Meta-Analysis of the efficacy of DPMAS-based artificial liver in the treatment of ACLF

Lina Ma
general hospital of ningxia medical university
Xu Zhang
general hospital of ningxia medical university
Wanlong Ma
general hospital of ningxia medical university
Xiangchun Ding (13619511768@163.com)
general hospital of ningxia medical university

Systematic Review

Keywords: acute-on-chronic liver failure(ACLF), plasma exchange(PE), double plasma molecular adsorption system(DPMAS), artificial liver support system(ALSS), meta- analysis

Posted Date: April 28th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1604197/v1

Title page

Meta-Analysis of the efficacy of DPMAS-based artificial liver in the treatment of ACLF

Le Zhang[1]， Li-Na Ma[2] ,Xu-Zhang[2],Wanlong Ma[2],Xiang-Chun Ding[2*]

1. Ningxia Medical University, Yinchuan, Ningxia, China

2.Department of Infectious Disease, General Hospital of Ningxia Medical University, Yinchuan, Ningxia.

***Corresponding Authors:**

Dr. Xiang-Chun Ding, Department of Infectious Disease, General Hospital of Ningxia Medical University, Yinchuan, Ningxia, 750004, China. Phone: (+86) 13619511768; Email: 13619511768@163.com. In the meantime, the institutional email address is dingxiangchun@nyfy.com.cn.

& These authors contributed equally to this work.

Abbreviations: ACLF: acute-on-chronic liver failure; ALSS: artificial liver support system; PE: plasma exchange; DPMAS: double plasma molecular adsorption system;

Keywords: acute-on-chronic liver failure(ACLF), plasma exchange(PE), double plasma molecular adsorption system(DPMAS), artificial liver support system(ALSS), meta-analysis

Lay Summary: ALSS is considered as the first-line treatment for HBV-ACLF, however, the certainty of their efficacy, safety and influence on survival rate are still controversial. In this study, the efficacy, safety, adverse reactions and survival rate of hepatitis B-caused acute-on-chronic liver failure treated with artificial liver support systems based on double plasma molecular absorption system (DPMAS) were evaluated by meta-analysis.

Running title: the efficacy of DPMAS-based artificial liver in the treatment of ACLF

Abstract:

Background & Aim: Many references have reported the feasibility of various artificial liver support systems in the treatment of acute-on-chronic liver failure caused by Hepatitis B. However, there is still controversy over their efficacy, safety, and impact on survival rates. Meta-analysis was conducted to assess the efficacy, safety, adverse reactions, and survival rate of hepatitis B-caused ACLF treated with artificial liver support systems based on the double plasma molecular absorption system (DPMAS).

Methods: The keywords or abstractions “liver failure, severe hepatitis, acute-on-chronic liver failure” were searched on the databases such as CBM, PubMed, Cochrane library,

etc. and the Revman5.3 software was used to analyze the literature data.

Results: After analysis, DPMAS improved total bilirubin and 90-day survival rate higher than plasma exchange (PE). However, there was no statistical significance in international standardized ratio (INR). the results of international normalized ratio (INR) were [MD=0.06, 95% CI (-0.38, 0.49), P>0.05], that of 90-day survival rate were [OR=3.07, 95% CI (1.87, 5.02), P<0.05]. The improvement of total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT), the adverse reactions, the 90-day survival rate and the improvement rate after treatment all were better in DPMAS+PE than PE. However, there were no statistical significance in prothrombin activity (PTA), prothrombin time (PT), blood platelet (PLT), international standardized ratio (INR), hemoglobin (HB), and creatinine (Cr).

Conclusion: Total bilirubin are reduced more in DPMAS than in PE after treatment, which might be related with the special bilirubin adsorption column (BS330II) in DPMAS. Whereas, the improvement in INR was not significant in DPMAS compared to PE, which may require additional investigation. The combination of DPMAS and PE reduced total bilirubin more effectively. Furthermore, while they were able to boost ALB, there was no difference in coagulation function, owing to the fact that PE could supply the proteins and coagulation components required by the human body. This meta-analysis also demonstrated that DPMAS+PE reduced the incidence of adverse reactions, increased the effective rate following treatment, and improved 90-day survival rate. Perhaps it's because DPMAS reduces the use of plasma products and removes more toxic substances like bilirubin and inflammatory agents.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is defined as acute or subacute liver decompensation within a short time on the basis of chronic liver disease, mainly manifested as jaundice, coagulation dysfunction, and hepatic encephalopathy within 4 weeks. It is a common severe liver disease syndrome and progresses rapidly, with high mortality rate in a short time[1]. In China, hepatitis B virus infection is the primary cause of ACLF[2]. Liver transplantation is the only certain way for liver failure, but is limited by the lack of donors and high cost[3]. Artificial liver support system (ALSS) is considered as the first-line treatment to promote the recovery of liver function or act as the bridge for transplantation[4]. ALSS utilizes the equipment to remove toxic substances temporarily, replenish some necessary matters needed by patients. ALSS can be divided into biological artificial liver, non-biological artificial liver and hybrid artificial liver system. Biological artificial liver support system and hybrid artificial liver are mainly composed of bioreactor and cell sources, which not only have detoxification function but also can replace partial liver functions, such as synthesis and metabolism. Nevertheless, the alternative animal cells are limited by the spread of pathogens and incompatibility of immune and physiological function. Recently, the human embryonic stem cells and bone marrow cells are used, but due to the tumor cells being able to pass through filtration membrane, Lan-Juan Li scientist predominantly resolved this matter by gene insertion way. It has been applied in clinical practice in Europe, but is clinical trial in China[5]. Among the ALSS methods, non-biological artificial liver (NBAL) is the most mature and most frequently used in clinic. NBAL gives priority to albumin channel

adsorption therapy including molecular adsorbent recirculating system (MARS) and Prometheus system in foreign countries, which can get rid of the protein binding and water-soluble toxics.

Molecular adsorbent recirculating system (MARS) consists of blood circulation, albumin circulation and typical renal circulation. Blood enters into a high-flux dialysate containing albumin through MARS FLUX dialyzer. In this manner, the MARS makes the albumin-bound toxins, but not albumin itself, to dissolve from the patient albumin. The secondary circuit undergoes dialysis to remove the water-soluble toxins, and the albumin dialyzer is generated via two adsorbers that contain charcoal and anion resin. Then the albumin is returned to the patient's circulatory system. According to previous studies[6-7], its distinctive ability in removing water-soluble and protein binding substances can reduce some complications such as hepatic encephalopathy and hepatorenal syndrome. The more interesting is that it can eliminate cytokines which are indispensable in the hap of liver failure and multiple organ failure[8-9]. It is limited in clinic due to the disadvantages such as complex pathway, expensive cost. In addition, it can't supply the required albumin and coagulation factors. Therefore, it cannot improve the prognosis of HBV-ACLF.

