



# Effect of artificial liver blood purification treatment on the survival of critical ill COVID-19 patients

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## Abstract

Our aim was to investigate the effect of artificial liver blood purification treatment on the survival of severe/critical patients with coronavirus disease 2019 (COVID-19). A total of 101 severe and critical patients with coronavirus SARS-CoV-2 infection were enrolled in this open, case-control, multicenter, prospective study. According to the patients' and their families' willingness, they were divided into two groups. One was named the treatment group, in which the patients received artificial liver therapy plus comprehensive treatment ( $n = 50$ ), while the other was named the control group, in which the patients received only comprehensive treatment ( $n = 51$ ). Clinical data and laboratory examinations, as well as the 28-day mortality rate, were collected and analyzed. Baseline data comparisons on average age, sex, pre-treatment morbidity, initial symptoms, vital signs, pneumonia severity index score, blood routine examination and biochemistry indices etc. showed no difference between the two groups. Cytokine storm was detected, with a significant increase of serum interleukin-6 (IL-6) level. The serum IL-6 level decreased from 119.94 to 20.49 pg/mL in the treatment group and increased from 40.42 to 50.81 pg/mL in the control group ( $P < .05$ ), indicating that artificial liver therapy significantly decreased serum IL-6. The median duration of viral nucleic acid persistence was 19 days in the treatment group (ranging from 6 to 67 days) and 17 days in the control group (ranging from 3 to 68 days), no significant difference was observed ( $P = .36$ ). As of 28-day follow-up, 17 patients in the treatment group experienced a median weaning time of 24 days, while 11 patients in the control group experienced a median weaning time of 35 days, with no significant difference between the two groups ( $P = .33$ ). The 28-day mortality rates were 16% (8/50) in the treatment group and 50.98% (26/51) in the control group, with

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a significant difference ( $z = 3.70$ ,  $P < .001$ ). Cytokine storm is a key factor in the intensification of COVID-19 pneumonia. The artificial liver therapy blocks the cytokine storm by clearing inflammatory mediators, thus preventing severe cases from progressing to critically ill stages and markedly reducing short-term mortality.

### KEYWORDS

artificial liver blood purification, COVID-19, cytokine storm, mortality

## 1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, resulting from infection with the novel coronavirus SARS-CoV-2 is currently the source of public health concern worldwide. However, treatment of this infection has been clinically challenging in many patients, especially in severe and critical cases. As of 30 May 2020, there have been approximately 6 million patients overseas and over 360 000 deaths, corresponding to a total crude mortality of 6.19%.<sup>1</sup> In China, a total of 83 001 have been diagnosed, and 4634 died, for a fatality rate of 5.58%.<sup>2</sup> It was reported that in the early stage of the COVID-19 pandemic, the fatality rate was as high as 61.5% in severely and critically ill patients,<sup>3</sup> so better treatment strategies are urgently needed.<sup>4,5</sup> In addition to China, many other countries are now facing high mortality in severe conditions. Without a specific medicine for COVID-19, how to decrease the fatality rate of severe COVID-19 patients has become a great challenge.

According to the treatment experience of severe H7N9 patients, artificial liver blood purification treatment (hereinafter referred to as "artificial liver therapy/treatment") has

proven effective at significantly blocking the cytokine storm and improving the survival rate.<sup>6,7</sup> COVID-19 and H7N9 are similar to some extent in lung pathology, both having inflammatory cytokine storm processes. However, whether artificial liver therapy can decrease the mortality of severe COVID-19 patients as well as it does for H7N9 patients remains unknown.

This open, case-control, prospective, multicenter study aimed to investigate the effect of artificial liver therapy in blocking the cytokine storm and improving the survival rate of severe and critical patients with COVID-19.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design and participants

This study was approved by the Ethics Committee of Shulan (Hangzhou) Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, the First Affiliated Hospital to College of Medicine of Zhejiang University and Renmin Hospital of Wuhan University. In



total, 101 severe/critical patients with COVID-19 were enrolled from 28 January 2020 to 30 May 2020.

