

Effects of Clinical Factors on Medical Burden in Non-Severe COVID-19 Patients

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Abstract

Background: To date, the medical resources and the important clinical risk factors of non-severe patients with the 2019 coronavirus disease (COVID-19) have not been investigated.

Methods: we retrospectively analyzed 104 patients with COVID-19 admitted to the isolation ward in Hubei, China, from February to March 2020. The general information, clinical symptoms, blood test and CT imaging characteristics were analyzed.

Results: The median length of stay (LOS) is 14 days, and the cost of hospitalization (COH) is ¥2,522.86. The main influencing factors include the following: CT imaging: lesions of the lungs were bilateral and multiple. The range of involved and interstitial changes affect the medical burden significantly ($P=0.009$ and $P=0.013$, respectively); Treatments: Patients were more severe with high flow nasal cannula oxygen therapy (HFNC) or used methylprednisolone more than 1mg / kg; Blood test indicators: lymphocyte (LC) count level $<1,000$ and increased LDH (Lactate dehydrogenase) level have impact on medical burden; These indicators have significant impact on medical resource after regression analysis except for LDH.

Conclusions: The hospitalization cost of non-severe COVID-19 is higher than that of the common CAP patients. The main influencing factors are multiple extensive interstitial changes on CT scans, absolute lymphocyte level $<1,000$, use of high-dose methylprednisolone and HFNC.

Background

Coronavirus is an enveloped positive RNA virus with a diameter ranging from 60 nm to 140 nm. It has spike-shaped protrusions on its surface and appears crowned under an electron microscope. Therefore, it was named coronavirus [1]. The virus that causes COVID-19 is a genus β coronavirus [2]. According to analysis of the virus sequence alignment, it is speculated that the natural host may be wild animals such as bats [3]. In the process of transmission from bat to human, there is also a possibility of an unknown intermediate host vector [3].

As of mid-April 2020, COVID-19 has achieved widespread prevalence worldwide [4]. According to real-time statistical data from Johns Hopkins University in the United States, the cumulative number of COVID-19 diagnoses in the world exceeds 1.6 million, and the number of deaths exceeds 160,000. Hubei Province of China has experienced a period of large outbreaks of the disease in the last two months. Of the 84,225 diagnosed patients in China, 68,128 were in Hubei, accounting for 80.88%. With the Chinese government's control measures and medical disease prevention and control staff, the spread of COVID-19 in China has been controlled.

To limit the spread of COVID-19, 1. more susceptible people need to be screened; and 2. active treatment should be administered to non-critical patients who have been diagnosed. It is important to manage these mild patients to prevent further transmission. There are no indicators to assess the severity of the disease for these mild COVID-19 patients. Viral pneumonia easily deteriorates during treatment, even if it starts as

very mild. In this retrospective study, we tried to find meaningful clinical indicators that can reflect the extent of medical resource usage as well as an indicator of the severity of non-severe COVID-19 pneumonia in patients with successful treatment.

Methods

patients

All patients with COVID-19 came from the isolation ward of the respiratory department in a prefecture city-level central hospital in Hubei Province, China. This was a single-centre retrospective study. The research plan has been reviewed and approved by the Sichuan Provincial People's hospital medical ethics committee. The doctors responsible for the isolation ward were from other provinces in China. Critical patients with invasive mechanical ventilation or ECMO were excluded, as were those without complete clinical medical records. Finally, 104 patients were included.

criteria

We referred to the Chinese guidelines regarding the diagnostic criteria for suspected cases of COVID-19.

Epidemiological history: (1) travel history or residence history in the Wuhan area or other areas with continuous transmission of local cases within 14 days before onset; (2) Pre-onset (within the past 14 days) contact with patients with fever or respiratory symptoms from Wuhan City or other areas where local cases continue to spread; (3) a cluster of incidence cases or an epidemiologic association with COVID-19 infection.

Clinical manifestations: (1) fever; (2) viral pneumonia indicated by imaging characteristics; (3) the number of white blood cells (WBCs) is normal or decreased in the early stage, and the LC is reduced. Anyone with an epidemiologic history and any two clinical manifestations was diagnosed as a suspected case.

Patient inclusion criteria: (1) COVID-19 suspected case; and (2) sputum, pharyngeal swabs, lower respiratory tract secretions, and other specimens were tested with RT-PCR to detect COVID-19 nucleic acid and were positive.

