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# Plasma exchange combining with plasma bilirubin adsorption effectively removes toxic substances and improves liver functions of hepatic failure patients

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**Abstract.** – **OBJECTIVE:** Hepatic failure (HF) is a kind of complex disease characterizing with liver dysfunction and a few clinical complications. Artificial liver support system (ALSS) has been applied to HF patients to improve dysfunctional liver in recent years. This study aims to evaluate therapeutic effects of ALSS approaches, including plasma exchange (PE), plasma diafiltration (PDF) and plasma bilirubin adsorption (PBA), on liver function of HF patients.

**PATIENTS AND METHODS:** This study is a retrospective analysis involving 516 patients diagnosed as HF between February 2014 and February 2015. Patients were randomly divided into PE, PDF, PE plus PBA, and PDF plus PBA group. Meanwhile, single-drug group and combined-drug group were also divided. The liver functions, capability of removing toxic substances and coagulation functions were evaluated both pre-treatment and post-treatment. The side effects and hospital improvement rate were also observed post-treatment.

**RESULTS:** Hospital improvement rate achieves to 69.6%. TBIL levels and MELD scores were significantly decreased post-treatment compared to pre-treatment ($p<0.05$). PTA values were significantly increased post-treatment compared to pre-treatment ($p<0.05$). Reduction value in PE+PBA group was significantly higher compared to PE and PDF group ($p=0.002$, 0.002, respectively). MELD scores were significantly decreased post-treatment compared to pre-treatment in each group ($p<0.05$). Combined-drug treatment is superior to single-drug treatment for removing toxic substances and improving liver functions. PE treatment, PDF treatment and PE+PBA treatment induced more side effects compared to PDF+PBA treatment.

**CONCLUSIONS:** PE combining with PBA plays a better role in removing toxic substances, improving liver functions of HF patients.

*Key Words:*
Hepatic failure, Artificial liver support system, Plasma exchange, Plasma bilirubin adsorption, Toxic substances.

## Introduction

The hepatic failure (HF) is a kind of complex disease characterizing with liver dysfunction and clinical complication. HF is always caused by various factors, the morbidity of which ranges from 60% to 80% in clinical[1,2]. In clinical, the HF mainly divided into three types, including acute HF, acute-on-chronic hepatic failure (ACHF) and chronic hepatic failure (CHF)[3]. The HF onsets rapidly without any hepatic disorders before occurrence[3]. The ACHF results from drugs, alcohol or the virus caused acute exacerbation of the chronic hepatic diseases[3]. The CHF occurs in any types of the end-stage hepatic diseases[4]. Among these types of HF, the ACHF is the most frequently occurred type. Meanwhile, HF constitutes a worse symptom characterizing with diversified manifestations, sophisticated etiology and a higher short-term mortality[5]. Till now, the liver transplantation has been considered to be the most common applied method for the ACHF. However, even seldom patients benefit from the liver transplantation due to the costly operation and the shortage of the healthy livers[6]. In 1970s, in order to improve the functions of liver, the artificial liver support system (ALSS) was firstly applied to therapy the AHF[7]. In the past fifty years, many types of ALSS have been applied to improve the dysfunctional liver, and proved to be the effective method[5,8]. Meanwhile, the ALSS has



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also been developed to bridge the patients with HF to transplantation of liver or to support temporarily the failing liver, till liver can regenerate[7,8]. Though the ALSS can't replace the full liver functions, which could improve some basic liver function effectively[9,10]. Previous studies[11,12] have been exhibited a few effective ALSS approaches, including plasma exchange (PE), plasma diafiltration (PDF) and plasma bilirubin adsorption (PBA)[13]. All of above, ALSS approaches could remove and replace the toxic substances, prevent the bleeding, and improve the coagulopathy. Following with the development of ALSS technology, the survival of HF patients has been achieved to 60%[14,15]. Although the previous studies[10-12,14] have illustrated that ALSS could reduce patients' mortality efficiently, most of these studies conducted the single-treatment for patients. Meanwhile, the effects of combined-drug treatment of PE, PDF and PBA on removing toxic substances and improving coagulation function have not been investigated till now. In this investigation, we employed the ALSS approaches to compare therapeutic effects of various combinations of PE, PDF and PBA on liver function in HF patients.