## 2.2 | Criteria of enrollment

The severe and critical COVID-19 patients were diagnosed by referring to the Notice on Diagnosis and Treatment Protocol of Novel Coronavirus Pneumonia (the 4th trial version), No. 2020.7.7 of the General Office of the National Health Commission.<sup>8</sup>

### 2.2.1 | Confirmed cases

The diagnostic criteria for COVID-19 included any of the epidemiological histories and any two of the clinical manifestations plus any one of the etiological factors, as follows.

Epidemiological histories: (a) a history of travelling or living in Wuhan and surrounding areas or other communities with continuous transmission of COVID-19 cases within 14 days before onset, (b) a history of contact with febrile patients or patients with respiratory symptoms who came from Wuhan or other areas with continuous transmission of COVID-19 within 14 days before onset, (c) clustered onset or epidemiologic association with COVID-19-infected persons.

Clinical manifestations: (a) fever, (b) radiologic characteristics of pneumonia: multiple small, patchy shadows and interstitial changes, especially in the lung periphery at the early stage, which then developed into multiple ground-glass shadows and infiltrating shadows in both lungs. In severe cases, lung consolidation may occur, but pleural effusion was rare, (c) at the early stage, a normal or low total number of leukocytes or a low lymphocyte count.

Etiological factors: (a) positive result for the new coronavirus nucleic acid detected by real-time fluorescence polymerase chain reaction (PCR) on respiratory tract specimens or blood specimens, (b) a viral gene of respiratory tract specimens or blood specimens that was highly homologous with the known novel coronavirus, as identified by genetic sequencing.

### 2.2.2 | Severe and critical confirmed cases

Those who met any of the following conditions were defined as having severe COVID-19: (a) respiratory distress, RR > 30 times/min, (b) oxygen saturation <93% at rest, and (c) alveolar oxygen partial pressure/fraction of inspiration  $O_2$  ( $PaO_2/FiO_2$ )  $\leq$  300 mm Hg (mm Hg = 0.133 kPa).

Those who met any of the following conditions were defined as having critical COVID-19: (a) respiratory failure

requiring mechanical ventilation, (b) shock, (c) other organ failure that needed ICU monitoring and treatment.

### 2.2.3 | Significant rise in serum inflammatory factors

The concentrations of serum inflammatory factors (such as IL-6) were greater than or equal to 5 times the upper limit or normal or rose faster than 100% per day.

### 2.2.4 | Rapid progress of lung imaging

The percentage of lung involvement progressed by 10% or more per day as suggested by CT or X-rays.

### 2.2.5 | Exclusion criteria

Exclusion criteria included (a) women in pregnancy, (b) patients with pre-treatment morbidity that may affect the judgement of treatment efficacy, such as malignant tumors and long-term administration of immune inhibitors, and (c) patients with contraindications for artificial liver blood purification treatment, such as severe active hemorrhage or disseminated intravascular coagulation, allergies to blood products or drugs (plasma, heparin and protamine), acute cerebrovascular accidents or severe craniocerebral injury, cardiac insufficiency with uncorrected hypotension or shock.

Those severely/critically confirmed patients who had either a significant rise in serum inflammation (2.2.3) or rapid progression of lung imaging (2.2.4) without any exclusion criteria (2.2.5) were enrolled, regardless of sex, but all patients had to be above 18 years old.

## 2.3 | Treatment

### 2.3.1 | Groups

The enrolled patients were divided into two groups according to the patients' and their families' willingness. One was named the treatment group, in which the patients received artificial liver therapy plus comprehensive treatment, while the other was named the control group, in which the patients received only comprehensive treatment.

### 2.3.2 | Artificial liver therapy

Plasma exchange (PE) was the basic method used, and hemofiltration was added for those patients with severe renal



impairment. The therapy was applied in a single treatment ranging from 3 to 24 hours, and the time of the treatment was decided according to the disease condition.

### 2.3.3 | Criteria for discontinuation

Once the patients obtained clinical remissions of normal body temperature for 3 days and obvious improvement of respiratory symptoms plus any of the following three improvements, they were considered for ending artificial liver therapy:

1. Inflammatory factors (such as IL-6) decreased to below twice the normal values for 3 continuous days;
2. Weaning from the ventilator;
3. Obvious improvement of lung imaging after 1 week (lung lesions absorbed  $\geq 30\%$  over before therapy).

