Bleeding Complications Associated with the Molecular Adsorbent Recirculating System: a retrospective observational study

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ABSTRACT

Background: The molecular adsorbent recirculating system (MARS) is an artificial liver support system that supports excretory liver function in patients with liver failure and is used as bridge therapy for patients waiting for liver transplantation. However, MARS may increase the tendency for bleeding. The objective of this study was to determine how MARS affects coagulopathy and identify specific factors associated with bleeding complications.

Methods: We retrospectively analyzed data from 15 patients undergoing a total of 36 MARS sessions. Complete blood count, coagulation profiles, and blood chemistry values were compared before and after MARS. To identify pre-MARS factors associated with increased bleeding after MARS, we divided patients into bleeder and non-bleeder groups and compared their pre-MARS laboratory values.

Results: MARS significantly reduced bilirubin and creatinine levels. MARS also increased prothrombin time and activated partial thromboplastin time and reduced fibrinogen, thus negatively impacting coagulation. Seven patients had bleeding complications and were classified into the bleeder group. Pre-MARS hemoglobin was significantly lower in the bleeder group (8.3 mg/dl) than in the non-bleeder group (10.0 mg/dl, P=0.014). When comparing the upper and lower 25% of MARS sessions based on the hemoglobin reduction rate, hemoglobin reduction was significantly greater in MARS sessions involving patients with low pre-MARS hemoglobin and factor V (P=0.008 and P=0.032, respectively).

Conclusions: MARS appears to alter coagulation-related factors and increase the risk of bleeding complications. However, individual differences among patients were large, and various factors, such as low hemoglobin and factor V levels, appear to be involved.
Keywords: albumin dialysis; bleeding complication; coagulopathy; extracorporeal liver support; molecular adsorbent recirculating system; liver failure
BACKGROUND

The treatment of acute liver failure encompasses symptomatic supportive care as a medical treatment and liver transplantation as a surgical treatment. The need for intensive critical care is based on the severity of symptoms, such as hemodynamic instability, encephalopathy, bleeding, and hepatorenal syndrome [1]. Liver transplantation should be considered upon progression to decompensated liver failure [2]. However, as liver failure progresses rapidly and exhibits a varying course, it is difficult to make early decisions regarding liver transplantation in practice. In addition, finding living donors for liver transplantation is difficult, and obtaining appropriate cadaveric donors takes a considerable amount of time.

The molecular adsorbent recirculating system (MARS) is an artificial liver support system that supports excretory liver function in patients with liver failure. It is widely used as a bridge therapy for patients waiting for liver transplantation [3, 4]. MARS improves hepatic encephalopathy, cerebral blood flow, renal function, and systemic hemodynamics [5]. Although it may be a good option for patients with end-stage liver failure [6], many clinicians are reluctant to apply MARS due to its high price, various side effects, and lack of evidence that it reduces mortality and improves survival rate [7-9]. Adverse effects of MARS include infection, hypotension, severe coagulopathy, bleeding, respiratory failure, cardiac failure, acute pancreatitis, severe thrombocytopenia, and seizure. Of these, bleeding complications are closely linked to mortality among liver failure patients [10], and even if donors are obtained, bleeding complications can impose a major constraint on liver transplantation.

Since MARS has been employed in our hospital, bleeding complications have occurred in many patients during or after MARS, even though coagulation-preventing agents, such as heparin or nafamostat, are not administered. One patient died of bleeding complications, and
many others could not proceed with additional MARS sessions. However, other patients showed no bleeding-related complications. Therefore, we sought to determine which patients are more likely to experience bleeding complications and any predictive factors. The objective of this study was to examine the association between MARS and bleeding complications, and to identify pre-MARS factors associated with bleeding complications.

