Received: 1 April 2024 | Revised: 14 June 2024 | Accepted: 9 July 2024

DOI: 10.1002/jca.22140

RESEARCH ARTICLE

Journal of Clinical Apheresis ASFA WILEY

Comparative efficacy of double plasma molecular adsorption system combined with plasma exchange versus plasma exchange in treating acute-on-chronic liver failure due to hepatitis B: A meta-analysis

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Funding information
Natural Science Foundation of Ningxia, Grant/Award Number: 2022AAC02065; Natural Science Foundation of China, Grant/Award Numbers: 81760363, 81460301, RGGJJ-2021-024

Abstract

This meta-analysis aims to evaluate the effectiveness of the double plasma molecular adsorption system (DPMAS) in combination with plasma exchange (PE) compared to plasma exchange alone in the treatment of Acute-on-Chronic liver failure (LF) caused by hepatitis B. Until August 31, 2023, a comprehensive search of databases including Embase, Chinese Medical Journal Full-text Database, China Biomedical Literature Database, Wan Fang Medical Network, PubMed, and the Cochrane Library was carried out using keywords like "liver failure," "acute-on-chronic liver failure," "PE," "DPMAS," and related terms. The quality of the included studies was evaluated using QUADS (quality assessment of diagnostic accuracy studies). Software Revman 5.3 was used to examine the data, while Stata 15.1 was used to run Egger's test. Following thorough screening, 452 patients who received PE alone and 429 patients who received DPMAS in addition to PE were included. Every study that was included was of a high caliber. When comparing the DPMAS plus PE group to the PE alone group, the total bilirubin reduction was considerably higher (mean difference [MD] = −49.09, 95% confidence interval [CI]: −54.84 to −43.35, $p < .00001$). Prothrombin activity (PTA; MD = −1.53, 95% CI: −3.29 to −0.22, $p = .09$), albumin (ALB; MD = −0.58, 95% CI: −1.57 to 0.41, $p = .25$), prothrombin time (PT; MD = −0.07, 95% CI: −1.47 to 1.34, $p = .92$), and platelet count (PLT; MD = −0.08, 95% CI: −1.33 to 1.66, $p = .90$) did not differ significantly. The improvement in international standardized ratio (INR) was significantly greater in the PE group (MD = 0.07, 95% CI (0.03, 0.10), $p = .0001$). When combined with DPMAS, PE has been shown to be more effective in lowering total bilirubin levels. PE can also lower INR in individuals who have hepatitis B-related ACLF. This therapeutic strategy also lessens the need for plasma transfusions.

KEYWORDS
artificial liver support, double plasma molecular adsorption system, liver failure, meta-analysis, plasma exchange

1 | INTRODUCTION

The severe clinical illness known as acute on-chronic liver failure (ACLF) is typified by acute liver decompensation, extrahepatic organ damage, and a significant short-term mortality rate.[1] Notably, one of the main causes of ACLF in our area is hepatitis B infection. Long-term hospital stays, quick disease development, 60%–80% short-term death rates, and limited effectiveness of standard medical treatments are the hallmarks of ACLF, which presents a substantial healthcare cost.[1,2]

The only effective treatment for ACLF at this time is liver transplantation, although it is expensive and difficult to find donor organs.[3] Artificial liver support systems (ALSS) have been the main therapeutic method in response to these constraints. The three types of ALSS are biological, non-biological, and hybrid.[4,5] Non-biological ALSS use extracorporeal circulation equipment to eliminate toxins, restore vital nutrients, and lengthen the period of time before liver transplantation. These systems include hemodialysis, hemofiltration, plasma exchange (PE), and double plasma molecular adsorption system (DPMAS). They have been used extensively and have demonstrated some effectiveness.[6–9]