The main principle of the Prometheus system is that the patient's blood is dialyzed through a high-flux hollow fiber hemodialysis filter, then the albumin-bound toxins and albumin are detoxified by a special adsorbent consisting of neutral resin and anion resin. The detoxifying blood is then purified by a high-flux hemodialyzer before entering the body. The difference with MARS is that the dialysate is discarded after being passed

through the filter. Studies have shown that it is superior in removing bilirubin, blood ammonia, bile acids[10]. In addition, MARS has an influence on stabilizing hemodynamics because it can clear vascular factors such as NO. However, we can't find this effect in the Prometheus system.

In China, non-biological liver support system includes hemodialysis, plasma exchange, etc. At present, the plasma exchange (PE) is the most common artificial liver support method in China. PE can nonspecifically dissolve toxic substances such as endotoxin and bilirubin [11], and fresh frozen plasma or blood albumin can be replaced to provide patients with coagulation factors or immunoglobulin and opsonin. It can be divided into selective and ordinary plasmaphereses. The latter is always used in immune system diseases, including SLE and myasthenia gravis. The former can eliminate toxins selectively. Studies have demonstrated that it can reduce not only the amount of plasma but also the low osmotic pressure related to the plasma exchange. However, PE is poor in the removal of water-soluble substances and blood ammonia[12]. Meanwhile, it requires a large number of blood products, which is easy to cause infections and allergies, metabolic alkalosis and hypocalcemia. Hence, PE often combines with hemofiltration to correct electrolyte imbalance. In the process of PE, it can destroy some nutritious substances, such as hepatocyte growth factors, which lead to the occurrence of loss syndrome. In addition, the shortage of plasma products restricts its application in clinic.

The double plasma molecular absorption system (DPMAS) is composed of anion exchange resin (BS330) and neutral microporous resin (HA330-II). The resin in

HA330-II can absorb medium and macromolecular toxins such as inflammatory factors. These factors are the main mediators that cause multiple organ failure in ACLF. The resin in BS330 can adsorb bilirubin specifically. But because of its prolonged absorption, it can destroy coagulation factors. Furthermore, due to its strong adsorption in albumin binding substances, it can destroy albumin as well. Compared with PE, DPMAS doesn't need a lot of blood products, so it can save plasma and reduce the possibility of infections and allergies[6].

Thus far, various artificial liver support systems are used in ACLF. For hepatic encephalopathy, plasma exchange and plasma perfusion are combined. For patients with renal insufficiency, PE combined with HD or HF can be chosen. After searching and strict screening, the literature that met the standard were mainly DPMAS and PE in the treatment ways. There were many studies involving the treatment of ACLF of HBV with DPMAS or PE, but the efficacy and safety still lack evidence-based medical evidence. Therefore, a meta-analysis was adopted to explore the efficacy and safety of DPMAS-based artificial liver support in the treatment of ACLF to offer a new opinion for clinical treatment in our study.

Methods

Two researchers completed literatures selection independently and checked the results each other. The main contents included treatment methods, indexes, results, etc. "Double plasma molecular absorption system, plasma exchange, severe hepatitis, liver failure, acute-on-chronic liver failure" as the key words or abstractions were searched in PubMed、Cochrane Library, Embase, CNKI, WANFANG Medical network and

CBM. Selection criteria: ①the language was limited to Chinese or English; ②due to the limitation of time and literature research results, the diagnostic criteria of ACLF were in line with the 2012 Guidelines for the Diagnosis and Treatment of Liver Failure. The indications for the application of artificial liver support system corresponded with the guidelines of Abiotic artificial liver therapy for liver failure in 2016; ③the patients were older than 18 years old and not pregnant individual. There was no limitation on gender, nationality; ④DPMAS as observation group and PE as control group or DPMAS+PE as observation group and PE as control group. Exclusion criteria: ①several basic diseases, such as respiratory diseases, hemopathy and tumors and so on; ②allergic to the blood products and easy to bleed; ③ The paper was reported repeatedly or only had abstractions, or had no complete data. Objectives: total bilirubin (TBIL); alanine aminotransferase (ALT); prothrombin time activity (PTA); prothrombin (PT); albumin (ALB) and incidence of adverse reactions and survival rates. Then the literatures that met the requirements were screened by reading the abstract. After careful readings, the full text, and the inclusion and exclusion criteria were combined to determine the included literature. Quality of our literatures were evaluated by the Cochrane collaboration method and heterogeneity was assessed using RevMan5.3. Data were meta-analyzed by RevMan5.3 software. Mean difference (MD) was used for measurement data group, odds ratio (OR) was used for counting data, and 95% confidence interval was used for effect sizes. In the meanwhile, heterogeneity analysis was carried out on the selective papers. No heterogeneity on studies using fixed effects model ($P>0.1$, $I^2<50\%$) and heterogeneity exists on studies using random effects model ($P<0.1$, $I^2>50\%$). $P<0.5$

means statistical significance.

Results

A total of 1710 articles were researched and 11 articles met the criteria at last[13-24]. A total of 4 articles involved the treatment of DPMAS compared with PE in HBV-ACLF, and the specific characteristics were shown in Table 1. There were 7 papers compared DPMAS+PE with PE in the treatment of ACLF caused by hepatitis B. The features were shown in Table 2. And the heterogeneity of literatures was assessed in Table 3.

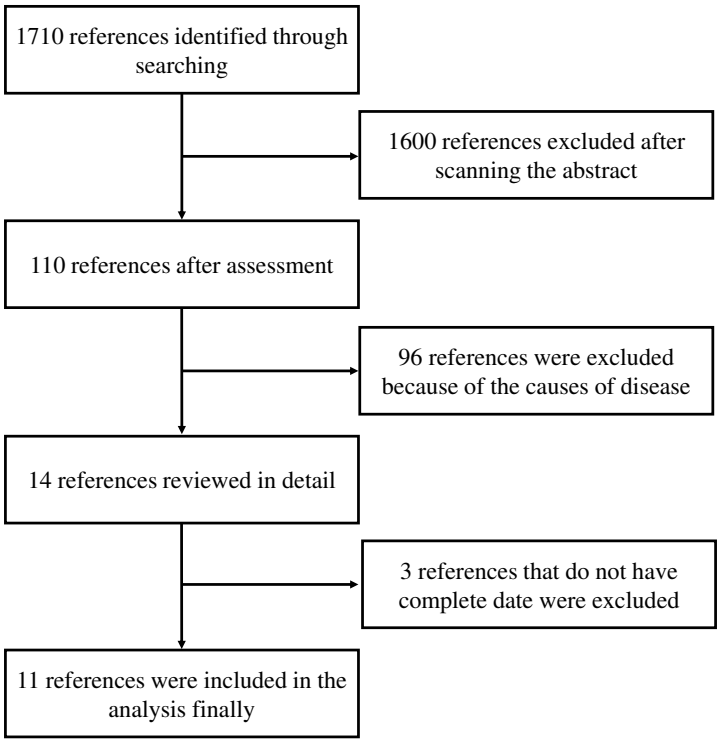

Figure1.Flowchart of our study

Tab.1 Baseline Characteristics of included literature

Included literatures	number of cases (T1/C1)	cause/diagnosis/stage	indexes
Liu Chuntao (2019)	40/40	HBV/ACLF /early stage	①⑧⑨⑫⑩⑪⑰
Jiao Yueqin (2021)	60/60	HBV/ACLF/early stage	①⑧⑨⑩⑪⑫⑰
Xie Lan (2020)	22/20	HBV/ACLF/early stage	①②④⑤⑧⑫
Jin Hua (2020)	42/42	HBV/ACLF/early stage	①②④③⑤⑫⑰

