

## ORIGINAL ARTICLE

# The effect of molecular adsorbent recirculating system treatment on survival, native liver recovery, and need for liver transplantation in acute liver failure patients\*

Taru Kantola,<sup>1</sup> Anna-Maria Koivusalo,<sup>1</sup> Krister Höckerstedt<sup>2</sup> and Helena Isoniemi<sup>2</sup>

1 Department of Anaesthesiology and Intensive Care Medicine, Surgical Hospital of Helsinki, Helsinki University Hospital, Finland

2 Department of Transplantation and Liver Surgery, Surgical Hospital of Helsinki, Helsinki University Hospital, Finland

## Keywords

acute liver failure, liver transplantation, molecular adsorbent recirculating system, survival.

## Correspondence

Dr. Taru Kantola, Department of Anaesthesiology and Intensive Care Medicine, Helsinki University Hospital Box 263, FIN-00290 HUCH, Helsinki, Finland. Tel.: +358 40 843 1551; e-mail: taru.teikari@gmail.com

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## Summary

Acute liver failure (ALF) is a medical emergency. Molecular adsorbent recirculating system (MARS), an artificial liver support system, can partly compensate for the detoxifying function of the liver by removing toxins from blood. To analyze the efficacy of MARS treatment, the outcomes of 113 ALF patients, treated with MARS between 2001 and 2007, were compared with a historical control group of 46 ALF patients treated without MARS between 1995 and 2001. Overall survival of transplanted patients was 94% in the MARS group and 77% in the control group ( $P = 0.06$ ). Without transplantation, survival was 66% and 40% ( $P = 0.03$ ), respectively. However, the etiological distribution of ALF differed significantly between the groups. In ALF patients with unknown etiology, groups were comparable at baseline; 91% and 69% of transplanted patients survived the MARS and control groups and the native liver recovered in 20% and 8% of the patients, respectively. Of the originally non-encephalopathic patients of unknown etiology, 36% underwent liver transplantation in the MARS group compared to 100% in the control group. Interpretation of the results was difficult in toxic etiology patients on account of differing baseline statuses. MARS treatment might partly explain the trend toward increased survival of ALF patients with unknown etiology.

## Introduction

Acute liver failure (ALF), a life-threatening medical emergency, is defined as a condition in which a patient with no previous liver disease develops a rapidly progressing coagulation deficiency and altered mental status, i.e., hepatic encephalopathy [1,2]. Other characteristics include cholestasis, hypoglycemia, acid-base and electrolyte imbalances, renal impairment, hemodynamic instability [3], and susceptibility to infections [4,5]. Death is usually caused by a fatal rise in intracranial pressure, an uncontrollable infection, or multi-organ failure [6]. Without liver transplantation (Ltx), mortality in ALF is 60%–90%, depending on the etiology of the condition [7,8]. Despite improved intensive care unit (ICU) treatment

and a possibility of Ltx, mortality resulting from ALF remains at 20%–40% [6–13]. Unfortunately, donor organs are scarce, and some patients die while awaiting a suitable graft [8,9]. After successful Ltx, patients require lifelong follow-up by medical professionals and immunosuppressive medication. Additionally, some patients have a small likelihood of native liver recovery or contraindications to Ltx. Therefore, new treatments that avoid transplantation are being investigated.

Molecular adsorbent recirculating system (MARS) treatment is an artificial liver support system that can partly compensate for the detoxifying function of the liver by removing albumin-bound and water-soluble toxins from the blood [14–16]. Thus, in theory, MARS treatment can sustain the patient until a graft becomes

available or the native liver recovers. To date, the effect of MARS treatment on patient outcome has been studied mainly in acute-on-chronic liver failure patients, and there are no controlled studies addressing ALF patients.

The aim of this study was to determine if MARS treatment has an effect on survival, native liver recovery, or the need for Ltx in 113 ALF patients compared with a historical control group of 46 ALF patients. All patients were treated with the same best standard medical therapy in an ICU setting.

## Patients and methods

This controlled single-center study was conducted with a prospectively collected group of 113 consecutive adult ALF patients who received MARS treatment in our ICU during the period from May 2001 to March 2007. Comparisons were made to a retrospectively collected historical control group of 46 consecutive adult ALF patients who required ICU treatment from January 1995 to April 2001. All patients had life-threatening ALF and were evaluated for Ltx. Our liver disease-specialized ICU is the only transplantation center in Finland, and all critical ALF cases are referred to our tertiary liver unit. The ethics committee of Helsinki University Hospital approved the study.

