (80.0)	18 (100.0)
Conventional oxygen therapy through mask.	10 (12.3)	6 (11.32)	2 (20.0)	2 (11.1)
High flow nasal cannula	31 (38.3)	18 (34.0)	6 (60.0)	7 (38.9)
Non-invasive ventilation	22 (27.2)	12 (24.5)	3 (30.0)	6 (33.3)
Invasive ventilation	10 (12.3)	0 (0.0)	7 (70.0)	3 (16.7)
Extracorporeal membrane oxygenation	1 (1.2)	0 (0.0)	1 (10.0)	0 (0.0)

Other support				
Parenteral nutrition — no. (%)	17 (21.0)	14 (26.4)	3 (30.0)	0 (0.0)
Prone position therapy— no. (%)	16 (19.8)	11 (20.8)	3 (30.0)	2 (11.1)
Median duration of prone position therapy (IQR) — day	10.0 (4.0-19.5)	10.0 (2.0-20.0)	8.0 (5.0-19.0)	17.0 (3.0-32.0)
Blood transfusion — no. (%)	6 (7.4)	2 (3.77)	4 (40.0)	0 (0.0)
Drugs				
Lopinavir or Ritonavir — no. (%)	71 (87.7)	47 (88.7)	6 (60.0)	18 (100.0)
Abidol — no. (%)	25 (30.9)	13 (24.5)	5 (50.0)	7 (38.9)
Ribavirin— no. (%)	12 （14.8）	9 (17.0)	0 (0.0)	3 (16.7)
Nebulized recombinant human interferon α2b — no. (%)	57 (70.4)	32 (60.4)	9 (90.0)	16 (88.9)
Thymosin α — no. (%)	33 (40.7)	19 (35.8)	6 (60.0)	8 (44.4)

Immunoglobulin — no. (%)	15 (18.5)	10 (18.9)	2 (20.0)	3 (16.7)
Methylprednisolone — no. (%)	44 (54.3)	27 (50.9)	6 (60.0)	11 (61.1)
Median maximum dose (IQR) — mg	80.0 (40.0-80.0)	80.0 (40.0-80.0)	100.0 (80.0-160.0)	80.0 (40.0-80.0)
Median duration (IQR) — day	5.0 (4.0 -7.0)	5.0 (3.0 -7.0)	4.0 (3.0 -8.0)	6 (4.0-9.0)
Antibiotics — no. (%)	58 (71.6)	39 (73.6)	8 (80.0)	11 (61.1)
Analgesics or sedatives — no. (%)	13 (16.1)	5 (9.4)	6 (60.0)	2 (11.1)
Neuromuscular-blocking drug— no. (%)	1 (1.2%)	0 (0.0)	1 (10.0)	0 (0.0)

Figure legend

Figure 1. Distribution and referral routes of severe Covid-19 cases in Sichuan Province.

