Original Article

Analysis of implementation status and effectiveness of treatments in the *Chinese diagnosis and treatment recommendation for COVID-19* at local hospitals

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ABSTRACT

Background: Since the outbreak of coronavirus disease 2019 (COVID-19), China updated a total of seven editions of the official guidelines. We analyzed the treatment of patients to understand how the several editions of diagnosis and treatment recommendation guided the local medical institutions from a regional perspective. **Methods:** This study included a total of 93 patients who were suspected or confirmed cases of COVID-19. We analyzed the use of antiviral treatments, antibiotics, steroid, and life support measures in these patients. Based on the time of admission and the update of the official recommendations, we compared the treatments complied with the updated versions of the diagnosis and treatment recommendation. **Results:** All the 93 cases received different types of antiviral drugs. There were 41 cases of the use of antiviral drugs did not comply with the recommendations. There were 82 cases who received antibiotics, and 31 cases did not comply with the recommendations. 53 patients who received steroids, but only 3 patients comply with the recommendations. One patient was treated with extracorporeal membrane oxygenation (ECMO), but the timing was delayed compared with the recommendations. 91 patients were cured and discharged, one died, and one was still treated in hospital for other diseases after being tested negative. **Conclusions:** The antiviral treatment initially involved too many types of drugs, and the duration of medication was too long. There was also an overuse of antibiotics. In addition, the use of steroids did not comply with the recommendations. The timing of intubation for mechanical ventilation and the timing of using ECMO were more conservative.

Key words: Coronavirus disease 2019, recommendation, implementation status, antiviral treatment, steroids

BACKGROUND

Since the outbreak of coronavirus disease 2019 (COVID-19), China has enforced a variety of effective prevention and control measures that have been applauded by the international community. On February 24, 2020, the World Health Organization (WHO)-

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China Joint Mission on COVID-19 reported in the press conference that "China has taken unprecedented public health response measures, which effectively slowed down the spread of the epidemic and reduced person-to-person transmission of the virus. These measures have prevented hundreds of thousands of COVID-19 cases or at least mitigated the epidemic in China." China is also relentlessly exploring the treatment of COVID-19. Between January 15, 2020 and March 3, 2020, the China National Health Commission and the State Administration of Traditional Chinese Medicine updated a total of seven editions of the official guidelines, *Diagnosis and Treatment Recommendation for COVID-19*, which reflected the collective wisdom of healthcare workers and researchers in China.[1–7] To date, some publications from China have reported the outcomes of COVID-19 patients,[8–10] including the average length of stay, duration of viral shedding, recovery rate, and mortality rate. However, do these results fully reflect the intervention effectiveness of the official *Diagnosis and Treatment Recommendation for COVID-19*? Do the actual treatment measures carried out in each region comply with the official recommendation? How effective are the actual treatment measures carried out by the local medical institutions across China? None of these questions have been addressed. We analyzed the treatment of patients with COVID-19 to understand from a regional perspective how the several editions of diagnosis and treatment recommendation guided the local medical institutions from a regional perspective. This will provide a more comprehensive overview to evaluate the causal relationship between the current diagnosis and treatment recommendation, as well as the current status of COVID-19 treatment in China.

METHODS

Patients

This study included a total of 93 patients who were suspected or confirmed cases and admitted to 19 hospitals in 8 cities of Jilin Province between January 21 and February 22, 2020. A confirmed COVID-19 case is defined as a positive result in nucleic acid testing of nasal or pharyngeal swab specimens sent to the Jilin Provincial Center for Disease Control and Prevention (JPCDC). We followed the above patients until March 15, 2020, when all patients were discharged.

We analyzed the use of antiviral treatments, antibiotics, steroids, and life support measures in these patients. All the data was checked by three physicians. Some patients underwent the update of multiple guidelines during the courses of treatment, but there was no change in treatment between the third and fifth edition of the guidelines. However, the sixth edition of the guidelines was updated in terms of treatment. Compared with the overall study, the guidelines were released later and involved fewer patients.

Based on the time of admission and the update of the official recommendations, we compared how the above-mentioned treatments complied with the updated versions of the diagnosis and treatment recommendation. We also analyzed the outcomes of these patients after receiving the above-mentioned treatments. All patients underwent two or more nucleic acid tests at the time of discharge. This study was approved by the ethics committee of the First Hospital of Jilin University (2020-620).