MATERIALS AND METHODS

Data collection

Data from all patients receiving MARS in the intensive care unit (ICU) at Jeonbuk National University Hospital between December 2016 and February 2020 were analyzed retrospectively, which included 15 patients undergoing a total of 36 MARS sessions. Laboratory data, hospitalization records, progress records, ICU record sheets, nursing records, transfusion records, and medication history were reviewed. The following data were collected: gender; age; predisposing factors; pre-existing liver disease or bleeding; computed tomography abdomen and biopsy findings; alpha-fetoprotein (AFP); Child-Turcotte-Pugh (CTP) score; Simplified Acute Physiology Score 3 (SAPS3); Model For End-Stage Liver Disease (MELD) score; Acute Physiology and Chronic Health Evaluation 2 (APACH2) score; use of continuous renal replacement therapy (CRRT); need for mechanical ventilation and/or vasopressor support during MARS; timing and duration of MARS sessions; pre-, on-, and post-MARS aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, albumin, creatinine, ammonia, lactate dehydrogenase (LD), hemoglobin, platelet count, prothrombin time international normalized ratio (PT INR), activated partial thromboplastin time (aPTT), fibrinogen degradation product (FDP), anti-thrombin III (ATIII), D-dimer, and factors II, V, VII and X; transfused red blood cells (RBCs), platelet concentrate (PC), fresh
frozen plasma (FFP), cryoprecipitate, fibrinogen, and ATIII; occurrence of liver transplantation surgery; and current patient status. Most pre- and post-MARS laboratory values were collected shortly before and after MARS, respectively. However, in cases of RBC transfusion during MARS, some post-MARS laboratory values were replaced by on-MARS laboratory values to exclude the effect of transfusion. Coagulation factor values were obtained pre-MARS, 2 hours after the start of MARS, and post-MARS. The Institutional Review Board of Jeonbuk National University Hospital approved this study (approval number CUH 2020-03-064). As the study is a retrospective observational one, the need for patient consent was waived.

**MARS procedure**

MARS was considered when total bilirubin exceeded 30 mg/dl or increased rapidly and/or upon the appearance of hepatic encephalopathy or hepatorenal syndrome. In addition, due to its high cost, a comprehensive judgment was made considering factors such as the patient’s age, possibility of transplantation, and the opinions of the patient or their family members. Additional MARS sessions were considered based on total bilirubin levels and changes, complications and effects of previous MARS sessions, and further consent of the patient or their family members. The Baxter GAMBRO MARS® kit was used, and heparin priming was performed. A Becton Dickinson™ arterial cannula was inserted into the radial or brachial artery, and an Arrow®s You-Bend™ two-lumen hemodialysis catheter and Arrow®s multi-lumen central venous catheter (7 French, 3-lumen) were inserted into the subclavian or femoral vein. No agent for preventing coagulation, such as heparin or nafamostat, was administered.

**Data analysis**

We first sought to determine the effect of MARS by comparing laboratory values before and
after MARS. To control for temporal changes due to liver failure, the amount of change in values before and after MARS was compared with the amount of change in values between two time points of the same duration before MARS.

To identify pre-MARS factors associated with increased bleeding after MARS, we first divided patients into bleeder and non-bleeder groups, according to whether there was visually confirmed or strong suspicion of bleeding after MARS and compared their pre-MARS laboratory values. The bleeder group included patients with suddenly increased catheter oozing or ecchymosis, hemoglobin reduction by ≥2 g/dl, need for RBC transfusion with two or more packs, or a marked increase in bleeding after MARS. The non-bleeder group consisted of patients not included in the bleeder group (i.e., patients without catheter oozing or ecchymosis, hemoglobin reduction <2 g/dl after MARS, need for RBC transfusion with one or fewer packs, and no marked increase in bleeding after MARS). Second, we compared individual MARS sessions involving bleeder and non-bleeder patients (i.e., bleeder and non-bleeder sessions). Third, we compared the upper and lower 25% of MARS sessions based on the amount of hemoglobin reduction after MARS, which were designated as bleeding and non-bleeding sessions, respectively.