## Patients and Methods

### Patients

The present work is a retrospective analysis, involving 516 patients diagnosed as HF between February 2014 and February 2015 at Infectious Disease Department, the First Affiliated Hospital of Chongqing Medical University (Chongqing, China). The diagnosis of the hepatic failure was conducted according to Diagnostic and Treatment Guidelines for Liver Failure (2012 version)[16]. Patients according to liver failure diagnostic criteria were included in this study. Among these 516 patients, there were 366 males and 150 females. The age of patients ranges from 19 to 68 years (mean age, 44.82±12.99). This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. The protocol of this study was strictly conformed to the Ethical Guidelines of Declaration of Helsinki[17]. The written informed consents were obtained from all of the patients included in this study.

### Study Design

Among the 516 patients, 108 cases were diagnosed as AHF, 20 cases were diagnosed as subacute HF, 204 cases were diagnosed as ACHF and 194 cases were diagnosed as CHF. These patients were randomly divided into four groups, including single PE group (n=129), single PDF group (n=129), PE plus PBA group (n=129) and PDF plus PBA group (n=129). According to the different therapeutic modes, PE group and PDF group were also called single-drug group (n=258). Meanwhile, the PE+PBA group and PDF+PBA group were also called combined-drug group (n=258). The baseline demographics were listed in Table I.

**Table I.** Base-line data for the four treatment methods.

| Items | PE | PDF | PE+PBA | PDF+PBA | $X^2$ | *p* |
|---|---|---|---|---|---|---|
| Gender (male/female) | 95/41 | 81/41 | 156/48 | 34/20 | 0.923[a] | 0.820 |
| Age (years) | 44 (28-63) | 51 (30-68) | 43 (20-64) | 40 (19-65) | 2.363[b] | 0.078 |
| ALB | 30±5.60 | 26.44±3.18 | 30.67±5.92 | 29.13±4.09 | 2.685[b] | 0.053 |
| TBIL | 279.66±42.19 | 291.57±87.16 | 327.36±120.84 | 286.76±95.57 | 1.891[b] | 0.139 |
| ALT | 461.60±51.60 | 522.11±70.973 | 566.00±61.58 | 406.88±33.42 | 0.904[c] | 0.824 |
| AST | 260.30±26.89 | 277.67±29.42 | 374.33±29.67 | 296.00±24.32 | 2.764[c] | 0.43 |
| PT | 24.07±11.04 | 23.39±7.33 | 22.41±8.1 | 25.58±11.93 | 0.299[b] | 0.826 |
| INR | 2.12±1.13 | 2.10±0.83 | 1.96±0.93 | 2.16±1.02 | 0.158[b] | 9.924 |
| PTA | 44.41±11.35 | 46.82±16.32 | 48.15±14.16 | 38.49±7.09 | 0.396[b] | 0.756 |
| Cr | 71.40±20.25 | 70.11±18.31 | 77.87±11.68 | 68.63±22.86 | 0.375[b] | 0.771 |
| NH | 47.88±12.07 | 61.94±18.97 | 43.18±13.80 | 64.88±6.18 | 1.669[b] | 0.181 |
| MELD | 20.23±6.91 | 21.64±6.42 | 21.30±6.51 | 21.78±4.28 | 0.240 | 0.868 |
| Acute hepatic failure | 4 | 2 | 7 | 3 | 10.699[a] | 0.297 |
| Sub-acute hepatic failure | - | - | 2 | 1 | | |
| Acute-on-chronic hepatic failure | 10 | 6 | 13 | 3 | | |
| Chronic hepatic failure | 6 | 10 | 8 | 1 | | |

Note: "a" represents the enumeration data, which is tested by quadruple tabular formed $x^2$-test. "b" represents the normal distribution data, which is tested by Student's *t*-test. "c" represents the abnormal distribution data, which is tested by non-parametric test following with Kruskal-Wallis test.