Plasma exchange can replace fresh frozen plasma or human albumin (ALB), replacing coagulation components and immunoglobulins that the body needs. It can also non-selectively remove toxins from patients' plasma, including bilirubin and endotoxins. In China, PE is hence a commonly utilized ALSS.[10–12] However, ACLF patients already have immune disorders and PE consumes 2000–2500 mL of plasma per session, and that will indicate increased risk of allergic transfusion reactions.[1] Consequently, DPMAS has been used and has shown encouraging outcomes. Using neutral macroporous resin (HA330-II) and anion exchange resin (BS330) adsorption columns, it may effectively remove medium and large molecular toxins, such as inflammatory mediators. HA330-I is a broad-spectrum adsorption resin. Nevertheless, there are certain restrictions because the resin in the BS330 adsorption column only targets bilirubin and is unable to supply proteins or coagulation factors.[13]

Therefore, we wondered whether DPMAS combined with PE therapy may address the drawbacks of the aforementioned forms of care. Though opinions vary, studies have indicated that combining the two can ameliorate the aforementioned weaknesses.[14,15]

In order to provide thorough and impartial evidence to support clinical decision-making, we therefore carried out a meta-analysis to assess the improvement of patients' liver function and coagulation following various treatment modalities for ACLF caused by hepatitis B, as well as adverse reactions occurring during treatment, primarily including allergy, bleeding, coagulation, hypotension, and other adverse reaction.

2 | MATERIALS AND METHODS

Literature Retrieval:Search terms like "double plasma molecular absorption system," "plasma exchange," "severe hepatitis," "liver failure," "acute-on-chronic liver failure," "plasma exchange," and "double plasma molecular adsorption therapy" were used to perform a thorough search across Pubmed, Cochrane Library, and Embase databases. We searched for the terms "severe hepatitis," "liver failure," "acute-on-chronic liver failure," "plasma exchange," and "double plasma molecular adsorption therapy" in Chinese databases (China National Knowledge Network, Wanfang Medical Network, and China Biomedical Literature Database).

2.1 | Inclusion criteria and exclusion criteria

Inclusion criteria: 1. Studies in either Chinese or English; 2. Cases of liver failure that satisfy the "Guidelines for Diagnosis and Treatment of Liver Failure" published in 2012. The included literature must also mention individuals treated with plasma exchange or double plasma molecular adsorption therapy paired with plasma exchange in addition to combined medical treatment. All patients were diagnosed with chronic acute liver failure caused by hepatitis B; 3. Only randomized controlled trials (RCTs) studies are included; 4. Pre- and post-treatment data should be included in the evaluation parameters, which should be founded on thorough medical management. 5. Studies published up to August 30, 2023.

Exclusion criteria: 1. Patients receiving neither plasma exchange nor plasma combination with double plasma molecular adsorption as a form of treatment for persistent acute liver failure unrelated to hepatitis B; 2. Non-randomized controlled trials; 3. Research without information before and after therapy; 4. Missing information or duplicate publications.

Data extraction: Two researchers separately extracted the data following a thorough screening process. Disagreements were settled by conversation, and in cases where they persisted, a third researcher was consulted. Among the observation indices were: 1. Total bilirubin (TBIL). 2. Prothrombin time (PT, synthesized in liver cells, prothrombin is a crucial coagulation factor related to coagulation factors II, V, VII, and X. Prothrombin time is a crucial indicator for determining the prognosis of severe hepatitis; it typically ranges from 12 to 14 s. The prognosis is not good if PT is extended to 20 s). 3. Prothrombin time activity (PTA) has a normal range of motion of 75%–100%. Prothrombin activity and prothrombin time have the same relevance and can more precisely reflect the activity of clotting factors. It is also a significant measure of the function of the liver reserve and strongly correlated with the disease severity. Prothrombin activity (%) is calculated as follows: (normal prothrombin time − 8.7)/(patient's prothrombin time − 8.7)*100%. 4. ALB. 5. Adverse reaction frequency (mostly encompassing allergies, bleeding, coagulation, and hypotension). 6. Survival rate (following therapy, survival rates were recorded at 7, 14, 28, and 90 days. The total number of persons less the total number of deaths is the survival rate, which is then divided by the total number of people).

2.2 | Quality assessment

As our study is observational, we used the QUADS (quality assessment of diagnostic accuracy studies) to assess study quality.