## 2.4 | Data collection

Demographic data, epidemiological history, medical history, symptoms, signs, laboratory findings and lung imaging examinations were collected from patients' medical records. Laboratory results included routine blood tests, liver function (AST and ALT), kidney function (Cr and BUN), myocardial enzyme (CK), lactate dehydrogenase (LDH), coagulation function (INR, D-dimer and APTT), inflammatory cytokines (IL-6) and arterial blood gas analysis. Adverse events were also recorded.

## 2.5 | Real-time reverse transcriptase–polymerase chain reaction assay

A confirmed COVID-19 case was defined as positive by means of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay on pharyngeal swabs, sputum and bronchoalveolar lavage according to the WHO guidelines. On receipt of the samples, viral RNA extraction was performed using the Smart Labassist-32 extraction system (Taiwan Advanced Nanotech Inc, China) according to the manufacturer's instructions, followed by PCR screening for the presence of specific 2019-nCoV sequences with the Roche Light Cycler 480II (Applied Biosystems, Hong Kong, China). The 25  $\mu\text{L}$  PCR mixture contained 5  $\mu\text{L}$  viral RNA, 4  $\mu\text{L}$  new coronavirus reaction solution, 7.5  $\mu\text{L}$  RT-PCR buffer, 5  $\mu\text{L}$  reverse transcriptase/Taq mixture from the kit and 3.5  $\mu\text{L}$  RNase water from Jiangsu Bioperfectus Technologies Co., Ltd, Taizhou, China. Thermal cycling was performed at 50°C for 30 minutes to conduct reverse transcription, followed by 95°C for 5 minutes, 95°C for 10 seconds for 45 cycles, and

finally 55°C for 40 seconds. A cycle threshold value (Ct value)  $\leq 36$  and an S-shaped curve with significant exponential growth was defined as a positive test, following the recommendation by the National Institute for Viral Disease Control and Prevention.

## 2.6 | Cytokine IL-6 detection

The serum cytokine IL-6 level was detected by flow cytometry with the FACSCanto II instrument (produced by Becton, Dickinson, Franklin Lakes, NJ, USA).

## 2.7 | Clinical prognostic indicator

The main indicator was the 28-day mortality of severe/critical COVID-19 patients after treatment. The secondary indicators included clinical improvement, ventilator application, successful ventilator weaning, serum IL-6 level changes and the time it took for viral nucleic acid to turn negative.

## 2.8 | Statistical analysis

SPSS 20.0 software was used for statistical analysis of the data. The normally distributed measurement data were evaluated by *t* test. Non-normally distributed data are expressed as median (M) and interquartile spread (P25, P75). The Wilcoxon test was used for comparisons between paired data, and the Mann-Whitney *U* test was applied for comparisons between groups. The enumeration data were expressed as cases (percentage) and were compared by the Mann-Whitney *U* test. A *P* value lower than .05 indicated a statistically significant difference.

# 3 | RESULTS

## 3.1 | Demographic and clinical characteristics of severe/critical patients with COVID-19

This study involved 101 severe/critical cases of COVID-19, among which 50 cases were in the treatment group, while the other 51 were in the control group. Patients were treated from 28 January 2020 to 28 April 2020 and were followed up from 28 January 2020 to 30 May 2020.

The baseline demographic and clinical characteristics of the 101 patients are shown in Table 1. Data comparisons between the treatment group and the control group were as follows: average age (60.96, 60.69 years), sex ratio (80% male, 68.63% male), incidence of main pre-treatment morbidity



(22% and 25.49% for diabetes, 52% and 41.28% for hypertension, 18% and 9.8% for cardio-cerebrovascular diseases), initial symptom (74% and 68.63% for fever, 48% and 31.37% for cough), systolic pressure ( $126.27 \pm 17.08$  mm Hg,  $130.57 \pm 17.43$  mm Hg), diastolic pressure ( $74.71 \pm 12.95$  mm Hg,  $73.36 \pm 12.41$  mm Hg), heart rate ( $93.39 \pm 18.81$  beats/min,  $92.20 \pm 24.33$  beats/min), respiratory frequency ( $26 \pm 8.21$  breaths/min,  $26.63 \pm 9.53$  breaths/min), oxygenation index (112.4 mm Hg, 114.5 mm Hg), pneumonia severity index score (108, 91), peripheral white blood cell count