### Therapeutic Approaches

All of the 516 patients were conducted due to following recommendations, including usage of hepatocyte growth factor, absolute bed rest, eating liquid, infusion of albumin, preventing and curing complications and maintaining acid-base equilibrium or electrolyte. ALSS were conducted by using plasma separator Plasmaflo KM-9000 (Kuraray, Tokyo, Japan) and membrane plasma separator (Evacure filter, Tokyo, Japan). The sing-drug treatment and combined-drug treatment were performed according to the previous studies[4,18]. Briefly, the combined-drug groups were performed the PBA treatment firstly for 2 h, and later conducted the PDF or PE treatment. The total amounts of 1600 ml fresh plasma were exchanged per time, following with blood flow of 130-140 ml/min and plasma separation rate of 30%. The anti-coagulant scheme was designed according to the prothrombin activity (PTA) of patients, and the heparin sodium (250 U/ml) was used as the anticoagulant in this study. For the first injection, 8 ml were injected when PTA ≥ 50%, 5.5-7 ml were injected when PTA ranging from 40% to 50%. Meanwhile, 4-5 ml were injected when PTA ranging from 26% to 39%, and never injecting when PTA ≤ 25%. For the additional treatment amounts, 4 ml/h for PTA ≥ 40% and 2.5 ml/h for PTA < 40%. Moreover, 5 mg dexamethasone were applied to prevent allergy reaction before the treatment. A total of 1 mg calcium gluconate was also injected when exchanged plasma achieved to 800 ml, to prevent the hypocalcaemia. Meanwhile, 1 mg protamine was also administrated to inhibit blood coagulation post the therapy.

### Observation Indexes

The laboratory parameters, including serum total bilirubin (TBIL), alanine aminotransferase (ALT), creatinine (Cr), aspartate aminotransferase (AST), international normalized ratio (INR), were examined by using commercial kits (Sigma-Aldrich, St. Louis, MO, USA). In this study, the Model for End-Stage Liver Disease (MELD) scores were evaluated and calculated as the following formula 9.57×loge (Cr mg/dl)+3.78×loge (TBIL mg/dl)+11.20×loge (INR)+6.43, according to the previous study[19]. The drugs received and adverse-events were recorded during the whole study period.

### Statistical Analysis

The quantitative data were illustrated as mean ± SD or median, and the categorical variables were illustrated by the count. The data were analyzed by using the SPSS 17.0 software (SPSS Inc, Chicago, IL, USA). The quantitative data were analyzed by using Student's *t*-test. The categorical data were analyzed by using $\chi^2$ or Fisher exact test. The comparison among multiple groups were conducted by using Kruskal-Wallis test. $p<0.05$ was considered as the statistically significant.

## Results

### Hospital Improvement Rate

For all of the patients involved in this study, the physical strength and appetite for food were improved, and the mental state was gradually recovery. A total of 618 ALSS treatments were administrated for the 516 patients, and 1-3 ALSS treatments were administrated to each patient. Among all of the 516 patients, 359 patients were improved and left the hospital with an hospital improvement rate of 69.6%.

