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Molecular Adsorbent Recirculating System for Acute Liver Failure and Acute-on-Chronic Liver Failure: A Meta-Analysis

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Abstract

Objective: To systematically evaluate the efficacy and safety of Molecular adsorbent recirculating system (MARS) in the clinical treatment for acute liver failure (ALF) and acute-on-chronic liver failure (AOCLF).

Methods: Search EMABSE, PUBMED, and COCHRANE library database for the RCTs and Cohort Studies of MARS in the treatment of ALF and AOCLF up to June 2020. Two independent researchers screened and assessed the quality of the literature and extracted the data. Rev Man 5.2 software was applied for meta-analysis. Trial Sequential Analysis was used to evaluate the risk of random error and effectiveness of conclusion by using TSA software.

Results: A total of seven RCTs, two prospective cohort studies and 2 retrospective cohort studies were included. The analysis showed that MARS decreased total bilirubin [MD=-8.34, 95%CI=(-12.85, -3.82), P=0.0003], improved hepatic encephalopathy [RR=1.95, 95% CI=(1.43, 2.67), P<0.0001] and reduced mortality in the short-term (3 days to 30 days) group [RR=0.63, 95%CI=(0.47,0.84), P=0.002] rather than the long-term (90 days to 3 years) group [RR=0.85, 95% CI=(0.72, 1.00), P<0.04]. TSA of improvement of hepatic encephalopathy, mortality and total bilirubin passed the cumulative Z-Score, the conventional boundary value and the require information size, proving it reliable.

Conclusion: MARS in ALF and AOCLF was still indeterminate for the decrease of total bilirubin, the improvement of hepatic encephalopathy and the reduction of mortality. The MARS improved the short-term (3 days to 30 days) rather than the long-term (90 days to 3 years) survival rates. Future multicenter, large-scale, randomized controlled trials are necessary to further research of MARS therapy.

Keywords: MARS; ALF; ACLF; meta-analysis

1. Introduction

Liver failure includes a group of clinical syndromes with high mortality that is characterized by low coagulation function, jaundice, hepatorenal syndrome, hepatic encephalopathy and ascites.[1] It results from dysfunctions of synthesis, detoxification, metabolism, secretion, immune and decompensation, which are caused by various factors. Unfortunately, there is no specific therapies exist for liver failure. At present, liver transplantation is the most effective method for the treatment. And the long waiting time for liver transplantation could be overcome by the liver support systems. Therefore, over the past decades, many in vitro liver support systems have been developed to overcome liver transplantation in patients with liver failure, or as potential therapies for tissue regeneration and liver function recovery.[2]

In the 1960s, the concept of "artificial liver" was first proposed.[3] Since then, numerous different artificial liver technologies have been developed, which mainly divided into biological artificial liver and non-biological artificial liver.

The bioartificial liver is supposed to restore the physiological functions of the liver, such as synthesis, metabolism, detoxification, immunity and secretion because it contains hepatocytes or liver tissues. The bioartificial liver has been used in preclinical experiments on large animals providing the survival advantage.[3] The overall effect of the bioartificial

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liver on mortality in patients with liver failure was insignificant[4]. In addition, the potential risks of porcine endogenous retrovirus infection after treatment remained a concern.[5] Thus, it appears that the bioartificial liver is still in its infancy.

On the other side, non-biological artificial liver technology has been successfully applied in clinical practice, which is effective *in vitro* liver support therapy.[6] Compared with the complex triumphant function of the liver, the role of the abiotic artificial liver is relatively particular. It mainly uses artificial membranes or adsorbents to detoxify the blood of patients with liver failure.

Following the further development of medical technology, MARS was developed in 1990s.[7] Molecular adsorbent recirculating system (MARS) is one of the most widely used non-biological artificial liver systems. It combines hemodialysis and blood perfusion technology to remove water-soluble toxic substances and albumin-bound toxic substances, such as bilirubin, bile acid, ammonia, nitrotyrosine and fatty acids[8], thus cleansing the body of toxic catabolites accumulated from liver failure. There were controversies about the clinical benefits of MARS. Some studies have indicated that MARS can significantly reduce mortality rate,[9] while some other studies suggested the opposite tendency.[10] To evaluate the effects and safety of MARS for the patients with ALF or AOCLF, we conducted a meta-analysis of all RCTs and cohort studies published so far, systematically reviewing the effects of MARS on the survival rates, the wide-ranging clinical, as well as its biochemical parameters in ALF and AOCLF.

