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Kidney Outcomes Following Utilization of Molecular Adsorbent Recirculating System

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Introduction: Molecular adsorbent recirculating system (MARS) is an extracorporeal system combining conventional veno-venous hemodiafiltration and adsorption to provide rescue support in fulminant hepatic failure. Acute kidney injury (AKI) is common in patients with hepatic failure warranting continuous kidney replacement therapy (CKRT). Our primary aim was to characterize a cohort of patients who received MARS therapy and examine kidney events given the current paucity of available data.

Methods: Patients initiating MARS in a tertiary care setting from January 2014 through December 2020 were assessed for treatment indications, transplantation, CKRT, kidney recovery, and death. Data was collected using the REDCAP software.

Results: A total of 49 patients (67% female; 75% White) received MARS therapy with 29 patients (59%) requiring concomitant CKRT. Hepatic encephalopathy (HE) was the most common indication for MARS initiation (55%). In-hospital mortality was 41% (12/29) among patients who received CKRT versus 10% (2/20) among those not requiring CKRT (relative risk [RR] 4.15, 95% confidence interval [CI] 1.04 to 16.52, $P = 0.044$); this persisted following adjustment for prespecified patient characteristics (all RR $\geq$ 3.76, all $P \leq 0.060$). One-year mortality post-MARS initiation was high overall but highest among the CKRT group (59% [17/29] vs. 25% [5/20] unadjusted RR 2.92, 95% CI 1.08 to 7.94, $P = 0.035$). Liver transplant after MARS occurred in 41% of patients (20/49). After CKRT, 39% of patients (9/29) recovered kidney function prior to hospital discharge.

Conclusions: Patients requiring MARS frequently have AKI warranting the use of concomitant CKRT, which is associated with a high rate of in-hospital and 1-year mortality.

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Acute liver failure and acute on chronic liver failure are associated with high morbidity and mortality especially when liver transplantation is not a viable option.[1] In the United States, fulminant liver failure is most commonly precipitated by drug injury from acetaminophen[2] whereas hepatitis C, alcoholism, and nonalcoholic fatty liver disease are the leading etiologies of liver cirrhosis.[3] Nephrologists are often asked to comanage patients with liver failure due to considerable risk for AKI, electrolyte derangements, and labile hemodynamics.[4,5] Patients requiring the use of kidney replacement therapy have a significantly reduced rate of survival compared to patients without AKI (57% vs. 93%).[6]

Select tertiary medical centers utilize extracorporeal liver support systems off-label as a bridging mechanism in the intensive care unit while waiting for liver transplantation.[7] These systems eliminate hydrophobic metabolites that accumulate during liver failure via chemical gradients and adsorption.[8] Modalities include MARS (Baxter, Deerfield, IL), Prometheus (Fresenius, Waltham, MA) fractionated plasma separation and adsorption system, single-pass albumin dialysis,

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selective plasma filtration therapy, and plasma exchange with hemodiafiltration.[1]

MARS consists of an albumin dialysate circuit in combination with hemodiafiltration.[7] A specialized high-flux filter allows water-soluble and protein-bound toxins to move across the membrane into the albumin circuit, which is detoxified using columns of activated charcoal and ion-exchange resin.[9] Remaining ammonium and other water-soluble toxins diffuse across the low-flux dialyzer for hemodiafiltration. MARS is approved by the US Food and Drug Administration for the treatment of drug overdose and poisonings in addition to HE due to decompensated liver disease.[10]

Previous studies have reviewed the efficacy of MARS for the treatment of various liver related conditions without extensive focus on kidney consequences. This study evaluated kidney-related outcomes of MARS in a retrospective cohort of patients over a 7-year period. Our aim was to characterize the indications, frequency, survival, and kidney recovery with MARS therapy. We further examined the effect of concomitant CKRT on survival and renal outcomes after MARS therapy in addition to the impact on liver biomarkers.