Statistical analysis

If the continuous measurement is a normal distribution, the data are presented as mean ± standard deviation (SD); otherwise as median (IQR). The classification variable is presented as count (%). Chi-squared or Fisher's exact test was used for comparing the differences between the groups. Levene's test was performed for variance homogeneity and Kruskal-Wallis test was applied when analysis of variance was not applicable. The statistical analysis was using the Statistical Package for Social Sciences version 19 software (IBM Corp., Armonk, NY, USA). A *P* value less than 0.05 was

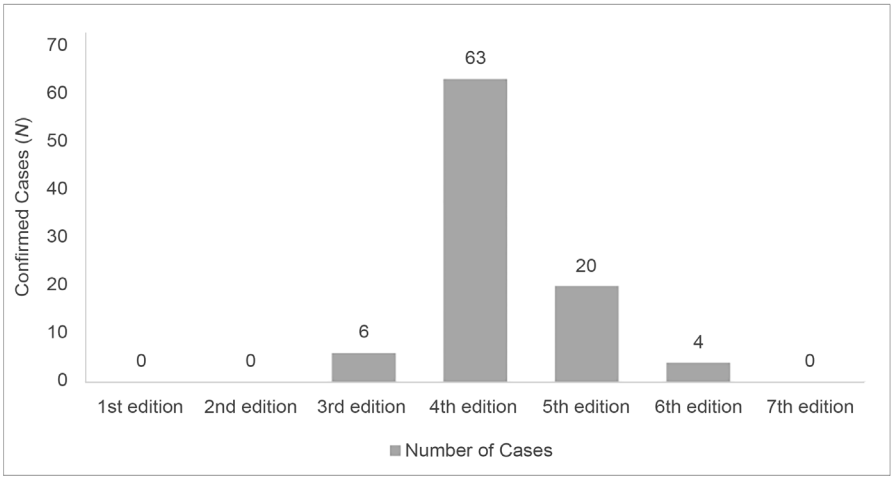

Figure 1. Correspondence between the dates of confirmed cases and the update time of the diagnosis and treatment recommendation.

Table 1. Hospital distribution of COVID-19 patients in Jilin province

Location	Hospital	Patients (*N*)
Changchun	Changchun Hospital for Infectious Diseases	43
	First Hospital of Jilin University	4
	China-Japanese Union Hospital of Jilin University	2
	China-Japanese Union Hospital of Jilin University (South Lake Branch)	1
Jilin	Jilin Hospital for Infectious Diseases	4
Siping	Siping Hospital for Infectious Diseases	11
	Shuangliao Central Hospital	2
	Gongzhuling Central Hospital	6
Liaoyuan	Liaoyuan Chest Hospital	6
	Liaoyuan Central Hospital	1
Tonghua	Tonghua Hospital for Infectious Diseases	3
	Tonghua Central Hospital	2
	Meihekou Central Hospital	1
Baicheng	Zhenlai County People's Hospital	1
Yanbian Korean Autonomous Prefecture	Helong People's Hospital	1
	Longjing People's Hospital	1
	Tumen People's Hospital	1
	Yanbian University Affiliated Hospital	2
Songyuan	Songyuan People's Hospital	1

Patients were grouped according to their treatment. The average time from symptom onset to hospitalization was 3.95 days for the 93 patients. COVID-19: coronavirus disease 2019.

considered as statistically significant.

RESULTS

The first confirmed case in Jilin Province was diagnosed on January 22, 2020, at which time the third edition of the diagnosis and treatment recommendation was followed. All the patients admitted to 19 hospitals in 8 cities of Jilin Province. The names of these hospitals and number of respective inpatients are listed in Table 1.

Patients were grouped according to their treatment. The average time from symptom onset to hospitalization was 3.95 days for the 93 patients. Figure 1 showed how the dates of the subsequent diagnoses correspond to the update time of the recommendations.

Treatments

Antiviral treatment: All the 93 patients received different types of antiviral drugs recommended in the diagnosis and treatment recommendation. The characteristic of these patients were listed in Table 2. Among them, 25 patients were administered three or more antiviral drugs. Then, nine of these 25 patients were administered three or more antiviral drugs after February 18, 2020 (the 6th edition of the recommendation suggested against using three or more antiviral drugs in combination). 59 patients were administered two antiviral drugs. 62 patients were administered a single antiviral drug for more than 10 days, 39 of whom received the drug after the publication of the sixth edition of the recommendation (the sixth edition recommended against using a single antiviral drug for more than 10 days). 44.10% (41 cases) of the use of antiviral drugs did not comply with the recommendations. The modifications on antiviral treatment in the diagnosis and treatment recommendation were shown in Table 3. The use of antiviral drugs did not comply with the recommendation was associated with an increased risk of secondary infection ($P < 0.01$).