2. Materials and Methods

2.1 Literature Search

The RCTs and Cohort Studies of EMABSE, PUBMED, and COCHRANE library database (up to June 2020) were searched using the following terms: (“acute liver failure” or” acute-on-chronic liver failure”) and (“molecular adsorbent recycling system” or “molecular adsorbent recirculating system”). The tracing method was also used to search for relevant literature. All data used in this study were from previously published studies; thus, no ethical approval and patient consent were required.

2.2 Study Selection

Two independent coauthors screened the literature step by step by reading the title, abstract, and reading the full text. A third author resolved the disagreements through discussion. Inclusion criteria were as follows: 1) the search strategy was limited to human studies; 2) treatment groups included MARS, and the control groups adopted SMT; 3) the survival or mortality outcome data provided in articles were sufficient and had a critical endpoint and follow-up period; 4) randomized controlled trials (RCTs) or cohort studies that involved patients with objective diagnosis of ALF or ACLF were included in the meta-analysis; 5) the study with the largest sample size among the repeated publications of the same author or team was included; 6) publication language did not influence selection.

Exclusion criteria were as follows: 1) all the patients in trials received liver transplant, or the trials contained patients after hepatectomy, gravidas, or the patient's aged over 70 years old or less than 18 years old; 2) the studies lacking following outcome indicators: title, first author, year of publication, country, study design, the number of research centers, sample size, duration of follow-up, outcome indicators, types of liver failure, etiologies of failure, diagnostic criteria, therapy (including the method, the number of sessions, duration per session, blood flow rate, etc.) results (including decrease in circulating levels of total bilirubin, ammonia, improvement of hepatic encephalopathy and reduction of all-cause mortality etc.). We extracted the mean value at the baseline and end of the study period, the net change, as well as the number of subjects to assess the outcomes. 3) Reviews, case reports, and comments were excluded.

2.3 Data Extraction

Two researchers extracted the data from the included articles. A third researcher resolved the disagreements through discussion. The characteristics collected in each study were as follow title, first author, year of publication, country, study design, the number of research centers, sample size, duration of follow-up, outcome indicators, types of liver failure, etiologies of failure, diagnostic criteria, therapy (including the method, the number of sessions, duration per session, blood flow rate, etc.) results (including the decrease in circulating levels of total bilirubin, ammonia, the improvement of hepatic encephalopathy and the reduction of all-cause mortality etc.). We extracted the mean value at the baseline and end of the study period, the net change, as well as the number of subjects to assess the outcomes.

2.4 Quality assessment

In this study, the Cochrane Collaborative risk assessment tool was used to evaluate the quality of RCTS. Two independent subjects rated RCTS as

"high risk", "low risk" and "unclear" in five aspects: selection bias, implementation bias, measurement bias, follow-up bias and reporting bias. The Newcastle - Ottawa Scale (NOS) was used to assess the quality of the cohort study. In case of any disagreement during quality assessment, the third researcher will intervene to resolve the disagreement.

2.5 Statistical Analysis

RevMan 5.2 was used for meta-analysis in this study. Relative Risk ratio (RR) and 95% confidence interval (95%CI) were used as outcome indicator statistics for binary variables, Mean difference (MD) and 95% CI were used as outcome indicator statistics for continuous variables. Statistical heterogeneity was determined according to the chi-square test. If I^2<50% and P>0.05, there was no statistical heterogeneity among the studies and the Fixed effects model (FEM) was used. If I^2>50% and P<0.05, statistical heterogeneity existed between studies and the random-effects model (REM) was used. If the heterogeneity was too large, sensitivity analysis or descriptive analysis were performed. When the number of included literatures was more than 10, the funnel plot was used to detect publication bias in the included studies.

2.6 Trial Sequential Analysis

When the number of trials and sample size included in the study were not large enough, the results would show a significant difference, but probably exaggerated the efficacy. Repeated tests of significance increased the risk of I error and false positive rate. Trial Sequential Analysis was used to evaluate the risk of random error and effectiveness of conclusion in the study. Setting I error as 5% and accumulated sample size as information axis. The value of required information size (RIS) was dependent on the value above. If the Z-curve exceeded the line of sequential monitoring boundary or RIS, the study wouldn't need for further research because of having enough evidence to prove the intervention effect. If the Z-curve didn't reach any boundary line, the study would be regarded as insufficient evidence for the conclusion.