( $9.47 \times 10^9/L$ ,  $8.47 \times 10^9/L$ ), lymphocyte count ( $0.61 \times 10^9/L$ ,  $0.55 \times 10^9/L$ ), hemoglobin content (125 g/L, 123 g/L), platelet count ( $175.5 \times 10^9/L$ ,  $162 \times 10^9/L$ ), rate of abnormal ALT (52%, 35.92%), rate of abnormal AST (32%, 31.37%), rate of abnormal CK (8%, 19.61%), rate of abnormal LDH (68%, 78.43%), rate of abnormal BUN (58%, 43.14%), rate of abnormal CR (16%, 21.57%), D-dimer (2.65  $\mu\text{g/L}$ , 4.42  $\mu\text{g/L}$ ), INR (1.09, 1.10), and APTT (30.10 seconds, 31.95 seconds). No significantly differences in age, gender, pre-treatment morbidity, initial symptom, peripheral white blood cell count,

**TABLE 1** Comparison of baseline data on demographic and clinical characteristics between the treatment group and the control group

Item	The treatment group (n = 50)	The control group (n = 51)	P value
Age (years)	60.96 $\pm$ 13.41	60.69 $\pm$ 15.70	.93
<i>Sex</i>			
Female	20% (10/50)	31.37% (16/51)	.19
Male	80% (40/50)	68.63% (35/51)	
<i>Incidence of combination/underlying diseases</i>			
Hypertension	52% (26/50)	41.28% (21/51)	1
Diabetes	22% (11/50)	25.49% (13/51)	.28
Cardio-cerebrovascular disease	18% (9/50)	9.80% (5/51)	1
<i>Initial symptom</i>			
Fever	74% (37/50)	68.63% (35/51)	1
Cough	48% (24/50)	31.37% (16/51)	
<i>Diagnosis</i>			
Severe type	30% (15/50)	29.41% (15/51)	.95
Critical type	70% (35/50)	70.59% (36/51)	
<i>Signs</i>			
Systolic pressure (mm Hg)	126.27 $\pm$ 17.08	130.57 $\pm$ 17.43	.22
Diastolic pressure (mm Hg)	74.71 $\pm$ 12.95	73.36 $\pm$ 12.41	.60
Heart rate (bpm)	93.39 $\pm$ 18.81	92.20 $\pm$ 24.33	.79
Respiratory rate (bpm)	26 $\pm$ 8.21	26.63 $\pm$ 9.53	.73
<i>Assay index</i>			
Oxygenation index (mm Hg)	112.4 (81.5, 156.5)	114.5 (82.65, 176)	.94
Pneumonia severity index (PSI) score	108 (84.75, 133.25)	91 (71, 126)	.10
Peripheral white blood cell count ( $\times 10^9/L$ )	9.47 (5.70, 12.51)	8.47 (5.80, 11.64)	.36
Lymphocyte count ( $\times 10^9/L$ )	0.61 (0.36, 0.83)	0.55 (0.40, 0.71)	.28
Hemoglobin (g/L)	125 (111.75, 136.25)	123 (106.5, 135)	.54
Platelet count ( $\times 10^9/L$ )	175.5 (113.5, 214.25)	162.0 (118.5, 229.25)	.86
Alanine aminotransferase (ALT, U/L)	38.5 (18.75, 82)	37.5 (22.25, 59)	.74
Aspartate aminotransferase (AST, U/L)	29.5 (22, 47)	33 (21, 53.5)	.29
Creatine kinase (CK, U/L)	93 (46, 159)	84 (29.25, 313.05)	.92
Lactate dehydrogenase (LDH, U/L)	412.5 (348, 621.5)	495.5 (374, 712.5)	.13
Blood urea nitrogen (BUN, mmol/L)	9.15 (5.72, 13.70)	8.23 (5.39, 17.08)	.89
Creatinine (Cr, $\mu\text{mol/L}$ )	63 (47, 82.75)	64 (45.5, 85)	.31
D-dimer ( $\mu\text{g/L}$ )	2.65 (1.0, 9.31)	4.42 (1.16, 13.26)	.29
International normalized ratio (INR)	1.09 (0.98, 1.17)	1.10 (1.01-1.23)	.12
Activated partial thromboplastin time, APTT(s)	30.10 (26.15, 43.48)	31.95 (26.10, 39.28)	.93