## Monitoring and standard medical therapy

The main principles of standard medical therapy were the same in the MARS and the control groups. Patients were monitored with arterial and central venous catheter. Swan-Ganz catheter was used as necessary. All nephro- and hepatotoxic medications were discontinued. The mean arterial pressure was maintained above 65 mmHg with fluid resuscitation and vasoactive medication (mainly noradrenaline infusion). Vigilant surveillance of infection and prophylactic antibacterial and antifungal therapies were used. The level of consciousness was monitored, and sedatives were not used in nonintubated patients. If the grade of encephalopathy was 3 or 4, the patient was sedated, intubated, and mechanically ventilated. A regimen of lactulose, proton pump inhibitors, and *N*-acetylcysteine was used, and normoglycemia was maintained. Enteral nutrition was employed where possible, and urinary output was monitored. Initial laboratory tests evaluating the etiology and severity of ALF were extensive. Coagulation parameters were assessed daily, and clotting abnormalities were corrected only in cases of active bleeding or invasive procedures. Blood counts, creatinine, urea, bilirubin, ammonia, and liver enzymes were analyzed daily. Blood gases, electrolytes, hemoglobin, and glucose were assessed hourly.

## Extracorporeal treatments in the control group

Renal replacement therapy (mainly continuous venovenous hemodiafiltration) was used in the control group if renal failure ensued. Before the era of MARS treatment, normal-volume plasmapheresis was used for some patients if their clinical condition deteriorated despite the best standard medical care. High-volume plasmapheresis has been used since 1998 for 12 patients enrolled in an ongoing randomized multi-center study. Our center ceased to participate in the study when MARS became available. Inclusion criteria for high-volume plasmapheresis were hyperacute or acute liver failure with hepatic encephalopathy grades 2–4.

## MARS treatment

The criterion for initiating MARS treatment was the rapidly deteriorating clinical condition of the patient despite the best possible standard medical therapy (described above). Additionally, patients either fulfilled the criteria for high urgent Ltx [17] or had ingested a lethal amount of a known toxin with a high probability of death on account of liver failure [18,19]. In some cases, MARS treatment was commenced without encephalopathy, if patients had ingested a lethal amount of toxin and laboratory markers indicated progressive liver failure despite the best possible standard medical therapy. Each MARS session was planned to last 22 h, and sessions were continued daily until the native liver recovered, the patient received a transplant, or treatment was discontinued on account of irreversible organ damage. The flow rates of the blood and albumin circuits were 150 ml/min, and the flow rate of bicarbonate-buffered dialysate was 500 ml/min. Ultrafiltration was adjusted to control intravascular volume balance. Anticoagulant (daltaparin or epoprostenol) was administered when permitted by the coagulation status. A more detailed description of the operational principles of the MARS machine can be found in our previous article [19].

## Measurements

For the MARS group, from 2001 onwards, we have prospectively collected data from every patient and treatment session on a specially designed data collection sheet. All data from the control group were retrieved from patient file archives. In the MARS group, the baseline demographic, clinical, and laboratory data were recorded at the beginning of each MARS session. In the control group, the first data-collecting point was arrival at the ICU. The last grade of encephalopathy was recorded either at the end of the last MARS treatment, at discharge from

the ICU for the control group, before transplantation, or before death. The model for end-stage liver disease (MELD) score was calculated applying the standard formula by UNOS [20–22]. Survival, native liver recovery (defined as survival for at least 3 months without Ltx), and the need for Ltx were recorded. All patients were followed for at least 6 month.

## Statistics

All data were analyzed with SPSS for Windows, version 15.0. Pearson's chi-square and Fisher's exact tests were used to compare outcomes and binomial results between groups. The Mann–Whitney *U*-test was employed to analyze scale measurements between groups. A *P* value  $\leq 0.05$  was considered statistically significant. The Kaplan–Meier method was used for survival curves, and the difference between groups was analyzed with the log-rank test.

## Results

### Characteristics and comparability of groups

The demographics, clinical conditions, and laboratory parameters for the MARS and control groups are shown in Table 1. Three subgroups were formed according to the etiology of ALF, i.e., unknown, toxic, and others with a known etiology. The toxic group was then subdivided into paracetamol-toxicity patients and nonparacetamol toxicity-related patients (toxicity on account of another drug or toxin). The etiological distribution of ALF differed substantially between the MARS and control groups ( $P = 0.002$ ; Fig. 1). Toxic etiology was the most common in the MARS group (56%) and unknown etiology in the control group (57%) (Fig. 1). ALF of other known etiology, the third subgroup, included patients with pregnancy-related ALF, viral hepatitis, ischemia, trauma, and Budd-Chiari syndrome.