### ALSS Treatments Significantly Remove Toxic Substances

In this study, the ALSS approaches, including single PE, single PDF, PE+PBA and PDF+PBA, were administrated to HF patients. The results indicated that TBIL levels were significantly decreased post the treatment compared to the pre-treatment (Figure 1A, $p<0.05$). There were significant differences for the reduce values among all of the four groups (Figure 1A, $F=5.161$, $p=0.002$). The TBIL levels in PE+PBA group decreased from 327.36 ± 120.84 µmol/L post the treatment to 193.83 ± 83.3 µmol/L pre-treatment (Figure 1A, $p=0.002$). The reduction value in PE+PBA group was significantly higher compared to the PE and PDF group (Figure 1A, $p=0.002$, 0.002, respectively). All of the PTA values were significantly increased post-treatment compared to pre-treatment in every group (Figure 1B, $p<0.05$). There were no significant differences for the increase values among all of the four groups (Figure 1B, F=2.532, $p=0.062$). The Cr levels were also decreased post-treatment compared to pre-treatment; however, there were no significant differences (Figure 1C, $p>0.05$). There were also no significant differences for reduce values among all four groups (Figure 1C, F=3.573, $p=0.311$). The MELD scores were significantly decreased post-treatment compared to pre-treatment in each group (Figure 1D, $p<0.05$). There were also no significant differences for

