Use of the Molecular Adsorbent Recirculating System in Acute Liver Failure: Results of a Multicenter Propensity Score-Matched Study*

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OBJECTIVES: The molecular adsorbent recirculating system removes water-soluble and albumin-bound toxins and may be beneficial for acute liver failure patients. We compared the rates of 21-day transplant-free survival in acute liver failure patients receiving molecular adsorbent recirculating system therapy and patients receiving standard medical therapy.

DESIGN: Propensity score–matched retrospective cohort analysis.

SETTING: Tertiary North American liver transplant centers.

PATIENTS: Acute liver failure patients receiving molecular adsorbent recirculating system at three transplantation centers ($n = 104$; January 2009–2019) and controls from the U.S. Acute Liver Failure Study Group registry.

INTERVENTIONS: Molecular adsorbent recirculating system treatment versus standard medical therapy (control).

MEASUREMENTS AND MAIN RESULTS: One-hundred four molecular adsorbent recirculating system patients were propensity score–matched (4:1) to 416 controls. Using multivariable conditional logistic regression adjusting for acute liver failure etiology (acetaminophen: $n = 248$; vs nonacetaminophen: $n = 272$), age, vasopressor support, international normalized ratio, King's College Criteria, and propensity score (main model), molecular adsorbent recirculating system was significantly associated with increased 21-day transplant-free survival (odds ratio, 1.90; 95% CI, 1.07–3.39; $p = 0.030$). This association remained significant in several sensitivity analyses, including adjustment for acute liver failure etiology and propensity score alone ("model 2"; molecular adsorbent recirculating system odds ratio, 1.86; 95% CI, 1.05–3.31; $p = 0.033$), and further adjustment of the "main model" for mechanical ventilation, and grade 3/4 hepatic encephalopathy ("model 3"; molecular adsorbent recirculating system odds ratio, 1.91; 95% CI, 1.07–3.41; $p = 0.029$). In acetaminophen-acute liver failure ($n = 51$), molecular adsorbent recirculating system was associated with significant improvements (post vs pre) in mean arterial pressure (92.0 vs 78.0 mm Hg), creatinine (77.0 vs 128.2 µmol/L), lactate (2.3 vs 4.3 mmol/L), and ammonia (98.0 vs 136.0 µmol/L; $p \leq 0.002$ for all). In nonacetaminophen acute liver failure ($n = 53$), molecular adsorbent recirculating system was associated with significant improvements in bilirubin (205.2 vs 251.4 µmol/L), creatinine (83.1 vs 133.5 µmol/L), and ammonia (111.5 vs 140.0 µmol/L; $p \leq 0.022$ for all).

CONCLUSIONS: Treatment with molecular adsorbent recirculating system is associated with increased 21-day transplant-free survival in acute liver failure and improves biochemical variables and hemodynamics, particularly in acetaminophen-acute liver failure.

KEY WORDS: acute liver failure; critical care management; extracorporeal liver support; liver transplantation; molecular adsorbent recirculating system; transplant-free survival

***See also p. 346.**

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Acute liver failure (ALF) is a rare syndrome characterized by acute hepatic injury resulting in hepatic encephalopathy (HE) and impaired hepatic function in patients without preexisting liver disease (1, 2). Critically ill patients with ALF may develop intracranial hypertension (ICH) and cerebral edema (CE) associated with significant morbidity and mortality (3, 4). Management is primarily supportive and aims to maintain hemodynamic stability and correct metabolic abnormalities while awaiting potential hepatic recovery (5, 6). Prognosis varies with etiology, with acetaminophen-/paracetamol-induced ALF patients displaying greater recovery potential. For those failing medical therapy, liver transplantation (LT) may confer improved survival, with approximately 20% of North American ALF patients receiving LT (7). Critical illness and psychosocial factors may complicate listing decisions for LT, whereas many ALF patients may die waiting for a suitable donor graft in an era where organ demand greatly exceeds supply (8–10).

To address the need for treatment options for ALF, extracorporeal liver support (ELS) systems may represent a promising area in the medical management of ALF patients. The molecular adsorbent recirculating system (MARS; Baxter International, Deerfield, IL), an albumin-based dialysis system, removes water-soluble and albumin-bound toxins and may assist in bridging patients to donor organ availability or, alternatively, may supplement hepatic function while native organ recovery occurs (11). The MARS albumin dialysis system improves serum biochemistry and hemodynamics in ALF; however, studies have had small sample size, resulting in difficulty in evaluating the role of MARS in transplant-free survival (TFS), particularly in acetaminophen-ALF (12–14).