177

178 Tab.2 Baseline Characteristics of included literature

Included literatures	number of cases(T2/C2)	cause/diagnosis	indexes
Li Kai（2021）	55/55	HBV/ACLF	③④⑪
Qin Hua(2019)	32/37	HBV /ACLF	②⑤③⑨⑥⑮⑯
Guo Xiju（2019）	33/31	HBV /ACLF	①②③④⑦
Xie Nengwen（2021）	56/56	HBV /ACLF	①②③④⑨⑦
Du Zhen（2021）	34/38	HBV /ACLF	②①⑤⑨⑧⑮⑯
Qin Wei（2021）	114/134	HBV /ACLF	①②③⑮⑯
Qin Hao（2020）	43/43	HBV /ACLF	①②③④⑩⑪

179 Notes: T1: DPMAS; C1: PE; T2: DPMAS+ PE; C2: PE 。Indexes: ① total bilirubin(TBIL); ② alanine
180 transaminase(ALT); ③ prothrombin activity(PTA); ④ prothrombin(PT); ⑤ albumin(ALB); ⑥ adverse effects
181 rates; ⑦effective rate; ⑧creatinine(Cr); ⑨total bile acid(TBA); ⑩TNF-a; ⑪IL-6; ⑫INR; ⑬CD4+; ⑭CD8+;
182 ⑮4 weeks recovery rate; ⑯12 weeks recovery rate; ⑰3-month survival rate.

183 Tab.3 Quality assessment

Included studies	Li Kai,	Qin Hua,	Guo Xiju,	Xie Nengwen
Was the spectrum of patients representative of patients who will receive test in practice?	Yes	Yes	Ye s	Yes
Whether the selection criteria was clear?	Yes	Yes	Ye s	Yes
Was the gold standard likely to correctly classify the target disease?	Yes	Yes	Ye s	Yes
Did the patients receive the same reference standard?	Yes	Yes	Ye s	Yes
Was the gold standard independent of the test to be evaluated?	Yes	Yes	Ye s	Yes
Whether the gold reference results interpreted without knowing the results of index test?	Yes	Yes	Ye s	Yes
Was the interval between the gold standard and the test	Yes	Yes	Ye s	Yes
sufficiently short enough to avoid changes in disease?	Yes	Yes	Ye s	Yes
Whether all cases received the gold standard test?	Yes	Yes	Ye s	Yes
Was the implementation of gold standard tests fully explained and repeatable?	Yes	Yes	Ye s	Yes
Is the clinical information available when interpreting the results of the trial consistent with the clinical information available in practice?	Yes	Yes	Ye s	Yes
Could the cases dropped out of the study be illuminated??	No	No	N o	No
Were difficult to interpret test results reported?	No	No	N o	No

184

185 Tab.4 Quality assessment

Included studies	Du Zhen,	Qin Wei,	Qin Hao

Was the spectrum of patients representative of patients who will receive test in practice?	Yes	Yes	Ye s
Whether the selection criteria was clear?	Yes	Yes	Y es
Was the gold standard likely to correctly classify the target disease?	Yes	Yes	Y es
Did the patients receive the same reference standard?	Yes	Yes	Y es
Was the gold standard independent of the test to be evaluated?	Yes	Yes	Ye s
Whether the gold reference results interpreted without knowing the results of index test?	Yes	Yes	Yes
Was the interval between the gold standard and the test	Yes	Yes	Y es
sufficiently short enough to avoid changes in disease?	Yes	Yes	Y es
Whether all cases received the gold standard test?	Yes	Yes	Y es
Was the implementation of gold standard tests fully explained and repeatable?	Yes	Yes	Y es
Is the clinical information available when interpreting the results of the trial consistent with the clinical information available in practice?	Yes	Yes	Y es
Could the cases dropped out of the study be illuminated??	No	No	N o
Were difficult to interpret test results reported?	No	No	No

We found four studies that reported changes in total bilirubin and INR before and after treatment[13-16], with heterogeneity (P<0.1, I^2=53%) (P<0.1, I^2=100%).Total bilirubin decreased more after treatment in DPMAS than PE, according to a meta-analysis of random effects model [MD=-39.47, 95% CI （-54.29, -24.66）, P<0.05].(Figure 2). There was no statistically significant difference between DPMAS and PE [MD=0.06, 95%CI (-0.38, 0.49), P>0.05] (Figure 3). Meantime, here were 3 articles that reported the 90-day survival rate [13-14,16](P>0.1, I^2=8%),Meta-analysis of fixed effect model demonstrated that DPMAS might enhance 90-day survival rate than PE with statistical significance [OR=3.07, 95% CI (1.87, 5.02), P<0.05](Figure 4).

