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Application value of artificial liver support system in the treatment of cytokine storm in patients with COVID-19

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ABSTRACT

Objective: To explore the application value of artificial liver support system in the clinical treatment of coronavirus disease 2019 (COVID-19) patients with cytokine storm.

Methods: Six cases of severe or critically severe COVID-19 patients treated in The First Affiliated Hospital, College of Medicine, Zhejiang University from January 22 to February 4, 2020 were recruited, and all of them received artificial liver support treatment. Statistical analysis was carried out on the change of cytokines (TNF-α, IL-10, IL-6, IFN-γ, IL-2, IL-4), inflammation-related indicators (white blood cell, neutrophil, lymphocyte, C-reactive protein and procalcitonin), immune-related indicators (B lymphocyte percentage, natural killer cell percentage, $CD3^{+}CD4^{+}CD8$ T cell percentage), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the 6 patients before and after treatment, and the proportions of patients with abnormal indicators were analyzed as well. In addition, computed tomography (CT) was used to observe the absorption of pulmonary lesions before and after the artificial liver support treatment.

Results: The levels of cytokines (IL-6 and IL-10) were effectively reduced in the 6 patients after treatment with the artificial liver support system. Meanwhile, the proportions of patients with abnormal TNF-α, IL-10, IL-6 and IFN-γ were all decreased ($p < 0.05$). The levels of inflammation-related indicators including white blood cell, C-reactive protein and procalcitonin, and the proportions of patients with these abnormal indicators were both significantly reduced ($p < 0.05$). The level of neutrophil was not effectively reduced before and after the treatment, but the proportion was significantly reduced ($p < 0.05$). However, the abnormality of lymphocyte in the patients was not improved. There was no significant difference in immune-related indicators, AST and ALT before and after the treatment ($p > 0.05$). CT imaging showed that the artificial liver support treatment contributed to absorption of pulmonary lesions.

Conclusions: The artificial liver support system had a great clinical effect in the treatment of cytokine storm and inflammation in COVID-19 patients, and it could promote the absorption of infected lesions.

1. Introduction

Novel coronavirus 2019-nCoV (also known as severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) has caused a worldwide pandemic of the coronavirus disease 2019 (COVID-19) [1]. 2019-nCoV is the third deadly coronavirus in the past two decades, after SARS-CoV and Middle East respiratory syndrome (MERS) -CoV [2]. The numbers of confirmed COVID-19 cases and related deaths are increasing worldwide. There were 84,239 confirmed cases and 4642 deaths on the Chinese mainland up to April 20, 2020, while the total number of confirmed cases abroad was 2,327,486 and that of deaths was 160,693, with an overall mortality about 6.86% (165,335/2,411,725). Although the epidemic in China has been controlled steadily, it is still not optimistic all over the world.

Human coronaviruses (hCoVs) can be divided into low-pathogenic and high-pathogenic coronaviruses [3]. Low-pathogenic hCoVs can cause mild and cold-like respiratory diseases with infection of upper respiratory tract [3]. In contrast, high-pathogenic hCoVs, such as SARS-CoV and MERS-CoV, mainly infect the lower respiratory tract and cause fatal pneumonia [3]. Severe pneumonia caused by pathogenic hCoVs is

