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# Application of the Molecular Adsorbent Recirculating System in Type 1 Hepatorenal Syndrome in the Course of Alcohol-Related Acute on Chronic Liver Failure

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Data Interpretation D  
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**Background:** This study aimed to evaluate the Molecular Adsorbent Recirculating System (MARS) effectiveness in patients with alcohol-related acute-on-chronic liver failure (AoCLF) complicated with type 1 hepatorenal syndrome (HRS). So far, MARS efficacy and safety has been demonstrated in various acute liver failure scenarios.





**Material/Methods:** Data from 41 MARS procedures (10 patients with type 1 HRS, in the course of alcohol-related AoCLF) were considered for this study. Biochemical tests of blood serum were performed before and after each procedure. The condition of patients was determined before and after the treatment with the use of the model for end-stage liver disease – sodium (MELD-Na) and the stage of encephalopathy severity based on the West Haven criteria.

**Results:** During the observation period (20.5±13.9 days), 5 patients died, and the remaining 5 surviving patients were discharged from the hospital. In the group of 10, the 14-day survival, starting from the first MARS treatment, was 90%. The MARS procedure was associated with a 19% reduction in bilirubin (27.5±6.1 versus 22.3±4.0 mg/dL,  $P<0.001$ ), 37% reduction in ammonia (44.1±22.5 versus 27.6±20.9  $P<0.001$ ), 27% reduction in creatinine (1.5±1.0 versus 1.1±0.6 mg/dL,  $P<0.001$ ) and 14% reduction urea (83.8±36.1 versus 72.1±33.3,  $P<0.001$ ) in blood serum samples, with stable hemodynamic parameters. In the group of patients discharged from the clinic (n=5), the MARS treatments resulted in an improvement in hepatic encephalopathy (West Haven;  $P=0.043$ ), as well as a reduction in the MELD-Na score ( $P=0.015$ ).

**Conclusions:** MARS is a hemodynamically safe method for supporting the function of the liver and the kidneys. Application of the MARS reduces the symptoms of encephalopathy in patients with alcohol-related type 1 HRS.

**MeSH Keywords:** **Acute Kidney Injury • Dialysis • Hepatorenal Syndrome • Mars**

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## Background

Molecular Adsorbent Recirculating System (MARS) is a system of extracorporeal toxin removal using the albumin dialysis method. It was introduced into clinical practice by the German nephrologists Mitzner and Stang in 1993, in order to support the detoxification function of the liver in cases of acute liver failure as well as previously existing acute-on-chronic liver failure (AoCLF) [1]. This technique is based on extracorporeal removal of toxins associated with plasma proteins which result from liver failure. This system allows for the simultaneous elimination of water-soluble uremic and non-uremic toxins. The main goal of the MARS method is to remove small and medium molecules from the circulation. This is achieved by a specially constructed highly permeable membrane [1]. Procedures using MARS are well tolerated, safe, stabilize the function of cardiovascular system, reduce the degree of hepatic encephalopathy, and have a positive effect on selected biochemical markers, which has been confirmed in numerous studies – including the randomized trial named RELIFE [2–4].

The most common factors causing AoCLF include alcohol consumption. Although alcohol abuse and/or addiction are not a prerequisite for the development of alcoholic liver disease, they still frequently correlate with alcoholic liver disease. One of the stages of alcoholic liver disease can be liver cirrhosis. The bases for the diagnosis of alcoholic liver disease are the following: medical history, clinical symptoms of liver disease, and abnormal results of additional tests. One of the elements of the medical history review interview may be a questionnaire such as the AUDIT (alcohol use disorders identification test).

One of the most severe AoCLF complications is kidney damage. Even a slight increase of creatinine concentration in the serum indicates a significant decrease in glomerular filtration in patients with chronic liver failure and is associated with poor prognosis. The occurrence of acute kidney injury (AKI) in the form of type 1 hepatorenal syndrome (HRS) as a component of multiorgan failure in patients with AoCLF is associated with high short-term mortality (28-day mortality greater than 15%) [5]. In a prospective, randomized, controlled clinical trial, Mitzner et al. in the group of patients with type 1 HRS found that the mortality in the control group on day 7 of the study was 100%. In the MARS group, the mortality rate on day 7 was 62.5%, and on day 30, the mortality rate was 75%. The authors found that the removal of substances associated with albumins using the MARS method can contribute to improving the survival of patients with type 1 HRS [6].