3. Results

3.1 Literature search

There were 4224 potentially relevant articles. Figure 1 shows the trial flow diagram for article selection. After browsing the full text, 11 articles met the inclusion criterion, including 7 RCTs,[10-16] 2 prospective cohort studies[9, 17] and 2 retrospectives cohort studies.[18, 19]

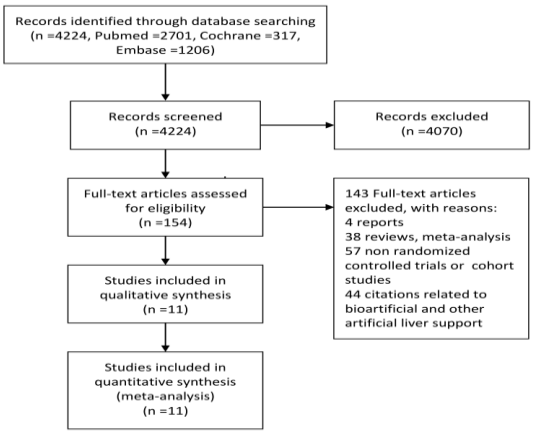

Figure 1. **The trial flow diagram for article selection**

3.2 Study Characteristics

The eleven studies involved a total of 214 ALF patients and 566 AOCLF patients, among whom 419 were treated with MARS, and 361 were treated with SMT. There were 4 multicenter studies and 7 single-center studies. Countries involved in these studies included Germany, the USA, UK, Belgium, Denmark and so on. The shortest follow-up period was 3 days[18] and the longest follow-up period was 3 years.[17] The characteristics are shown in Table 1.

Nine out of the 11 studies explained the causes of liver failure in the patients. Most patients with liver failure developed from alcoholic or viral liver disease.

In eight studies that provided relevant results,[10-17] overall male ratio ranged from 40.3% to 70.4%. The average age of the MARS group ranged from 44 to 60.5 years. Seven studies provided participants with initial average MELD scores, ranging from 16.5 to 33 score in MARS groups or ranging from 19.4 to 35 in Control groups. But only one study provided average MELD scores after MARS treatment.[14] However, only 2 studies showed the net change or the endpoint levels of serum protein in patients. [14, 15]

All clinical studies met one of the following diagnostic criteria: Asian Pacific Association for the Study of the Liver (APASL), European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD).

All the studies applied the MARS in their intervention groups with some differences in therapeutic strategies. The mean number of MARS sessions per patient ranged from 1 to 10 sessions, which continued 2 to 8 hours in each session. The strength of albumin dialysate in seven studies ranged from 10% to 25%. Seven studies reported

the applications of anti-coagulation during the MARS sessions.[10, 11, 13-16, 19] MARS was run with blood flow rates of 100–250 ml/ min, where reported.[9-13, 15, 16]

Table 1. **The characteristics of the selected studies**

Author Year	Country	Etiology of Liver Failure	Study Design	Study Period	No. of Patients		Age		Outcome indicators
					T	C	T	C	
Mizner2000[11]	Germany	AOCLF (HRS type1)	RCT	30 days	8	5	49.6	43.8	④⑤
Heemann2002[12]	Germany	AOCLF drug	RCT	30 days	12	12	50.2	52.6	③⑤
Sen2004[14]	UK	AOCLF alcoholic cirrhosis	RCT	7 days	9	9	45	44	①②③④⑤
Banayosy2004[13]	Germany	ALF acute hypoxic liver failure	RCT	14 days	14	13	60.5	62.7	④⑤
Laleman2006[15]	Belgium	AOCLF acute hypoxic liver failure	RCT	3 days	6	6	54.5	55.8	②④
Hassanein2007[16]	USA/Germany/ Denmark	AOCLF drug, biliary cirrhosis	RCT	180 days	39	31	49	56	③④⑤
Kantola2008[9]	Germany	ALF Acetaminophen	Prospective cohort studies	6 months	113	46	45	40	⑤
Hessel2010[17]	Finland	AOCLF alcoholic, intoxications, autoimmune hepatitis	Prospective cohort studies	3 years	67	82	48.8	48.5	⑤
Banares2013[10]	European	AOCLF drug non-alcoholic, biliary cirrhosis	RCT	90 days	90	89	51.8	50.0	③⑤
Bailey2016[19]	USA	ALF	Retrospective cohort studies	30 days	14	14	44	54	④⑤
Gerth2017[18]	Germany	AOCLF	Retrospective cohort studies	28 days	47	54	53.1	53.7	⑤

① Chang of Mean MELD Score; ② Change of serum albumin(g/L); ③ Improvement in West-Haven Grade of Hepatic Encephalopathy; ④ Chang of Serum Total Bilirubin(mg/dl); ⑤ Thirty-day mortality（%）

3.3 Risk bias assessment

The included literatures were distributed from 2000 to 2017, and the sample size was different. The risk bias of the included literature is shown in Figure 2. Although almost all of the literature found moderate or higher risk of bias in different aspects, including selection bias, implementation bias, measurement bias, follow-up bias, and reporting bias, these studies still met the inclusion requirements.