2.3 | Statistical methods

We used RevMan 5.3 software to analyze the data. For measurement data, mean differences (MD) were utilized, and for categorical data, odds ratios (OR) were used. For each effect size, 95% confidence intervals (CI) were computed. A fixed-effect model was employed for studies that did not exhibit substantial heterogeneity ($p > .1$, $I^2 < 50\%$) when heterogeneity among the studies was assessed. A Stata 15.1 Egger Test was used to analyze publication bias for all results ($p > .5$ indicates no substantial publication bias).

3 | RESULTS

3.1 | Literature search results

After conducting preliminary investigation, we found that the database had 405 entries related to Chinese and English-language studies. Ten pertinent papers were chosen in the end after thorough screening to ensure they met the inclusion criteria.[5,16–22,25] Excluded studies were those that did not fit the inclusion requirements. Out of the trials that were chosen, 429 patients were treatment using DPMAS + PE, while 452 patients were treated with PE. The comprehensive flowchart that shows the procedure for screening literature is located in Figure 1.

3.2 | Characteristics of included studies

One English study source[5] and nine Chinese literature sources[16–22,25] made up the randomized controlled trials (RCTs) that made up all of the included studies in this analysis. A comprehensive summary of the observational indicators, outcome measures, and particular plasma exchange volumes present in the chosen RCT is given in Table 1.

3.3 | Results and publication bias

3.3.1 | Effects of DPMAS + PE and PE on liver function

There were nine papers with total bilirubin data.[5,16–22,25] Six RCTs[5,17,18,20,22] with a total of 459 individuals were included following a thorough heterogeneity analysis. Of these, 219 patients received DPMAS + PE and 240 received PE therapy. Minimal heterogeneity was found in the analysis ($p = .36$, $I^2 = 9\%$). Our research, which made use of a fixed-effect model, showed that DPMAS + PE was statistically significantly more effective than PE at lowering TBIL levels (MD = −49.09, 95%CI [−54.84, −43.35], $p < .00001$). Although Jie Liu and JingLi make up a sizable section of the literature, the inclusion of all literature data demonstrated that combination therapy led to a decrease in TBIL.

Seven RCTs in total that reported on serum ALB levels were included in our analysis.[5,16,18–22] Following a comprehensive analysis to check for heterogeneity, 3 publications[16,18,23,24] with a total of 175 participants were approved for inclusion. Of them, 85 received therapy with DPMAS + PE and 90 received PE treatment. Minimal heterogeneity was found in the analysis ($p = .55$, $I^2 = 0\%$), and a fixed-effect model showed that there was no statistically significant difference in ALB levels between DPMAS + PE and PE (MD = −0.58, 95% CI [−1.57, 0.41], $p = .25$) (Figure 2).

3.3.2 | Effects of DPMAS + PE and PE on coagulation function

International standardized ratio (INR) was included in seven RCTs in total.[5,16,18,19,21,22,25] Following