**Statistical analysis**

Patient demographics and baseline values were compared using independent T tests or Chi square test, as appropriate. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether data were normally distributed, after which groups were compared using independent T tests or Mann-Whitney nonparametric tests as appropriate. Changes over time in factors were tested using repeated measures analysis of variance (RM ANOVA). Statistical analysis was performed using IBM SPSS Statistics ver. 26 (SPSS, Chicago, IL, USA).
RESULTS

We examined data from 15 patients undergoing a total of 36 MARS sessions (Table 1). The average age of patients was 49 years. Ten were men, and five were women. Four patients had acute liver failure (2 hepatitis A virus, 1 pregnancy-induced, 1 toxic hepatitis), and 11 patients had acute-on-chronic liver failure (8 alcoholic, 3 hepatitis B virus-related liver cirrhosis). MARS was administered one to six times per patient. Seven of the 15 patients died, 7 were discharged and were on an outpatient follow-up, and 1 was transferred to another hospital. Seven patients received liver transplantation and one of them died 3 days after surgery. Eight patients did not receive liver transplantation and 2 of them spontaneously recovered. Thirty-five MARS sessions were uninterrupted, but one MARS session was stopped after 1 hour due to malfunction of the blood leak detector. The average duration of MARS sessions was 8 hours and 18 minutes.

Seven of the 15 patients presented clinical bleeding complications during or after MARS and were classified into the bleeder group. Six of these 7 patients had catheter bleeding, and 3 had worsening ecchymosis. In one patient, hemoglobin decreased by <2 mg/dl, and in two patients, more than two packs of RBCs were transfused. One patient exhibited subdural hematoma 3 days after MARS and eventually died. In addition, various bleeding events including oral bleeding, bloody sputum, hematuria, melena, or vaginal bleeding occurred or worsened in one or more patients. Patients in the bleeder group received a daily average of 2.18 packs of RBCs, 7.20 packs of PC, 3.82 packs of FFP, and 5.02 packs of cryoprecipitate from the start to the end of MARS. None of these bleeding events led to the interruption of a MARS session, but they influenced whether additional MARS sessions were administered. The remaining 8 out of 15 patients were classified into the non-bleeder group. Five patients exhibited little bleeding, and 3 had ecchymosis and catheter bleeding, but did not show much change after MARS.
start to the end of MARS, patients in the non-bleeder group received a daily average of 0.54 packs of RBCs, 2.73 packs of PC, 2.77 packs of FFP, and 2.95 packs of cryoprecipitate.

**Effects of MARS on laboratory values**

The amount of change in laboratory values before and after MARS was compared across all patients (Table 2). We found significant changes before and after MARS in total bilirubin, direct bilirubin, creatinine, PT-INR, aPTT, fibrinogen, FDP, and D-dimer. Total bilirubin and direct bilirubin increased by 0.2 and 1.4 mg/dl on average before MARS but decreased by 4.7 and 4.3 mg/dl after MARS (P=0.001 and P<0.001, respectively). Creatinine decreased by 0.2 mg/dl before MARS and by 0.6 mg/dl after MARS (P<0.001). Changes in coagulation profiles after MARS were indicative of a negative coagulation effect. That is, increases in PT-INR, aPTT, FDP, and D-dimer and a decrease in fibrinogen were significantly greater after MARS. PT-INR was nearly unchanged before MARS but increased by 1.9 INR after MARS (P=0.048), and aPTT increased by 1.7 sec before MARS but increased by 33.7 sec after MARS (P=0.014). Fibrinogen increased by 4.7 mg/dl before MARS but decreased by 47.4 mg/dl after MARS (P=0.021). There were no significant differences in the amount of change before and after MARS in other chemistry profiles, complete blood count, or inflammatory markers. Figure 1 shows changes in coagulation factors measured before MARS, 2 hours after the start of MARS, and after MARS.

**Comparison of pre-MARS values between bleeder and non-bleeder groups**

Table 1 presents pre-MARS values for patients in the bleeder and non-bleeder groups. Pre-MARS hemoglobin was significantly lower in the bleeder group (8.2 mg/dl) than in the non-bleeder group (10.0 mg/dl; P=0.014). Apart from hemoglobin, however, there were no significant differences between patient groups.
However, after classifying individual MARS sessions into bleeder and non-bleeder sessions, there were significant differences between groups in vasopressor use, pre-MARS hemoglobin, and pre-MARS factor V (Table 3). Bleeding complications were more common in MARS sessions involving vasopressor use (58.3%) than in those not involving vasopressor use (12.5%; P=0.045). In addition, pre-MARS hemoglobin and factor V were significantly lower in bleeder sessions than in non-bleeder sessions (8.3 vs. 9.5, P=0.001; 19.2 vs. 38.3, P=0.033, respectively).