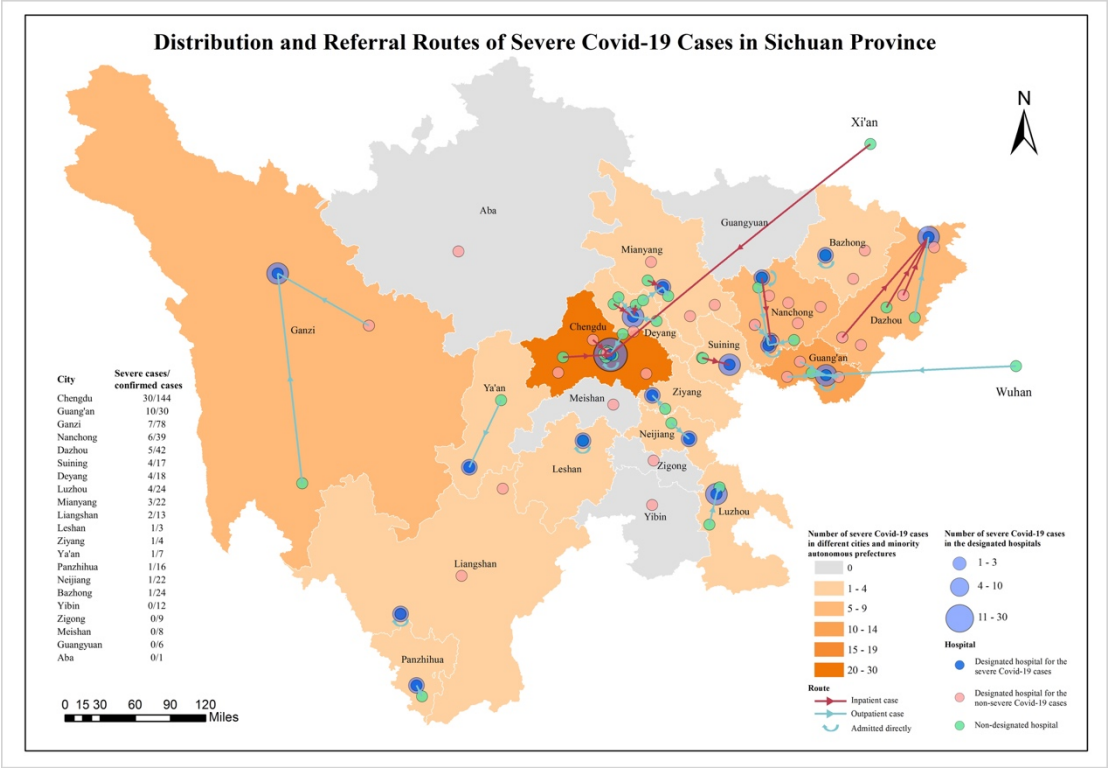
Distribution of all the 81 patients with severe Covid-19 from 13 cities and 2 minority autonomous prefectures of Sichuan province were shown in the figure. The blue dot denotes the 18 designated hospital for severe cases, pink dot denotes 30 designated hospital for non-severe cases, and green dot denotes non-designated hospital. The red and green arrow represent the route taken by inpatient and outpatient cases, respectively. Centralization mode of the severe cases is clearly demonstrated.

Figure 2. Daily organ support for 81 patients with severe Covid-19 from D1 to D28.

Daily organ support, including respiratory support and renal replacement therapy, for each of the 81 patients with severe Covid-19 are shown from the day diagnosed severe (D1) to death, discharged from hospital, or D28.

Figure 3. Daily respiratory support needs for patients with severe Covid-19 from January 16 to March 15.

The bar plot shows, for each calendar day, counts of the respiratory support used for patients with severe Covid-19. Daily number of newly diagnosed patients with Covid-19 disease in Sichuan, newly diagnosed severe cases, and cumulative severe cases hospitalized are shown in lines.