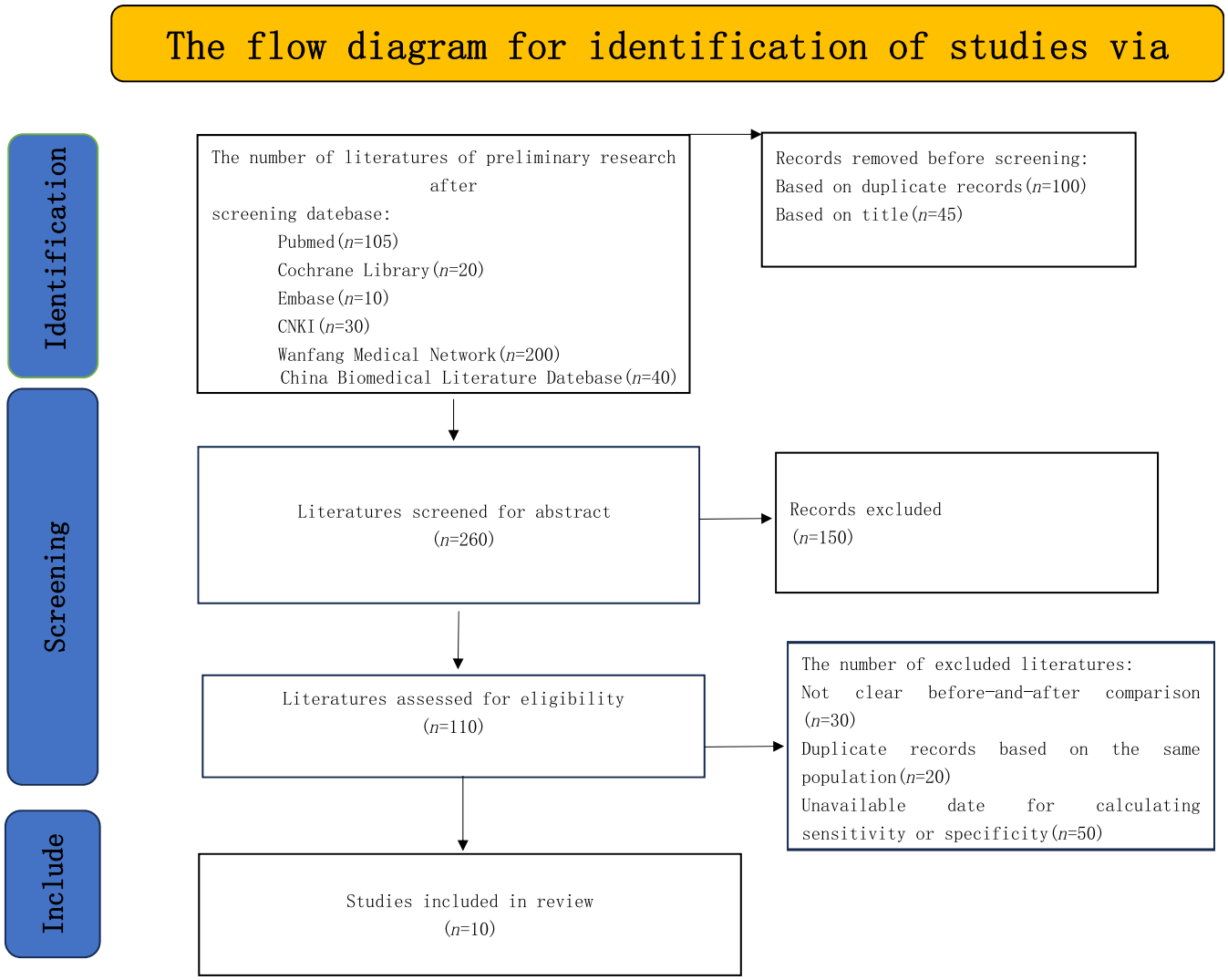
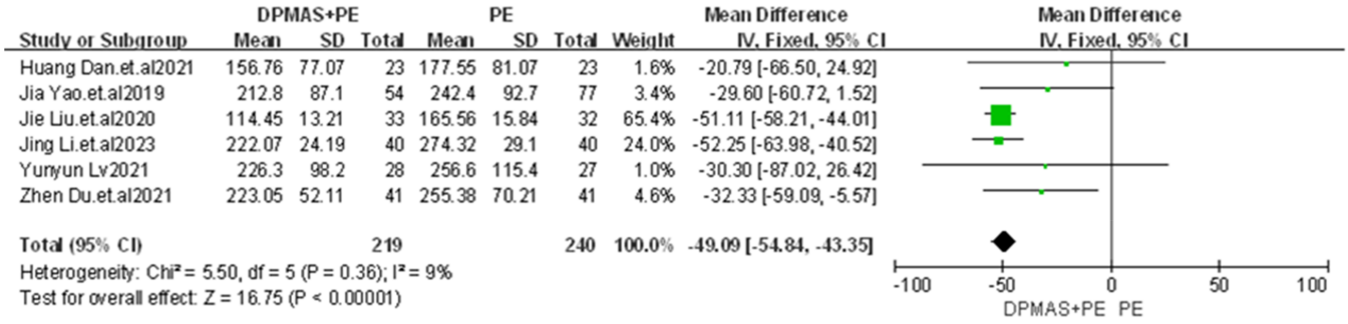


FIGURE 1 Literature screening flow chart.