METHODS

A retrospective study reviewing consecutive hospitalized patients treated with MARS from January 1, 2014 through December 31, 2020, at Mayo Clinic Florida, a facility with a liver transplant program. Baseline characteristics of study participants including race and ethnicity (self-reported by participant), comorbidities, medications, treatment indications, laboratory results, use of kidney replacement therapy, and transplantation were obtained from the electronic medical record. Inclusion criteria consisted of patients of age 18 years or older, minimum of 1 MARS treatment of any length, and intensive care unit hospitalization. Patients receiving MARS in the outpatient setting for refractory pruritis were excluded. Institutional review board approval was obtained through the local ethics board. Data was collected using the REDCAP software. Primary aim evaluated in-hospital and 1-year mortality of patients receiving MARS with or without CKRT. Secondary aims included total number of MARS treatments, frequency of liver transplantation, impact of therapies on laboratory studies, and recovery of kidney function for patients necessitating CKRT.

All patients received MARS therapy using a Prismaflex (Baxter) dialysis machine in combination with MARS with the following parameters: dialysate rate 1000 ml/hr, replacement rate 1500 ml/hour, Prismaflex blood flow rate 200 ml/min, MARS albumin pump flow rate 200 ml/min, no extra fluid removal, temperature 37 °C, and duration 7 to 24 hours per physician discretion or timing of nursing shift changes. Each treatment utilizes PrismaSol 4K dialysate/replacement fluid, 16.7% albumin in 0.9% saline, MARS FLUX 2.1 dialyzer, diaFLUX 1.4 dialyzer, diaMARS AC250 carbon adsorber, and diaMARS IE250 ion exchanger. Pretreatment and intertreatment laboratory values were obtained including chemistry panel with ionized calcium, hepatic panel, ammonia, and coagulation panel. The patients received a minimum of 3 MARS treatments to determine responsiveness to therapy. The total number of MARS treatments was dictated by clinical response, the timing of liver transplantation, or deterioration from comorbid conditions. MARS was the only liver support system utilized at the investigation site during the study period. CKRT was performed using the NxStage System One S (Fresenius) machine set to continuous veno-venous hemofiltration with the following initiating parameters: blood flow rate 300 ml/min, replacement fluid rate 35 ml/kg/hour, PrismaSol 4K or 2K replacement fluid, hemofilter CAR-505, no anticoagulation, and variable net loss, The inpatient nephrology service was responsible for ordering and managing MARS and CKRT when consulted by the critical care team

Statistical Analysis

Numeric variables were summarized with the sample median and interquartile range. Categorical variables were summarized with the frequency and percentage of patients. For the primary analysis, we estimated the RR of in-hospital death among those who had concomitant CKRT versus no CKRT using a modified Poisson regression approach with robust error variance estimation.[11] Considering the low number of in-hospital deaths ($n = 14$) and to avoid including more than 1 variable for every 10 patients who experienced the outcome, we repeated our primary analysis adjusting for prespecified potential confounders one at a time (age, sex, chronic kidney disease, diabetes, hypertension, and liver cirrhosis or end-stage liver disease).[12,13]

The Kaplan-Meier method was used to estimate survival after MARS initiation according to concomitant CKRT status. We additionally estimated the RR of death within 1 year after MARS initiation with concomitant CKRT versus no CKRT using single variable and multivariable Cox regression censoring at the earlier of date of last follow-up or 366 days for those who had not died within 1 year after MARS initiation. The modified Poisson regression approach was used to estimate the RR of liver transplant receipt after MARS initiation with CKRT compared to no CKRT. Other comparisons using either the Wilcoxon rank sum test or the Fisher's exact test are described in the results.

All 95% CI and statistical tests were 2-sided. Statistical analyses and graphics were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, a total of 53 patients received MARS with 4 patients excluded from the analysis due to outpatient indication of refractory pruritis. Our cohort included 49 patients (67% female; 75% White) of which 29 patients (59%) required concomitant CKRT (Table 1). Timing of MARS initiation occurred simultaneously with CKRT initiation in 12 patients (41%) and after CKRT initiation in 17 patients (59%). Among the remaining 20 patients, 15 only received MARS and 5 received CKRT after MARS discontinuation. In these 5 patients, MARS was utilized for 3 to 5 days followed by CKRT within a 7-day timespan for 4 of the patients. Indications for initiation of CKRT included volume overload and refractory metabolic acidosis in setting of undifferentiated shock. Chronic kidney disease was present in 18% of MARS patients ($n = 9$) including 1 patient with end-stage kidney disease. Although HE was the most common indication for initiation of MARS (55%), the top 3 indications among the CKRT group included HE ($n = 14$), primary nonfunction or dysfunction of liver transplant ($n = 6$), and bridge to liver transplantation ($n = 6$) (Table 2). Duration of MARS treatments ranged from 6 to 8 hours for 14