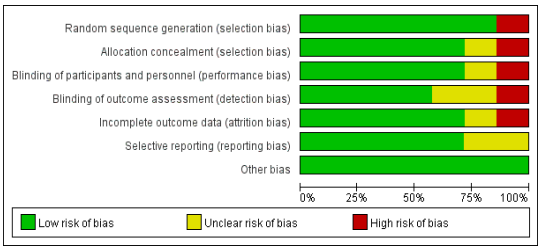

Figure 2**. Risk of bias**

3.4 A decrease in Total Bilirubin

As described in Figure 3, six trials recorded baseline levels of total bilirubin, as well as total bilirubin levels or net changes of total bilirubin after treatment.[11, 13-16, 19] A significant heterogeneity was detected (I^2=63%, P=0.0003). Compared with SMT, MARS reduced total bilirubin further [MD=-8.34, 95%CI= (-12.85, -3.82), P=0.0003]. According to subgroup analysis of the types of liver failure (Figure 4), whether in ALF [MD=-10.58, 95%CI= (-18.34, -2.81), P=0.008] or AOCLF [MD=-7.12, 95% CI= (-13.74, -0.50), P=0.04], MARS was more advantage than SMT.

3.5 Improvement of Hepatic Encephalopathy

Four studies reported the improvement of the West-Haven grade of hepatic encephalopathy.[10, 12, 14, 16] Meta-analysis revealed that compared with SMT, MARS resulted in a significant increase of improvement in hepatic encephalopathy [RR=1.95, 95% CI= (1.43, 2.67), P<0.0001], as shown in **Figure 5**. The heterogeneity test was performed but no significant heterogeneity detected (I^2=49%, P<0.0001). There were too few trials to conduct meaningful subgroup analyses

3.6 Reduction of Mortality

Figure 6 displays a comparison of the effects of MARS and SMT on mortality. Ten trials recorded the endpoints of mortality in the participants.[9-14, 16-19]

Overall, compared with SMT, MARS significantly reduced the mortality of patients without liver transplantation [RR=0.78, 95%CI= (0.68, 0.90), P=0.0007]. No remarkable heterogeneity was detected (I^2=0%, P=0.0007). Subgroup analysis revealed that MARS had a significant effect on reducing mortality both in ALF group [RR=0.63, 95%CI= (0.46, 0.85), P=0.003], and AOCLF group [RR=0.83, 95%CI= (0.71, 0.97), P =0.02] (Figure 7). However, as shown in Figure 8, another subgroup analysis indicated that MARS reduced mortality in the short-term (3 days to 30 days) group [RR=0.63, 95%CI= (0.47, 0.84), P=0.002] rather than the long-term (90 days to 3 years) group [RR=0.85, 95% CI= (0.72, 1.00), P<0.04].