The aim of this study was to evaluate the effectiveness of MARS in patients with alcohol-related AoCLF complicated with type 1 HRS.

## Material and Methods

The study included 10 patients with type 1 hepatorenal syndrome HRS, in the course of alcohol-related AoCLF, treated in the years 2016–2019. A total of 41 procedures were performed. The indication for treatment was the occurrence of AoCLF meeting the criteria of the European consensus for MARS [7]. Before and after each procedure the following biochemical tests from blood serum samples were performed: albumin and total bilirubin determined by colorimetric method (cobas c 501), ammonia and creatinine determined by enzymatic method (cobas c 501), urea determined by enzymatic method (kinetic with urease and glutamate dehydrogenase with cobas c 501), sodium and potassium determined by indirect ion-specific electrode (ISE) method (cobas c 501). During the procedure, non-invasive monitoring of blood pressure, heart rate, blood saturation, hourly diuresis, and body temperature was performed. In addition, before and after the treatment, the condition of patients was determined on the basis of 2 scales: the model for end-stage liver disease-sodium (MELD-Na) and the stage of hepatic encephalopathy severity based on the West Haven criteria.

All treatments were performed without any technical problems or adverse events. The criteria for premature termination of the MARS procedure included the following: decrease in systolic pressure below 90 mmHg for more than 30 minutes, without reaction to administered drugs and changes in treatment settings, clinically significant, recurrent hypoglycemia with glucose concentration in the serum below 50 mg/dL, bleeding threatening the life of the patient, significant aeration of the dialyzer system or albumins, coagulation of albumins in the MARS system or line positioning for hemodialysis, damage to the column system or dialyzer.

The decision not to perform subsequent MARS procedures was made in the case of the following: obtaining stable and acceptable improvement of liver function, lack of improvement or deterioration of the general condition and prognosis as to the improvement of the state of health, despite the lack of direct MARS complications.

All study procedures were performed according to the Helsinki Declaration of Human Rights of 1975, modified in 1983 and 1989. The Bioethics Committee of the Military Chamber of Physicians in Warsaw (Poland) raised no objections to the design of our work.

## Statistical analysis

The test results were evaluated using the Statistica 12.0 software. Due to the small sample size, the basic results are presented in the form of means with standard deviations as well

as in the form of medians with minimum and maximum values. Differences between the results obtained before and after the procedure were tested using the *t*-test for dependent variables or the Wilcoxon matched-pairs signed-rank test, depending on the fulfillment of the normal distribution condition. Differences between survivors and non-survivors were evaluated using the *t*-test for independent variables or the Mann-Whitney U test if the normal distribution was missing. The results were considered statistically significant at  $P < 0.05$ . The survival rate of patients within 14 days from the start of therapy was determined by the Kaplan-Meier method.

## Results

The study included 10 patients (7 males, 3 females, age  $52.1 \pm 11.1$  years) with alcohol-related AoCLF, without hepatitis B virus or hepatitis C virus infections. The clinical characteristics of the study group are shown in Table 1. The parameters of the performed procedures are presented in Table 2.

During the hospital observation of  $20.5 \pm 13.9$  days on average, covering the period from the first MARS treatment to discharge or death, 5 patients (4 males, 1 females) died, and the remaining 5 (3 males, 2 females) were discharged from the hospital. Initial sepsis was recognized in 1 survivor patient and 1

deceased patient. Concomitant bleeding complications (nasal, esophago-gastrointestinal) occurred in 1 discharged patient and 3 deceased patients, but these complications were not closely related to the MARS procedures. A comparison of baseline data of survivors and non-survivors is presented in Table 3.

In the entire study group, the 14-day survival, starting from the first MARS treatment, was 90%, but the 21-day survival was only 39% (Figure 1).

The MARS treatments were associated with a significant reduction in blood serum of bilirubin by 18.9%, ammonia by 37.4%, creatinine by 26.7%, and urea by 14%, with stable hemodynamic parameters (Table 4).

The observed improvement of blood circulation parameters in the form of a slight increase in both systolic blood pressure (approximately 3.2%) and diastolic blood pressure (approximately 4.1%) during the procedure was not significant. Examining the entire group, we initially found no significant improvement in hepatic encephalopathy ( $P = 0.06$ ) or in the MELD-Na score ( $P = 0.95$ ). However, in contrast to deceased patients with significant worsening in the MELD-Na score, within the group of patients discharged from the clinic, MARS treatments resulted in a significant improvement in hepatic encephalopathy and in lowering the MELD-Na score (Table 5).