The mean number of MARS treatments per patient was 2.9 (range 1–12), and the mean duration of one session was 15.2 h ( $\pm 4.6$  h). A contraindication to Ltx existed in 14% (16/113) of patients in the MARS group and 13% (6/46) of patients in the control group at the beginning of treatment. Contraindications included substance abuse problems, serious psychiatric illness, serious concomitant disease (e.g., malignancy), and old age (over 80 years). In addition, contraindications that developed during treatment included serious uncontrollable infection in 4% (5/113) of the MARS patients and 7% (3/46) of the control-group patients, and multi-organ failure or brain death in 7% (8/113) of the MARS patients and 11% (5/46) of the control-group patients.

The control group was analyzed and patients receiving high-volume, normal-volume, and no plasmapheresis

were compared with each other. There were no statistically significant differences among these groups in the distribution of ALF etiology, survival, number of transplantations, or native liver recovery rate.

### Overall survival, native liver recovery, and need for liver transplantation in the MARS and control groups

There was no statistically significant difference in survival between the MARS and the control group patients (Fig. 2). At 28 days, survival was 80% (90/113) in the MARS group and 72% (33/46) in the control group. At 6 months, survival was 75% (85/113) in the MARS group and 61% (28/46) in the control group ( $P = 0.07$ ). In patients who underwent Ltx, survival was 94% (31/33) in the MARS group and 77% (20/26) in the control group ( $P = 0.06$ ). Survival without Ltx was 66% (53/80) in the MARS group and 40% (8/20) in the control group ( $P = 0.03$ ). The percentage of all treated patients who died on account of tentorial herniation was 4% (4/113) in the MARS group and 15% (7/46) in the control group ( $P = 0.014$ ).

In the MARS group, the native liver recovered in 49% (55/113) of patients, compared with 17% (8/46) in the control group ( $P < 0.001$ ). Twenty-nine percent (33/113) of patients received Ltx in the MARS group compared with 57% (26/46) in the control group ( $P = 0.001$ ).

These overall results include all patients with toxic, unknown, and other known etiologies of ALF. The small other ALF subgroup (Table 1.) consisted of heterogeneous group of different ALF etiologies in the MARS and control group and therefore these groups were not analyzed or compared in more detail.

### Subgroup analysis according to etiology

#### Unknown etiology

With regard to demographics, clinical state, and laboratory parameters, as well as the distribution of hepatic encephalopathy grades, patients with unknown etiology were comparable between the two groups at baseline (Table 1; Fig. 3c). The mean MELD scores were  $34 \pm 6$  and  $36 \pm 9$  in the MARS and control groups, respectively.

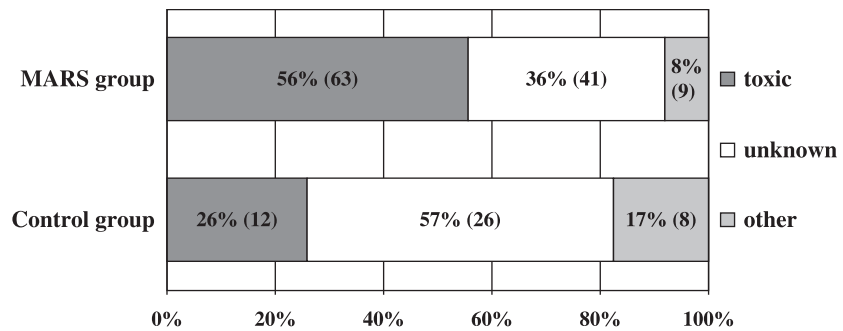
The overall survival was 71% (29/41) in the MARS group and 50% (13/26) in the control group ( $P = 0.09$ ). The native liver recovered in 20% (8/41) of the MARS patients and 8% (2/26) of the control patients (Fig. 4). Fifty-six percent of patients (23/41) underwent Ltx in the MARS group and 62% (16/26) in the control group. Six-month patient survival following transplantation was 91% (21/23) in the MARS group and 69% (11/16) in the control group ( $P = 0.1$ ) (Fig. 5). The mean time on the transplantation waiting list was  $4.8 \pm 7.6$  days in the