Analyzing MARS-treated ALF patient data from three tertiary liver transplant centers and standard medical therapy (SMT)–treated ALF patient data from the multicenter U.S. ALF Study Group (U.S. ALFSG) registry, we compared MARS therapy with SMT in ALF patients. Our objectives were to test the following hypotheses:

1) TFS is significantly greater for ALF patients treated with MARS therapy compared with SMT.
2) MARS therapy significantly improves serum biochemistry and hemodynamics.

MATERIALS AND METHODS

Study Design

A propensity score (PS)–matched retrospective cohort study of all ALF patients treated with MARS at three North American tertiary care hospitals (Emory University Hospital, Atlanta, GA; University of Alberta Hospital, Edmonton, AB, Canada; University of Kansas Medical Center, Kansas City, KS) between January 2009 and January 2019 was performed. Participating MARS recruitment centers were U.S. ALFSG member institutions. Eligible SMT controls were prospectively enrolled in the U.S. ALFSG registry between January 2010 and December 2019. All protocols were approved by the institutional review boards/health research ethics boards at participating sites (tertiary liver transplant referral centers). Consent/assent was obtained from each participant/next of kin. All research procedures were conducted according to the principles of the 1975 Declaration of Helsinki. Therapeutic interventions, including SMT algorithms and initiation and cessation of MARS, were implemented in accordance with institutional standards of care. Criteria for listing and performing LT were determined based on protocols at participating transplant centers. Full details regarding standard-of-care medical therapy in ALF are published elsewhere (15–17).

Participants

Enrollment criteria were as follows: 1) primary diagnosis of ALF as determined by the site investigator, 2) participant age greater than or equal to 18 years, and 3) receipt of MARS therapy (MARS patients) or absence of receipt of MARS therapy (SMT patients). SMT patients with missing values for any matched variable(s) used in the PS calculation (age, sex, acetaminophen-ALF etiology, use of renal replacement therapy [RRT], use of vasopressors, mechanical ventilation, presence of grade 3/4 HE, international normalized ratio [INR], bilirubin, creatinine, fulfillment of King's College Criteria [KCC]) were not considered. Missing data in the eligible SMT patient pool were minimal.

Operational Definitions

ALF was defined using the following criteria: 1) INR greater than or equal to 1.5, 2) HE of any grade (West

Haven Criteria) (18), 3) illness duration less than 26 weeks, and 4) absence of existing cirrhosis (note: patients with liver failure secondary to acute Wilson's disease or de novo presentation of preexisting subclinical liver disease were considered). The KCC predict poor outcomes in ALF (19). In acetaminophen-ALF, KCC are defined as either 1) arterial pH less than 7.3 or 2) all three of the following criteria: a) INR greater than 6.5, b) creatinine greater than 300 μmol/L, and c) the presence of grade 3/4 HE. In nonacetaminophen ALF, KCC are defined as 1) INR greater than 6.5 or 2) three of the following five criteria: a) age less than 11 years or greater than 40 years, b) non-hepatitis A virus/non-hepatitis B virus viral hepatitis or indeterminate or idiosyncratic drug-induced etiology, c) jaundice-to-HE interval greater than 7 days, d) INR greater than 3.5, and e) bilirubin greater than 300 μmol/L.

Clinical Variables and Endpoints

MARS patient covariates were manually collected through retrospective electronic medical record review at each contributing center. Data were then pooled to create a complete MARS case cohort dataset (maintained at the University of Alberta, Edmonton, AB, Canada).

The U.S. ALFSG registry (maintained at the Medical University of South Carolina, Charleston, SC) contains prospectively collected clinical, biochemical, and outcome data from 32 tertiary care hospitals since January 1998. Eligible SMT patients included those enrolled between January 2010 and December 2019. Control data were pulled from the U.S. ALFSG registry electronic data warehouse for analysis.