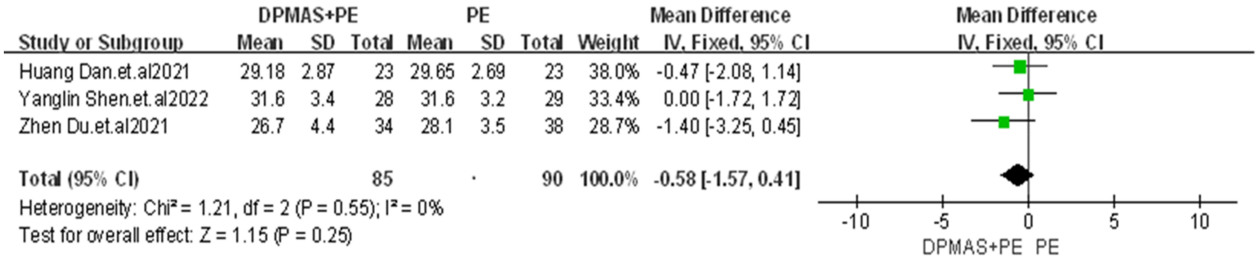
TABLE 1 The basic information of included publications.

Included RCTs	Year	Sample size (DPMAS + PE/PE)	Plasma exchange volume (ML) (T)	Plasma exchange volume (ML) (C)	Indicators
Shen Yanglin	2022	31/33	1000–2000	2000–3000	①②④
Liu Jie	2020	33/32	800–1000	2200–2800	①③⑥⑦
Du Zhen	2021	34/38	1100–1200	2500–3000	①②③④⑤
Li Yongchao	2020	30/30	1000–2000	2000–3000	①②③④⑥
Lv Yunyun	2021	41/41	1000	2000	①②③⑥⑦
Li Chunyu	2021	35/32	1000–2000	2000–3000	①②④⑤
Huang Dan	2021	23/23	1000–1500	2500–3000	①②③⑤
Yang Jingyi	2021	108/106	1000–1500	3000–3500	③④⑤⑦
Yao Jia	2018	54/77	1100–1200	2200–2400	①②③④
Li Jing	2013	40/40	1200–1500	2500–3000	①③④⑤⑥⑦

Note: T: experimental group (patients treated by DPMAS + PE); C: control group (patients treated by PE); ① total bilirubin (TBIL); ② albumin (ALB); ③ prothrombin activity (PTA); ④ International normalized ratio of prothrombin (INR); ⑤ prothrombin time (PT); ⑥ platelets (PLT); ⑦ improved effective rate after treatment.