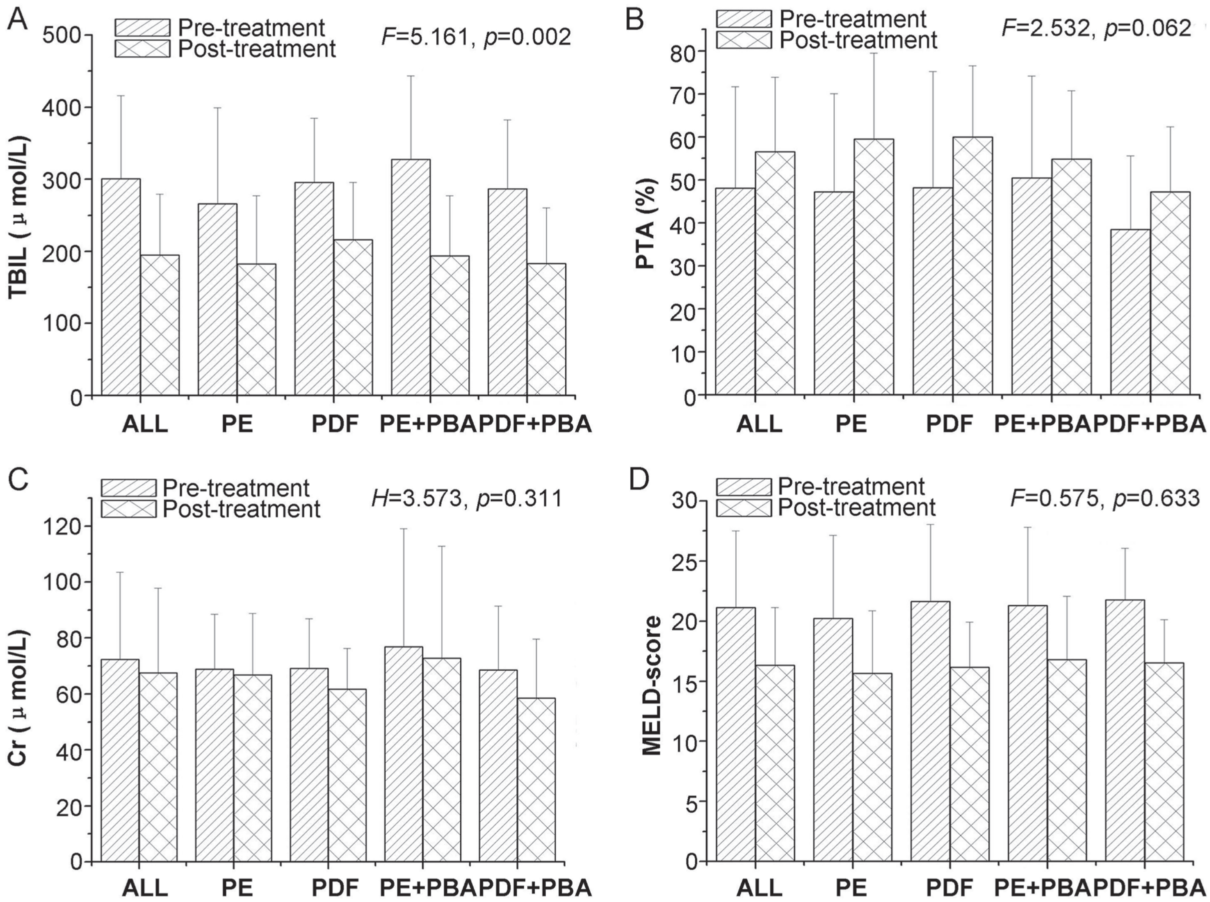


**Figure 1.** Therapeutic comparison for the ALSS among all of the PE, PDF, PE+PBA and PDF+PBA. ***A,*** Comparison for the TBIL levels. ***B,*** Comparison for the PTA values. ***C,*** Comparison for the Cr levels. ***D,*** Comparison for the MELD-scores. The statistical values were listed in the images.

reduce values among all four groups (Figure 1D, F=0.575, $p$=0.633).

### *Combined-Drug Treatment is Superior to Single-drug Treatment for Removing Toxic Substances and Improving Liver Function*

The results showed that the TBIL levels were significantly decreased post-treatment compared to pre-treatment in both single-drug group (279.02 ± 115.64 μmol/L *vs.* 197.51 ± 88.99 μmol/L) and combined-drug group (320.59 ± 113.08 μmol/L *vs.* 192.08 ± 81.59 μmol/L) (Figure 2A, both $p$<0.05). The reduce values for the TBIL were significantly different between the single-drug and combined-drug group (Figure 1A, F=13.870, $p$=0.000). The PTA values were also significantly increased post-treatment compared to pre-treatment in both single-drug group (47.62 ± 24.51% *vs.* 59.68 ± 18.36%) and combined-drug group (48.49 ± 23.00% *vs.* 53.55 ± 15.91%). The increase values of PTA were significantly different between the single-drug and combined-drug group (Figure 2B, F=6.912, $p$=0.010). The Cr levels were also decreased post the treatment compared to pre-treatment in both single-drug and combined-drug group; however, there were no significant differences (Figure 2C, $p$>0.05). There were also no significant differences for reduce values of Cr levels between two groups (Figure 1C, F=2.042, $p$=0.153). The MELD scores were significantly decreased post-treatment compared to pre-treatment in both single-drug and combined-drug group (Figure 2D, $p$<0.05). There were also no significant differences for reduce values of MELD scores between single-drug and combined-drug group (Figure 2D, F=0.040, $p$=0.842).

**Table II.** Side-effects distribution in different items.

| Items | Bleeding tendency (*n*) | Hypotension (*n*) | Skin rashes (*n*) | Numb (*n*) | Total (*n*) |
|---|---|---|---|---|---|
| PE | - | 5 | 14 | 15 | 34 |
| PDF | - | | 5 | 5 | 10 |
| PE+PBA | 5 | 10 | 15 | 10 | 40 |
| PDF+PBA | - | 5 | - | - | 5 |
| Total | - | 20 | 34 | 30 | 89 |

### *Combined-Drug Treatment Triggers Lower Side Effects*

All of the patients successfully administrated the ALSS therapy with better tolerance. There were 89 times of side effects in all of 516 patients (89/516, 17.20%). The side effects mainly include bleeding tendency, hypotension, skin rashes and numb. The results indicated that PDF+PBA treatment only induced 5 cases of hypotension, and no other side effects (Table II). However, the PE treatment, PDF treatment and PE+PBA treatment induced more side-effects compared to the PDF+PBA treatment (Table II).

## Discussion

HF mainly caused by two aspects of pathogenic factors, including toxic substances accumulation in liver and inflammatory factors production[20,21].