Use of antibiotics: The diagnosis and treatment recommendation did not specify indications for the use of antibiotics. It only recommended to avoid blind or inappropriate use of antibiotics, especially the combination of broad-spectrum antibiotics. It is important to test bacterial cultures and use antibiotics in a timely manner when there is evidence of secondary bacterial infection. In this study, 11 of the 93 patients did not receive antibiotics, while the other 82 patients all received antibiotics. According to the medical records, no indications for the use of antibiotics were found in the 11 patients who did not receive antibiotics. Among the 82 patients who received antibiotics, 31 did not exhibit any indication for the use of antibiotics. In addition, 33.33% (31 cases) of the use

of antibiotics did not comply with the recommendations.

Use of steroids: Since the second edition of the diagnosis and treatment recommendation, it was recommended to use steroids "according to the severity of patient's dyspnea and disease progression shown by chest imaging. Steroids can be used for a short period of time (three to five days), and the recommended dose was the equivalent of 1–2 mg/kg·d of methylprednisolone or below." Since the fourth edition, it was recommended that only severe or critical cases should be administered steroids in accordance with the above principles (see Table 4). Among the total of 53 patients who received steroids in this study, 42 were mild or moderate cases (35 of whom received steroids after the publication of the fourth edition), five were severe cases, and six were critical cases. The characteristic of these patients was listed in Table 5. The highest daily dose of steroids administered was 200 mg. There were 36 patients were administered steroids for more than five days, of whom one was a mild case, 27 were moderate cases, three severe cases, and 5 were critical cases. And 53.76% (50 cases) of the use of steroids did not comply with the recommendations. The patients who complied with the recommendations had a shorter duration of viral shedding than the patients did not comply with the recommendations ($P < 0.05$).

Mechanical ventilation: All six critical cases were treated with non-invasive ventilation, and the indications were 100% consistent with

Table 2. Demographics and clinical characteristics of patients under antiviral treatment

	Total ($N = 93$)	Comply with the recommendation ($N = 52$)	Do not comply with the recommendations ($N = 41$)	Statistic value	*P* value
Age, years	43.61 ± 17.32	43.02 ± 16.32	44.37 ± 18.70	-0.373*	0.71
Gender (Male/Female), *N*	54/39	31/21	24/17	0.011#	0.92
Average days from symptom onset to hospitalization, days	3.96 ± 4.27	3.96 ± 3.86	3.93 ± 4.78	0.075*	0.97
Clinical classification (Mild and moderate/Severe and critically ill), *N*	82/11	45/7	37/4	0.302#	0.75
Complication (Any/None), *N*	11/82	6/46	5/36	0.009#	0.92
Duration days of viral shedding, days	17.92 ± 5.82	17.87 ± 5.76	18.00 ± 5.98	-0.319*	0.91
Average length of hospital stay days, days	18.13 ± 5.92	18.40 ± 7.01	17.78 ± 4.22	1.211*	0.60
Fever duration days after admission, days	4.95 ± 4.39	5.06 ± 4.30	4.80 ± 4.55	0.592*	0.68
Secondary infections (Yes/No), *N*	52/41	20/32	32/9	14.574#	<0.01
Abnormal of liver function (Yes/No), *N*	17/76	11/41	6/35	0.652#	0.42
Lymphocyte absolute value at discharge, $\times 10^9$/L	1.39 ± 0.63	1.33 ± 0.64	1.46 ± 0.61	-2.596*	0.32

Data are presented as mean ± standard deviation (SD) or the absolute number. *Kruskal-Walls test. #Chi-squared or Fisher's exact test.

Table 3. Modifications on antiviral drugs in the diagnosis and treatment recommendation

Edition	Comparison of antiviral treatments
1st	No mention of antiviral treatment
2nd	Proposed taking lopinavir/ritonavir and inhaling nebulized alpha-interferon
3rd	Same as the second edition
4th	Same as the third edition
5th	Proposed the use of ribavirin in addition to the fourth edition
6th	Based on the fifth edition, proposed the use of chloroquine phosphate and arbidol, and recommended the combination of ribavirin and interferon or lopinavir/ritonavir. Recommended against the use of three or more antiviral drugs at the same time. Standardized the course of drug use and called for close monitoring of adverse reactions.
7th	Based on the sixth edition, adapted the dosage of chloroquine phosphate according to body weight, and added precautions for the use of antiviral treatment in pregnant women.

those in the diagnosis and treatment recommendation. Among these cases, two switched to invasive mechanical ventilation later. In both cases, however, the switch was delayed compared with the timing specified in the recommendation.

Extracorporeal membrane oxygenation (ECMO) treatment: one patient was treated with ECMO, and the indications were in compliance with the diagnosis and treatment recommendation, but the timing was delayed compared with the recommendation.