Patients needed to meet the following conditions to be eligible for discharge: clinical symptoms were alleviated, lung injury improved significantly on CT scan, and the COVID-19 nucleic acid test was negative more than 2 consecutive times. Patients returned to society after being discharged to home for another 14 days.

Statistical analysis

SPSS 23.0 software was used, and the normally distributed measurement data are expressed as the mean \pm SD. The t test was used to compare the means of two samples, and ANOVA was used to compare the means of more than two samples. The median was used to describe the measurement data that did not meet the normal distribution, and the rank sum test was used for comparisons; count data were tested by χ^2 , and multivariate regression analysis and analysis of variance (ANOVA) were performed.

Results

1 General Information

Limited by conditions of the isolation ward, 6 patients under the age of 18 were admitted to the department. The youngest was 3 years old, the oldest was 86, and the average age was 47.94 ± 18.13 years. The average LOS and cost of hospitalization were 12.26 days (95% CI 10.33–14.19) and \$2,522.86 (95% CI \$1,956.95–\$3,088.77), respectively. There was no relapse among the patients after being discharged.

1.1 Comorbidities at different ages As shown in Table 1, there was no difference in the basic diseases among patients of different ages.

1.2 Treatments All patients received different symptomatic therapies. Mild patients either did not receive oxygen therapy or received oxygen by nasal catheters. Five patients were given HFNC because of dyspnoea. The drugs administered mainly include the following four categories: (1) antiviral drugs: ribavirin, lopinavir, ritonavir, and abidol were administered orally or intravenously (the usage rates were 12.9%, 64.5%, and 50%, respectively); (2) anti-inflammatory treatment: methylprednisolone (max 240 mg/d, min 40 mg/d; the dosage varied according to the severity of lung injury and clinical symptoms); (3) antibiotics: administered for patients with evidence of combined bacterial infection, including elevated WBC, purulent secretions in sputum; the most frequently used antibiotics were quinolones (used in 26 patients, approximately 1/4), and some teenagers used macrolides; and (4) decoctions and traditional Chinese medicines: all patients were given symptomatic treatment with Chinese medicines for cough or phlegm; forty-five patients received traditional Chinese medicine decoction treatment.

1.3 Imaging characteristics The CT imaging features varied in patients with COVID-19. Viral pneumonia was commonly bilateral, accounting for 86.4%. Typical imaging changes included ground glass shadows (89.8%), small nodular changes (18.6%), reticular lesions (55.9%), infiltrative foci (64.4%), and interstitial pneumonia (61%). Some patients had a wide range of involvement (45.7%), which is consistent with severe pneumonia in terms of imaging characteristics, as shown in Fig. 1.

Table 1
Basic diseases in patients with non-severe COVID-19 at different ages

Age group (years)	Total patients	Diabetes	Hyperlipidaemia	Hypertension	Basic lung disease	Heart disease	Immune diseases*
≤ 18	6	0	0	1	0	0	0
19–59	68	6	7	9	4	0	1
≥ 60	30	5	1	7	4	1	0
Total	104	11	8	17	8	1	1

Note: *Immune problems include systemic immune diseases, haematological tumours, etc.

2 Duration of symptoms before admission

All patients with COVID-19 had different degrees of fever, cough, dyspnoea, fatigue, abdominal pain, and diarrhoea. The most important symptom that prompted the patient to see a doctor was dyspnoea ($R = 0.488$, $P < 0.001$). There was no difference in the length admission delay among people of different ages and sexes.

3 Effects of LOS and the cost of hospitalization

3.1 Chest imaging features The degree of lung injury on CT scan is an important indicator of severity in lung disease, and it also affects the hospitalization LOS and costs. The influence of image characteristics on LOS, according to the regression analysis, is shown in Table 2. The most relevant clinical factors related to hospitalization costs are range of involvement on CT followed by interstitial pneumonia, and then unilateral/bilateral pneumonia. These imaging changes are consistent with the impact of LOS.