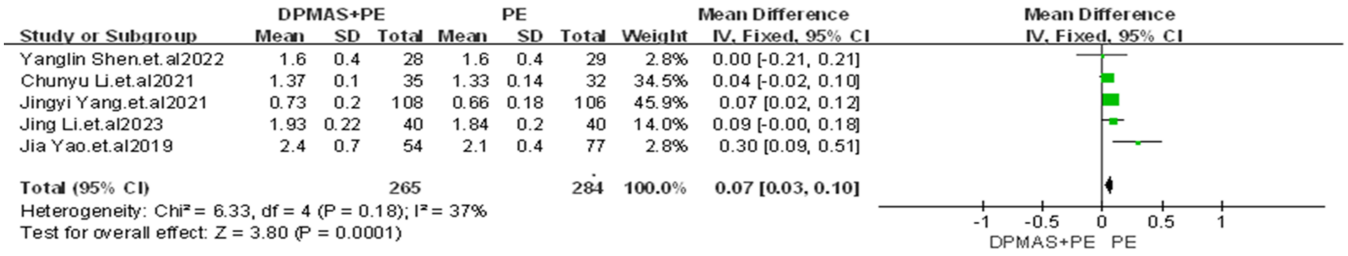


Forest map of meta-analysis of TBIL

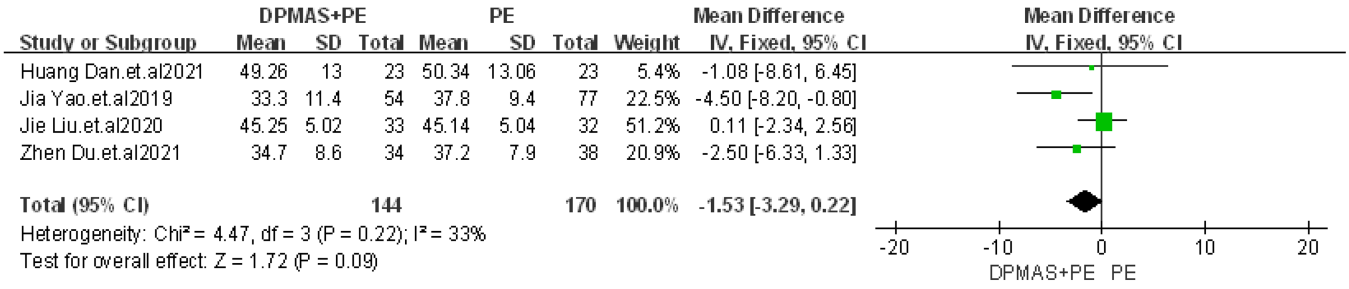


Forest map of meta-analysis of ALB levels

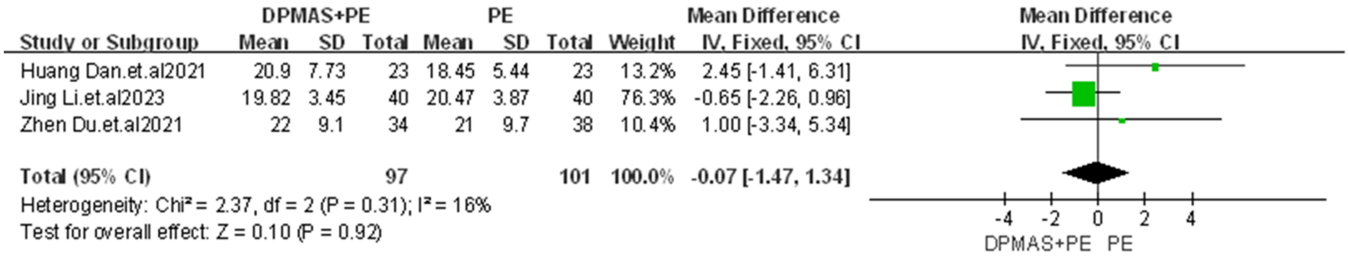
FIGURE 2 Forest map of meta-analysis of ALB levels.



Forest map of meta-analysis of INR level



Forest map of meta-analysis of PTA level



Forest map of meta-analysis of PT level

FIGURE 3 Forest map of meta-analysis of PT level. PT, prothrombin time.

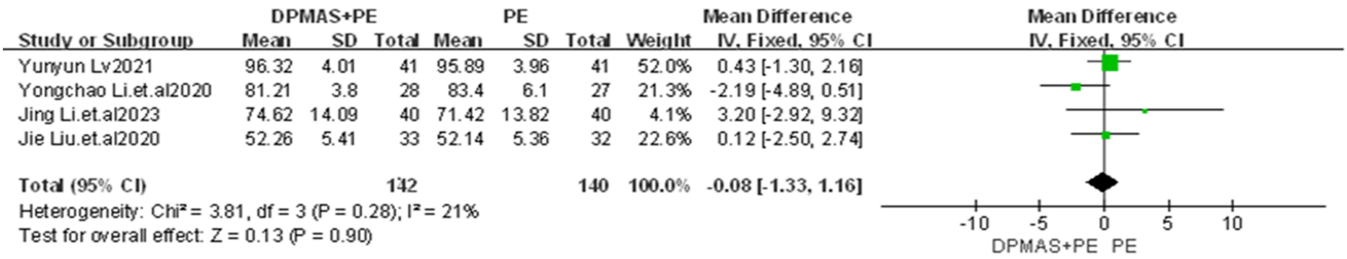


FIGURE 4 Forest map of meta-analysis of PLT levels. PLT, platelet count.