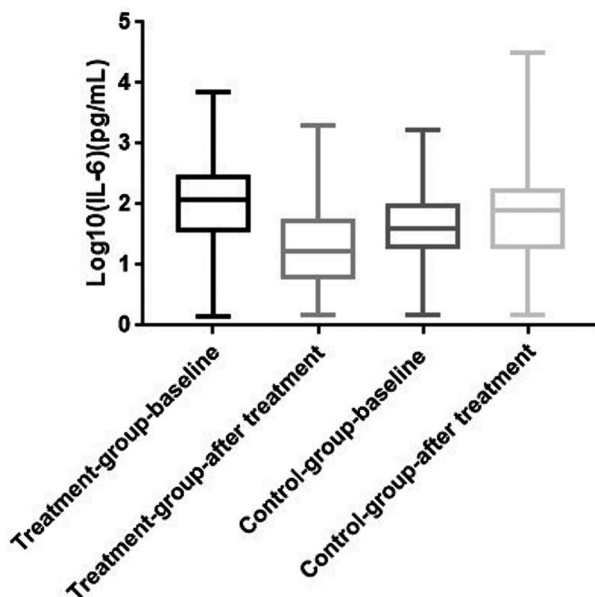
lymphocyte count, hemoglobin, platelet count, abnormal rate of biochemical indicators were obtained between the artificial liver therapy group and the control group (all  $P > .05$ ), indicating to be comparable at baseline.

### 3.2 | Serum IL-6 levels and cytokine storm

The median duration from disease onset to cytokine storm was 12 days (7.5-15 days). The median level of serum interleukin-6 (IL-6) was 51.12 pg/mL when the cytokine storm happened (22.1-146.05 pg/mL).

The serum IL-6 level decreased from 119.94 to 20.49 pg/mL in the treatment group and increased from 40.42 to 50.81 pg/mL in the control group. Significant differences were obtained between the two groups both before and after treatment ( $P < .05$ ) (Figure 1), indicating that artificial liver therapy can significantly decrease the serum level of IL-6.

In the treatment group, all 15 patients in the early stage of the cytokine storm improved and were discharged without the use of invasive assisted respiration, while in the control group, 6 of the 15 patients (40%) in the early stage of the cytokine storm progressed to the critically severe type and died. The prognosis of the patients who experienced early cytokine storms in these two groups was significantly different ( $P = .007$ ), indicating that applying artificial liver therapy in the early stage of the cytokine storm can decrease the fatality rate.



**FIGURE 1** Comparison of serum IL-6 level changes between the artificial liver treatment group and the control group. The serum average IL-6 level decreased from 119.94 to 20.49 pg/mL in the treatment group and increased from 40.42 to 50.81 pg/mL in the control group ( $P < .05$ ), indicating that artificial liver therapy decreased the serum level of IL-6

### 3.3 | Comparisons of assisted respiration duration and successful weaning rate from invasive ventilation

The duration of ventilator-assisted respiration in these two groups was compared (Figure 2). In total, 17 patients in the treatment group and 11 patients in the control group experienced successful weaning from the invasive ventilator. The median assisted duration in the treatment group and the control group was 24 days (25%-75%, 6-46 days) and 35 days (25%-75%, 8-60 days), respectively. There was no significant difference ( $P = .33$ ), indicating that artificial liver therapy did not have an obvious effect on shortening the duration of invasive assisted ventilation in severe/critical COVID-19 patients.