Overall treatment effect: The relationship between the use of drugs and outcome was shown in Table 6. Whether the use of antiviral drugs, antibiotics, and steroids was compliant with the recommendation was not significantly correlated with the outcome ($P > 0.05$). As of the date of publication, 91 patients were cured and discharged, one died, and one was still treated in hospital for other diseases after being tested negative.

DISCUSSION

In December 2019, the first case of pneumonia of unknown cause was reported in China which was later confirmed to be caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical condition caused by novel coronavirus is referred to as COVID-19.[11–13] The severe cases showed respiratory,

Table 4. Modifications on steroids treatment in the diagnosis and treatment recommendation

Edition	Comparison of the use of steroids
1st	No mention of steroids
2nd	According to the severity of patient's dyspnea and disease progression shown by chest imaging, glucocorticoids can be administered for a short period of time (three to five days), and the recommended dose was the equivalent of 1–2 mg/kg·d of methylprednisolone or below.
3rd	Same as the second edition
4th	Based on the third edition, added that steroids should only be used in severe and critical cases.
5th	Based on the fourth edition, warned that a high dose of steroids would extend the duration of viral shedding.
6th	Based on the fifth edition, specified that steroids should be used in patients with progressive deterioration of oxygenation index, rapid progression shown in imaging, and excessive activation of inflammatory response in body.
7th	Same as the sixth edition

Table 5. Demographics and clinical characteristics of patients under steroid treatment

	Total ($N = 53$)	Comply with the recommendation ($N = 3$)	Do not comply with the recommendations ($N = 50$)	Statistic value	*P* value
Age, years	46.45 ± 17.43	41.67 ± 13.01	46.74 ± 17.72	-0.376*	0.63
Gender (Male/Female), *N*	33/20	2/1	31/19	0.026#	1.00
Average days from symptom onset to hospitalization, days	4.47 ± 4.50	4.00 ± 4.36	4.50 ± 4.55	-0.474*	0.85
Clinical classification (Mild and moderate/Severe and critically ill), *N*	42/11	3/0	39/11	0.833#	1.00
Complication (Any/None), *N*	10/43	0/3	10/40	0.740#	1.00
Duration days of viral shedding, days	17.15 ± 5.78	10.33 ± 7.64	17.56 ± 5.49	-5.780*	0.03
Average length of hospital stay days, days	17.58 ± 5.80	16.67 ± 5.03	17.64 ± 5.88	-1.093*	0.78
Fever duration days after admission, days	5.94 ± 4.35	7.33 ± 4.72	5.86 ± 4.36	1.237*	0.57
Secondary infections (Yes/No), *N*	41	2/1	39/11	0.208#	0.55
Abnormal of liver function (Yes/No), *N*	11	0/3	11/39	0.833#	1.00
Lymphocyte absolute value at discharge, $\times 10^9$/L	1.17 ± 0.44	1.17 ± 0.47	1.17 ± 0.44	-0.030*	0.98

Data are presented as mean ± standard deviation (SD) or the absolute number. *Kruskal-Walls test. #Chi-squared or Fisher's exact test.

Table 6. The relationship between the use of drugs and outcome (*N* = 92)

Items	Discharge (*N* = 91)	Death (*N* = 1)	Statistic value	*P* value
Antiviral drugs, *N*			0.813[#]	1.00
Comply with the recommendations	50	1		
Do not comply with the recommendations	41	0		
Antibiotics, *N*			0.514[#]	1.00
Comply with the recommendations	60	1		
Do not comply with the recommendations	31	0		
Steroids, *N*			1.204[#]	0.46
Comply with the recommendations	41	1		
Do not comply with the recommendations	50	0		

[#]Chi-squared or Fisher's exact test.

hepatic and neurological complications that can leads to mortality. The transmission of COVID-19 is reported to be human-to-human transmission via direct contact or respiratory droplets with the infected patients.[14–17] In view of the current global spread of COVID-19, China is again facing the risk of imported cases. China's achievements in the first stage will undoubtedly provide valuable experience for the next stage of the prevention of the epidemic. The recently published *Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (nCoV) Infection is Suspected* (second edition) from WHO[18] adopted many of the clinical treatment experience in China. Here, China's clinical experience is mainly reflected in the continuously updated editions of the official *Diagnosis and Treatment Recommendation for COVID-19* from the China National Health Commission and the State Administration of Traditional Chinese Medicine. However, the actual treatment measures implemented by local medical institutions in China do not comply with the recommendation.