3.2 Effect of treatment As mentioned in Sect. 1.2, most patients received one of the following symptomatic treatments. (1) Traditional Chinese medicine decoction: The LOS in the traditional Chinese medicine group and the comparison group were 18.44 ± 7.086 days and 7.47 ± 9.079 days, respectively ($P < 0.001$). However, the patients who used traditional Chinese medicine had lower lymphocyte levels and longer hospital stays. (2) Antibiotics: A total of 43.5% of COVID-19 patients used antibiotics during hospitalization, but antibiotics had no effect on hospital stay. The LOSs in the patients who used antibiotics and the patients who never used antibiotics were 16.82 days and 19.63 days, respectively ($P = 0.141$). (3) Methylprednisone: A total of 12 patients used methylprednisolone. Patients who used a large dose of methylprednisolone (> 1 mg/kg) had longer hospital stays and higher hospital costs than those who did not use methylprednisolone or patients who used methylprednisolone less than 1 mg/kg (ANOVA, $P = 0.004$). (4) Oxygen therapy methods: The length and cost of hospitalization were both related to the methods of oxygen therapy in non-severe patients; both were significantly higher in patients who used HFNC than in those who either used nasal catheters or did not receive oxygen therapy (see Table 3).

3.3 Effect of blood tests In the routine blood tests, the lymphocyte count (LC) and LDH levels affected the length of hospital stay. The lower the lymphocyte level, the longer the LOS ($P < 0.001$); the opposite association with LDH was observed ($P < 0.001$).

Table 2
Pulmonary imaging features correlated with hospital length of stay

Imaging lesion	Correlation coefficient	P value
The range of involvement *	0.309	0.009
Interstitial pneumonia **	0.291	0.013
Unilateral/bilateral pneumonia	0.296	0.012
Mixed patchy shadows	0.227	0.043
Single/multiple lesions	0.220	0.048
Note: * The extent of infectious lesions in the lung: infectious lesions limited to one lung segment or lobe were rated as 0; lesions involving more than two lobes or segments were rated as 1; lesions exceeding 50% of the lung were rated as 2.		
** Interstitial pneumonia changes: grid-like changes, exudative lesions distributed along the tracheal vascular bundle.		

Table 3

The impact of different respiratory support methods and blood tests on the length of hospital stay and the cost of hospitalization

Influence factors	The length of hospitalization (days, mean \pm standard)	The cost of hospitalization (\$, mean \pm standard)
Respiratory support methods		
No oxygen therapy	17.5 \pm 6.5	1824.699 \pm 1267.781
Oxygen via nasal catheter	17.2 \pm 5.39	2618.626 \pm 2013.406**
HFNC	26.0 \pm 8.77**#	6130.488 \pm 3983.335**#
LC		
Normal	11.84 \pm 9.44	2,208.21 \pm 2226.19
Reduced	13.74 \pm 11.372**	3,423.88 \pm 1973.42**
Total	12.039 \pm 9.858	2,529.79 \pm 2215.70
LDH		
normal	5.50 \pm 9.008	2,497.77 \pm 2231.25
Elevated	14.74 \pm 9.04**	2,795.69 \pm 2218.17**
Total	12.127 \pm 10.43	2,529.82 \pm 2216.14
Note: ** P < 0.001 compared with the group without oxygen therapy; #P < 0.05 Oxygen therapy via nasal catheter compared with the high flow oxygen inhalation group.		

4 Comprehensive evaluation of medical resource use for patients with non-severe COVID pneumonia

Three imaging characteristics and one treatment factor had effects on LOS by multifactor regression analysis ($R = 0.446$, $P = 0.019$). The imaging factors were the range of involvement ($P = 0.013$), interstitial pneumonia ($P = 0.021$), and unilateral/bilateral lung lesions ($P = 0.031$); the treatment factor was the dosage of methylprednisolone ($P = 0.003$).

The factors associated with the cost of hospitalization were different from those associated with LOS. There were 5 influencing factors for hospitalization cost: the range of involvement on CT scan ($P < 0.001$), interstitial pneumonia ($P = 0.003$), LC < 1000 ($P = 0.041$), type of oxygen therapy ($P < 0.001$) and dosage of methylprednisolone ($P < 0.001$), ($R = 0.601$, ANOVA test $P < 0.001$).