**Table 1.** Clinical characteristics of the studied group.

| Variable                         | Mean  | Median | Minimum | Maximum | SD    |
|----------------------------------|-------|--------|---------|---------|-------|
| Age (year)                       | 52.1  | 55.0   | 31.0    | 64.0    | 11.1  |
| Time to discharge or death (day) | 20.5  | 17.0   | 3.0     | 45.0    | 13.9  |
| Natrium (mmol/L)                 | 135.1 | 136.0  | 129.0   | 143.0   | 4.33  |
| Potassium (mmol/L)               | 4.1   | 3.8    | 3.5     | 5.3     | 0.6   |
| Bilirubin (mg/dL)                | 28.2  | 30.2   | 17.6    | 38.6    | 7.48  |
| Ammonia ( $\mu\text{mol/L}$ )    | 49.9  | 45.5   | 22.0    | 92.0    | 25.04 |
| Creatinine (mg/dL)               | 1.85  | 1.20   | 0.70    | 4.20    | 1.26  |
| Urea (mg/dL)                     | 92.8  | 94.5   | 32.0    | 182.0   | 42.7  |
| Albumin (g/dL)                   | 2.9   | 2.9    | 2.2     | 3.5     | 0.4   |
| MELD-Na – pre                    | 34.9  | 35.0   | 28.0    | 44.0    | 5.2   |
| MELD-Na – post                   | 35.1  | 35.0   | 23.0    | 44.0    | 6.9   |
| MARS/patient                     | 4.0   | 3.5    | 1.0     | 9.0     | 2.2   |
| West Haven – pre                 | 1.6   | 1.0    | 1.0     | 3.0     | 0.8   |
| West Haven – post                | 1.1   | 0.5    | 0.0     | 4.0     | 1.4   |

MARS – Molecular Adsorbent Recirculating System; MELD-Na pre/post – model for end-stage liver disease – sodium scale score before or after MARS treatment; West Haven pre/post – West Haven scale score before or after MARS treatment; SD – standard deviation.

**Table 2.** Characteristics of MARS procedures.

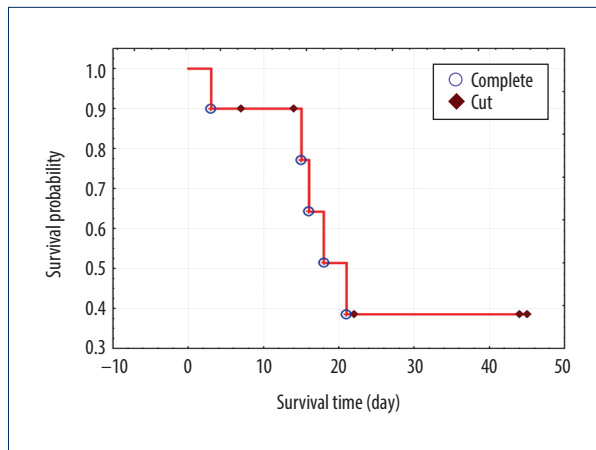
| Variable                     | Mean  | Median | Minimum | Maximum | SD    |
|------------------------------|-------|--------|---------|---------|-------|
| MARS duration (h)            | 6.0   | 6.0    | 1.0     | 7.0     | 0.8   |
| Blood flow (mL/min)          | 189.0 | 180.0  | 150.0   | 200.0   | 11.8  |
| Albumin flow (mL/min)        | 189.0 | 180.0  | 150.0   | 200.0   | 11.8  |
| Ultrafiltration (mL/h)       | 22.0  | 0.0    | 0.0     | 250.0   | 59.2  |
| Dialytic fluid flow (mL/min) | 831.7 | 1000.0 | 300.0   | 1500.0  | 390.2 |
| SBP (mmHg)                   | 116.1 | 114.5  | 95.0    | 133.4   | 9.7   |
| DBP (mmHg)                   | 71.5  | 72.5   | 56.4    | 89.0    | 7.9   |
| HR (bpm)                     | 84.0  | 82.2   | 62.9    | 109.4   | 11.3  |
| MAP (mmHg)                   | 86.5  | 86.2   | 73.7    | 103.8   | 7.3   |
| Time to next MARS (day)      | 3.0   | 2.0    | 2.0     | 10.0    | 1.7   |

MARS – Molecular Adsorbent Recirculating System; SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial blood pressure; HR – heart rate; bpm – beats per minute; SD – standard deviation.