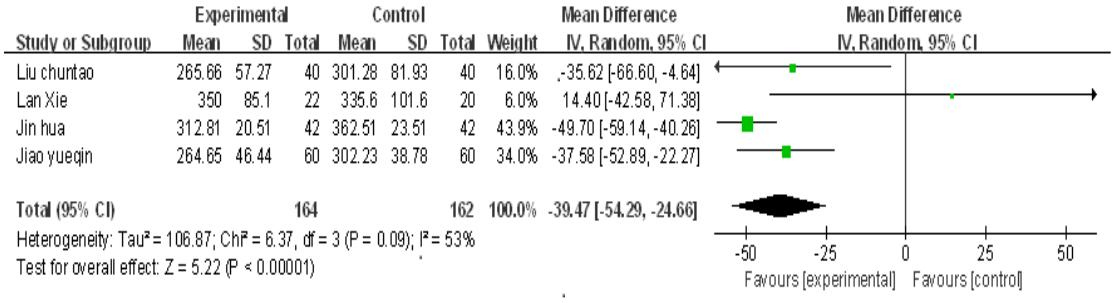

Figure2. TBIL after treatment between DPMAS and PE

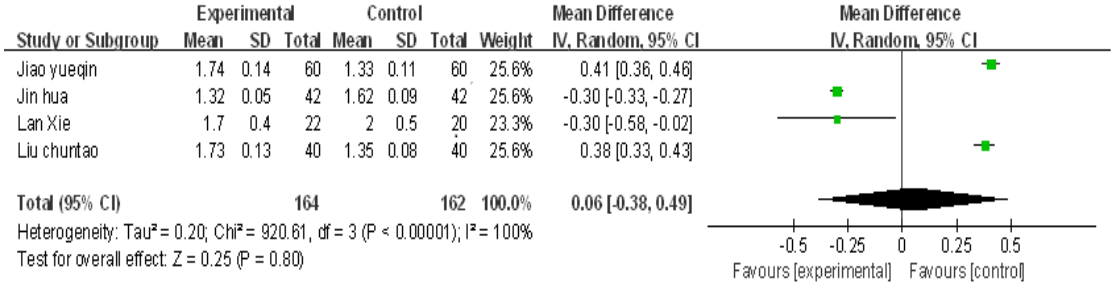

Figure3. INR after treatment between DPMAS and PE

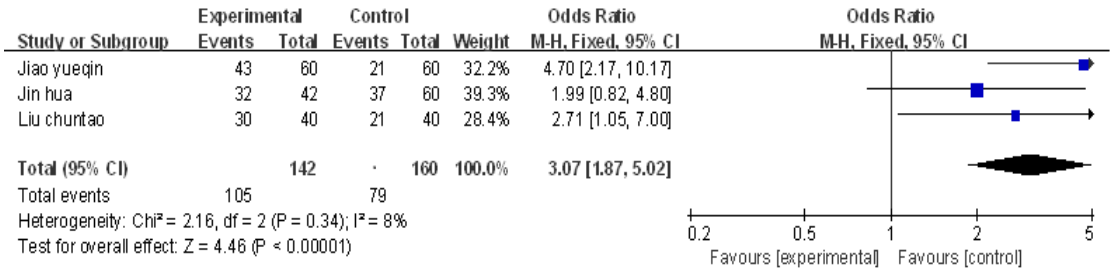

Figure4. 90-day survival rate after treatment between DPMAS and PE

Here were results about DPMAS+PE with PE. TBIL was described 7 literatures[18-24], with variability between studies (P<0.1, I^2=94%). TBIL dropped more in DPMAS+PE than PE, according to a meta-analysis of random effect models [MD=-28.77, 95% CI (-56.50, -1.04), P<0.05] (Figure5). There were 3 papers that showed ALB[19,20,24],with no significant differences between investigations (P>0.1, I^2=0%). A meta-analysis of fixed effect model revealed that DPMAS+PE improved ALB more than PE, with statistical significance [MD=-1.71, 95%CI (-2.63, -0.79), P<0.05] (Figure 6).There were 5 studies that reported ALT [18,19,21,22,25] and there was heterogeneity between them (P<0.1, I^2=97%). Using a meta-analysis of random effect model, the results showed that statistical significance [MD=-

52.95, 95% CI (-99.15, -6.75), P<0.05] (Figure 7). Cr was reported in four literatures [19,20,24,25], and there was no variability between studies (P>0.1, I^2=37%).There was no difference between DPMAS+PE and PE in a meta-analysis of fixed effect model [MD=-1.58, 95% CI (-5.32, 3.56), P>0.05]. (Figure8). There were 4 papers that involved HB [18,19,21,25] and the studies were heterogeneous (P<0.1, I^2=90%). There was no statistically significant difference in the random effect model, according to a meta-analysis. [MD=0.09, 95%CI(-9.42, 9.59), P>0.05]. (Figure 9)