Table 1. Baseline demographics and comorbidities at MARS initiation

Demographics/comorbidities	MARS without concomitant CKRT ($n = 20$)	MARS with concomitant CKRT ($n = 29$)	All MARS (N = 49)
Age, yrs	48 (43, 61)	57 (46, 66)	55 (44, 63)
Male gender	6 (30%)	10 (34%)	16 (33%)
Race			
American Indian/Alaska Native	0 (0%)	1 (3%)	1 (2%)
Asian	0 (0%)	1 (3%)	1 (2%)
Black or African American	3 (15%)	4 (14%)	7 (14%)
White	15 (75%)	20 (69%)	35 (71%)
Unknown/not reported	2 (10%)	3 (10%)	5 (10%)
Body mass index, kg/m^2	45.1 (39.0, 53.3)	47.5 (39.5, 58.8)	46.9 (39.5, 57.4)
Prior diagnosis of liver cirrhosis or end stage liver disease	12 (60%)	21 (72%)	33 (67%)
Alcohol abuse	8 (40%)	6 (21%)	14 (29%)
Hepatitis B diagnosis	1 (5%)	2 (7%)	3 (6%)
Hepatitis C diagnosis	3 (15%)	2 (7%)	5 (10%)
Nonalcoholic fatty liver disease	3 (15%)	11 (38%)	14 (29%)
Previous liver transplant	1 (5%)	5 (17%)	6 (12%)
TIPS procedure	2 (10%)	3 (10%)	5 (10%)
Esophageal varices history	9 (45%)	14 (48%)	23 (47%)
Ascites requiring paracentesis			
No	12 (60%)	19 (66%)	31 (63%)
Yes	7 (35%)	10 (34%)	17 (35%)
Unknown	1 (5%)	0 (0%)	1 (2%)
Spontaneous bacterial peritonitis history	3 (15%)	5 (17%)	8 (16%)
Chronic kidney disease	3 (15%)	6 (21%)	9 (18%)
Diabetes mellitus	4 (20%)	8 (28%)	12 (24%)
Heart failure	0 (0%)	0 (0%)	0 (0%)
Systemic hypertension	3 (15%)	11 (38%)	14 (29%)
Portal hypertension	10 (50%)	18 (62%)	28 (57%)
Peripheral vascular disease	0 (0%)	0 (0%)	0 (0%)
Depression or anxiety			
No	12 (60%)	25 (86%)	37 (76%)
Yes	7 (35%)	4 (14%)	11 (22%)
Unknown	1 (5%)	0 (0%)	1 (2%)
Tobacco use history			
No	11 (55%)	17 (59%)	28 (57%)
Yes	9 (45%)	11 (38%)	20 (41%)
Unknown	0 (0%)	1 (3%)	1 (2%)
Time from hospital admission to MARS initiation, d	2.5 (0.0, 4.0)	5.0 (1.8, 11.5)	4.0 (1.0, 8.3)

CKRT, continuous kidney replacement therapy; MARS, molecular adsorbent recirculating system; TIPS, transjugular intrahepatic portosystemic shunt.
Sample median (25th percentile, 75th percentile) is given for continuous data. Number (percentage) of patients is given for categorical data.