**Table 1.** Demographic, clinical state, and laboratory data of patients at the beginning of treatment.

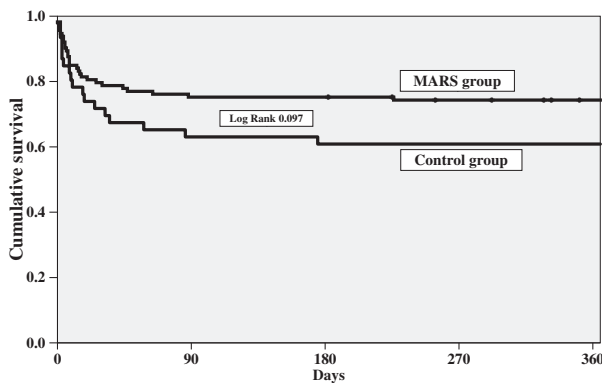
	Toxic etiology					
	Paracetamol-related			Nonparacetamol-related		
	MARS	Control	P	MARS	Control	P
<b>Demographic data</b>	MARS	Control	P	MARS	Control	P
Number of patients (n)	113	46		32	6	
Age in years (±SD)	45 (4)	40 (14)	NS	39 (14)	54 (13)	0.019
Male % (n)	41% (46)	35% (16)	NS	41% (13)	0%	0.076
BMI (±SD)	26 (5)	27 (6)	NS	25 (5)	30 (4)	0.011
Contraindication to Ltx % (n)	14% (16)	13% (6)	NS	16% (5)	16% (1)	NS
MARS treatments/patients (±SD)	2.9 (1.9)	0		2.3 (1.3)	0	3.1 (1.9)
Mechanically ventilated % (n)	33% (37)	33% (15)	NS	28% (9)	33% (2)	NS
Vasoactive-infusion used % (n)	31% (35)	33% (15)	NS	41% (13)	33% (2)	NS
Renal insufficiency % (n)	35% (40)	44% (20)	NS	34% (11)	50% (3)	NS
MELD-score (±SD)	29 (10)	35 (8)	0.02	23 (10)	35 (9)	0.016
<b>Encephalopathy grade</b>						
Before treatment (±SD)	1.8 (1.5)	2.0 (1.4)	NS	1.4 (1.6)	2.0 (1.3)	NS
After treatment (±SD)	1.4 (1.7)	2.6 (1.7)	P < 0.001	1.0 (1.6)	2.5 (2.0)	0.088
Hemoglobin g/l (±SD)	112 (21)	114 (21)	NS	114 (22)	125 (8)	NS
Platelets ×10 <sup>9</sup> (±SD)	156 (91)	143 (85)	NS	138 (75)	138 (40)	NS
Creatinine μmol/l (±SD)	137 (157)	152 (149)	NS	152 (230)	203 (242)	NS
Urea mmol/l (±SD)	8.2 (7.0)	10.1 (9.8)	NS	6.5 (6.0)	9.0 (7.1)	NS
NH <sub>4</sub> -ion μmol/l (±SD)	95 (75)	102 (66)	NS	79 (55)	114 (45)	0.078
Bilirubin μmol/l (±SD)	289 (231)	355 (210)	NS	104 (170)	221 (169)	0.017
ASAT U/l (±SD)	2.537 (4.731)	3.415 (7.735)	NS	4.015 (1.317)	5.025 (8.067)	NS
ALAT U/l (±SD)	2.233 (3.026)	1.925 (2.757)	NS	3.653 (3.731)	3.815 (3.730)	NS
γ-GT U/l (±SD)	189 (276)	127 (130)	NS	155 (165)	253 (283)	NS
TT (%)	24 (16)	19 (11)	NS	27 (19)	18 (13)	NS
				MARS	Control	P
				31	6	
				47 (15)	49 (10)	NS
				33% (2)	55% (17)	NS
				25 (7)	23 (12)	NS
				16% (6)	0%	NS
				3.1 (1.9)	0	3.1 (2.1)
				29% (9)	33% (2)	NS
				26% (8)	33% (2)	NS
				32% (10)	50% (3)	NS
				28 (11)	38 (5)	0.043
				1.8 (1.6)	2.7 (1.5)	NS
				1.7 (1.8)	2.5 (2.0)	NS
				118 (17)	120 (17)	NS
				172 (96)	168 (113)	NS
				123 (105)	235 (236)	NS
				8.6 (8.2)	14.0 (15.0)	NS
				120 (107)	130 (60)	NS
				289 (234)	397 (146)	NS
				2.627 (5.578)	1.747 (1.862)	NS
				1.968 (2.620)	1.189 (823)	NS
				227 (340)	73 (63)	NS
				27 (18)	22 (16)	NS
				MARS	Control	P
				41	26	
				48 (13)	45 (14)	NS
				32% (13)	31% (8)	NS
				27 (5)	26 (5)	NS
				20% (8)	31% (8)	NS
				3.1 (2.1)	0	
				34% (14)	31% (8)	NS
				27% (11)	28% (7)	NS
				37% (15)	42% (11)	NS
				34 (5)	36 (9)	NS
				MARS	Control	P
				2.0 (1.4)	1.9 (1.4)	NS
				1.5 (1.7)	2.6 (1.6)	0.01
				109 (20)	111 (23)	NS
				167 (101)	137 (68)	NS
				131 (120)	125 (96)	NS
				8.4 (6.3)	9.6 (9.5)	NS
				90 (51)	99 (77)	NS
				424 (178)	400 (214)	NS
				1.463 (3.331)	1.577 (3.276)	NS
				1.467 (2.491)	1.305 (2.046)	NS
				156 (149)	117 (92)	NS
				18 (9)	19 (11)	NS