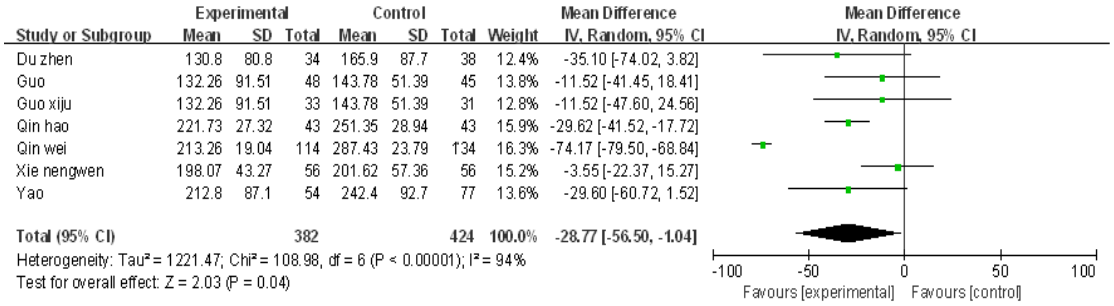

Figure5. TBIL after treatment between DPMAS+PE with PE

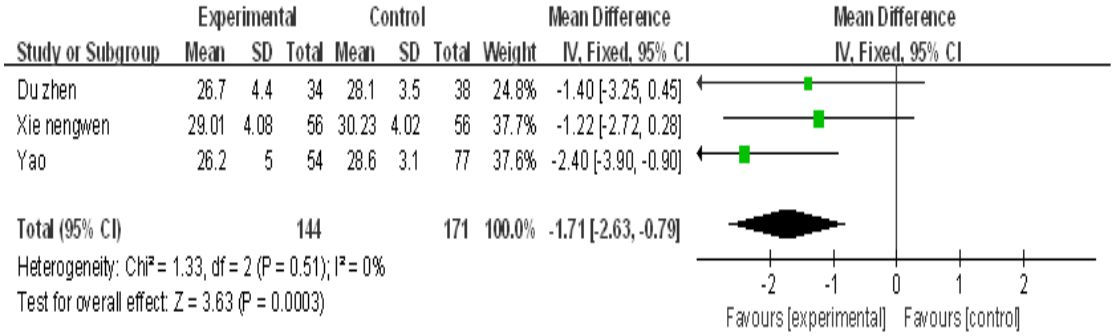

Figure6. ALB after treatment between DPMAS+PE with PE

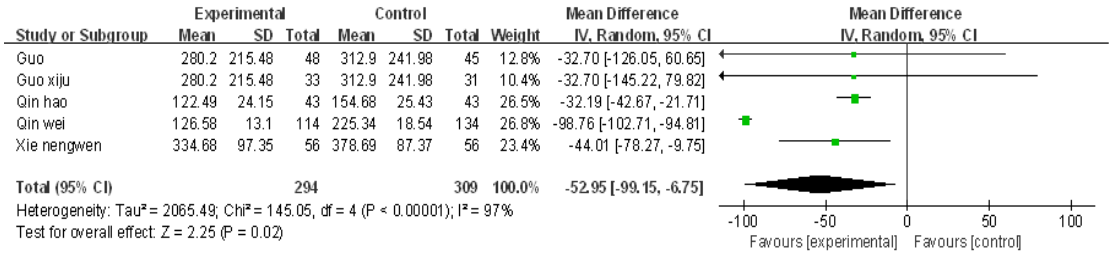

Figure7. ALT after treatment between DPMAS+PE with PE

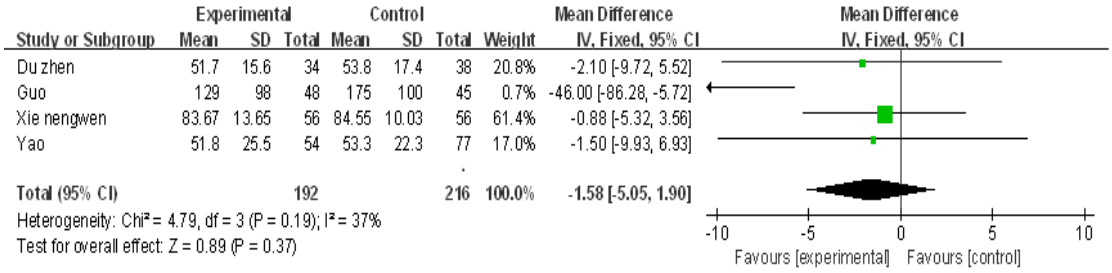

Figure8. Cr after treatment between DPMAS+PE with PE

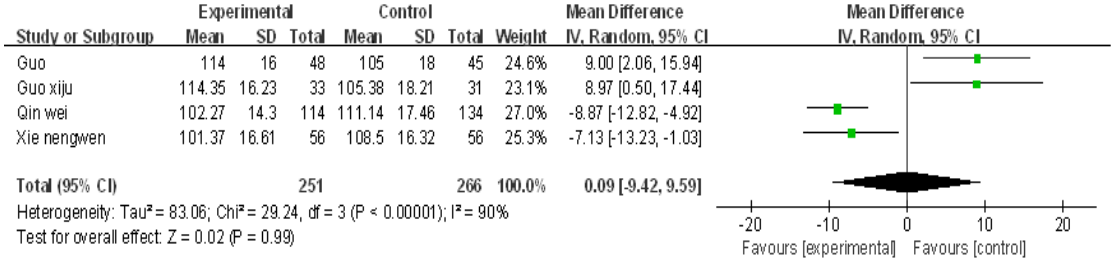

Figure9. HB after treatment between DPMAS+PE with PE

A total of 4 literatures reported INR [19,20,24,25] and there was heterogeneity among studies (P<0.1, I^2=59%). Meta-analysis of random effect model revealed that there were no difference between DPMAS+PE with PE [MD=-0.06, 95% CI (-0.21, 0.10), P>0.05](Figure 10).There were 5 papers involved PLT[18,19,21,22,25] and there was heterogeneity among studies (P<0.1, I^2=63%).Meta-analysis of random effect model showed there were no difference between DPMAS+PE and PE [MD=-4.07, 95%CI(-10.06, 1.92), P>0.05].(Figure 11). There were 5 literatures involved PT[17-20,25], and there was heterogeneity among studies(P<0.1, I^2=71%).Meta-analysis of random effect model showed no statistical difference in prothrombin time between DPMAS combined with PE and PE. [MD=0.12, 95%CI(-2.19, 2.43), P>0.05] (Figure12). There were 6 papers involved PTA[17,18,20,21,22,25]and there was heterogeneity among studies(P<0.1, I^2=97%). Meta-analysis of random effect model showed there were no difference between DPMAS+PE and PE in PTA[MD=2.95, 95%CI(-3.12, 9.010, P>0.05] (Figure 13)

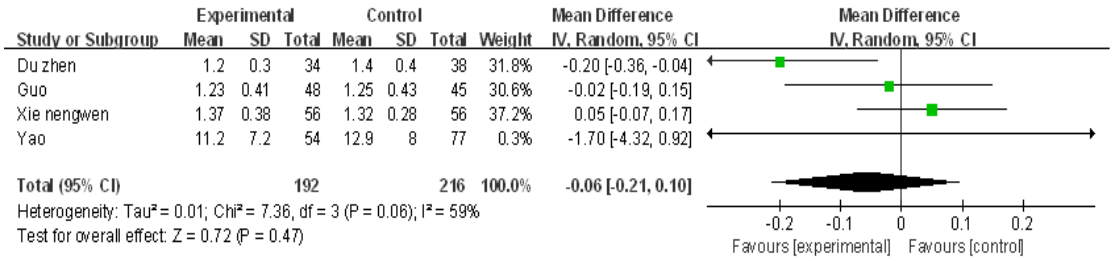

Figure10. INR after treatment between DPMAS+PE with PE

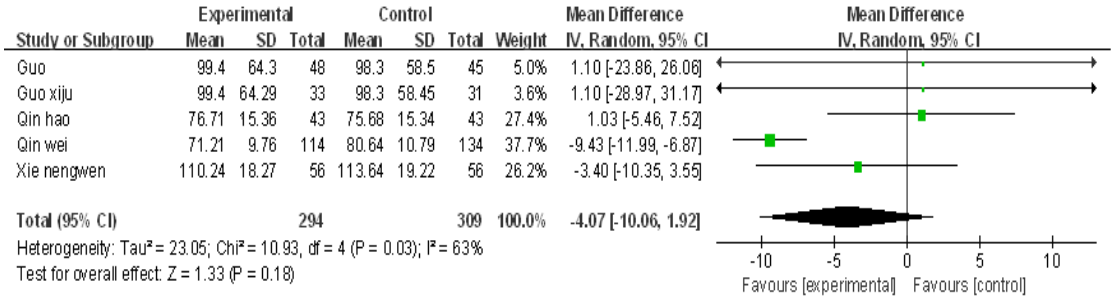

Figure11. PLT after treatment between DPMAS+PE with PE

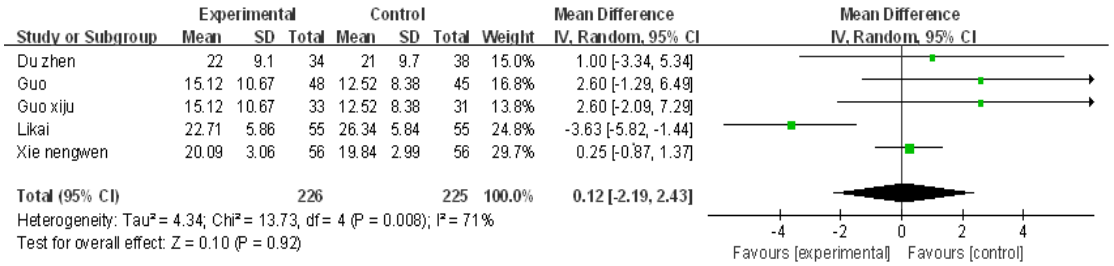

Figure12. T after treatment between DPMAS+PE with PE

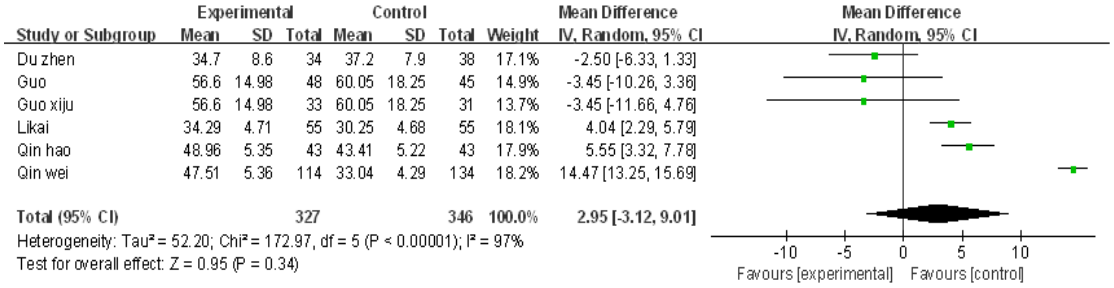

Figure13. PTA after treatment between DPMAS+PE with PE

There were 3 papers reported 90-day survival rate[20,21,23], with no heterogeneity between studies (P>0.1, I^2=16%). Meta-analysis of fixed effect model showed that DPMAS+PE improved 90-day survival rate than PE, and there was statistical significance [OR=2.52, 95%CI(1.55, 4.10), P<0.05](Figure 14). A total of 4 literatures reported therapeutic efficacy with no heterogeneity among studies (P>0.1, I^2=35%)[18-19,21-22]. Meta-

analysis of fixed effect model revealed that DPMAS+PE can improve effective rate more than PE and had statistical significance [OR=2.36, 95% CI (1.60, 3.50), P<0.05](Figure 15). There were 3 articles reported the occurrence of adverse reactions[19,22,23] and there was no heterogeneity between the studies (P>0.1, I^2=46%). Meta-analysis of fixed effect model displayed that DPMAS+PE could reduce the incidence of adverse reactions than PE. The main adverse reactions mainly included allergy, hypotension, rash, etc. which could be relieved after symptomatic treatment. (Figure 16)