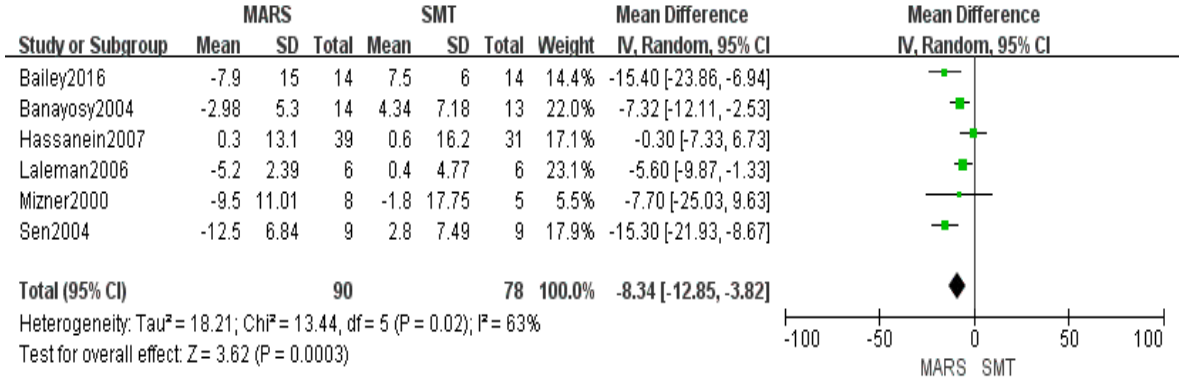

Figure 3. **Forest plot of total bilirubin**

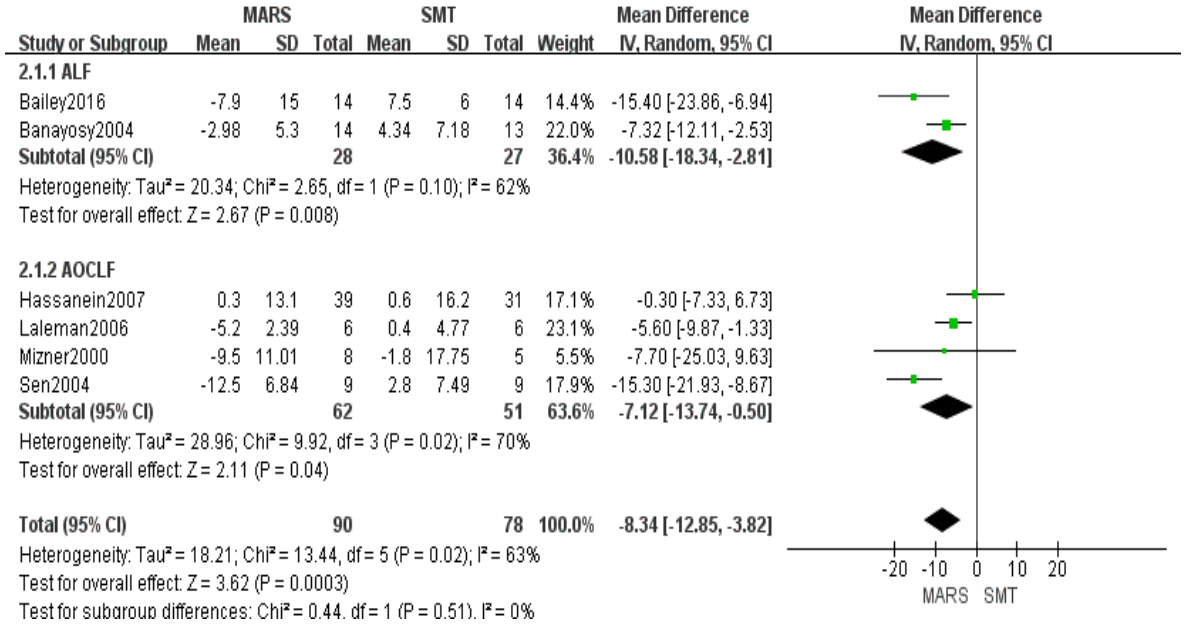

Figure 4. **Forest plot of subgroup analysis of the types of liver failure**

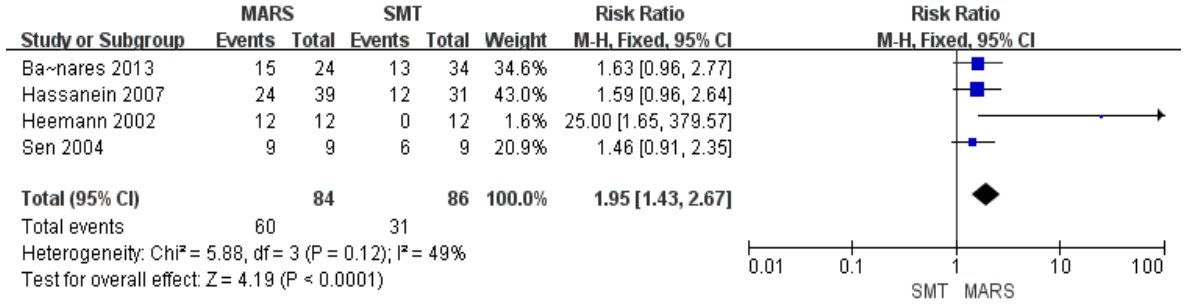

Figure 5. **Forest plot of improvement of hepatic encephalopathy**