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usually associated with rapid virus replication, massive inflammatory cell infiltration, and elevated pro-inflammatory cytokine/chemokine responses, which leads to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [3]. According to a paper in *The Lancet*, 17 out of the 99 early COVID-19 cases developed ARDS, among which 11 cases worsened in a short period of time accompanied by respiratory failure, and eventually died of multiple organ failure [4]. It is a kind of diffuse damage of pulmonary capillary endothelial cells and alveolar epithelial cells caused by cytokine storm that makes massive accumulation of exudate, thereby leading to airway obstruction and consequently resulting in ARDS [5]. As more clinical data are compiled and published, an enormous amount of data suggest that there is mild or severe cytokine storm in severe or critically severe COVID-19 patients, which is also an crucial cause of death [6]. Cytokine storm is caused by overactivation of the immune system due to virus infection and is an important cause of serious complications in severe COVID-19 patients [7,8]. The way of cytokine storm reflecting virus infection is to induce and promote inflammatory responses. Inflammatory mediators in severe cytokine storm usually include interferons (IFNs), tumor necrosis factors (TNFs), interleukins (ILs), and chemokines [9,10]. In summary, more than 150 cytokines have been identified to cause cytokine storm, and their combination with cytokine/chemokine signaling is detrimental to the development of effective therapies [11]. Therefore, avoiding the cytokine storm response caused by COVID-19 may be important in reducing the probability of COVID-19 developing into a severe disease and decreasing the mortality of severe patients.

Artificial liver technology is an *in vitro* liver support technology developed in recent years, the principle of which is to create conditions and gain time for liver cell regeneration, as well as promote spontaneous self-recovery of liver function through temporary and partial replacement of liver function. In addition, in the case of severe liver injury, artificial liver support treatment can extend the survival time of patients, thus providing enough time for patients who are undergoing medical treatment to receive liver transplantation [12,13]. The artificial liver support system consists of plasma exchange (PE), plasma adsorption, blood/plasma filtration and other blood purification modules. This method has been used in the treatment of patients with H7N9 influenza that can effectively remove cytokines/chemokines, block the cytokine storm, correct shock, reduce lung inflammation and improve respiratory function [14]. Meanwhile, this treatment is conducive to the recovery of immune homeostasis, improvement of metabolic spectrum disorders *in vivo*, accurate management of capacity, improvement of liver, kidney and other organ functions, cure rate improvement of severe and critically severe patients, and reduction of mortality [15]. The artificial liver support system may also play an important role in the treatment of severe and critically severe COVID-19 patients through blocking cytokine storm.

Therefore, this study evaluated the application value of the artificial liver support system in the treatment of COVID-19 by analyzing cytokines, inflammation- and immune-related indicators, and lesion absorption in 6 patients with severe or critically severe COVID-19 before and after treatment.

2. Materials and methods

2.1. Patients enrollment

Six COVID-19 patients (including 1 female and 5 males, 1 severe case and 5 critically severe cases) admitted to The First Affiliated Hospital, Zhejiang University School of Medicine from January 22 to February 4, 2020 were recruited. Ages of the patients range from 48 to 74. All patients received 3 days of artificial liver support treatment during the treatment period. The criteria for identifying severe and critically severe cases are based on Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment issued by the China National Health Commission. Severe cases should meet any of the following conditions: (1) shortness of breath, respiratory rate (RR) $>$ 30 beats/min; (2) oxygen saturation $\leq$ 93% at resting state; (3) arterial partial oxygen pressure (PaO_2) /blood oxygen concentration (FiO_2) $\leq$ 30 mmHg (1 mmHg = 0.133 kPa). Critically severe cases should meet any of the following conditions: (1) respiratory failure which requires mechanical ventilation; (2) presence of shock; (3) combined with other organ failure which requires ICU monitoring and treatment. The study was approved by the Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine. All the patients and their families had signed informed consent before the study.