Discussion

Transmission of the virus that causes COVID-19 from human-to-human through unknown intermediate animals began in December 2019 in Wuhan, Hubei Province, China. This infection can spread through droplets produced by coughing and sneezing in symptomatic patients before onset, or it may occur in asymptomatic individuals [5]. The incubation period varies from 2 to 14 days. Studies have shown that the viral load in the nasal cavity is higher compared to that in the throat, but there is no difference in viral load between symptomatic and asymptomatic people [6]. In certain populations (especially elderly patients and patients with multiple comorbidities), pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction can develop. Some patients may be asymptomatic, showing no clinical signs of infection. The overall mortality of COVID-19 is estimated to be 2–3%. However, COVID-19 shows mild clinical symptoms in most people. These patients can cause the disease to spread in the community for as long as the symptoms persist, even during clinical recovery. If patients are isolated at home, they may die accidentally because the disease can suddenly worsen. If patients are active in the community, they will become the main source of widespread infection. Therefore, early and adequate treatment in the isolation department is necessary. The amount medical resources are needed to treat these non-severely infected patients and how to evaluate the cost of treatment remain uncertain. Previous studies did not answer these questions. The normal community-acquired pneumonia severity score is not suitable for these mild patients, and their CURB-65 scores are very low.

Published studies have found that the median time from symptom onset to onset of dyspnoea is 5 days, and the median hospital stay is 7 days [7]. Our retrospective study found that the average hospital length of stay for noncritical patients was 12.26 days (median time was 14 days), which was significantly higher than that of other centres. The patients cured in our centre did not relapse. Other centres with shorter hospital stays have different proportions of relapsed patients. Adequate treatment may reduce the rate of relapse. The average cost of hospitalization in our study was \$2,522.86, which is also higher than the average cost of mild community-acquired pneumonia (\$1,919.98) in China [8]. However, in 2012, the cost of hospitalization for CAP in the Netherlands was 8,301 euros; their hospitalization cost was much higher than that observed for the COVID-19 patients in this study. The high cost is mainly related to the age of the patients they included in the study (generally between 65–75 years old). There were more basic diseases in these elderly individuals, which results in higher costs for combined diseases [9].

The current treatment for COVID-19 is symptomatic support [10–11]. The principle is to maintain the balance of water, electrolytes and nutritional support and to control clinical symptoms such as fever, dyspnoea, and cough. In hypoxic patients, it is recommended to use nasal catheters, masks, HFNC or noninvasive ventilation. Of the 104 mild patients, only 5 patients used HFNC. There were no patients who were treated with ECMO or CRRT, and no patients died.

Traditional Chinese medicine is recommended for adjuvant treatment of COVID-19 in multiple centres in China. Our study found that the length of hospital stay was not significantly reduced after combining other treatments with traditional Chinese medicine. In contrast, these patients treated with combined therapies were hospitalized for a longer time. These patients may have had more symptoms requiring the use of more drugs.

The role of corticosteroids in the treatment of COVID-19 has not been confirmed. However, the current international consensus and the World Health Organization advocate against the use of corticosteroids. The use of low- to medium-dose corticosteroids in the treatment of ARDS is still recommended by Chinese guidelines in the short term [12–14]. Until now, there has been no clear recommendation for the use of steroids in the treatment of COVID-19. Some patients may be prescribed a certain dose of methylprednisone for a short time because of dyspnoea or rapid progression of lung injury on CT scan. In our study, 3 patients used 40 mg of methylprednisolone for 3 days, and 9 patients used methylprednisolone at a dose greater than 1 mg/kg. Patients in the high-dose treatment group had significantly longer hospital stays than those who used a small dosage or did not use it, which may suggest that these mild patients do not benefit from steroid use.

In terms of antiviral therapy, in a controlled study of SARS, patients treated with lopinavir-ritonavir combined with ribavirin had a better prognosis than those given ribavirin alone [15]. There was a report of an anecdotal experience using remdesivir, a broad-spectrum anti-RNA drug developed for Ebola virus, in the treatment of COVID-19 [16]. No patient used a remdesivir in the current study. Antiviral therapy or combined therapy did not affect LOS in non-severe COVID-19 patients.

Mild patients with COVID-19 achieved good clinical results after active treatment. Based on LOS and hospitalization cost, we can see the extent of medical resource utilization in these patients. These parameters may indicate that there is still a difference between the relatively severe and the relatively mild cases among these non-severe COVID-19 patients. After multiple regression analysis, the main factors affecting the condition of mild COVID-19 patients were chest imaging characteristics and LC level. After controlling for treatment, this finding is consistent with the clinical process of treatment in COVID-19. Clinicians use the peripheral blood lymphocyte count and chest imaging characteristics to diagnose or stratify the severity of the disease. Minimizing the use of methylprednisolone in mild patients is related to reducing the medical burden of mild COVID-19.