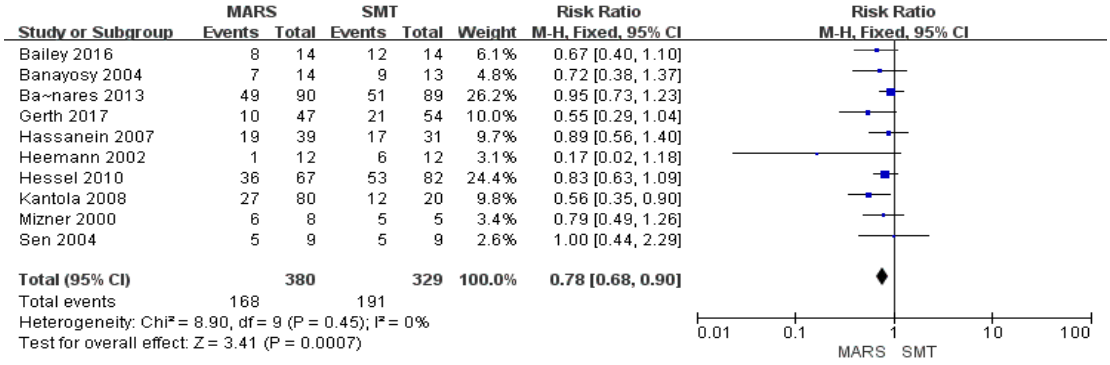

Figure 6**. Forest plot of mortality**

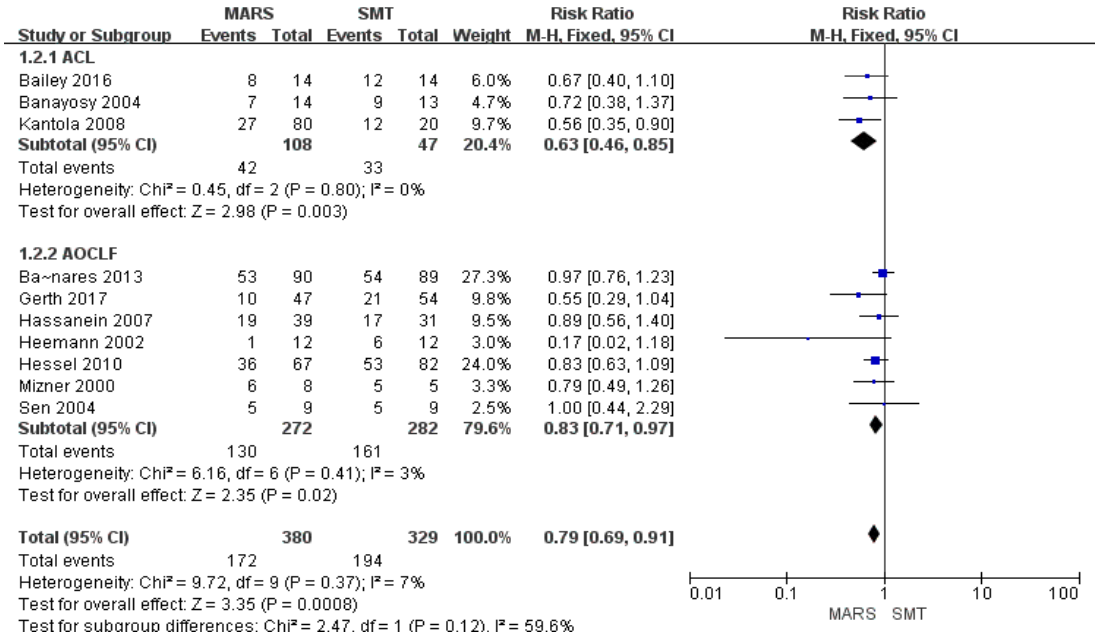

Figure 7. **Forest plot of subgroup analysis of mortality in ALF group and AOCLF group**

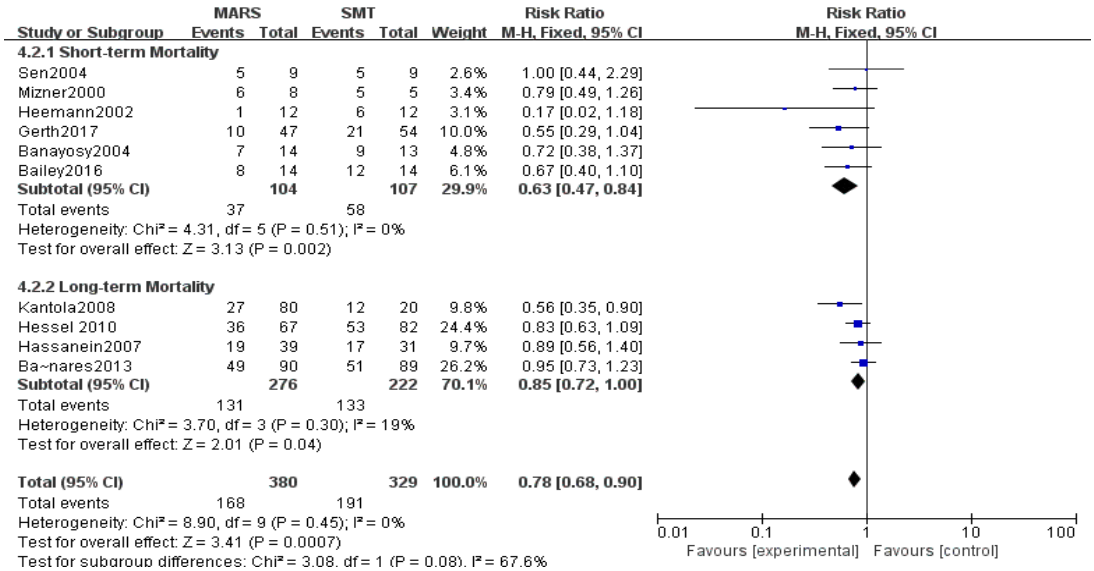

Figure 8. **Forest plot of subgroup analysis of mortality in short-term group and long-term group**