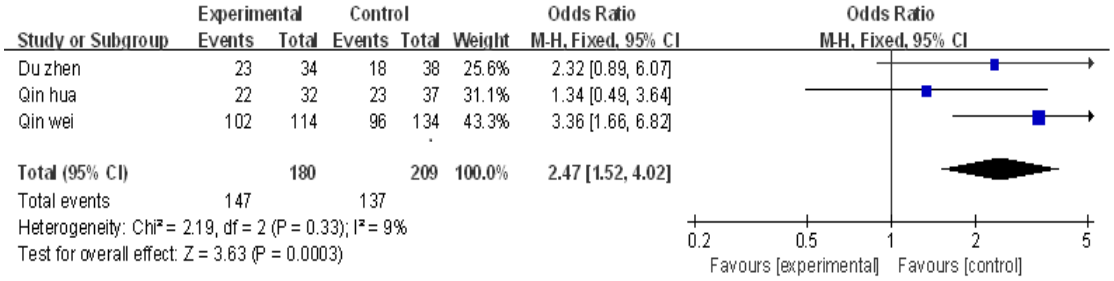

Figure14. 90-day survival rate after treatment between DPMAS+PE with PE

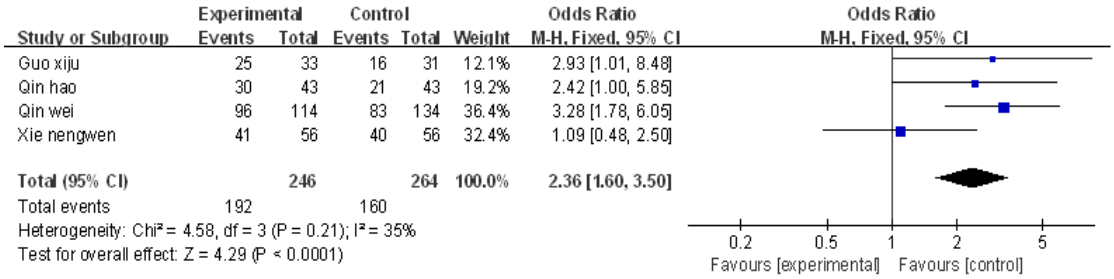

Figure15. Efficacy rate after treatment between DPMAS+PE with PE

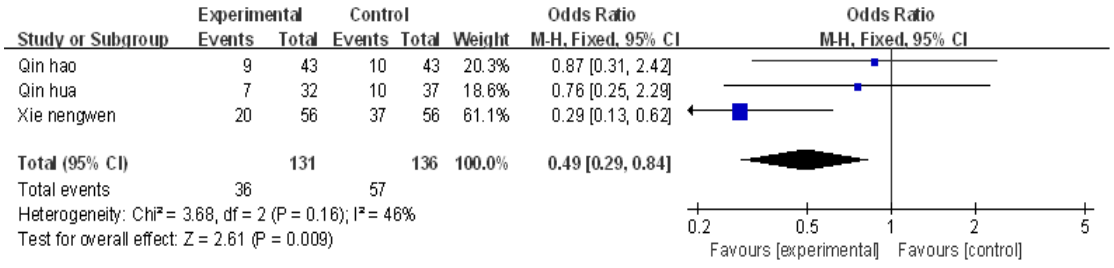

Figure16. Adverse reaction rate after treatment between DPMAS+PE with PE

Discussion

Acute-on-chronic liver failure (ACLF) is a sudden and rapid deterioration of liver function on the basis of chronic liver disease, which is mainly manifested as jaundice,

coagulopathy. It has a high mortality rate using comprehensive medical treatment. Liver transplantation is the only confirmed effective method, however, it is limited by the high cost and the lack of donors[27]. Artificial liver support system utilizes mechanical, chemical or biological devices to remove toxic substances or temporarily replace the liver function as well as replenishes some necessary substances, such as albumin, coagulation factors. So, it can support and promote the liver function and prolong waiting time for liver transplantation[28].

We analyzed the treatment for ACLF caused by hepatitis B by DPMAS based artificial liver support. We could see that total bilirubin decreased more in DPMAS than PE, which was related to the specific BS330 bilirubin adsorption column in DPMAS. And the result is consistent with Wan[30]. As we all know, the pathogenesis with liver failure is inflammatory response caused by cytokine mediated inflammatory mediators. The adsorption column in HA330II can strengthen the clearance for medium and large molecules such as inflammatory factors which may be related to the improvement of 90-day survival rate in DPMAS. Meanwhile, using DPMAS, the MELD score could decrease, however, the lower score the better prognosis. Furthermore, some studies showed that the improvement of coagulation was better in PE than DPMAS, but in our study, the result of INR had no difference with PE, which might have something with the small number of literatures and need further confirmation.

Our results indicated that the total bilirubin and alanine aminotransferase decreased higher in DPMAS+PE than PE, and could increase the albumin. In fact, the fundamental pathology of liver failure is liver cell necrosis of different degrees, TBIL is

mainly metabolized by liver, and ALT is stored in liver cells. Therefore, we could conclude that DPMAS combined with PE might improve liver metabolism and strengthen the clearance of inflammatory factors which could improve the liver microenvironment and decrease the destroy of the liver cells. Albumin as one of the main components of nutritional status can improve the prognosis of HBV-ACLF. The column in DPMAS can damage albumin in the process of absorption of albumin binding toxins. It could be concluded that combined therapy can supplement albumin needed by human body improving the condition of patients. The improvement of creatinine, hemoglobin, international prothrombin ratio, platelet, prothrombin time and prothrombin activity were not significantly different from pure PE, which were in consistent with Guo[25]. As a result of the long contact between the adsorption column and the blood of patients, which certainly causes damage to coagulation factors and tangible substances in blood. Our study demonstrated that there was no significant difference in the improvement of coagulation function in DPMAS+PE and PE. So, we could infer that PE could compensate the damage in the process of adsorption in DPMAS to some extent. Moreover, DPMAS is the suitable treatment option for patients with abnormal elevated bilirubin and repeated transfusion of plasma product as it doesn't need more blood products than PE. Our study also confirmed that the incidence of adverse reactions was lower than PE, the 90-day survival rate was higher in DPMAS+PE than PE, these results were consistent with Li[32-33]. It may be related to the specific adsorption columns in DPAMS, which strengthen the adsorption for inflammatory factors and bilirubin and, improve the microenvironment in liver. PE can supplement

coagulation factors and albumin required by human body. In order to avoid metabolic alkalosis, cerebral edema, hyperkalemia, allergies, and other adverse reactions produced by repeated transfusion of plasma products in ACLF patients caused by hepatitis B, DPMAS+PE can be selected to increase short-term survival rate and reduce adverse reactions.