Finally, our study was a single-centre retrospective study, and these data were limited. Multicentre research data results will be more instructive. What we need to emphasize is that the treatment of these mild patients can reduce the source of infection and has a positive significance for controlling the spread of COVID-19 pneumonia until mass immunization is possible.

Conclusions

Active treatment of COVID-19 patients can help control the spread of the infectious disease. From the point of view of the medical burden and hospitalization time of patients with non-severe COVID-19, the main factors affecting the severity of these mild patients are the extensive changes of interstitial pneumonia on chest CT and low peripheral blood LC count. In terms of treatment, reducing the use of hormones in patients with mild disease can reduce the medical burden of patients with mild new pneumonia.

Abbreviations

COVID-19: 2019 coronavirus disease

LOS: length of stay

COH: cost of hospitalization

HFNC: high flow nasal cannula oxygen therapy

LC: lymphocyte

LDH: Lactate dehydrogenase

CAP: community acquired pneumonia

ECMO: Extracorporeal Membrane Oxygenation

WBCs: white blood cells

CRRT: continuous renal replacement therapy

Declarations

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Authors' contributions

Jian-Bin He and Gao-Zhong Yi conceived and designed the research. Lin Chen and Yang Yang analyzed data and wrote the paper. Didarul Alam analyzed data and modified the paper. Gao-Zhong Yi, Wen-Feng Chen, Yun-Shi Mi, and Yu-Hang Zou collected patient samples. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due individual privacy of patients could be compromised, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study has been approved by the ethics committee of Sichuan Provincial People's Hospital. The data used in this study was anonymised before its use. These patients have not been reported in any other submissions.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests to disclose.

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Figures

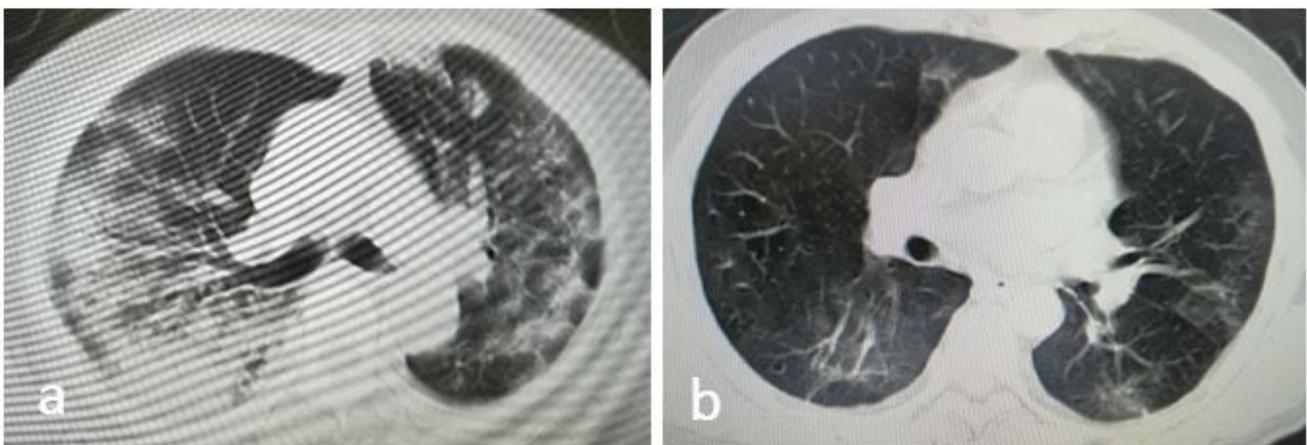


Figure 1

Chest CT images of patients with COVID-19 a chest CT images of a female patient with COVID-19 by nucleic acid detection after presenting with fever and cough for 5 days. CT images showed widely distributed multiple ground glass shadows, partially fused into patches and with fibrous cords present, and lesions involving multiple segments and leaves. The patient was discharged after 27 days of treatment. b chest CT images of a male patient with COVID-19 after presenting with intermittent fever for 9 days. CT images also showed multiple ground glass shadows, which were located near the pleura and the distal vascular bundle. He was discharged 23 days later.