Data assessed included baseline patient characteristics (age, sex, ALF etiology), requirement of organ support (mechanical ventilation, vasopressors, RRT), biochemical variables (complete blood count, INR, transaminases, bilirubin, pH, ammonia, creatinine, lactate), HE grade, and clinical outcomes (21 d TFS, overall 21 d survival, and transplantation). Additionally, hemodynamic variables were evaluated in MARS patients. Baseline variables were defined as those most recently recorded prior to the initiation of MARS therapy (MARS patients) or those at admission (SMT patients). Post-MARS patient variables were defined as those recorded immediately following cessation of MARS therapy. The primary endpoint for this study was 21-day TFS. Transplant-free survivors were considered to be those surviving without LT at 21 days following enrollment. Those receiving LT within the first 21 days or those experiencing mortality within the first 21 days were considered as failures in the outcome of interest. Time zero was defined as follows: at ICU admission in MARS patients and on enrollment in the U.S. ALFSG study in SMT patients. Secondary outcomes included changes in biochemical and hemodynamic variables following MARS therapy in the exposed cohort.

Statistical Analysis

We used a PS-matched, retrospective cohort design, which aimed to balance baseline characteristics and minimize potential confounding between MARS and SMT patients. Using logistic regression, baseline covariates (age, sex, acetaminophen-ALF etiology, use of RRT, use of vasopressors, mechanical ventilation, presence of grade 3/4 HE, INR, bilirubin, creatinine, fulfillment of KCC) were identified to generate exposure PS values. Each PS represented the predicted probability of treatment with MARS therapy. A random matching of patients to controls within a maximum PS radius of 0.2 without replacement was used to select SMT patients for each MARS patient in a 1:4 ratio (20). The radius method matches based on an allowable maximum difference between PSs. Matching was completed using a 1:4 ratio to maximize statistical power while addressing residual heterogeneity between groups (21). Matched cohort covariate balance was assessed using standardized mean differences (SMDs). A covariate SMD threshold greater than 0.2 (absolute value) was considered unbalanced and accounted for using adjustment in multivariable modeling (22).

PS matching was completed by the U.S. ALFSG registry statistical team. Subsequent analyses based on the pulled SMT control sample were completed by an independent research team.

The association of therapy (MARS vs SMT) and 21-day TFS was evaluated using conditional logistic regression. The primary analysis included adjustment for age, use of vasopressors, INR, fulfillment of KCC (all $|SMD| > 0.2$), acetaminophen-ALF etiology, and continuous PS values (main model). We conducted several sensitivity analyses to assess the consistency of

the effect of MARS therapy with inclusion of different covariates. First, we evaluated MARS therapy adjusting for acetaminophen-ALF etiology and continuous PS values (model 2). Additionally, we further adjusted the "main model" for mechanical ventilation and grade 3/4 HE (|SMD| > 0.1; "model 3").

Using data from MARS patients before and after treatment, we conducted a subgroup analysis comparing ALF etiology (acetaminophen vs nonacetaminophen). Pre- and post-MARS categorical covariates were presented as proportions and compared using the chi-square test. Complete pair pre-/post-MARS continuous covariates were presented as medians with interquartile ranges (IQRs) or means with SDs following assessment for normality using skewness (± 0.5) and kurtosis (± 2). Continuous covariates were compared using the Wilcoxon signed-rank test or paired Student *t* test, where appropriate.

All analyses were two tailed. We used a threshold for statistical significance of 0.05. Statistical analysis was performed using Stata (Version 16.1; StataCorp, College Station, TX) and SAS (Version 9.4; SAS Institute, Cary, NC).

RESULTS

Baseline Patient Variables

A total of 104 patients were treated with MARS between December 2009 and January 2019. The majority of patients receiving MARS therapy were admitted to the ICU on the same day as hospital admission (n = 89; 85.6%).The unmatched SMT population included 1,544 eligible patients enrolled across 17 centers within the U.S. ALFSG registry between January 2010 and December 2019. PS matching yielded a cohort of 520 ALF patients; 104 MARS patients matched 1:4 with 416 SMT control patients (**Fig. 1**). Following PS matching, ALF etiology (acetaminophen vs nonacetaminophen), sex, use of RRT, mechanical ventilation, presence of grade 3/4 HE, serum bilirubin, and serum creatinine SMDs (absolute values) were less than 0.2 between treatment groups, indicating acceptable covariate balance. Patient age, use of vasopressors, INR, and fulfillment of KCC were unbalanced between matched treatment groups, requiring adjustment consideration in subsequent modeling. Matched demographic and clinical variables are described in **Table 1**. PS variables in the eligible unmatched SMT population are summarized in **Supplementary Table 1** (http://links.lww.com/CCM/G582). Additional, nonmatched, baseline variables in the matched SMT cohort are summarized in **Supplementary Table 2** (http://links.lww.com/CCM/G582).