2.2. Treatment plans

All patients underwent artificial liver support therapy on the basis of the conventional treatment for COVID-19. Artificial liver support therapy was initiated in the patients with following indications: (1) The concentration of inflammatory factors (such as IL-6) was 5 times the upper limit of normal or higher, or the daily rising rate was more than 1 time; (2) Rapid disease progression could be seen from pulmonary imaging, with computed tomography (CT) or X-ray suggesting a daily progression of 10% or more of lung involvement; (3) Underlying diseases which required artificial liver support treatment. The patients should have both the indications (1) and (2) at the same time, or have the indication (3) alone. The treatment methods of artificial liver support therapy included PE, molecular absorbent recirculating system, PE combined with hemofiltration, and other combined non-bioartificial liver. The conditions of PE: blood flow = 100 ml/min, plasma separation rate = 30%, plasma exchange dosage= (1–1.3) times the patient plasma volume. Patient plasma volume = weight (kg) $\times$ 70 $\times$ [(1.0 - Hct) $\times$ 0.91] $\times$ 1.15, where Hct represents hematocrit. Molecular absorbent recirculating system: 6 h of treatment time. Bedside hemofiltration: pre-dilution or post-dilution, (16–20) L/time of replacement fluid for 6–8 h.

During the treatment, the vital signs of the patients, the transmembrane pressure and arterial pressure of the plasma separator applied were closely observed. The speed was adjusted in time according to the blood pressure changes so as to maintain a balance between filtration and replenishment, which should be recorded in a proper way. Hypotension was easy to develop during artificial liver support treatment and it could be improved by slowing down blood flow velocity and balancing fluid dilatation. The input of a large amount of fresh plasma, albumin, amino acids and other substances during PE would cause allergic reactions. Therefore, patients were given 5 mg of dexamethasone by intravenous injection before the treatment for prevention.

2.3. Evaluation indicators

Artificial liver support therapy usually lasted for 3 days. Here, three time points, including the day before the beginning of support treatment (before treatment), the third day of treatment (in treatment), and the day after the end of treatment (after treatment), were set to observe the change of the following evaluation indicators. The indicators included (1) cytokine indicators, such as TNF-α, IL-10, IL-6, IL-4, IL-2, IFN-γ; (2) inflammatory indicators including white blood cell (WBC), neutrophil, lymphocyte, C-reactive protein (CRP), procalcitonin (PCT); (3) immune indicators, such as B lymphocyte (%), natural killer (NK) cell (%), $CD3^+CD4^+CD8$ (%); (4) alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Changes on the levels of the above indicators and on the proportions of patients with these abnormal indicators were recorded. In addition, the changes of lesion absorption before and after treatment were observed by CT imaging.

2.4. Statistical analysis

SPSS 16.0 software was applied to conduct statistical analysis on all the data and GraphPad Prism 7.0 was used for plotting. All data were

Table 1
The level of cytokines in 6 patients before and after treatment ($\overline{X} \pm S$).

Indicators	TNF-α	IFN-γ	IL-10	IL-6	IL-2	IL-4
Before treatment	28.3 ± 23.0	4.7 ± 1.8	8.7 ± 2.2	38.3 ± 22.1	1.4 ± 0.6	1.8 ± 0.0
In treatment	20.8 ± 14.3	3.8 ± 0.9	3.5 ± 1.8	7.2 ± 3.3	1.1 ± 0.3	1.7 ± 0.2
After treatment	17.8 ± 8.2	4.6 ± 1.8	2.8 ± 0.8	6.5 ± 3.7	1 ± 0.2	1.6 ± 0.2
P value	0.31	0.93	0.0001	0.006	0.15	0.64

Normal reference range: TNF-α, (0–33.2) pg/ml; IFN-γ, (0–6) pg/ml; IL-10, (0–2.31) pg/ml; IL-6, (0–6.61) pg/ml; IL-4, (0–8.37) pg/ml; IL-2, (0–4.13) pg/ml; Beyond the normal reference range is considered abnormal.

expressed in the form of mean ± standard deviation. Student's *t*-test was used for data comparison before and after treatment. Fisher's exact test was used for enumeration data comparison. Finally, $p < 0.05$ was regarded as statistically significant.