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; BMI, body mass index (weight in kg/height in m<sup>2</sup>); γ-GT, gamma glutamyltransferase; TT (%), measure of coagulation status (coagulation factors II, VII, and X); normal range, 70%–130%.

All encephalopathy and laboratory values are expressed as mean (±standard deviation).



**Figure 1** Etiological distribution of acute liver failure patients in the molecular adsorbent recirculating system (MARS) and control groups.

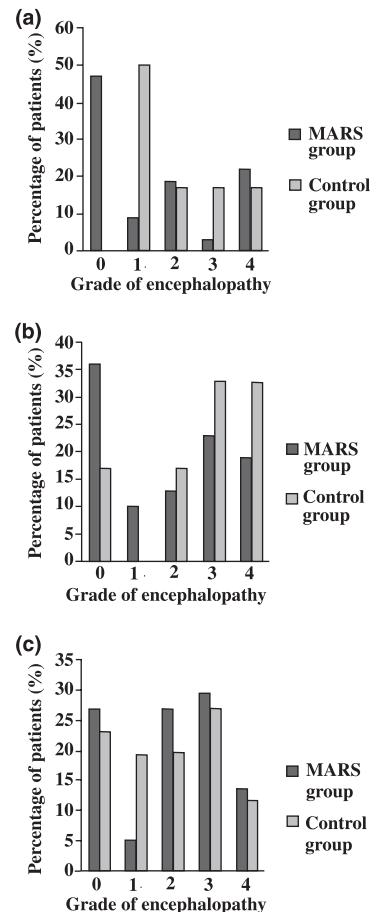


**Figure 2** Kaplan–Meier survival curves for all patients with acute liver failure.

MARS group and  $3.1 \pm 3.6$  days in the control group (ns). Two transplanted patients in the MARS group and three transplanted patients in the control group died of multi-organ failure or sepsis. In addition, in the control group, two transplanted patients died of tentorial herniation.

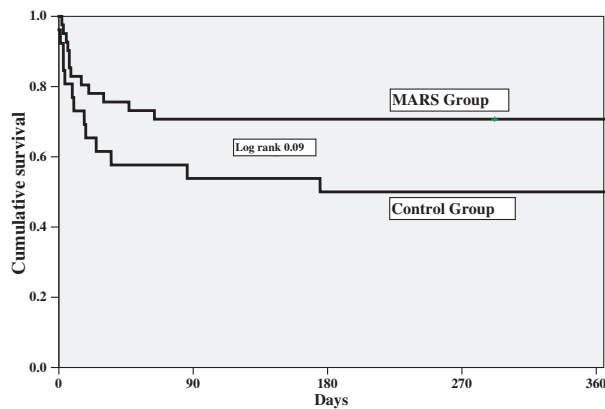
Analysis of nonencephalopathic patients at baseline showed a survival rate of 82% (9/11) in the MARS group and 50% (3/6) in the control group. A new liver was transplanted into 36% (4/11) of these patients in the MARS group, whereas all patients with no initial encephalopathy (6/6) received a transplant in the control group ( $P = 0.035$ ). The 6-month survival of these transplanted patients was 100% (4/4) in the MARS group versus 50% (3/6) in the control group. Death after Ltx was caused by tentorial herniation in one patient and sepsis in two control patients.

The demographic and clinical data of patients in both groups with encephalopathy grade 2 or higher at baseline were comparable including the mean MELD scores ( $35 \pm 7$  for MARS group versus  $33 \pm 8$  for control group). The survival rate of MARS group patients was 68% (19/28), whereas 40% (6/15) survived in the control group ( $P = 0.078$ ). Ltx was performed on 64% (18/28) of



**Figure 3** Grade of hepatic encephalopathy at the beginning of treatment. (a) Paracetamol-related toxic etiology acute liver failure (ALF) subgroups; (b) nonparacetamol-related toxic etiology ALF subgroups; (c) unknown etiology ALF subgroups.

the MARS group patients and 40% (6/15) of the control group patients ( $P = 0.126$ ). Three patients (11%) in the MARS group and four patients (27%) in the control group became untransplantable during treatment, and the native liver recovered in three (11%) MARS patients and two (13%) control patients.