MARS Protocols

Treatment with MARS was initiated a median (IQR) of 1 day (0–1 d) following ICU admission. Case patients received a median (IQR) of 3 (1.5–4) MARS therapy sessions, with a median (IQR) total treatment duration of 24.0 hours (9.0–33.1 hr). Use of citrate anticoagulation was most common (55.8%), followed by no anticoagulation (31.7%). Notably, all participating institutions utilized PRISMAFLEX (Baxter International, Deerfield, IL) RRT as part of MARS therapy setup. **Supplementary Table 3** (http://links.lww.com/CCM/G582) summarizes MARS therapy protocol variables.

Multivariable Analyses: Associations With TFS

Multivariable conditional logistic regression was performed to determine associations with 21-day TFS in the PS-matched cohort. Adjusting for ALF etiology, continuous PS values, and unbalanced matched covariates (age, use of vasopressors, INR, and fulfillment of KCC), MARS therapy was significantly associated with 21-day TFS (odds ratio [OR], 1.90; 95% CI, 1.07–3.39; p = 0.030) (**Supplementary Table 4**, http://links.lww.com/CCM/G582). **Figure 2** summarizes associations with 21-day TFS in the "main model." The effect of MARS therapy was statistically significant in several sensitivity analyses: adjusting for ALF etiology and continuous PS values ("model 2": MARS OR, 1.86; 95% CI, 1.05–3.31; p = 0.033) (**Supplementary Table 5**, http://links.lww.com/CCM/G582) and further adjustment of the "main model" for mechanical ventilation and grade 3/4 HE ("model 3": MARS OR, 1.91; 95% CI, 1.07–3.41; p = 0.029) (**Supplementary Table 6**, http://links.lww.com/CCM/G582). **Table 2** summarizes model associations of MARS therapy with 21-day TFS. The breakdown of patients who were listed for transplant, received a transplant, survived, and TFS at day 21 are summarized in **Supplementary Table 7** (http://links.lww.com/CCM/G582).

Comparisons of Pre-MARS and Post-MARS Variables

Changes in clinical and biochemical variables following receipt of MARS therapy (compared with those