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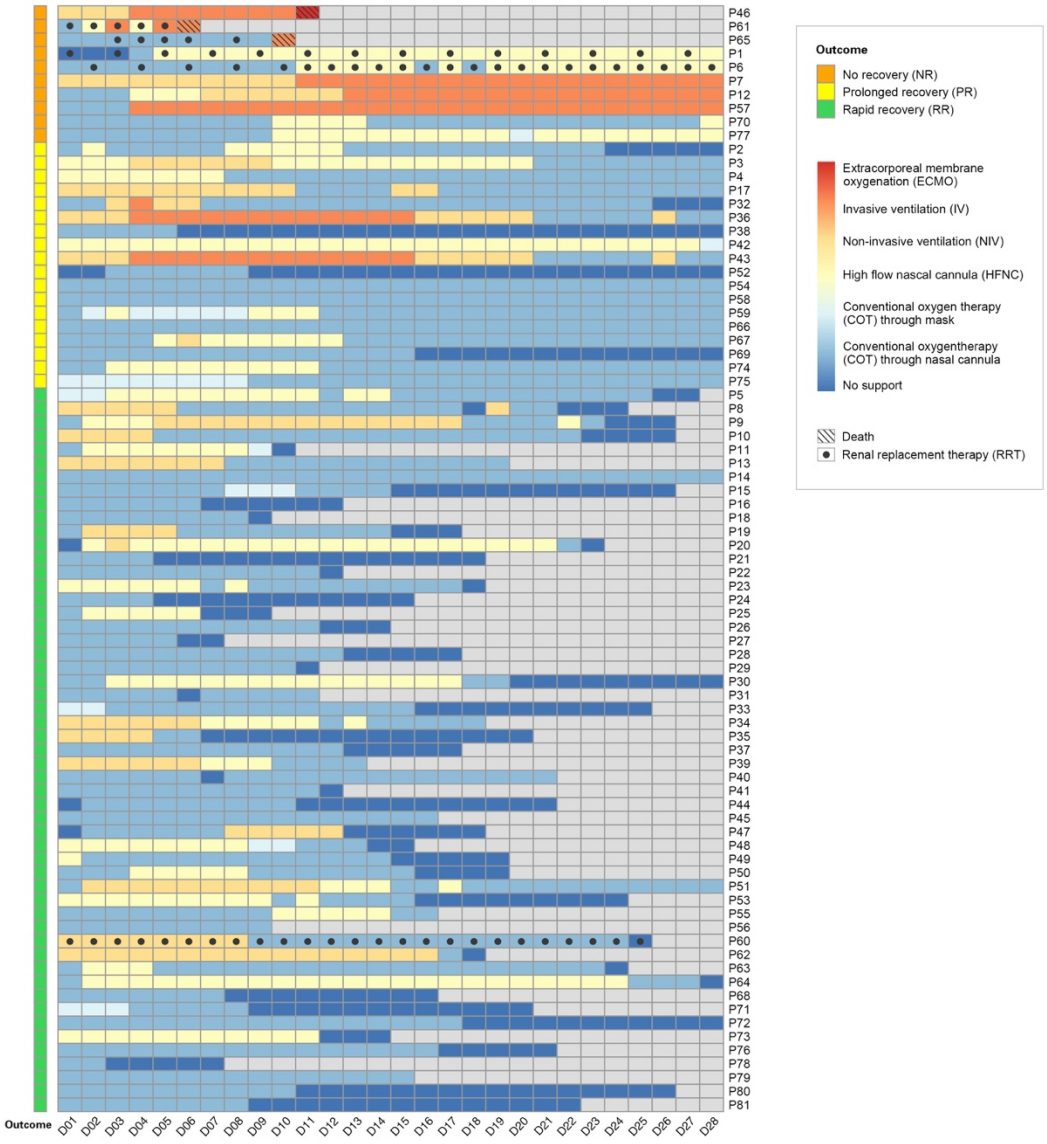
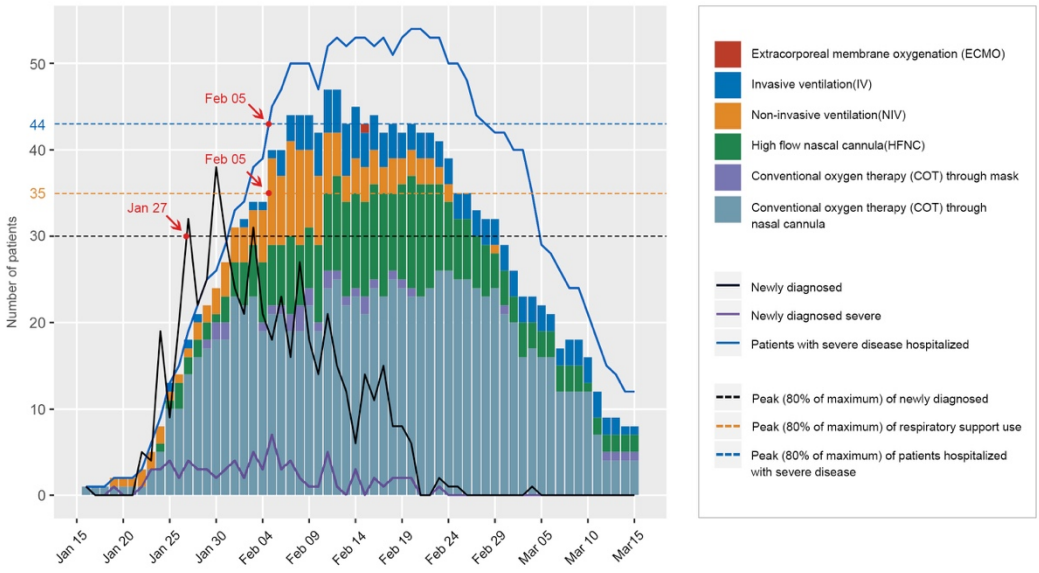


Figure 2. Daily organ support for 81 patients with severe Covid-19 from D1 to D28.



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