Table 4 shows a comparison of the upper and lower 25% of MARS sessions based on hemoglobin reduction rate. After MARS, hemoglobin decreased by 1.43 g/dl on average in the upper 25% of sessions (i.e., bleeding sessions) and increased by 0.29 g/dl in the lower 25% of sessions (i.e., non-bleeding sessions). Pre-MARS hemoglobin was significantly lower for bleeding sessions (8.5 mg/dl) than for non-bleeding sessions (10.2 mg/dl; P=0.008). Also, pre-MARS factor V was significantly lower for bleeding sessions (21.6%) than for non-bleeding sessions (45.5%; P=0.032). Other values did not significantly differ between groups.

**DISCUSSION**

Our results show that MARS acts as a liver support system by reducing total bilirubin, direct bilirubin, and creatinine. However, MARS may increase the risk of bleeding by increasing PT and aPTT and reducing fibrinogen. When comparing MARS sessions between bleeder and non-bleeder groups, parameters that differed significantly between groups were vasopressor use, pre-MARS hemoglobin, and pre-MARS factor V. Lower pre-MARS hemoglobin in the bleeding group suggests that bleeding, including micro-bleeding, may have been present prior to MARS, unless the patient had underlying anemia, chronic kidney disease, or hematological disease. There were no differences in pre-MARS parameters between bleeder and non-bleeder groups except for hemoglobin, and no patient had underlying chronic kidney disease. Thus, our
results suggest that MARS increases bleeding risk when a tendency toward bleeding already exists. Pre-MARS platelet count, PT, and aPTT did not significantly differ between groups. As individual differences in bleeding tendency exist, laboratory values may not fully reflect a patient's bleeding tendency.

The liver is the site of synthesis of fibrinogen and factors II, V, VII, IX, X, XI, and XII. In patients with hepatic insufficiency, levels of these factors are low due to protein dysfunction and poor synthetic function. Defects in r-carboxyglutamic acid residues introduced by vitamin K-dependent carboxylase result in deterioration of the functions of factor II, VII, IX, and X and anticoagulant proteins C and S. By contrast, although factor V is mainly synthesized in the liver, it is a vitamin K-independent coagulation factor. As it has a relatively short plasma half-life of ~12 hours, it rapidly decreases in acute liver failure. Factor V is a major cofactor that converts prothrombin to thrombin and plays an important role in the coagulation pathway by regulating factor VIII activity [11]. For this reason, many studies suggest that factor V levels are related to survival and can serve as a prognostic indicator [12-14].

Many studies suggest that MARS reduces bilirubin and creatinine and improves hepatic encephalopathy [4]. However, its side effects and survival rate are somewhat controversial. According to a meta-analysis published in 2012 [5], MARS decreases total bilirubin and clinical symptoms of hepatic encephalopathy, but the incidence of bleeding complications was 24.1% compared with 10.2% among patients receiving standard medical support (P=0.007), and a consistent interpretation of mortality reduction across studies was difficult. In a meta-analysis published in 2019 [7], there was no difference in the survival of patients receiving standard medical support or MARS, but patients receiving high-intensity therapy with five or more MARS sessions showed better survival than those receiving low-intensity therapy with four or fewer sessions. Furthermore, a meta-analysis published in 2020 [15] reports that MARS
reduces mortality (relative risk (RR), 0.84; 95% confidence interval (CI), 0.74-0.96; moderate certainty) among patients with acute or acute-on-chronic liver failure and is associated with bleeding-related side effects, such as hypotension (RR, 1.46; 95% CI, 0.98-2.20; low certainty), bleeding (RR, 1.21; 95% CI, 0.88-1.66; moderate certainty), and thrombocytopenia (RR, 1.62; 95% CI, 1.00-2.64; very low certainty). Bleeding complications of MARS can induce an unstable hemodynamic state, increase blood transfusion demand, and impede the procedure. Bleeding complications can also promote disseminated intravascular coagulation in patients with liver failure, making medical staff hesitant to proceed with liver transplantation.