3. Results

3.1. The change of cytokines in patients

In order to clarify the effect of artificial liver support treatment on the level of cytokines in patients, three time points, including before treatment, in treatment and after treatment, were selected to observe the change of cytokine indicators for more accurate analysis. The results exhibited that the levels of IL-2 and IL-4 in the 6 patients were in normal range before and after treatment, while the levels of IL-6 and IL-10 were effectively reduced after treatment ($p < 0.05$). TNF-α and IFN-γ were decreased during treatment, but the overall levels showed no significant difference before and after treatment ($p > 0.05$). Next, the proportions of patients with abnormal indicators before and after treatment were accounted, and the results indicated that the proportions of patients with abnormal IFN-γ, TNF-α, IL-10 and IL-6 were all effectively reduced after treatment, indicating that the artificial liver support treatment had an obvious effect on cytokines and could effectively reduce the level of cytokines in patients ($p < 0.05$). More details are shown in Table 1 and Fig. 1.

3.2. The change of inflammation-related indicators in patients

Changes of inflammation-related indicators including WBC, neutrophil, lymphocyte, CRP and PCT were observed at the same three time points. It was exhibited that the levels of WBC, CRP and PCT all showed a decreasing trend after the artificial liver support treatment ($p < 0.05$). Although the level of neutrophil was decreased as well, there was no significant difference before and after the treatment ($p > 0.05$). In the meantime, the level of lymphocyte was reversely increased. Then, the proportions of patients with these abnormal indicators were statistically analyzed. It turned out that the proportions of patients with abnormal WBC (100% *vs.* 16.7%), neutrophil (100% *vs.* 33.3%), PCT (100% *vs.* 16.7%) and CRP (66.7% *vs.* 0%) except lymphocyte were effectively reduced after treatment, with a significant difference before and after treatment ($p < 0.05$). Details can be seen in Table 2 and Fig. 2.

Table 2
Changes of inflammation-related indicators before and after treatment ($\overline{X} \pm S$).

Indicators	WBC	Neutrophil	Lymphocyte	CRP	PCT
Before treatment	13.8 ± 2.9	26.2 ± 33.7	0.58 ± 0.3	22.6 ± 13.4	0.07 ± 0.02
In treatment	9.7 ± 3.9	8.1 ± 3.5	0.72 ± 0.3	5.3 ± 4.2	0.04 ± 0.01
After treatment	8.7 ± 4.3	7.8 ± 3.9	0.67 ± 0.3	2.2 ± 2.1	0.03 ± 0.01
P value	0.04	0.21	0.61	0.004	0.001

Normal reference range: WBC, (4–10) × 10^9/L; neutrophil, (2–7) × 10^9/L; lymphocyte, (0.8–4) × 10^9/L; CRP, (0–2.87) mg/L; PCT, (0–0.05) ng/ml; Beyond the normal reference range is considered abnormal.