**Figure 4** Survival in acute liver failure (ALF) of unknown etiology patients subgroup.

#### Toxic etiology

The percentages of paracetamol-related toxic etiology cases were approximately the same in the two groups: 51% (32/63) in the MARS group and 50% (6/12) in the control group. Other drugs, such as disulfiram, nimesulide, anti tuberculosis medications, antibiotics, and chemotherapeutic agents were the cause of toxicity-related ALF in 33% (21/63) of patients in the MARS group and 42% (5/12) of patients in the control group. Mushroom poisoning (*Amanita phalloides*) and herbal products caused liver failure in 16% (10/63) of the patients in the MARS group and 8% (1/12) of the patients in the control group.

#### Paracetamol-related toxic etiology

The demographic data and clinical state at baseline differed between groups (Table 1). MARS-treated patients ( $n = 32$ ), had significantly lower mean MELD scores compared with the controls ( $n = 6$ ). Additionally, at base-

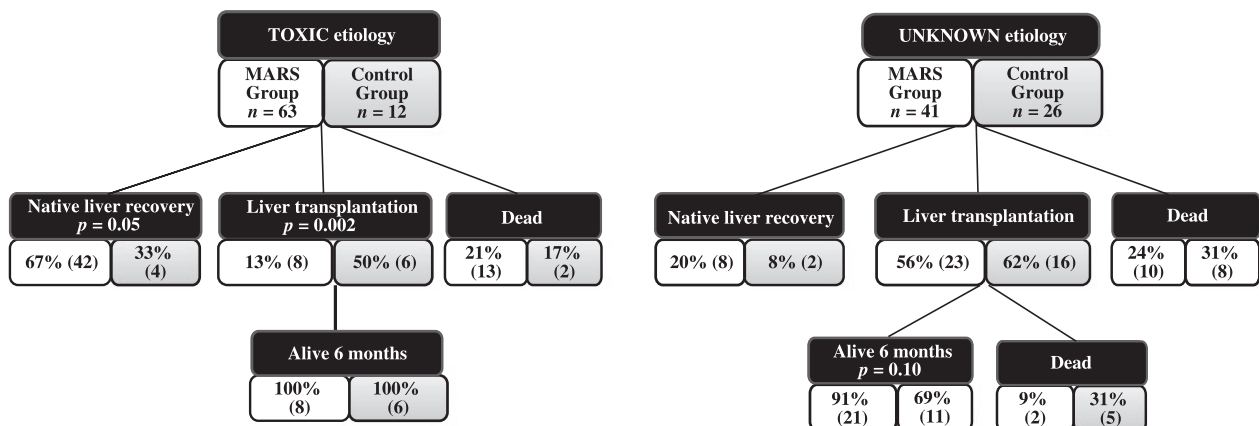
line, 47% (15/32) of the MARS group patients were non-encephalopathic, while all six control patients had encephalopathy (Fig. 3a). During treatment, the mean grade of encephalopathy decreased in the MARS group but increased in the control group (Table 1). Six-month survival was 84% (27/32) in the MARS group and 67% (4/6) in the control group (ns). The native liver recovered in 81% (26/32) of the MARS patients and 33% (2/6) of the control patients ( $P = 0.031$ ). In the MARS group, one patient (3%) received Ltx, compared with two (33%) in the control group. All three transplanted patients survived (Fig. 5).

In a subgroup of patients with encephalopathy grade 2 or higher at baseline, MARS patients ( $n = 14$ ) had lower mean MELD scores compared with control patients ( $n = 3$ ),  $23 \pm 13$  vs.  $35 \pm 14$ , respectively. Sixty-four percent (9/14) of MARS patients survived for 6 months, whereas only one patient survived in the control group. The native liver recovered in 57% (8/14) of the MARS patients and in one of the three control patients.

#### Nonparacetamol-related toxic etiology

Patients with nonparacetamol-related toxic etiology were otherwise comparable, but the mean MELD score was lower in MARS patients ( $P = 0.043$ ) (Table 1). Additionally, 36% (11/31) of MARS group patients were nonencephalopathic at baseline, while there was only one (17%) such patient in the control group (Fig. 3b).