Table 2. Indication for MARS therapy

Indication	MARS without concomitant CKRT (n = 20)	MARS with concomitant CKRT (n = 29)	All MARS (N = 49)
Hepatic (portosystemic) encephalopathy	13 (65%)	14 (48%)	27 (55%)
Primary nonfunction or primary dysfunction of liver transplant	1 (5%)	6 (21%)	7 (14%)
Bridge to liver transplant	0 (0%)	6 (21%)	6 (12%)
Acute intoxication or overdose	1 (5%)	2 (7%)	3 (6%)
Acute severe alcoholic hepatitis	1 (5%)	0 (0%)	1 (2%)
Intractable pruritus in cholestasis	1 (5%)	0 (0%)	1 (2%)
Other	3 (15%)	1 (3%)	4 (8%)

CKRT, continuous kidney replacement therapy; MARS, molecular adsorbent recirculating system.
Number (percentage) of patients is given.

patients (29%), 12 hours for 7 patients (14%), 24 hours for 4 patients (8%), and mixed treatment lengths for 24 patients (49%). There were no observable differences in baseline laboratory values between MARS without CKRT versus MARS with CKRT, specifically for creatinine (1.06 vs. 1.09 mg/dl), ammonia (87.0 vs. 69.5 μmol/l), INR (2.4 vs. 2.8), alanine transaminase (95 vs. 97 U/l), aspartate transferase (118 vs. 142 U/l) and alkaline phosphatase whereas total bilirubin was higher in the MARS with concomitant CKRT group (12.7 mg/d compared to 3.1 mg/dl) (Supplementary Table S1).

Survival After MARS Initiation

The overall Kaplan-Meier survival probabilities after MARS according to concomitant CKRT status are shown in Figure 1. As demonstrated, overall mortality was much higher in the CKRT group compared to the no CKRT group. In-hospital mortality was 41% (n = 12) among patients who received CKRT and 10% (n = 2) among patients without CKRT (RR 4.15, 95% CI 1.04 to 16.52, P = 0.04). Similar results were observed when adjusted for prespecified patient characteristics one at a time (Table 3, all RR ≥3.76, all P ≤0.060). Within 1 year of MARS initiation, 59% of patients (n = 17) who received CKRT died compared to 25% (n = 5) among those who did not receive CKRT (unadjusted RR 2.92, 95% CI 1.08 to 7.94, P = 0.035). The association of CKRT with death within 1 year remained statistically significant after adjusting for age, sex, chronic kidney disease, diabetes mellitus, hypertension, and end-stage liver disease (adjusted RR 2.95, 95% CI 1.03 to 8.50, P = 0.045).

Secondary Outcomes

When comparing patients with concomitant CKRT to those without CKRT, patients requiring CKRT had a longer time interval from date of admission to MARS initiation (median 5 vs. 2.5 days, P = 0.035), but had similar number of MARS treatments (Table 4, median 3 vs. 3 days, P = 0.51). Sixty-one percent of MARS patients (n = 30) were approved for liver transplantation, and receipt of a liver transplant after MARS initiation occurred in 45% of patients (n = 13) with concomitant CKRT compared to 35% of patients (n = 7) without CKRT. This association was not statistically significant (modified