### 3.4 | Comparison of the viral nucleic acid negativity time

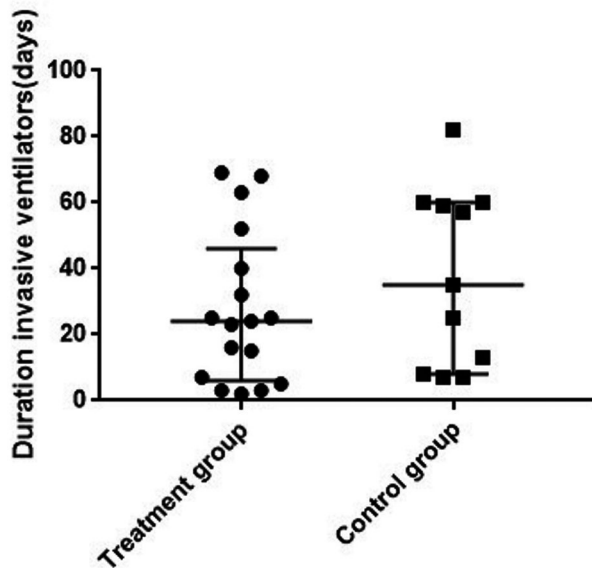
As shown in Figure 3, the median duration of persistent nucleic acid positivity was 19 days (25%-75%, 14.5-44 days) in the treatment group and 17 days (25%-75%, 13-28 days) in the control group. No significant difference was obtained ( $P = .36$ ), suggesting that artificial liver therapy had no obvious effect on the conversion to viral nucleic acid negativity in severe/critical COVID-19 patients.

### 3.5 | Comparisons of clinical improvement and 28-day mortality

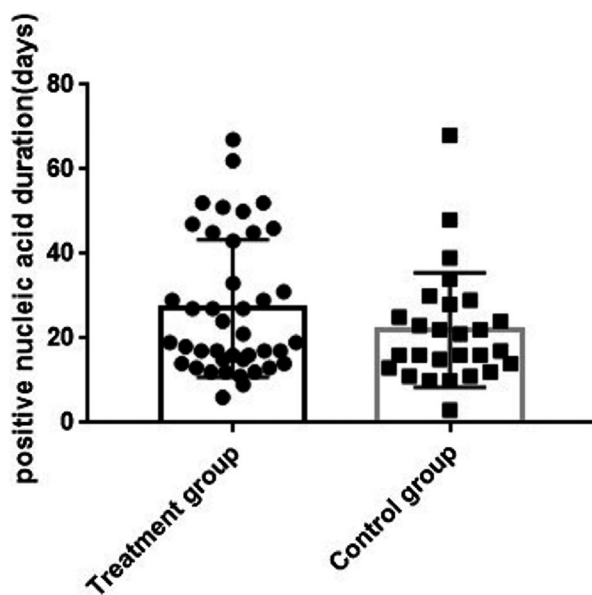
Following up to 30 May 2020, 64% (32/50) of the patients in the treatment group were clinically improved and discharged from the hospital, while 39.22% (20/51) were in the control group, a significant difference ( $z = 2.48, P = .01$ ). The fatality rates of patients 28 days after enrollment were 16% (8/50) in the treatment group and 50.98% (26/51) in the control group, with a significant difference ( $z = 3.70, P < .001$ ). These differences showed that artificial liver blood purification treatment was helpful to improve clinical outcomes.

## 4 | DISCUSSION

The artificial liver blood purification system integrates technologies of PE, hemoperfusion, continuous veno-venous hemofiltration, hemodialysis, bilirubin adsorption and filtration, and others. It has proven helpful for clearing inflammatory mediators, endotoxins and small-medium molecular toxicity, as well as supplementing albumin, coagulation factors and other beneficial substances, resulting in water/electrolyte balance and homeostasis. Previous studies found high levels of pro-inflammatory cytokines/chemokines (eg, IL-2, IL-7, IL-10,



**FIGURE 2** Comparison of the duration of invasive assisted ventilation between the artificial liver treatment group and the control group. No significant difference was obtained ( $P = .33$ )



**FIGURE 3** Comparison of the duration of virus nucleic acid positivity between the artificial liver treatment group and the control group. No significant difference was obtained ( $P = .36$ )

GCSF, MCP-1, MIP1A and TNF- $\alpha$ ) in severely and critically ill patients with COVID-19 infection; furthermore, the presence of a cytokine storm was correlated with disease severity.<sup>9,10</sup> We also saw a distinct rise in IL-6 in severe and critical patients. Cytokine storm usually occurred 1-2 weeks after onset in severe and critical COVID-19 patients. At this time, the cytokine level rises significantly, 5 times or more the upper limit of normal. The median time from disease onset to early cytokine storm was 12 days (7.5 to 15 days). However, a larger sample is required to further study severe COVID-19 patients.