Six-month survival was 74% (23/31) in the MARS group and 100% (6/6) in the control group (ns). In the MARS group, all nine of the amanita mushroom-poisoning patients survived. Also in the MARS group, half of the nonsurviving patients suffered from toxicity resulting from either a chemotherapeutic agent or an anti tuberculosis antibiotic; Ltx was contraindicated in these patients on account of the underlying diseases.



**Figure 5** Effect of molecular adsorbent recirculating system (MARS) treatment on patient outcome in the toxic and unknown etiology subgroups.

The native liver recovered in 52% (16/31) of MARS patients and in 33% (2/6) of control patients ( $P = \text{ns}$ ). Twenty-three percent (7/31) of patients in the MARS group received Ltx compared with 67% (4/6) in the control group ( $P = 0.05$ ), and all transplanted patients survived (Fig. 5).

In the MARS group all 11 nonencephalopathic patients at the beginning of treatment survived, but two of them underwent transplantation. The only nonencephalopathic control patient had a native liver recovery.

Patients with encephalopathy grade 2 or higher did not differ significantly at baseline. Survival was 53% (9/17) in the MARS group and 100% (5/5) in the control group (ns). Liver transplantation was performed in 24% (4/17) of the MARS patients and 80% (4/5) of the control patients ( $P = 0.039$ ). The native liver recovered in five of the MARS patients and in one control patient.

### Side-effects and complications

There were no serious complications associated with MARS treatment, but development of mild thrombocytopenia was observed. One patient in the control group died on account of transfusion-related acute lung injury.

### Discussion

Prior to this study, the effect of MARS treatment on ALF patient outcome had not been investigated in a controlled study. Our study was the first to include a large number of patients with ALF. Previously, only a handful of uncontrolled small case series (7–50 patients) on the subject had been published [23–27].

Our study, comprising data gleaned from 159 ALF patients, represents the largest patient population investigated thus far. However, on account of the large difference in etiological distribution, the MARS and control groups could not be compared directly in this study. Over the past decade, there has been a trend toward etiologies resulting in lower mortality, such as paracetamol toxicity, in many countries [28,29]. In the past, the majority of ALF cases were caused by an unknown etiology, but presently toxic etiologies are dominant in Finland, the United Kingdom, and the United States [8,9,12,30]. It has been stated that the etiology of ALF determines the prognosis and outcome [8,9,31,32]. In our study, subgroups according to ALF etiology were analyzed to compare patient with similar prognoses.

The most important findings of this study were in the unknown etiology subgroup, where the prognosis is usually the poorest. The clinical condition at baseline was comparable between the MARS and control groups. A trend toward better overall survival (71% vs. 51%) and

survival following Ltx (91% vs. 69%) was found, and there was also a slightly increased rate of native liver recovery (20% vs. 8%) in the MARS group compared with control patients. All originally nonencephalopathic control patients with unknown etiology were transplanted, and only half of these patients survived, whereas only one-third of MARS patients underwent Ltx, and all of them survived. One possible explanation for this is that during MARS treatment, the encephalopathy grade decreased, whereas in the control group it increased. In the control group, more patients became unsuitable for transplantation or were in poorer clinical condition prior to Ltx. A similar higher tendency toward survival (68% vs. 40%) was noted in the small subgroup of unknown etiology patients with grade  $\geq 2$  encephalopathy at the beginning of treatment. In addition, fewer patients became unsuitable for transplantation (11% vs. 27%) in the MARS group. As the unknown etiology MARS and control groups were comparable at baseline, it seems likely that MARS treatment played a role in improving the survival of these patients.

In both the MARS and control groups there were ALF patients with different etiologies without encephalopathy at baseline, but we emphasize that this was only the time point at which active treatment was started in our ICU. Peak encephalopathy grade during treatment was not recorded in this study. Our goal was to start MARS treatment early in the natural course of ALF to enable rapid removal of endogenous and exogenous circulating toxins and thus attempt to halt further liver cell damage. The basis for this goal stems from a Scandinavian study, which showed that 65% of patients who were nonencephalopathic when placed on the transplant list died if they did not receive a transplant [17,33]. How to identify those patients who will deteriorate remains the question of foremost importance, particularly with regard to ALF patients with unknown etiology. In the control group, half of the transplanted patients who did not have encephalopathy at baseline died after Ltx indicating that treatment decisions were made too late.

In contrast to situations in unknown etiology, in situations of toxic etiology, the baseline demographics and clinical condition of the patients differed considerably between the control and MARS-treated patients. Therefore, it is difficult to draw any conclusions based on our results in these subgroups.