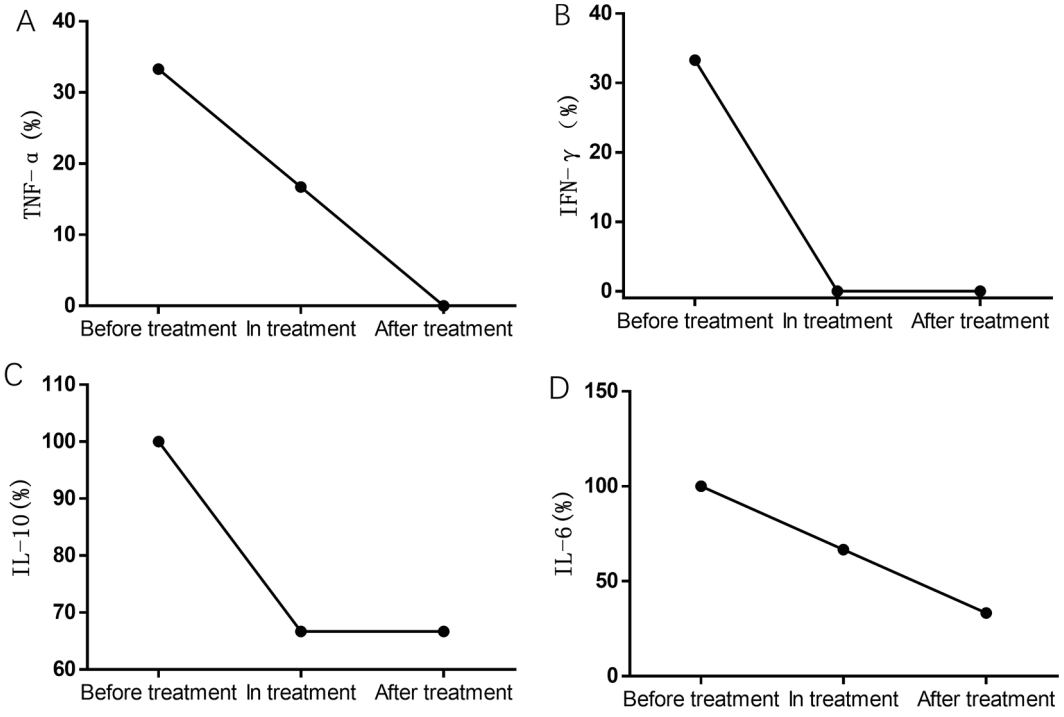

Fig. 1. The proportion of patients with abnormal cytokine level before and after treatment. Proportions of patients with abnormal TNF-α (A), IFN-γ (B), IL-10 (C), IL-6 (D) before and after treatment. Normal reference range: TNF-α, (0–33.2) pg/ml; IFN-γ, (0–6) pg/ml; IL-10, (0–2.31) pg/ml; IL-6, (0–6.61) pg/ml; Beyond the normal reference range is considered abnormal.