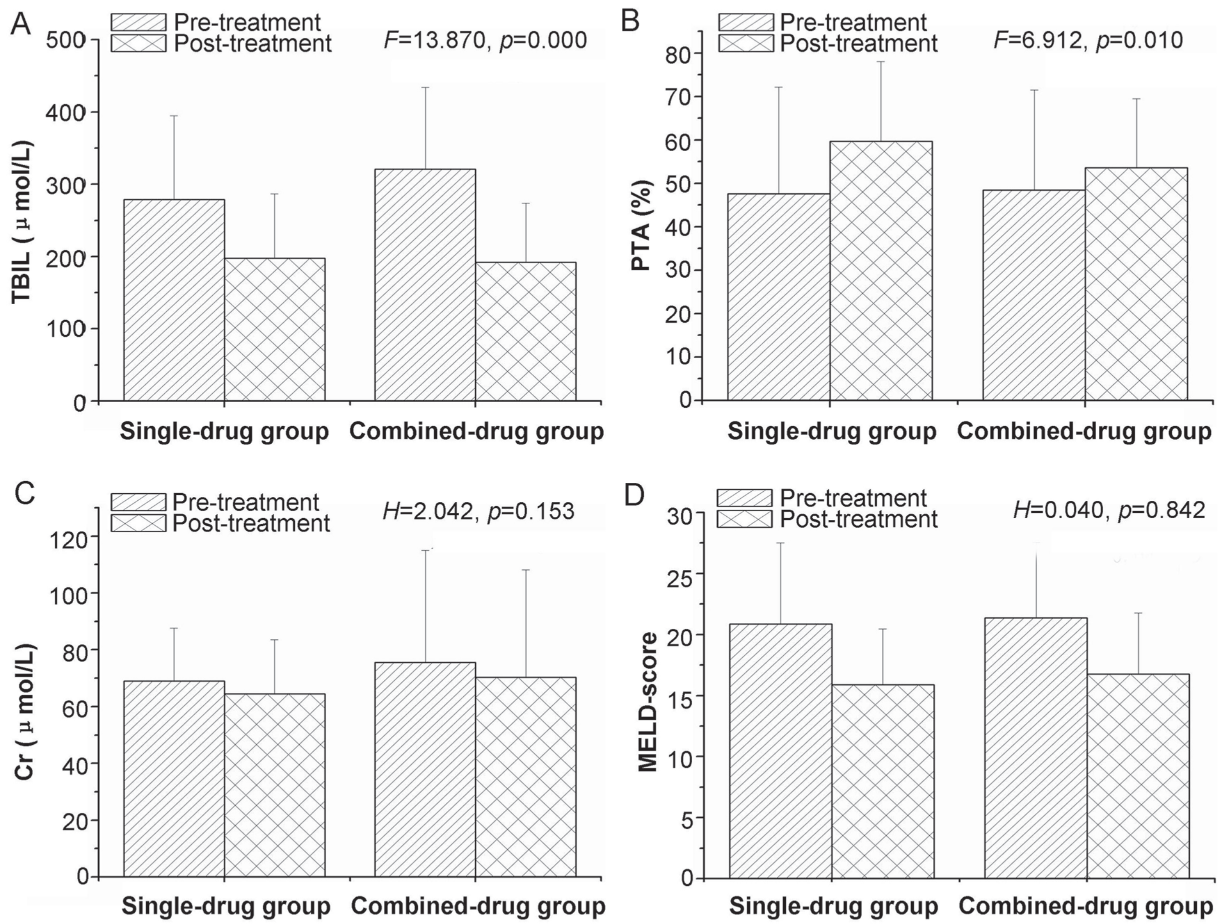


**Figure 2.** Therapeutic comparison for the ALSS between single-drug and combined-drug group. ***A,*** Comparison for the TBIL levels. ***B,*** Comparison for the PTA values. ***C,*** Comparison for the Cr levels. ***D***, Comparison for the MELD-scores. The statistical values were listed in the images.