In patients with paracetamol intoxication, a slight trend toward better outcome was observed in the MARS group, but it was probably attributable to the bias of better clinical condition at baseline rather than MARS treatment itself. This raises the question as to whether we should start MARS treatment in paracetamol-intoxicated patients

before they develop encephalopathy. Our study did not address whether MARS treatment improves outcome in nonencephalopathic paracetamol-intoxicated patients, as there were no such control patients in the study population. If the grade of encephalopathy was two or higher at baseline, the native liver recovered more often in MARS-treated paracetamol-intoxication patients; however, these subgroups were too small for any conclusions to be drawn.

In the nonparacetamol-related toxic etiology subgroup, MARS patients had a lower mean MELD score and grade of encephalopathy at the beginning of treatment, yet the survival was higher in the control group. This might be on account of the significantly higher percentage of transplantations (67% vs. 23%) in the control group. The majority of patients who died in this MARS subgroup had contraindications to transplantation on account of concomitant diseases with poor prognosis, such as cancer with chemotherapy treatment or active tuberculosis.

The percentage of patients who died on account of increased intracranial pressure was significantly lower in the MARS treatment group compared with the controls (4% vs. 15%). Additionally, in the paracetamol and unknown-etiology subgroups, the mean grade of hepatic encephalopathy decreased after MARS treatment was initiated, but not in any of the control subgroups. In these two groups, the risk of brain edema was perhaps lower in MARS-treated patients prior to Ltx, thus resulting in better survival following transplantation.

The number of patients referred to our ICU has increased substantially during the past decade, and the number of Ltx performed has more than doubled during this time. During the era of the control group, mainly the patients who could be considered for Ltx were admitted to our liver transplant unit. The reason for the increase in patient referrals is the increased overall knowledge of liver diseases. Also the introduction of MARS therapy as a possible detoxifying therapy has increased the number of patient referrals with toxic etiology to our ICU. Also, the percentage of toxic patients who are nonencephalopathic and in better clinical condition at the beginning of treatment has grown during the MARS era. We think that it is inappropriate to wait until encephalopathy develops before initiating MARS treatment if the ingested amount of toxin is lethal according to the literature.

To date, all of the randomized studies investigating the effectiveness of MARS treatment have focused on patients with acute decompensation of chronic liver failure, and have indicated that there are improvements in survival and laboratory parameters following treatment [34–36]. In review articles, MARS treatment has been considered an effective and safe treatment for life-threatening liver failure [37,38], although in a meta-analysis, MARS treat-

ment did not appear to reduce mortality significantly compared with the standard medical treatment [39].

There are no published controlled or randomized trials of ALF patients treated with MARS. Thus far, only case series involving very few patients have been published, with conflicting results. Improved survival and decreased need for Ltx have been reported [26]. Another study concluded that MARS is a futile tool in centers without active liver transplant support [27]. This study included acute exacerbations of chronic hepatitis B with only a few ALF patients without possibility of Ltx. Our MARS treatment protocol also differs from the other published series as they used only 6–8 h daily treatment, whereas our target has been to use MARS continuously in ALF patients.

The main shortcoming of this study is that MARS-treated patients were compared with historical control patients. Plasmapheresis, which was used in almost half of the control group patients, may also have introduced bias. During the past 12 years, although the main treatment protocols in our ICU have remained the same, intensive care management, the etiological distribution of ALF, and patient referral patterns have changed. All of these factors have undoubtedly improved patient survival during recent years. One of the biggest changes in ALF treatment in our ICU during the past decade has been the replacement of plasmapheresis by MARS treatment. Unfortunately, it has always been very difficult to conduct sufficiently powered, controlled studies on diseases that are characterized by high mortality and low incidence, such as ALF. In 1998, a multicenter study on high-volume plasmapheresis was launched but remains unpublished, further demonstrating the difficulty of conducting randomized, controlled clinical studies involving ALF patients.

In conclusion, the etiological distributions of ALF cases and referral patterns to our ICU have changed markedly over the past 12 years. We began to treat toxic ALF patients with more priority following the advent of MARS treatment, and, therefore, the clinical condition of patients at baseline differed considerably between the two treatment groups, making it difficult to interpret results. As those ALF patients with unknown etiology were comparable at baseline, MARS treatment might partly explain the trend toward better survival in these patients. Additionally, we noted that the worsening of hepatic encephalopathy was halted more often in MARS-treated patients, which might explain increased survival following Ltx.

## Authorship

TK, designed study, collected and analyzed data, and wrote the article; AMK, designed study, collected data and



co-wrote the article; KH, designed study; HI, designed study and co-wrote the article.

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