Serological indexes	TBIL	ALB	INR	PTA	PT	PLT
p	.084	.618	.446	.174	.279	.074

TABLE 2 Data publication bias detection results of DPMAS combined with PE and PE.

heterogeneity analysis, 5 studies were included,[5,16,21,22,25] involving a sample of 549 patients, 265 of whom received treatment in DPMAS + PE and 284 of whom received treatment in PE. Fixed-effect model analysis revealed that PE had a stronger effect on lowering INR, with statistical significance [MD = 0.07, 95% CI (0.03, 0.10), $p = .0001$], since there was less heterogeneity ($p = .18$, $I^2 = 37\%$).

A total of 8 publications provided data on Prothrombin Time Activity (PTA).[5,17–20,22,25] After heterogeneity analysis, 4 studies were deemed suitable for inclusion,[5,17,18] comprising a total of 314 participants, with 144 receiving DPMAS + PE and 170 undergoing PE treatment. Minimal heterogeneity was found in our study ($p = .22$, $I^2 = 33\%$). With a fixed-effect model, we discovered that there was no statistically significant difference in PTA levels between DPMAS + PE and PE [MD = −1.53, 95% CI (−3.29, 0.22), $p = .09$].

Prothrombin time (PT) data were obtained from a total of 5 RCTs.[18,21,22,25] After a thorough review of heterogeneity, three RCTs with 198 individuals overall—97 cases getting DPMAS + PE and 101 cases receiving PE treatment—were chosen for inclusion.[18,22] In the chosen studies, the analysis showed little heterogeneity ($p = .31$, $I^2 = 16\%$). Our analysis, which used a fixed-effect model, showed that there was no significant change in PT between the two groups (MD = −0.07, 95% CI [−1.47, 1.34], $p = .92$). Moreover, this difference was not statistically significant (Figure 3).

3.3.3 | Effects of DPMAS + PE and PE on blood routine

In total, 4 publications provided data on platelet count (PLT).[16,17,20,22] Following a meticulous heterogeneity analysis, all 4 RCTs were included in the final analysis,[16,17,20,22] encompassing a total of 282 participants, with 142 receiving DPMAS + PE and 140 undergoing PE treatment. Our analysis revealed minimal heterogeneity ($p = .28$, $I^2 = 21\%$). Using a fixed-effect model, we found no significant difference in PLT between the two groups, and this difference was not statistically significant (MD = −0.08, 95% CI [−1.33, 1.16], $p = .90$) (Figure 4).

3.4 | The publication bias of all results

After analysis, the *p* values of all data in this study were greater than .05, suggesting no significant publication bias, Table 2 shows the data publication bias detection results of DPMAS combined with PE and PE (Table 2).

4 | DISCUSSION

Acute-on-chronic liver failure (ACLF) is typified by a rapid decline in liver function underlying chronic liver disease; frequent clinical symptoms include jaundice and coagulation abnormalities. Between 60% and 80% is an extremely high short-term mortality rate linked to ACLF.[26] The main cause of ACLF in China is infection with the hepatitis B virus (HBV). ALSShave progressively replaced conventional medical treatment as the first-line therapeutic option due to the poor efficacy of such treatments. These systems show some degree of effectiveness in filling in for the liver's necessary roles in detoxification, synthesis, and metabolism while also providing the body with important nutrients.[27]

It is important to remember that bilirubin is a key factor in determining how well a patient with liver disease will fare. Bilirubin is a metabolite of heme, as is well known. Normally, direct bilirubin, which is secreted into the tubule bile and emptied into the gut, is created by liver cells from circulating indirect bilirubin.[28] Liver