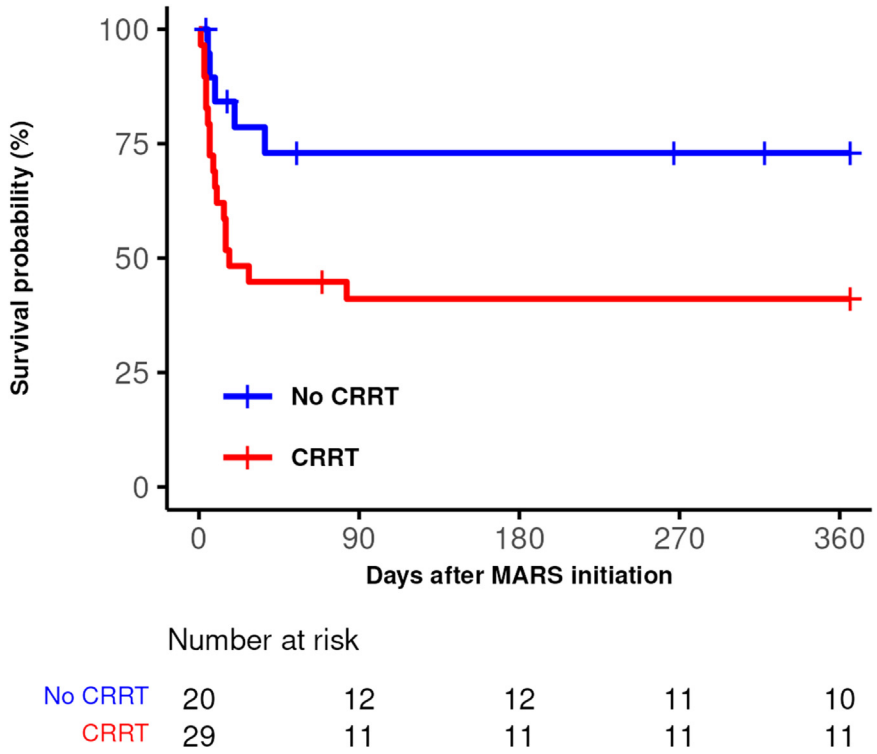

Figure 1. Survival probability after MARS initiation. CKRT, continuous kidney replacement therapy; MARS, molecular adsorbent recirculating system.

Table 3. Exploration of the impact of potentially confounding variables on the association of concomitant CKRT on in-hospital death following MARS initiation

	Association of concomitant CKRT with in-hospital death following MARS initiation	
Variables	RR (95% CI)	*P*
Unadjusted	4.15 (1.04, 16.52)	0.044
Adjusted for:		
- Age	3.85 (0.95, 15.62)	0.060
- Sex	4.24 (1.09, 16.47)	0.037
- History of chronic kidney disease	3.90 (1.01, 15.16)	0.049
- History of diabetes	3.76 (0.97, 14.54)	0.055
- History of hypertension	4.40 (1.01, 19.13)	0.048
- Prior diagnosis of liver cirrhosis/end stage liver disease	4.12 (0.99, 17.14)	0.052

CKRT, continuous kidney replacement therapy; MARS, molecular adsorbent recirculating system; RR, relative risk.
Relative risks (RR) of in-hospital mortality (yes or no) and corresponding 95% confidence intervals (CI) were estimated using modified Poisson regression with robust error variance estimation.

Poisson RR 1.28, 95% CI 0.62 to 2.63, $P = 0.50$). Overall, ammonia levels dropped by 45.9% 24 hours after MARS initiation (interquartile range -68.1% to 0.0%) (Supplementary Table S2, Supplemental Figure S1), but there was no evidence of a difference between CKRT and no CKRT in absolute change in ammonia test ($P = 0.75$) or percent change in ammonia ($P = 0.77$).

DISCUSSION

Our study is the first to describe the outcomes of MARS and CKRT. We found a higher probability for in-hospital mortality in patients requiring concomitant CKRT with MARS compared to MARS alone (RR 4.15, 95% CI 1.04–16.52, $P = 0.04$). The in-hospital mortality rate for CKRT with MARS was 41% (12 of 29) versus 10% (2 of 20) for MARS alone. We identified a lower in-hospital mortality for MARS patients compared to the literature averaging approximately 50% mortality rate.[14,15] In comparison, in-hospital mortality rates have been reported as high as 84% for patients requiring CKRT[16] although most studies approximate mortality closer to 50% to 60%.[17–19] Notably, patients with cirrhosis requiring initiation of kidney replacement therapy are at high risk for death within 6 months (85%), especially if not a candidate for liver transplantation.[20] The overall reduced in-hospital mortality observed in our study may be attributable to 41% of total MARS patients proceeding to liver transplant.

Table 4. Outcomes following MARS therapy

Outcomes	MARS without concomitant CKRT ($n = 20$)	MARS with concomitant CKRT ($n = 29$)	All MARS ($N = 49$)
Number of MARS treatments	3.0 (2.0, 4.3)	3.0 (2.5, 5.0)	3.0 (2.0, 5.0)
Liver transplant event(s)	7 (35%)	13 (45%)	20 (41%)
Liberation from KRT by hospital discharge		9 (31%)	
Averaged time to recovery of kidney function by hospital discharge, days, range of days in parenthesis		15 (11, 17)	
In-hospital death	2 (10%)	12 (41%)	14 (29%)
Death within 1 year from MARS initiation	5 (25%)	17 (59%)	22 (45%)

CKRT, continuous kidney replacement therapy; KRT, kidney replacement therapy; MARS, molecular adsorbent recirculating system.