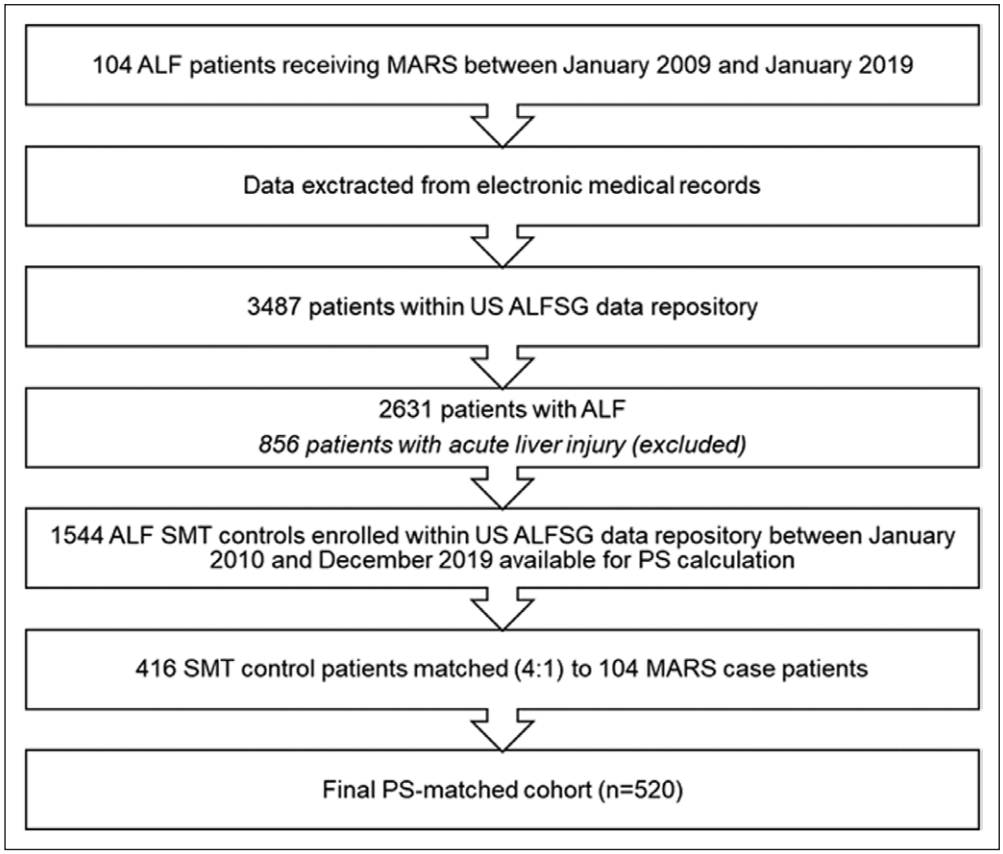

Figure 1. Patient selection flow diagram. ALF = acute liver failure, MARS = molecular adsorbent recirculating system, PS = propensity score, SMT = standard medical therapy, U.S. ALFSG = U.S. Acute Liver Failure Study Group.

prior to intervention), stratified by ALF etiology (acetaminophen and nonacetaminophen), are shown in **Table 3**. Among acetaminophen-ALF patients, significantly fewer required vasopressor support following MARS (post MARS: 37.3% vs pre MARS: 49.0%), in the setting of increased median mean arterial pressure (92.0 v. 78.0 mm Hg; $p \leq 0.002$ for all). Significant reductions in median INR (2.8 vs 4.3), creatinine (77.0 vs 128.2 μmol/L), lactate (2.3 vs 4.3 mmol/L), and ammonia (98.0 vs 136.0 μmol/L; $p < 0.001$ for all) were observed following MARS therapy. A statistically significant increase in median bilirubin (101.0 vs 82.1 μmol/L; $p = 0.041$) was seen following MARS.

In nonacetaminophen ALF patients receiving MARS, more patients required vasopressor support following intervention (post 43.4% vs pre 34.0%; $p < 0.001$). Significant reductions in median bilirubin (205.2 vs 251.4 μmol/L), creatinine (83.1 vs 133.5 μmol/L), and ammonia (111.5 vs 140.0 μmol/L; $p \leq 0.020$ for all) were observed following MARS therapy.

Details on specific modalities of RRT (intermittent or continuous) for both the patients receiving MARS and controls are outlined in **Supplementary Table 8** (http://links.lww.com/CCM/G582).

DISCUSSION

Key Results

Using a PS-matched ALF patient cohort, adjusting for covariates reflecting likelihood of MARS treatment, the odds of 21-day TFS for patients treated with MARS were 1.9 times that of patients treated with SMT. This association remained statistically significant in several sensitivity analyses. Following MARS, significant improvement in hemodynamic status was observed in acetaminophen-ALF patients, whereas significant improvements in biochemical variables were observed in both acetaminophen and nonacetaminophen ALF patients.

Comparison With the Literature

Various ELS systems have been developed to support ALF patients, with the MARS albumin dialysis system being the most studied. By removing hydrophilic and albumin-bound toxins, MARS therapy has been reported to significantly improve both biochemical variables and hemodynamics when compared with SMT (12, 13, 23). Literature evaluating an association between MARS and TFS is lacking, as ALF patients remain clinically heterogeneous, with LT frequently serving as a competing risk.

In the present study, significantly fewer acetaminophen-ALF patients required vasopressor support following MARS, with patients displaying increased mean arterial pressure. Further, significant reductions in creatinine, lactate, and ammonia in acetaminophen-ALF

TABLE 1.
Matched Baseline (Premolecular Adsorbent Recirculating System/Admission) Characteristics of Molecular Adsorbent Recirculating System and Standard Medical Therapy–Treated Patients After Propensity Score Matching