failure causes varying degrees of hepatocyte necrosis, which in turn causes a decline in liver function and varying degrees of hyperbilirubinemia.[29] Research has demonstrated that slightly higher bilirubin levels offer protection against oxidative stress-related illnesses, such as cancer and cardiovascular disease.[29] However, studies also show that excessive bilirubin will have a certain toxicity to nerve cells, which can lead to coma in patients.[30] In our study, we have demonstrated that the combination of the Double Plasma Molecular Adsorption System (DPMAS) with Plasma Exchange (PE) can more effectively reduce TBIL levels compared to PE alone. This may be attributed to the specific bilirubin adsorption column utilized in DPMAS.[29] Nearly all coagulation factors are created in the liver, with the exception of tissue factors and VW factors produced by endothelial cells. Prothrombin is a crucial coagulation factor that is produced in liver cells and is connected to coagulation factors II, V, VII, and X. The clinical importance of prothrombin activity and prothrombin time is equal. When the liver fails, the function of the liver to synthesize clotting factors decreases, which increases the risk of bleeding in the patient by prolonging PT, INR, and other parameters to variable degrees. At the same time, prothrombin activity is diminished to diverse degrees. Our study results indicate that PE can expedite the normalization of INR, which holds significant promise for improving the prognosis of ACLF patients.[29,31,32] One possible explanation for this improvement is the addition of fresh frozen plasma through PE. By substituting fresh frozen plasma, plasma exchange can help patients' PT and PTA, among other metrics. However, the results of our study showed that there was no significant difference in the improvement of PT and PTA between PE alone and combined therapy. Some studies have shown a significant decrease in PTA following sole DPMAS treatment, even though the adsorption column will destroy some influencing factors during the DPMAS treatment process and the use of anticoagulants will cause certain damage to the coagulation function.[28,32,33] However, following the combined therapy, our study finds no discernible difference between the two treatment modalities. This implies that PE can effectively supplement and improve coagulation function.

Another important measure of hepatic production activity is ALB. Studies have demonstrated that DPMAS possesses a strong adsorption capacity for protein-bound toxins, and this process may lead to the destruction of some ALB.[3,7,11] The results of our investigation, however, show that there was no discernible change in ALB levels following the combined treatment. This lack of discernible variation may be related to PE's capacity to complement ALB.

4.1 | Shortcomings of our study

1. Limited availability of foreign literature (The literature included in this work is subject to some limits because ALB binding is the primary therapeutic strategy for liver failure in foreign nations. Few studies have been conducted in this area, and many English-language literatures are investigated by local writers. With additional clinical case studies to add to the database in the future, we look forward to that).
2. Lack of classification for ACLF within the included literature (It would be better if the patients could be divided into different periods to observe. However, since our study mainly focuses on the efficacy of treatment methods, it is helpful to observe the improvement of indicators after treatment to draw conclusions).
3. Variations in the separation machines and membranes used in artificial liver support therapy across the selected studies (Although the material of adsorption column used in various literatures varies, the patients are all suffering from chronic acute liver failure caused by hepatitis B, and the material used in the same literature is identical. It has minimal bearing on the final result because we primarily study the changes that occur before and after therapy).
4. Absence of survival rate analysis in this study, necessitating further extensive research to determine the therapeutic efficacy of ALSS. (Since it is a meta-analysis, it necessitates that the research objects in the literature be consistent; hence, the survival rate study's period must also be consistent, allowing for the completion of the meta-analysis. The selected literature does contain reports on survival rate. However, because the studies' survival rates varied throughout time, a meta-analysis is not possible. Additional research is required to demonstrate its effect on the survival rate.)

In conclusion, the combination of DPMAS and PE helps to replenish the necessary amount of ALB for the human body while also lowering TBIL levels and enhancing coagulation function. In clinical practice, combination therapy may be the best option for patients suffering from both acute and chronic hepatitis B-related liver failure. It can also lessen financial strain, preserve plasma supplies, and lower the danger of metabolic alkalosis brought on by recurrent plasma use.

FUNDING INFORMATION

This study was supported by the Natural Science Foundation of Ningxia (2022AAC02065) and the Fund for Less, Developed Regions of the Natural Science Foundation of

China (81760363, 81460301) and the exploration of the application value of thrombologram in guiding anticoagulant dosage in artificial liver treatment of patients with chronic and acute liver failure (RGGJJ-2021-024).

CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

An ethics statement is not applicable because this study is based on published literatures.

PATIENT CONSENT STATEMENT

Because our study is a meta-analysis, it is not necessary to get patient's consent.

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How to cite this article: Zhang L, Ma Y, Wang X, Ma L-N, Ma W, Ding X-C. Comparative efficacy of double plasma molecular adsorption system combined with plasma exchange versus plasma exchange in treating acute-on-chronic liver failure due to hepatitis B: A meta-analysis. *J Clin Apher*. 2024;39(4):e22140. doi:10.1002/jca.22140