**Table 3.** Comparison of baseline parameters between survivors and non-survivors.

| Variable           | Survivors |      | Non-survivors |      | Significance P |
|--------------------|-----------|------|---------------|------|----------------|
|                    | Mean      | SD   | Mean          | SD   |                |
| Age (year)         | 48.0      | 12.3 | 56.2          | 9.0  | 0.265          |
| SBP (mmHg)         | 106.8     | 11.6 | 114.0         | 14.8 | 0.417          |
| DBP (mmHg)         | 66.6      | 12.0 | 71.2          | 10.6 | 0.540          |
| HR (bpm)           | 83.0      | 10.7 | 90.8          | 18.2 | 0.431          |
| Natrium (mmol/L)   | 135.6     | 5.0  | 134.6         | 4.0  | 0.738          |
| Potassium (mmol/L) | 4.0       | 0.8  | 4.2           | 0.6  | 0.465          |
| Bilirubin (mg/dL)  | 29.0      | 7.1  | 27.4          | 8.6  | 0.762          |
| Ammonia (µmol/L)   | 55.0      | 22.8 | 44.8          | 28.7 | 0.551          |
| Creatinine (mg/dL) | 2.5       | 1.5  | 1.2           | 0.6  | 0.118          |
| Urea (mg/dL)       | 104.2     | 47.4 | 81.4          | 39.1 | 0.430          |
| Albumin (g/L)      | 2.9       | 0.5  | 2.9           | 0.4  | 0.946          |
| MELD-Na – pre      | 38.0      | 4.9  | 31.8          | 3.4  | 0.049          |
| West Haven – pre   | 1.0       | 1.0  | 2.2           | 0.8  | 0.047          |

HR – heart rate; bpm – beats per minute; MELD-Na pre/post – model for end-stage liver disease – sodium scale score before or after MARS treatment; SBP – systolic blood pressure; DBP – diastolic blood pressure; SD – standard deviation; West Haven pre/post – West Haven scale score before or after MARS treatment.



**Figure 1.** Kaplan-Meier survival of AoCLF patients treated with MARS. AoCLF – acute-on-chronic liver failure; MARS – Molecular Adsorbent Recirculating System.

## Discussion

Acute-on-chronic liver failure (AoCLF) was first described in 1995 by Ohnishi et al. [8]. According to the authors, this disease entity is characterized by an acute deterioration of compensated or decompensated chronic liver disease leading to multiorgan failure. AoCLF most often manifests as a hepatic coma or hepatorenal syndrome. Clinically, on the basis of the time of increase in creatinine concentration, it can be divided into type 1 HRS with a serious prognosis and high mortality, and type 2 HRS with a relatively better prognosis. Type 1 HRS is burdened with 15% mortality within 28 days [5].

The incidence of renal failure in patients with liver cirrhosis is estimated at 7% to 65% [9–12]. One of the forms of acute kidney injury in patients with liver cirrhosis is HRS [13]. The risk of development of HRS in patients with liver cirrhosis and ascites

**Table 4.** Comparison of blood pressure and laboratory data before and after MARS treatment.

| Variable           | Before MARS |      | After MARS |      |
|--------------------|-------------|------|------------|------|
|                    | Mean        | SD   | Mean       | SD   |
| Bilirubin (mg/dL)  | 27.5        | 6.1  | 22.3       | 4.0  |
| Ammonia (µmol/L)   | 44.1        | 22.5 | 27.6       | 20.9 |
| Creatinine (mg/dL) | 1.5         | 1.0  | 1.1        | 0.6  |
| Urea (mg/dL)       | 83.8        | 36.1 | 72.1       | 33.3 |
| SBP (mmHg)         | 114.2       | 13.1 | 117.9      | 14.4 |
| DBP (mmHg)         | 70.6        | 10.9 | 73.6       | 9.8  |
| HR (bpm)           | 82.7        | 14.0 | 82.5       | 11.6 |

MARS – Molecular Adsorbent Recirculating System; SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial blood pressure; HR – heart rate; bpm – beats per minute; SD – standard deviation.