Matched Variables	Molecular Adsorbent Recirculating System (*N* = 104)	Standard Medical Therapy (*N* = 416)	Standardized Mean Difference[a]
Acetaminophen etiology, *n* (%)	51 (49.0)	197 (47.4)	0.03368
Age, mean (SD)	39.4 (14.9)	42.5 (15.4)	0.20398
Sex (male), *n* (%)	39 (37.5)	137 (32.9)	0.09573
Renal replacement therapy, *n* (%)	32 (30.8)	114 (27.4)	0.07415
Vasopressor support, *n* (%)	43 (41.3)	110 (26.4)	0.31883
Mechanical ventilation, *n* (%)	56 (53.8)	198 (47.6)	0.12526
Grade 3/4 hepatic encephalopathy, *n* (%)	55 (52.9)	192 (46.2)	0.13493
International normalized ratio, mean (SD)	4.7 (2.8)	3.8 (2.3)	–0.34565
Bilirubin (µmol/L), mean (SD)	213.4 (206.2)	180.6 (187.2)	–0.16665
Creatinine (µmol/L), mean (SD)	171.5 (129.1)	179.5 (132.6)	0.06135
King's College Criteria met, *n* (%)	52 (50.0)	142 (34.1)	0.32561

[a]A standardized mean difference < 0.2 (absolute value) was considered acceptable covariate balance.

and significant reductions in creatinine, bilirubin, and ammonia in nonacetaminophen ALF were recorded. High serum ammonia levels are believed to play a role in the pathogenesis of CE and are associated with worsening HE and ICH in ALF (24–26). Both MARS and continuous RRT (a component of the MARS setup) have been shown to significantly reduce serum ammonia levels (12, 23, 27–29), whereas continuous RRT has been further suggested to improve 21-day TFS (28).

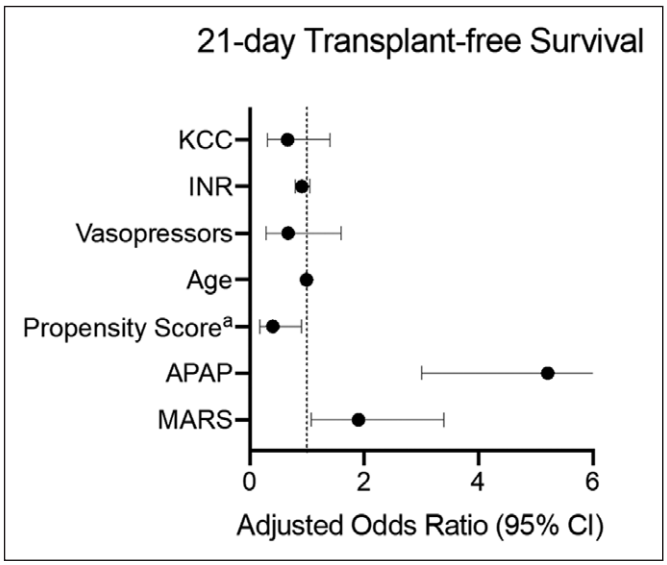

Figure 2. Adjusted associations with 21 d transplant-free survival in 520 propensity score–matched acute liver failure patients: "main model." [a]Per 10% increase in propensity score value. APAP = acetaminophen, INR = international normalized ratio, KCC = King's College Criteria, MARS = molecular adsorbent recirculating system.

Beyond informal case series, no mortality benefit following MARS therapy has been observed in previous controlled ALF studies (12, 13, 23). Saliba et al (14) reported results of the largest randomized controlled trial on MARS in ALF (FULMAR study). Comparing MARS ($n = 53$) versus SMT ($n = 49$) patients, 6-month survival did not differ between groups (85% vs 76%; $p = 0.28$). One significant confounding factor in this study was the short median listing-to-LT time (16.2 hr). Fourteen patients randomized to MARS received less than 5 hours of total MARS therapy prior to death or LT, confounding a robust assessment of MARS on clinical outcomes.

Larsen et al (30) reported a clinically and statistically significant increase in TFS in ALF patients receiving high-volume plasma (HVP) exchange. Of 182 patients randomized to receive HVP and SMT ($n = 92$) or SMT alone ($n = 90$), survival to hospital discharge was 58.7% for patients treated with HVP and 47.8% for patients who received SMT alone (hazard ratio for HVP vs SMT, stratified for LT status, 0.56; 95% CI, 0.36–0.86; $p = 0.0083$). No survival advantage was noted in patients ultimately receiving LT. This remains the only trial identifying a potential role for ELS in nontransplanted ALF patients.