3.7 Safety of MARS

Five studies reported significantly inconsistent adverse events, both in SMT groups and MARS groups.[9, 10, 12, 15, 16] The complications included neurological, gastrointestinal and hepatic, cardiovascular, respiratory, hematologic, renal, multi-organ, catheter-related events, such as alloimmunization, sepsis, mild thrombocytopenia, hemodynamic instability, gastrointestinal bleeding, inadequate intravenous access, and malfunction of the dialysis machine. One study suggested that adverse events during treatment were related to the use of MARS with no statistical results.[12] In another study, statistical analysis showed that in the number, proportion and type of adverse events there was no difference between MARS and SMT groups.[10] The other three studies recorded the types and quantities of adverse events in two groups without discussion.[9, 15, 16] Because the reported results were cluttered without the unified standard, the safety data could not be included in the meta-analysis to test for statistical significance in these studies.

3.8 Trial Sequential Analysis

TSA was applied to conduct the total bilirubin, improvement of hepatic encephalopathy and mortality. A total of 6 trials including 168 cases of the total bilirubin were included. RIS was 170 and the Z-curve didn't reach it but cross the cumulative Z-Score and the conventional boundary value (**Figure 9**), which meant the stability in the conclusion.

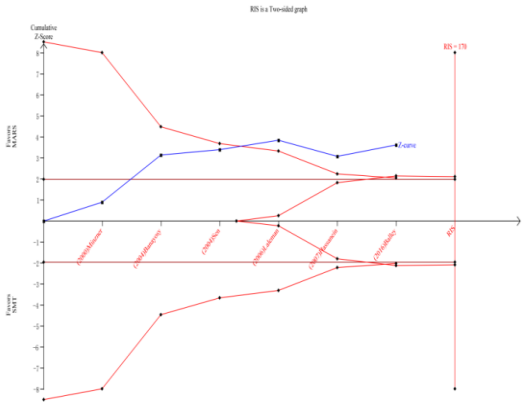

Figure 9. **Trial Sequential Analysis of total bilirubin**

Improvement of hepatic encephalopathy of 4 trials including 170 cases was conducted in the study. The Z-curve exceeded the cumulative Z-Score, the conventional boundary value and the RIS which was 159 (**Figure 10**), revealing that the trials was sufficient for the stable conclusion.n.

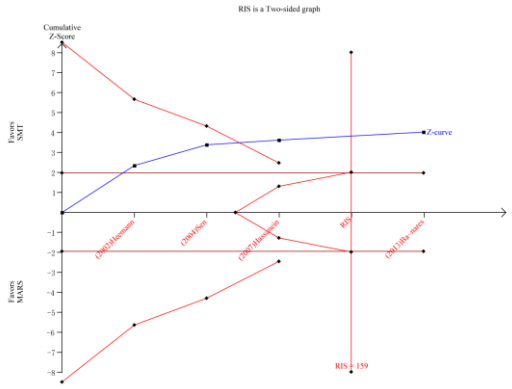

Figure 10. **Trial Sequential Analysis of improvement of hepatic encephalopathy**

10 trials with 709 cases of mortality were included. As **Figure 11** shown, the Z-curve went across the conventional boundary value, the cumulative Z-Score as well as the RIS with the value of 379. The TSA result suggested that the conclusion was reliable with enough trials.

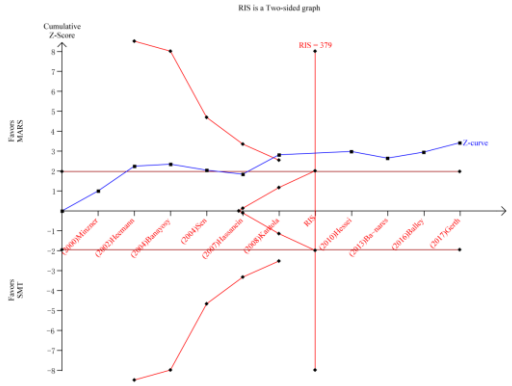

Figure 11. **Trial Sequential Analysis of mortality**

4. Discussion

MARS is an *in vitro* abiotic liver support system for patients with ALF and AOCLF that works as a bridge for liver transplantation or as a bridge for liver recovery by removing water-soluble toxic substances and albumin-bound toxic substances[20]. This meta-analysis aimed to study and analyze the differences in therapeutic effects and safety between MARS and SMT, including the decrease of total bilirubin in serum, the improvement of hepatic encephalopathy and the reduction of mortality.