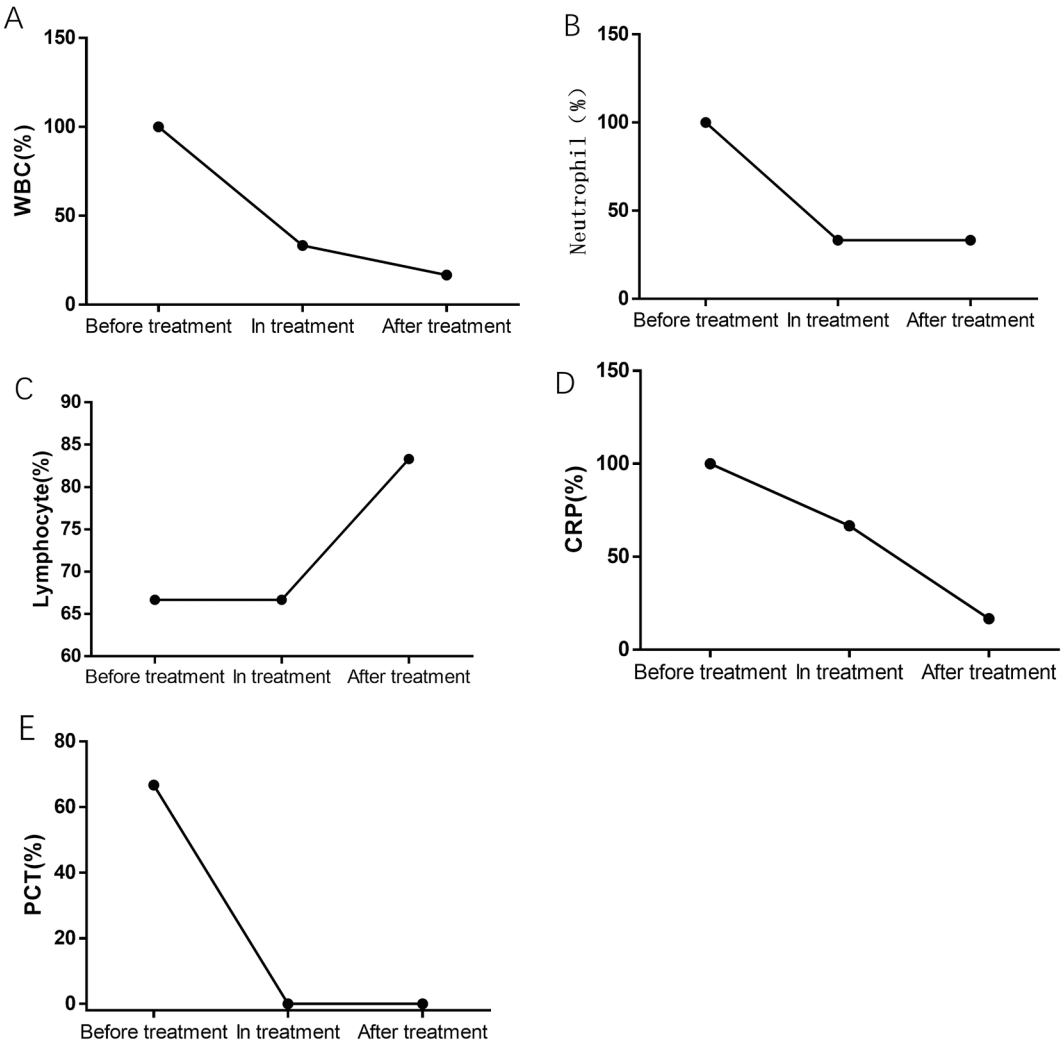

Fig. 2. Changes of inflammation-related markers before and after treatment. The proportions of patients with abnormal WBC (A), neutrophil (B), lymphocyte (C), CRP (D) and PCT (E) before and after treatment. Normal reference range: WBC, (4–10) × 10^9/L; neutrophil, (2–7) × 10^9/L; lymphocyte, (0.8–4) × 10^9/L; CRP, (0–2.87) mg/L; PCT, (0–0.05) ng/ml; Beyond the normal reference range is considered abnormal.

Table 3
Changes of immune-related indicators, AST and ALT in patients before and after treatment.

Indicators	Before treatment	In treatment	After treatment	*P* value
B lymphocyte (%)	19.3 ± 7.4	19.1 ± 6.2	23.4 ± 10.5	0.44
NK cell (%)	22.1 ± 7.8	14.3 ± 2.1	10.1 ± 2.8	0.005
$CD3^+CD4^+CD8$ T cell (%)	1.7 ± 2.2	1.4 ± 0.9	0.9 ± 0.9	0.43
ALT	18.8 ± 9.5	37.5 ± 32.5	42 ± 36.2	0.16
AST	21.8 ± 15.6	21.2 ± 9.5	24.2 ± 13.2	0.78

Normal reference range: B lymphocyte (%), (3–19) %; NK cell (%), (3–37) %; $CD3^+CD4^+CD8$ T cell (%), (0–1.5) %; ALT, male, (9–50) U/L, female, (7–40) U/L; AST, male, (15–40) U/L, female, (13–35) U/L; Beyond the normal reference range is considered abnormal.

3.3. The change of immune cells, AST, ALT and absorption of lesions

After evaluating cytokines and inflammation-related indicators, we analyzed immune- and safety-related indicators in patients. The results indicated that 4 out of 6 patients had abnormal B lymphocyte percentage before treatment, while 5 cases had abnormal B lymphocyte percentage after treatment. The overall level of B lymphocyte percentage was increased, but there was no significant difference before and after treatment (19.3 ± 7.4 *vs.* 23.4 ± 10.5, $p > 0.05$). The percentage of NK cells was decreased remarkably after treatment (22.1 ± 7.8 *vs.* 10.1 ± 2.8, $p < 0.05$), but there were no patients with NK cell percentage beyond normal reference range before and after treatment. There was no change in the proportion of patients with abnormal percentage of $CD3^+CD4^+CD8$ T cells before (2/6) and after treatment (2/6). The overall percentage of $CD3^+CD4^+CD8$ T cells showed a downward trend after treatment without significant difference with that before treatment (1.7 ± 2.2 *vs.* 0.9 ± 0.9, $p > 0.05$). In addition, there was no case with abnormal ALT before the treatment, while 2 cases developed abnormal ALT after the treatment. Moreover, the proportion of patients with abnormal AST after the treatment was decreased (4/6 *vs.* 3/6). The levels of ALT and AST of the patients both presented an upward trend after treatment, but there was no significant difference with those before treatment (18.8 ± 9.5 *vs.* 42 ± 36.2, 21.8 ± 15.6 *vs.* 24.2 ± 13.2, $p > 0.05$) (Table 3).