However, due to the small number of literatures (especially English literatures) included in our study, and the relevant data to electrolytes, inflammatory mediators, acid-base balance and other conditions were incomplete and were not concluded. Therefore, further studies are required to prove their efficacy. Because of the small number of literatures included in this paper, publication bias is not considered for the time being. Although this study can provide some reference value for the selection of clinical treatment options, there are some limitations of our study as follows: ①the quality of the included literatures is different, and there may be selection bias; ②the experimental allocation method of included literatures may be subjective, which may lead to selection bias; ③the number of artificial liver support was not mentioned, the number of included studies was small, the treatment regimen was not completely consistent, which may lead to publication bias; ④the selected literatures all are domestic researches, which may occur language, analysis and other biases.

Acknowledgments

Acknowledgments

This study was supported by the Fund for the Natural Science Foundation of Ningxia (2022AAC02065), the Key R&D Programs of Ningxia (2022CMG02039) and the Fund

for Less Developed Regions of the Natural Science Foundation of China (81760363, 81460301). These funding bodies played no role in study design, data collection and analysis, and decision-making regarding publishing or preparing the manuscript.

Availability of data and materials

The data in this study's findings are included within the reference articles selected from Cochrane Library, Pub med, CNKI, EMBASE, and the Wan fang database.

Authors' Contributions

Le Zhang and Li-Na Ma contributed equally to this study. Xiang-Chun Ding and Le Zhang received the study, picked the manuscript, and critically corrected it for important intellectual content. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no competing financial interests.

References

1. Group of Liver Failure and Artificial liver, Chinese Society of Infectious Diseases, Chinese Medical Association, Group of severe Liver disease and Artificial Liver, Chinese Society of Hepatology, Chinese Medical Association. Guidelines for diagnosis and treatment of Liver Failure(2018 edition). Chinese Journal of Clinical Infectious Disease. 2018, 11(6): 401-410. Doi: 10.3760/cma.j.issn. 1674-2397. 2018.06.001

2. Wu T, Li J, Shao L, Xin J, Jiang L, Zhou Q, Shi D, Jiang J, Sun S, J in L, Ye P, Yang L, Lu Y, Li T, Huang J, Xu X, Chen J, Hao S, Chen Y, Xin S, Gao Z, Duan Z, Han T, Wang Y, Gan J, Feng T, Pan C, Chen Y, Li H, Huang Y, Xie Q, Lin S, Li L, Li J; Chinese Group on the Study of Severe Hepatitis B (COSSH).. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut. 2018 Dec; 67(12): 2181-2191. Doi: 10.1136/gutjnl-2017-314641. E pub 2017 Sep 19. PMID: 28928275.

3. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. Hepatology. 2014 Dec; 60(6): 2099-108. Doi: 10.1002/hep.27406. E pub 2014 Oct 29. PMID: 25164003; PMCID: PMC4867229.

4. Inoue K, Watanabe T, Hirasawa H, Yoshiba M. Liver support systems as perioperative care in liver transplantation-historical perspective and recent progress in Japan. Minerva Gastroenterol Dietol. 2010 Sep;56(3):345-53. PMID: 21037550.

5. Kobayashi N, O kitsu T, Tanaka N. Cell choice for bioartificial livers. Keio J Med. 2003 Sep; 52(3): 151-157. Doi: 10.2302/kjm.52.151. PMID: 14529147.

6. Koivusalo AM, Teikari T, Höckerstedt K, Ison Iemi H. Albumin dialysis has a favorable effect on amino acid profile in hepatic encephalopathy. Metab Brain Dis. 2008 Dec; 23(4): 387-398. Doi: 10.1007/s11011-008-9110-9. E pub 2008 Sep 5. PMID: 18773287.

7. Novelli G, Rossi M, Pretagost Ini M, Pugliese F, Ruberto F, Novelli L, Nudo F, Bussotti A, Corradini S, Martelli S, Berloco PB. One hundred sixteen cases of acute liver failure treated with MARS. Transplant Proc. 2005 Jul-Aug; 37(6): 2557-2559. Doi: 10.1016/j.transproceed. 2005.07.015. PMID: 16182742.

8. Liu Q. Role of cytokines in the pathophysiology of acute-on-chronic liver failure. Blood Puri f. 2009; 28(4): 331-341.Doi: 10.1159/000232940.Epub 2009 Sep 1. PMID: 19729901.

9. Luo M, Guo JY, Cao WK. Inflammation: A novel target of current therapies for hepatic encephalopathy in liver cirrhosis. World J Gastroenterol. 2015 Nov 7; 21(41): 11815-11824. Doi: 10.3748/wjg.v21.i41.11815. PMID: 26557005; PMCID: PMC4631979.

10. Sauer IM, Goetz M, Steffen I, Walter G, Kehr DC, Schwartlander R, Hwang YJ, Pascher A, Gerlach JC, Neuhaus P. In vitro comparison of the molecular adsorbent recirculation system (MARS) and single-pass albumin dialysis (SPAD). Hepatology. 2004 May; 39(5): 1408-1414. Doi: 10.1002/hep.20195. PMID: 15122770.

11. Stahl K, Busch M, Fuge J, Schneider A, M an ns MP, See liger B, Schmidt JJ, Wiesner O, Schmidt BMW, Taubert R, Vondran FWR, Hoeper MM, David S. Therapeutic plasma exchange in acute on chronic liver failure. J Clin Ap her. 2020 Aug; 35(4): 316-327. Doi: 10.1002/jca.21799. E pub 2020 Jun 24. PMID: 32583446.

12. Zhou PQ, Zheng SP, Yu M, He SS, Weng ZH. Prognosis of acute-on-chronic liver failure patients treated with artificial liver support system. World J Gastroenterol. 2015 Aug 28; 21(32): 9614-9622. Doi: 10.3748/wjg.v21.i32.9614. PMID: 26327769; PMCID: PMC4548122.

13.Liu Chuntao, Wu Ru i, Yu Haiyan, Liu Shourong, Fu Xiaoqing. Therapeutic effect

of double plasma molecular adsorption system in the treatment of hepatitis B associated acute-on-chronic liver failure[J]. ZhejIng Medicine, 2019, 9(2): 125-127131. Doi: 10.12056/j. i SSN.1006-2785.2019.41.2.2018-1086.