In sum, seven RCTs and four cohort studies were screened out among over 4,000 documents that were searched in three databases from the construction of the libraries toJune 2020. This meta-analysis demonstrated that patients with ALF or AOCLF benefited from it. MARS could decrease total bilirubin, improve hepatic encephalopathy and

totally reduce mortality. Even if the artificial liver support system can partly replace the liver function and correct various biochemical parameters, the overall mortality rate is still high without liver transplantation.[5, 21] The TSA results of total bilirubin, improvement of hepatic encephalopathy and mortality show that the pooled trials were adequate enough to prove the conclusion reliable.

Although ammonia is the most representative neurotoxin in the pathophysiology of hepatic encephalopathy,[22] elevated serum ammonia levels are not sufficient to diagnose the disease. At the same time, 11 studies lacked sufficient laboratory data, such as baseline levels of blood ammonia and net changes. Therefore, in this meta-analysis, we did not perform a statistical analysis of blood ammonia. We tried to make subgroup analysis in view of the types of liver failure and found that did not have a significant impact on the heterogeneity of mortality. Besides, the time of follow-up periods was significantly different among all studies. We found that the survival benefits are significantly related to the length of the study period.

MARS reduces bilirubin, bile acid, ammonia, pro-inflammatory cytokines and NO to relieve liver failure. Therefore, patients in both the ALF group and the AOCLF group achieve survival benefits. However, patients only have short-term rather than long-term survival benefits. It is perhapes that the destruction of liver structure and cells is severe and rapid during liver failure. Functionally, MARS cannot effectively replace the liver. And the destruction of the liver cannot be effectively delayed. At the same time, when liver failure, the regeneration and restoration of the liver are affected. Additional biological or non-biological treatments to promote liver regeneration are needed. It should be noted that due to the development of cell technology, liver regeneration medicine such as autologous liver transplantation, biological artificial liver and tissue-engineered liver have become a new generation of treatment strategies.[23]

The present study has several significant limitations that need to be emphasized. More than 700 patients were included, but the number was still insufficient. The time and geography gap between the 11 trials were vast and uneven. This may be related to the formulation and implementation of search strategies, the literature sources of the three databases and so on. At the same time, there were some publishing deviations among these 11 experiments.

Because the reported data are incomplete and inconsistent, it was impossible to get statistically significant results. Therefore, with the change of the MARS treatment program, the trend and degree about the decrease of total bilirubin, the improvement of hepatic encephalopathy and the reduction of mortality were still indeterminate. Because of the lack of RCTs, some non-randomized studies were included in the analysis. In these studies, selection bias and confusion were inevitable.

The significant heterogeneity in the study limited our analysis of the effect of MARS on the improvement of total bilirubin. After excluding one of the studies,[14] the heterogeneity was significantly reduced to less than 50%. By reviewing the full text again, the reason for the high heterogeneity may be small sample size and the differences of the baseline level in this subject.

The severity of the liver failure, the diversity of etiology, and the different definitions of liver failure in each trial may lead to different therapeutic effects. The double-blind method was implemented in all trials, which may be another important source of bias in meta-analysis.

Future multicenter, large-scale, randomized controlled trials are necessary to further research or improve the efficacy of MARS therapy. However, in terms of clinical and ethical aspects, whether to conduct the trial needs serious consideration.

Last but not least, there is no comprehensive and accurate evaluation method that can accurately identify patients, select therapy and predict prognosis.[24-26] Therefore, it is necessary to explore appropriate evaluation methods and evaluation indicators. Besides, the current development of artificial liver is mainly based on adult patients. There is insufficient research on artificial liver support therapy for children with liver failure,[27, 28] which is why its effectiveness and safety need to be further explored.

Acknowledgments

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Conflict of interest

The authors declare no competing interests regarding the publication of this manuscript.

Contribution statement

Jian-Jun Liang is responsible for the project design, data analysis and writing papers; Wei-Hong Kuang is responsible for drafting the writing ideas, guiding the writing and finalizing the articles; Dong-Yong Lv is responsible for participating in the revision of the paper; Lu-Lu Zhu and Wan-Ning Lan

are responsible for selecting, extracting data and evaluating the literature; Han-Yu Wang is responsible for arbitrating the differences in literature screening, data extraction and literature evaluation.

Abbreviations

MARS: Molecular adsorbent recirculating system; ALF: Acute Liver Failure; AOCLF: Acute-on-chronic liver failure; RCTs: Randomized Controlled Trials; SMT: Standard Medical Therapy

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