Studies have verified COVID-19 as a systemic disease, with the pronounced release of vasoactive mediators (cytokine storm). A high IL-6 level was identified as a potential predictor of a fatal outcome COVID-19 disease as an increase in IL-6 levels results in pronounced vasodilatation and membrane leakage, which ultimately lead to refractory vasoplegia and multiple organ failure. Multiple therapeutic strategies, including antibody therapies (such as Tocilizumab, Sarilumab, Siltuximab), therapeutic plasma exchange, and even direct removal of cytokines, might mitigate the “cytokine storm”.<sup>11</sup>

The experience gained in the treatment of critically ill patients with H7N9 influenza infection and their cytokine storm revealed the high efficacy of plasma exchange modules in artificial liver blood purification systems, based on the extent of cytokine clearance.<sup>6</sup> The lethality of coronaviruses is related to their induction of an excessive and aberrant immune response associated with severe lung pathology, similar to what influenza viruses do. We hypothesized, inspired by other research,<sup>6,7,12,13</sup> that artificial liver blood purification systems block the cytokine storm, restore immune homeostasis and improve metabolic disorders in severe and critical COVID-19 patients, which might be responsible for reducing mortality. Our study enrolled 101 patients who were severely and critically ill with COVID-19. According to the patients' and their families' willingness, patients were divided into two groups: artificial liver therapy plus comprehensive treatment or only comprehensive treatment. There were no significant differences in age, sex, pre-treatment morbidity, initial symptoms, peripheral white blood cell count, lymphocyte count, hemoglobin, platelet count, or rate of abnormal biochemical indicators between the artificial liver therapy group and the control group, indicating they were comparable<sup>14</sup> at baseline. A significant decrease in the serum IL-6 level (accounting for 82.91%) was obtained in the artificial liver therapy group, while the cytokine storm persisted in the control group. Further study of disease progression and 28-day mortality yielded the following results: (a) The 28-day mortality of all 50 patients in the treatment group was 16% (8/50), significantly lower than that of the control group (50.98%). (b) Further classification by disease severity showed that thirty severe COVID-19 patients were in the early stage of the cytokine storm, of whom all 15 in the treatment group survived to the 28-day follow-up, while 40% of the 15 patients (6/15) in the control group progressed to the critically severe type and died. The above results suggested that artificial liver therapy blocked disease progression and resulted in reduced short-term mortality in COVID-19 patients.

On the other hand, our research showed that among the 68 patients whose viral nucleic acid turned negative during the observation period, 41 were in the treatment group and 27 were in the control group. There was no significant difference in the duration of nucleic acid positivity between the treatment group (median 19 days, ranging from 6 to 67 days)



and the control group (median average 17 days, ranging from 3 to 68 days). Similarly, in patients who survived more than 28 days and were successfully weaned from the ventilator, no significant difference was obtained in the assisted respiration duration between the treatment group (median average 24 days, ranging from 2 to 69 days) and the control group (median average 35 days, ranging from 7 to 82 days). No obvious advantage of artificial liver therapy was observed in clearing novel coronavirus or shortening the duration of assisted respiration with invasive ventilator, which may be related to the limited number of cases, so further specific studies are needed.

## 5 | CONCLUSION

Cytokine storm is a key factor in the intensification of COVID-19 pneumonia. The artificial liver blood purification system blocks the cytokine storm by clearing inflammatory mediators, thus preventing severe cases from progressing to critically ill stages and markedly reducing short-term mortality. Furthermore, the effect of artificial liver therapy can be more significant if applied in the early stage of the cytokine storm. However, there are limitations to this study, such as the small sample size, which may have led to biased conclusions. Further, more detailed studies on the mechanism and long-term follow-up are needed.

### COMPETING INTERESTS

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

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