TABLE 2.
Adjusted Associations of Molecular Adsorbent Recirculating System Therapy With 21-Day Transplant-Free Survival: A Summary of Three Models (Molecular Adsorbent Recirculating System: *n* = 104; Standard Medical Therapy: *n* = 416)

Models	Molecular Adsorbent Recirculating System OR[a]	95% OR CI	*p*
Main model[b]	1.90	1.07–3.39	0.030
Model 2[c]	1.86	1.05–3.31	0.033
Model 3[d]	1.91	1.07–3.41	0.029

OR = odds ratio.
[a]Reference group: standard medical therapy.
[b]Main model included adjustment for acute liver failure etiology, continuous propensity score values, and unbalanced matched covariates (|standardized mean difference| > 0.2; age, use of vasopressors, international normalized ratio, and fulfillment of King's College Criteria).
[c]Model 2 included adjustment for acute liver failure etiology and continuous propensity score values.
[d]Model 3 included further adjustment of the Main Model for additional unbalanced matched covariates (|standardized mean difference| > 0.1; mechanical ventilation, grade 3/4 hepatic encephalopathy).

In the present study, MARS therapy was significantly associated increased 21-day TFS. It has been hypothesized that ELS may create an environment for hepatic recovery and reverse underlying mechanisms of hepatocyte injury, thus, promoting TFS. Prognostic potential in ALF patients varies with underlying etiology (6, 7). Specifically, acetaminophen-ALF patients display greater potential for hepatic regeneration and survival without LT. In a subgroup analysis of FULMAR study acetaminophen-ALF patients, MARS therapy was associated with greater, although not statistically significant, 6-month overall survival compared with SMT alone (85% vs 68%; $p = 0.46$) (14). Ultimately, the FULMAR study may have been underpowered to reveal a MARS-related survival advantage in acetaminophen-ALF.

Furthermore, treatment with HVP has been shown to dampen systemic inflammatory response through reductions in neutrophil activation and circulating levels of damage-associated molecular patterns and pro-inflammatory cytokines (30). As acetaminophen-ALF is associated with an abrupt generalized inflammatory cascade, the potential role of MARS in immunomodulation necessitates further study (31).

Strengths and Limitations

Interpretation of this study should consider its strengths and limitations. Strengths include use of, to the best of our knowledge, the largest cohort of ALF patients receiving MARS therapy and inclusion of SMT controls using one of the largest ALF databases across multiple tertiary care centers, lending to reasonable generalizability. ALF is an orphan disease where controlled trials remain both ethically and practically challenging. This study's PS-matched design provides a feasible alternative and serves to address potential confounding interfering with determination of associations in observational studies. Rate of LT among MARS patients in the present study was low (22.1%); thus, LT is plausibly less likely to have confounded the association between TFS and MARS therapy.

Regarding its limitations, neither MARS nor SMT protocols were standardized across participating institutions, and this retrospective analysis of observational data may comment only on association (32). Although subjects were PS-matched, a number of covariates remained imbalanced between matched treatment groups, necessitating further adjustment. This residual imbalance may be considered as a form of selection bias. Furthermore, the delay between hospital presentation and the initiation of MARS therapy may have resulted in immortal time bias. However, this bias is likely minimal as patients who die within the first 24 hours would not be considered for MARS and would not be selected as controls after propensity matching. Decisions regarding LT were not standardized across U.S. ALFSG sites nor treatment cohorts; thus, the potential for selection bias exists. Classification of HE grade was established retrospectively using recorded Glasgow Coma Scale score values. As some of these patients were critically ill and required mechanical ventilation in the setting of multisystem organ failure, concomitant use of sedating medications cannot be excluded as a potential confounder. Vasopressor use was considered as a binary entity. Data regarding time from ICU admission to listing for transplant, minor bleeding events, serial phosphate levels, and complete data on patient race were unavailable. Changes in vasopressor dosing following MARS were not evaluated. Finally, as continuous RRT has been suggested to improve 21-day TFS, future studies should evaluate ELS against continuous RRT (28). In the present study, variations in RRT modalities were not considered. Despite

TABLE 3.
Comparative Analysis of Clinical and Biochemical Variables Following Molecular Adsorbent Recirculating System Therapy, Grouped by Acute Liver Failure Etiology