14. Jiao Yueqin, Zhao Yunfeng, Wang Li. Effects of DPMAS artificial liver in the treatment of chronic hepatitis B-associated acute liver failure[J]. Chinese Journal of Practical Medicine, 201, 48(09): 54-57.

15. Xie Lan. Comparison of short-term effects of two artificial liver treatment modes in chronic and acute hepatitis B liver failure[J]. Wisdom of health, 2020, 6(01): 101-103. Doi: 10.19335/j.cnki.2096-1219.2020.01.042.

16. Wang Y, et al. The efficacy of DPMAS artificial liver transplantation in the treatment of chronic acute liver failure[J]. Contemporary medicine, 2020, 26(01): 46-48.

17. Li Kai. Effect of plasmapheresis combined with dual plasma molecular adsorption system on inflammatory level and coagulation index in patients with chronic acute liver failure[J]. Modern Diagnosis and Treatment, 2021, 32(11): 1683-1685.

18. Guo Xiju, Wei Yunhua, Guo Weibo, Zhang Jiaqiang, Xu Juan, Lion Mingmei. Effects of artificial liver therapy on liver inflammation in patients with chronic acute liver failure[J]. Shaanxi Medical Journal, 2019, 48(09): 1167-1170.

19. Xie Nengwen, Zhu Longchuan, Gan Dakai, Fu Suhong, Jiang Jianhong, Xiong Morong. Efficacy and safety of dual plasma molecular adsorption combined with low volume plasma exchange in the treatment of chronic acute liver failure[J]. Chinese Modern Doctor, 201, 59(18): 1-5.

20. Du Zhen, Tang Xiaojun, Tao Yun, Cheng Hao, Zhou Wei. Effects of plasma exchange on liver and kidney function in patients with chronic acute liver failure[J]. Clinical research, 2021, 38 (6): 932-935. Doi: 10.3969/j.i SSN. 1671-7171.2021.06.038.

21. Qin Wei, Zhu Suping, Zheng Yanli, Huo Yuling, Wang Dan. Influence of PE combined with DPMAS on survival of patients with cirrhosis complicated with chronic acute liver failure[J]. Infectious Disease Information, 2021, 34(2): 140-143,147. Doi: 10.3969/j.issn.1007-8134.2021.02.010.

22. Qin Hao, Wang Yang, Wei Jinggang, Gao Pengbin, Wu Fengying, Ren Fei. Effects

of half-volume plasma exchange combined with dual plasma molecular adsorption system on inflammatory response, immune function and liver function in patients with chronic acute liver failure[J]. Venereology, 2020, 19(5): 485-89509. Doi: 10.3969 / j.i SSN. 1671-6450.2020.05.012.

23. Qin H, Wei L. Efficacy analysis of dual plasma molecular adsorption combined with plasmapheresis in treatment of chronic acute liver failure[J]. Clinical Meta-analysis, 2019, 34(7): 633-636. Doi: 10.3969/j.issn.1004-583X.2019.07.013.

24. Yao J, Li S, Zhou L, Luo L, Yuan L, Duan Z, Xu J, Chen Y. Therapeutic effect of double plasma molecular adsorption system and sequential half-dose plasma exchange in patients with HBV-related acute-on-chronic liver failure. J Clin Ap her. 2019 Aug; 34(4): 392-398. Doi: 10.1002/jca.21690. E pub 2019 Feb 13. PMID: 30758886; PMCID: PMC6767528.

25. Guo X, Wu F, Guo W, Zhang J, Yang Y, Lu Y, Yin C, Fan H, Xu J, Liao M. Comparison of plasma exchange, double plasma molecular adsorption system, and their combination in treating acute-on-chronic liver failure. J Int Med Res. 2020 Jun; 48(6): 300060520932053. Doi: 10.1177/0300060520932053. PMID: 32552092; PMCID: PMC7303772.

26. Wu RL, Zhao HC, Geng XP. [Current status of liver transplantation for adult patients with acute-on-chronic liver failure]. Zhong hua Wai Ke Za Zhi. 2022 Feb 1; 60(2): 182-188. Chinese. Doi: 10.3760/cma.j.cn112139-20210810-00369. E pub ahead of print. PMID: 35012279.

27. Liu H, Zhang Q, Liu L, Cao Y, Ye Q, Liu F, Liang J, Wen J, Li Y, Han T. Effect of artificial liver support system on short-term prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure. Artif Organs. 2020 Oct; 44(10): E434-E447. Doi: 10.1111/aor.13710. E pub 2020 May 12. PMID: 32320491.

28. Zhang J, Luo H, Han Y, Zhou X. Sequential versus mono double plasma molecular adsorption system in acute-on-chronic liver failures: A propensity-score matched study. Int J Arti f Organs. 2022 Jan; 45(1): 5-13. Doi: 10.1177/0391398820987565. E pub 2021 Jan 12. PMID: 33435806.

29. Wu Jianhua. Prognosis assessment of liver failure and related problems in clinical

application [J]. Hepatology Journal of Integrated Traditional and Western Medicine, 2017, 27(4): 193-197. Doi: 10.3969/j.issn.1005-0264.2017.04.001.

30. Chen YY, Li H, Xu BY, Zheng X, Li BL, Wang XB, Huang Y, Gao YH, Qian ZP, Liu F, Lu XB, Shang J, Li H, Wang SY, Zhang YH, Meng ZJ; Chinese Chronic Liver Failure (CLIF) Consortium. Plasma Exchange-Based Non-bioartificial Liver Support System Improves the Short-Term Outcomes of Patients With Hepatitis B Virus-Associated Acute-on-Chronic Liver Failure: A Multicenter Prospective Cohort Study. Front Med (Lausanne). 2021 Nov 16; 8: 779744. Doi: 10.3389/fmed.2021.779744. PMID: 34869500; PMCID: PMC8635207.

31.Wan YM, Li YH, Xu ZY, Yang J, Yang LH, Xu Y, Yang JH. Therapeutic plasma exchange versus double plasma molecular absorption system in hepatitis B virus-infected acute-on-chronic liver failure treated by enter cavir: A prospective study. J Clin Ap her. 2017 Dec; 32(6): 453-461. Doi: 10.1002/jca.21535. E pub 2017 Mar 17. PMID: 28304106.

32. Nong Li, Guo Graben, Wei Qiufang, Huang Jinli, Peng Xuehan. The short-term efficacy of DPMAS sequential plasmapheresis in patients with chronic hepatitis B virus associated acute liver failure[J]. Chongqing Medical Science, 2019, 48(4): 608-611. Doi: 10.3969/j.issn.1671-8348.2019.04.015.

33. Xiao LL, Xu XW, Huang KZ, Zhao YL, Zhang LJ, Li LJ. Artificial Liver Support System Improves Short-Term Outcomes of Patients with HBV-Associated Acute-on-Chronic Liver Failure: A Propensity Score Analysis. Biomed Res Int. 2019 Nov 29; 2019: 3757149. Doi: 10.1155/2019/3757149. Erratum in: Biomed Res Int. 2021 Jun 8; 2021: 9875940. PMID: 31871940; PMCID: PMC6907045.