Over the 7-year study period, frequency of MARS usage increased with each consecutive year ranging from only 1 treatment in 2014 up to 14 patients in 2020. Limited utilization of MARS occurred during the first 3 years due to constraints of needing trained nursing staff and faculty development in addition to inertia to incorporate extracorporeal liver support into clinical practice. No other liver support systems were available at our center during this time interval, and the number of liver transplants remained stable at approximately 150 per year. The most common indications for MARS were HE (55%) followed by dysfunction of liver transplant (14%) and bridge to liver transplant (12%). Usage of MARS to facilitate liver transplantation ($n = 17$), either pretransplant or posttransplant, is an off-label use of the system, which has been described favorably in the literature.[21–23] However, attempts to perform clinical trials evaluating this modality for this indication have fallen short due to challenges with study design and severity of illness of enrolled patients.[24] Nearly two-thirds of patients receiving liver transplantation had concomitant preoperative CKRT leading to higher Model for End-Stage Liver Disease scores. Interestingly, nearly all patients requiring CKRT were receiving vasopressors (93% vs. 50%) due to shock and had much higher total bilirubin level (12.7 vs. 3.1 mg/dl) at the time of MARS initiation potentially hinting at a superimposed cholemic nephropathy or bile cast nephropathy in addition to acute tubular necrosis.[25,26]

The estimated prevalence of AKI in liver cirrhosis ranges from 20% to 50%[27,28] dependent on patient characteristics such as the presence of ascites or sepsis and discrepancies in the definition of AKI. Most cirrhotics with AKI will be volume responsive; however, patients without response to volume challenge likely have hepatorenal syndrome or acute tubular necrosis.[29–31] Given the critical nature of our study patients necessitating MARS, no kidney biopsies were obtained to confirm the etiology of AKI; however, MARS patients requiring CKRT ($n = 27$) were at high risk for developing ischemic acute tubular necrosis given requirement of vasopressors to stabilize hemodynamic profile. Limited difference in creatinine levels were seen between patients

receiving concomitant CKRT versus no kidney replacement therapy. Our study collected laboratory data at the time of admission and pre/post MARS implementation in order to characterize the impact of MARS on common biomarkers. Use of cystatin-C or urinary biomarkers were not routinely measured during the investigation period. Seventeen of 29 patients (59%) requiring concomitant CKRT with MARS started CKRT prior to MARS most commonly for hypervolemia and/or refractory metabolic acidosis which impacted interpretation of pre-MARS creatinine levels. Secondary analysis showed that 31% of these patients were liberated from dialysis therapy by time of discharge from the hospital. All of these patients with kidney recovery ($n = 9$) received a liver transplant.

Limitations to our study include the single center design impacting the generalizability of the results and allowing for treatment bias based on several off-label uses of MARS ($n = 18$). The lack of a comparator cohort of matched patients with MARS indications but receiving the usual standard of care is not available with the retrospective approach. Furthermore, the number of MARS treatments provided, and duration of treatments were not standardized because physicians are given discretion in determining the necessity of extracorporeal therapy. Heterogeneity of MARS prescriptions exists because real-world logistical considerations may conflict with the US Food and Drug Administration indicated 7 to 8 hour treatment window.[32] Non-CKRT patients receiving MARS continuously for extended duration would also be exposed to continuous hemodiafiltration weakening separation between the 2 study groups. However, this distinction could be further studied in larger prospective clinical investigations.

In conclusion, MARS offers an extracorporeal modality for rescue support of patients with liver failure. Given the high rate of AKI in patients with decompensated liver disease, MARS patients frequently require CKRT for clearance and volume control which in combination is associated with a high rate of in-hospital and 1-year mortality. Future studies are needed to better examine utility of MARS as a bridging therapy for liver transplantation and impact on kidney function.

DISCLOSURES

All the authors declared no competing interests or source of funding for this study.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Change in ammonia from pre-MARS to 24 hours post-MARS according to concomitant CKRT status and indication for MARS.

Table S1. Laboratory studies at baseline.

Table S2. 24-hour change in ammonia.

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