**Table 5.** Comparison of the effectiveness of MARS treatments in West Haven and MELD-Na score results.

| Variable        | Before MARS |     | After MARS |     |
|-----------------|-------------|-----|------------|-----|
|                 | Mean        | SD  | Mean       | SD  |
| West Haven      | 1.6         | 0.9 | 1.1        | 1.4 |
| West Haven – s  | 1.0         | 0.0 | 0.0        | 0.0 |
| West Haven – ns | 2.2         | 0.8 | 2.2        | 1.3 |
| MELD-Na         | 34.9        | 5.2 | 35.1       | 6.9 |
| MELD-Na – s     | 38.0        | 4.9 | 29.2       | 3.8 |
| MELD-Na – ns    | 31.8        | 3.4 | 41.0       | 2.4 |

MARS – Molecular Adsorbent Recirculating System; MELD-Na pre/post – model for end-stage liver disease; s – survival; ns – non-survival; SD – standard deviation.

is estimated at 18% in the first year and approximately 40% after 5 years of observation [14]. For our study, patients with a positive history of alcoholic liver disease, liver cirrhosis, and ascites were qualified. All patients had HRS diagnosed on the basis of the International Ascites Club criteria [12]. In the study group treated with MARS, the 14-day survival was 90%, but the 21-day survival was only 39%. According to Moreau et al., patients with AoCLF are burdened with high mortality of 50% to 90% [15]. In order to assess the risk of death among patients and plan for their appropriate treatment, various point scales are used. One of them is the MELD scale, which was originally developed to predict the short-term survival of patients undergoing transjugular intrahepatic portosystemic shunt. Obtaining a result of over 25 points by a patient is an indication for urgent transplantation. Since January 1, 2016, the MELD scale has been used taking into account the concentration of sodium in the blood serum, the MELD-Na score [14]. In our group, the initial MELD-Na was 34.9. Paradoxically, in the group of deceased patients, the initial MELD-Na score was lower than in the group of discharged survivor patients; however, in both groups it was in the range of very high values (>30) and burdened with the highest mortality [16]. Some studies suggest that APACHE-II (Acute Physiology and Chronic Health Evaluation) is the best system of predictive assessment due to the fact that, in the case of AoCLF, prognosis depends on the degree of failure of other organs [17]. CLIF-SOFA (Chronic Liver Failure-sequencing Organ Failure Assessment) is a scale similar to APACHE-II that also accounts for multi-organ dysfunction. The scale estimates mortality based on the severity of multiorgan dysfunction in patients with AoCLF [18]. In other studies, it was found that MELD was a discriminatory factor similar to SOFA and APACHE II [19]. Data obtained from the CANONIC supported development of a simplified prognostic scale for AoCLF called the "CLIF Consortium ACLF score" (CLIF-C AoCLFs) [20,21]. The new scale shows much higher predictive accuracy of AoCLF severity than MELD and MELD-Na. On the other hand, a meta-analysis by Wu et al. showed that the scales referring to sodium concentration in the blood serum, i.e. MESO (MELD to Serum Sodium ratio) and MELD-Na had the highest accuracy in the prediction of mortality in decompensated liver cirrhosis [18].

At present, the administration of vasoconstrictor drugs (e.g., terlipressin) in combination with albumin infusions is recommended for the first-line treatment of type 1 HRS [22]. This strategy leads to improvement in kidney function in most patients, however, in more than 40% of cases it is ineffective [23,24]. The use of renal replacement therapy (RRT) in this syndrome is considered controversial, as it has not been associated with improvement in short- and long-term survival in both treated and untreated patients with RRT [25]. This method is only considered for candidates for liver transplantation (over 30% of individuals who have received RRT have

had a transplantation procedure). Compared to the standard RRT, the use of the MARS system can improve the prognosis of patients with HRS by simultaneous support of kidney and liver functions, and stabilization of the circulatory system without the need for the administration of additional catecholamines.

In the only correctly planned randomized study with the acronym RELIEF, Bañares et al. [4] showed that the use of the MARS system in AoCLF was characterized by a favorable safety profile, a significant dialysis effect, and a slight impact on the improvement of severe cerebral encephalopathy (statistically not significant), which is consistent with the results of our work. As in our work, the Bañares et al. study found it was not possible to demonstrate a beneficial effect of MARS on survival [4].