Nowadays, there were no effective therapies available except for the liver transplantation. However, the liver transplantation was limited due to the lack of healthy livers and costly operation[6, 22]. As a kind of alternative method of liver transplantation, the ALSS has become an effective approach for prolonging the survival period and improving the liver functions[23]. Therefore, the ALSS has been developed to bridge patient diagnosed as HF to liver transplantation. Previous studies[24-26] reported a few types of ALSS, such as PE, PDF, PBA. All of the above approaches could restore the liver functions by supplying the beneficial internal-environment for the liver cells. In this study, we evaluated the therapeutic outcomes (including remove of toxic substances and liver functions) of HF patients by employing different ALSS treating approaches. We mainly investigated the effects of four therapeutic modes, including PE, PDF, PE+PBA and PDF+PBA. According to the findings of Figure 1, all of these four modes play roles in removing toxic substances, improving coagulation function, and enhancing the kidney function. These results are consistent with Nakae et al[27] findings. Meanwhile, the capability of removing toxic substances in PE+PBA group was higher significantly compared to which in the other three groups. We speculated that the PE+PBA treatment method triggered two key processes for removing toxic substances. A method is to exchange the plasma containing toxins with the fresh plasma. The other one is to adsorb the toxic substances by the bilirubin adsorption column. The PDF, as a kind of blood purification method, plays the role of plasma filtration, dialysis and replacing blood[28]. Meanwhile, the efficient filtration area was inhibited competitively in the therapeutic processes[28]. Moreover, in the process of removing the water-soluble toxic substances, such as Cr, the filterability of the TBIL was decreased. Finally, the capability of removing toxic substances of PDF method was reduced.

The multiple combined ALSS approach has been become a therapeutic tendency for the HF treatment[28]. The plasma replacement as a kind of simple and good-effective non-biological artificial liver method, always combined with the other artificial liver methods in clinical. Schaefer et al[29] combined the plasma exchange and hemodialysis (HD), and compared to the therapeutic effect of molecular adsorbent recirculating system (MARS) in the HF children. They found that the efficacy of combined PE/HD was superior to the intermittent MARS. Huang et al[30] reported that PE combining with MARS therapy could reduce the serum TBIL levels more effectively for HF patients. Li et al[31] also found that the combination of PE, hemoperfusion and continuous veno-venous hemodiafiltration was more efficient for removing toxic substances, especially for the TBIL. The results of the present study are consistent with the above studies and the conclusions. The present findings suggest that multiple combined artificial liver methods could be better and more effectively remove toxic substances and improve liver functions. HF patients undergoing four kinds of artificial liver methods exhibited better tolerance, and completed the therapy successfully in this study. Although a few side effects were appeared in the therapeutic processes for some patients, the symptoms were controlled post the active interventions. Among the four kinds of therapeutic modes, PE+PBA mode triggered the most frequent side effects. These side effects may be associated with the injection of the massive fresh blood into the body, and no other supplementary of other liquids[4, 32,33]. Therefore, the PE+PBA mode may finally cause the hypocalcaemia, hypernatremia and allergy reaction. In clinical practice, it's critical to monitor the fresh frozen plasma infusion associated hypocalcaemia and allergy reactions.

## Conclusions

PE combining with PBA plays better role in removing toxic substances and improving liver functions compared to the other three therapeutic modes. Meanwhile, the ASLL illustrated the hospital improvement rate of 69.6%, and could effectively treat the HF. All of above suggests that it's promising to be vigorously promoted and developed for the application of combined ASLL therapeutic mode in clinical. This research is a retrospective analysis, and the samples will be enlarged in the following study. Also, the randomized controlled trial will be designed in the future, to better evaluate the applicable effects of combined ALSS on HF or other organ failure diseases.

### Conflict of Interest

The authors declare no competing financial or commercial interests in this manuscript.

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