Besides, we observed lesions in lungs by CT imaging before and after the artificial liver support treatment, and the results showed that during the treatment, the lesions of both lungs were improved or absorbed compared with those before the treatment. Datils are shown in Fig. 3.

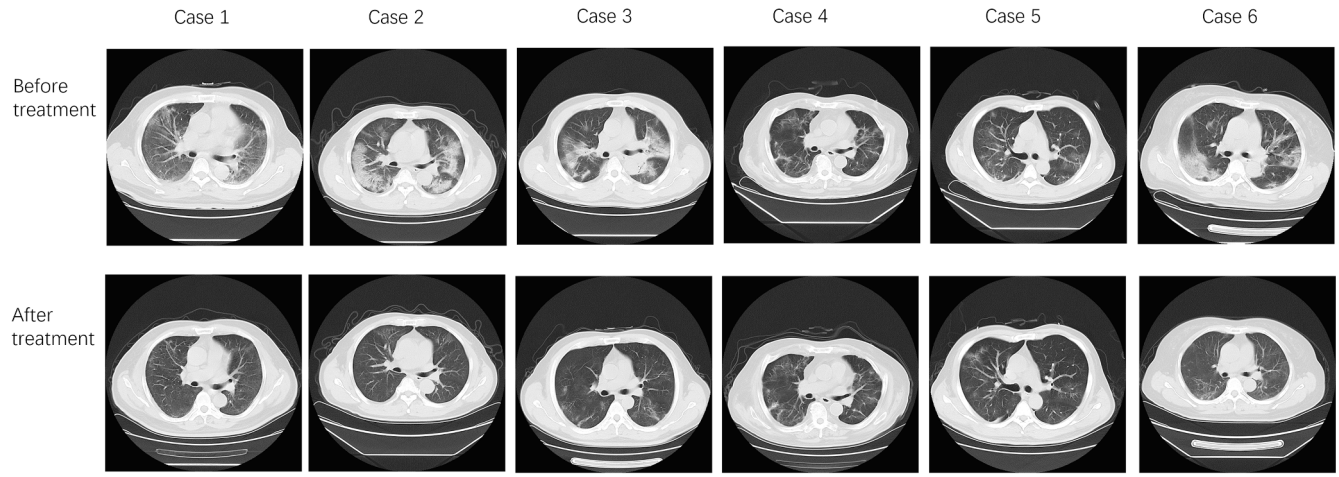

Fig. 3. CT imaging of the 6 patients before and after artificial liver treatment.