Jilin Province is located in Northeast China, with a population of 26.91 million. The first case of COVID-19 in Jilin Province was confirmed three days before the lockdown of Wuhan. As of February 22, 93 cases have been diagnosed, which was a smaller number than other provinces in China.[19–21] Therefore, 93 cases did not cause a shortage of healthcare resources in Jilin Province. The patients were all admitted to hospitals shortly after the onset of symptoms. Therefore, the COVID-19 patients in Jilin Province can be a good model to examine the implementation status and effectiveness of the official recommendation.

Our results showed that the use of antiviral drugs in Jilin Province was changed as the diagnosis and treatment recommendations changed, suggesting that doctors on the frontline were generally uncertain about the antiviral treatment of the COVID-19, although they were still some cases did not comply with the antiviral treatment recommendation. They actively followed every recommendation from the authority. The country's response to the virus was demonstrated by the lack of effective medicine at the initial stage, to using whatever medicine available, and to finally gaining some insight in medication. However, in the other three types of treatments (steroids, antibiotics, and life support measures), the treatment measures adopted in Jilin Province differed from the recommendations in the diagnosis and treatment, each of which reflecting a different problem.

The use of steroids was more unrestricted and active in local hospitals compared with the guidance in the official recommendation. Doctors in China have different opinions on the use of steroids, which may also be a common problem faced by doctors around the world. Among the 53 cases in Jilin Province in which steroids were used, the timing of the administration was within three days of disease onset in 43% of the cases because the early application of steroids was believed to help prevent the progression of the disease. With the updates of the recommendation and the strong recommendation against the use of steroids in mild or moderate cases, the use of steroids reduced gradually and became more conservative. Furthermore, in our study, the duration of viral shedding was affected by the appropriate use of steroids. The use of glucocorticoids remains controversial because there is very limited evidence of harm or benefit in the treatment of viral pneumonia, including COVID-19.[22,23] A retrospective study showed that the use of corticosteroids in critically ill SARS patients reduced mortality and length of hospital stay.[24] Another retrospective study showed that methylprednisolone treatment reduced the risk of death in patients with COVID-19 ARDS.[25] The results of most of these studies indicate significant clinical benefits of corticosteroid administration in patients with COVID-19 induced acute respiratory failure. However, another meta-analysis showed that systemic steroid therapy may not be effective for reducing mortality, duration of hospitalization, and period of viral shedding.[26]

As to the use of antibiotics, we can see that there was still some

irrational use in local hospitals. During the current pandemic, antibiotics are often given to COVID-19 patients admitted to intensive care units.[27] As scientists attempt to understand and contain the COVID-19 pandemic, it is also critical to prepare for the impact of the current and future viral pandemic on secondary bacterial infections, which will lead to antimicrobial resistance in the future. Data show that more than 90% of COVID-19 patients are taking antimicrobial drugs.[28–29] The rapid increase in antibiotic use may create strong selective pressure on bacterial pathogens to develop resistance, leading to an increased incidence of drug-resistant bacterial infections in the years following the COVID-19 pandemic. It is estimated that 10 million people will die from antibiotic-resistant bacterial infections in 2050,[30] but this forecast could change and be shortened due to the devastating impact of the COVID-19 pandemic on antibiotic use. The current pandemic highlights the need to understand the complex relationship between viral and bacterial infections. Of note, patients treated with higher doses of antibiotics may have more co-infections with resistant bacteria. As to the use of life support measures, whether they were used rationally or not depends on how developed the Intensive Care was in the region and how coordinated the different departments were.

Finally, we would like to state that the purpose of this study is not to discuss whether the various treatments were rational, but to show the implementation status and the outcomes of China's official *Diagnostic and Treatment Recommendation for COVID-19* at local hospitals. We anticipate data and reports from other regions to make a comprehensive evaluation of the effectiveness of the *Chinese Diagnosis and Treatment Recommendation for COVID-19*.

Conclusions

In the treatment of the 93 patients, the antiviral treatment initially involved too many types of drugs, and the duration of medication was too long. These problems were corrected partially after the diagnosis and treatment recommendation specified the recommendations. There was also an overuse of antibiotics. In addition, more than half of the cases using steroids did not comply with the recommendations. The timing of intubation for mechanical ventilation and the timing of using ECMO were more conservative. The overall effect was similar to existing case reports in China.

Author contributions

Li D designed the study and revised the manuscript. Liu H and Song L prepared the manuscript. Jie J and Luo J collected the data. Peng L did the statistical analysis. Hua S reviewed the results and made critical comments on the manuscript.

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Ethics approval

This study was approved by the ethics committee of the first hospital of Jilin University (2020-620).

Conflicts of interest

The authors declare that they have no competing interests.

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