	Acetaminophen (*N* = 51)			
Variables	***N***	**Pre MARS**	**Post MARS**	***p***
Vasopressor support, *n* (%)	51	25 (49.0)	19 (37.3)	0.001
Hemodynamics, median (interquartile range)				
Heart rate (beats/min)	51	102.0 (86.0–116.0)	92.0 (76.0–105.0)	0.016
Mean arterial pressure (mm Hg)	51	78.0 (69.0–96.0)	92.0 (75.0–100.0)	0.002
Biochemistry, median (interquartile range)				
Hemoglobin (g/L)	51	105.0 (91.0–120.0)	92.0 (83.0–104.0)	< 0.001
WBCs (10^9 cells/L)	51	8.8 (6.0–14.0)	8.5 (5.4–12.8)	0.322
Platelets (10^9 cells/L)	51	101.0 (64.0–166.0)	70.0 (34.0–113.0)	< 0.001
INR	50	4.3 (3.1–7.3)	2.8 (1.7–4.5)	< 0.001
ALT (U/L)	51	4,871.0 (2,909.0–6,650.0)	2,070.0 (1,061.0–3,402.0)	< 0.001
AST (U/L)	51	6,337.0 (2,600.0–10,833.0)	751.0 (200.0–1,721.0)	< 0.001
Bilirubin (µmol/L)	51	82.1 (59.9–114.6)	101.0 (61.6–171.0)	0.041
Creatinine (µmol/L)	51	128.2 (79.0–247.5)	77.0 (46.9–126.4)	< 0.001
Lactate (mmol/L)	45	4.3 (3.1–7.5)	2.3 (1.5–3.5)	< 0.001
Ammonia (µmol/L)	37	136.0 (110.0–261.0)	98.0 (71.0–154.0)	< 0.001
Pa_{O_2}/Fi_{O_2} ratio	50	390.2 (300.0–497.5)	406.1 (300.0–476.0)	0.783
	Nonacetaminophen (N = 53)			
Variables	***N***	**Pre MARS**	**Post MARS**	***p***
Vasopressor support, *n* (%)	53	18 (34.0)	23 (43.4)	< 0.001
Hemodynamics, median (interquartile range)				
Heart rate (beats/min)	53	91.0 (78.0–105.0)	91.0 (77.0–106.0)	0.581
Mean arterial pressure (mm Hg)	53	84.0 (68.0–98.0)	86.0 (74.0–93.0)	0.278
Biochemistry, median (interquartile range)				
Hemoglobin (g/L)	53	95.0 (84.0–113.0)	87.0 (75.0–103.0)	< 0.001
WBCs (10^9 cells/L)	51	11.1 (7.6–15.7)	12.6 (6.3–19.2)	0.913
Platelets (10^9 cells/L)	51	90.0 (60.0–143.0)	55.0 (40.0–95.0)	< 0.001
INR	51	3.5 (2.3–5.7)	3.1 (1.9–5.4)	0.725
ALT (U/L)	51	1,441.0 (100.0–3,890.0)	911.0 (166.0–1,496.0)	0.001
AST (U/L)	51	1,178.0 (175.0–4,099.0)	475.0 (162.0–1,955.0)	0.006
Bilirubin (µmol/L)	51	251.4 (135.0–435.0)	205.2 (147.1–347.1)	0.020
Creatinine (µmol/L)	51	133.5 (69.0–279.3)	83.1 (59.2–127.0)	< 0.001
Lactate (mmol/L)	42	4.2 (2.3–8.0)	3.9 (2.0–9.2)	0.956
Ammonia (µmol/L)	30	140.0 (88.0–273.0)	111.5 (51.0–210.0)	0.022
Pa_{O_2}/Fi_{O_2} ratio	48	334.7 (243.5–406.0)	322.1 (180.8–420.0)	0.123

ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio, MARS = molecular adsorbent recirculating system.

Comparisons of paired pre- versus post-MARS variables completed using Wilcoxon signed-rank test (only complete pairs analyzed; exact p value reported).

these limitations, this study represents the largest cohort of MARS-treated ALF patients evaluating its association with TFS. MARS therapy was associated improved 21-day TFS, underscoring the potential therapeutic role of MARS in ALF patients not receiving LT.

CONCLUSIONS

In a large multicenter PS-matched cohort study of ALF patients, treatment with MARS was associated with significantly increased 21-day TFS over SMT alone. MARS therapy significantly improved hemodynamic and biochemical variables, particularly in acetaminophen-ALF patients. Further robust clinical trials aiming to validate the efficacy of MARS therapy and to identify the subset of ALF patients who derive MARS-related survival advantage are warranted to determine if the therapy should be widely accepted for clinical management of ALF.

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