4. Discussion

Previous studies have found that cytokine storm is common. For example, it was noted in patients with H1N1 influenza in 2009, and caused uncontrolled excessive inflammation, sequentially leading to lung damage [16]. The elevated cytokines in cytokine storm mainly are IL-6, TNF-α, IFN-γ and so on [17]. In addition, phenomenon like cytokine storm has also been found in H7N9 patients, and severe H7N9 patients may have an overwhelming induction of IL-6 and IP-10, while the over-active cytokine-mediated inflammatory response may lead to destructive tissue inflammation [18]. A study discovered elevated plasma inflammatory cytokines in COVID-19 patients, such as TNF-α, IL-2, IL-6, IL-10, granulocyte colony stimulating factor (G-CSF), and INF-γ inducible protein 10, especially in ICU patients [8]. Yang, Y *et al.* [19] followed up 53 COVID-19 patients with moderate and severe clinical symptoms. They performed a multiplex screen of 48 cytokines and associated the results with laboratory tests, clinical features and viral load. A significant increase of 14 cytokines in patients with COVID-19 was found compared to the healthy control group. Sustained high levels of three cytokines (CXCL10, CCL7, and IL-1 receptor antagonist) were related to increased viral load, loss of lung function, lung injury, and mortality outcomes. Here, abnormal elevation of TNF-α, IL-10, IL-6 and IFN-γ in different degrees occurred in the 6 patients of our study, suggesting that cytokine storm might occur in these patients.

The treatment mechanisms of artificial liver support system consist of PE, plasma filtration dialysis and albumin dialysis [20]. In this study, the plasma complemented for patients was provided by healthy donors and the artificial liver therapy was performed only after the patients had shown corresponding indications. At present, glucocorticoids are mainly used to nonspecifically suppress inflammatory response in the clinical treatment of cytokine storm, but long-term use of glucocorticoids has obvious side effects and is prone to cause superinfection. A recent clinical study published in *The Lancet* revealed that according to the analysis of the clinical data based on previous treatment of SARS and other infections, the therapy with glucocorticoids is not recommended in the treatment of the lung damage caused by SARS-CoV-2 infection [21]. A subsequent study reported that the artificial liver support system is highly effective in the treatment of patients with severe H7N9 influenza infection and cytokine storm [15]. Consistently, our study found that after patients treated with artificial liver support system, fewer patients had abnormal cytokines including TNF-α, IL-10, IL-6 and INF-γ, proving that the artificial liver support treatment could effectively reduce the abnormal elevation of these cytokines. We also found that there was no statistical difference in the levels of TNF-α and INF-γ before and after treatment, but there was a difference in the proportion of people with these abnormalities, which might be attributed to the two different types of data. Normal levels of TNF-α and INF-γ are within a relatively wide range, and the occurrence of abnormality does not indicate a great magnitude of change in their levels. That's the reason for the above case. In addition, the artificial liver support treatment also reduced the proportion of patients with abnormal inflammation-related indicators such as WBC, neutrophil, CRP and PCT. Furthermore, CT examination showed that the artificial liver support treatment helped absorption of pulmonary infected lesions. Thus, it was concluded that the artificial liver support system had a great clinical effect on the clearance of cytokine storm and the treatment of inflammation in patients with COVID-19.

All patients in this study adopted a set of standard systematic treatment, and the only difference was whether the artificial liver treatment was applied, which was also the focus of our study. Therefore, we did not elaborate on the treatment methods beyond the study points. It is worth noting that due to the particularity of the disease and treatment, we only recruited 6 patients and analyzed their data before and after treatment. Though the results may be inaccurate in the case of limited sample size, we still tried to put forward different opinions based on these observations, which may provide some novel ideas and directions for subsequent treatment or research. Besides, long-term treatment effect of the patients should be observed or the sample size should be enlarged if possible, which may offer more valuable results.

In summary, the artificial liver support system is believed to be effective in the treatment of cytokine storm and inflammation in severe or critically severe COVID-19 patients. It is suggested that the follow-up study should focus on the therapeutic value of artificial liver support system in the treatment of COVID-19.

5. Ethics approval and consent to participate

Not applicable.

6. Consent for publication

Not applicable.

7. Availability of data and materials

The data and materials in the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Qi Xia: Conceptualization, Funding acquisition, Writing - original draft. **Kaijin Xu:** Data curation, Formal analysis, Investigation. **Liang**

Yu: Methodology, Project administration. **Huafen Zhang:** Visualization, Writing - review & editing. **Lanjuan Li:** Writing - review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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