Gerth et al. [26] retrospectively analyzed AoCLF patients treated with MARS in combination with standard therapy and patients only treated with standard medical treatment. Similar to our study, significant effects on bilirubin and creatinine in the serum were demonstrated in the patients treated with MARS [26]. Their study showed an increase in short-term 14-day survival in the MARS group [26], which was not observed in our study. Similar results were obtained by Heemann et al. who reported that MARS procedures in combination with standard therapy for AoCLF were associated with greater 30-day survival and a significant reduction in bilirubin in the serum [27]. In the study by Hessel et al. [28], the cumulative 3-year survival probability was shown to be higher in the MARS group treated for AoCLF. This study was created to assess the cost-effectiveness of MARS treatment in AoCLF, therefore the randomization methodology in the study was unclear [28].

The administration of MARS treatments in our group of patients with AoCLF caused a significant reduction in the concentration of renal dysfunction (as measured by creatinine and urea levels) and liver failure parameters (as measured by bilirubin and ammonia levels). Despite the declared permeability of filters used in MARS, available reports were not consistent with the significance of the reduction of these toxins during the procedure. Wolf et al. found that after 48 MARS treatments in 14 patients with AoCLF, there was a significant reduction in bilirubin, creatinine, and urea, but not ammonia [29]. Schaefer et al. did not observe a significant reduction in either bilirubin or ammonia after MARS procedures in children, in contrast to the plasmapheresis with hemodialysis (PE/HD) procedures alternating with MARS [30]. However, a significant decrease in ammonia concentration during PE/HD probably caused lower concentrations of this toxin before MARS, which affected the final lack of effectiveness of the method. On the other hand, Bourgoin et al., performing 17 albumin dialyses (MARSFLUX and MiniMARS) in 6 children, only found a significant reduction in ammonia concentration after the procedures, but without a decrease in bilirubin [31]. Undoubtedly, the results of

this study were affected by premature (<50% of the assumed time) completion of almost 30% of treatments. However, MARS treatments can serve as a bridge for liver transplantation in severe poisoning in children [32]. In a recently published retrospective, multicenter study by Cisneros-Garza et al., after 79 MARS treatments in 38 patients, the authors found a significant reduction in bilirubin, transaminases, and bile acids, and a decrease in symptoms of hepatic encephalopathy, without a reduction of creatinine [33]. In contrast to our study, where all patients presented with AKI in the course of AoCLF or type 1 HRS, in the work by Cisneros-Garza et al. only 5 patients (13%) had type 1 HRS. Taking into account the aforementioned observations, our study summarizes the research performed so far and shows the significant effectiveness of MARS in the elimination of selected liver and kidney toxins. Moreover, in our study a significant reduction in ammonia was accompanied by a significant decrease in symptoms of hepatic encephalopathy. In addition, studies have shown that plasma nitric oxide and both anti-inflammatory and pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin (IL)-6 or IL-10, involved in the pathogenesis of encephalopathy may be removed by the MARS method [34].

In our study group, performed MARS treatments were associated with a mild improvement in hemodynamic parameters in the form of a slight increase in blood pressure. During the procedures, there were no blood pressure drops that forced the reduction of planned ultrafiltration. Our observations are consistent with the results of the study by Schmidt et al. in which the improvement of hemodynamic conditions included

an increase in both systolic and diastolic blood pressure [35,36]. Similar to our study, these authors observed the constant catecholamine administration in spite of conducted ultrafiltration.

Our study documents the efficiency and safety of albumin dialysis in the form of MARS procedures in patients with type 1 HPS in the course of AoCLF. Despite promising observations, the results of our study are subject to limitations caused primarily by the small number of patients resulting from the selection of a homogeneous group of patients.

## Conclusions

Albumin dialysis using the MARS method is effective at removing selected liver toxins such as bilirubin or ammonia and kidney toxins such as creatinine or urea, reducing the symptoms of encephalopathy in the course of alcohol-related type 1 HRS. MARS procedures not only allow for the removal of selected toxins, which cannot be obtained using standard conservative therapy with the administration of terlipressin, but also might have a positive effect on the concentrations of selected cytokines. Hemodynamic stability during the MARS procedure without a necessity for a modification of the initial settings makes this method safe and well tolerated. No adverse events were observed during the procedures.

## Conflict of interests

None.

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