Many recent studies of MARS mention bleeding-associated side effects, such as thrombocytopenia, coagulopathy, hypofibrinogenemia, and anemia, but few studies focus on these outcomes. Among them, several studies using thromboelastography indicate that MARS induces platelet-mediated coagulopathy, both mechanically and immunologically [16, 17]. MARS is an extracorporeal circulation system that potentially activates coagulation by putting blood in contact with artificial materials, resulting in the consumption of platelets and coagulation factors. We found that MARS reduced platelet count by 17500/µl as well as levels of coagulation factors. In particular, factor V was markedly reduced relative to other factors. In addition, the large-bore venous cannulation required for MARS may be a factor that causes bleeding in liver failure patients with coagulopathy.

Unlike previous studies, we did not use heparin during MARS treatment and controlled the effects of blood transfusions such as RBCs, PC, and FFP. Central venous and arterial line catheters were inserted in all patients so that bleeding tendency could be evaluated under the same conditions. Above all, we compared coagulation factors and attempted to distinguish the effect of MARS from spontaneous coagulopathy caused by liver failure by comparing the amount of change rather than absolute laboratory values before and after MARS [18].
This study has several limitations. The number of patients was somewhat small, and the data collection period was long. Due to its retrospective design, the time that laboratory testing was performed differed slightly across patients. Moreover, there was an inevitable difference in timing because we had to select two time points between which blood transfusion was not performed. As we mainly classified patients into groups based on visible bleeding, researcher subjectivity cannot be completely excluded. The frequency of bleeding complications after MARS in this study was much higher than that in previous studies, even though heparin was not used. To explain this discrepancy, we reviewed the MARS procedure several times and contacted the MARS kit manufacturer to ensure that there were no changes in the kit or its recommended use instructions. We did not use thromboelastography and, therefore, could not evaluate platelet function, clot strength, or fibrinolysis.

**CONCLUSION**

MARS appears to alter coagulation-related factors, such as platelet count, PT, aPTT, fibrinogen, and coagulation factors, and increase the tendency toward bleeding complications in patients with liver failure. Therefore, the progression of coagulopathy should be considered when proceeding with MARS. However, the differences observed among patients were large, and various factors, such as vasopressor use and pre-MARS hemoglobin and factor V, appear to contribute to these differences. Further research on this subject is warranted given that the ability to predict bleeding complications, before their onset, would be useful to clinicians when making decisions regarding the use of MARS.
Research ethics and consent to participate

The Institutional Review Board of Jeonbuk National University Hospital approved this study (approval number CUH 2020-03-064). As the study is a retrospective observational one, the need for patient consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors’ contributions

Conceptualization: HBL. Data curation: SKK, DK, SWY. Formal analysis: SKK, SWY. Methodology: DKK, SWY, HBL. Project administration: MJK. Visualization: MJK. Writing – original draft: SWY. Writing – review & editing: HBL.

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Not applicable
Table 1. Patient demographics and baseline values before MARS

| Variable                          | All patients (n=15) | Bleeders (n=7) | Non-bleeders (n=8) | P-value  |
|----------------------------------|---------------------|----------------|--------------------|----------|
| Male sex                         | 10 (66.7)           | 4 (57.1)       | 6 (75.0)           | 0.608    |
| Age (yr)                         | 49.0                | 51.3±13.5      | 46.3±14.2          | 0.397    |
| Predisposing factor              |                     |                |                    |          |
| Hepatitis A virus                | 2 (13.3)            | 0              | 2 (25.0)           | 0.467    |
| Hepatitis B virus                | 3 (20.0)            | 1 (14.3)       | 2 (25.0)           | 0.554    |
| Alcohol                          | 8 (53.3)            | 5 (71.4)       | 3 (37.5)           | 0.214    |
| Toxin                            | 1 (13.3)            | 0              | 1 (12.5)           | 0.467    |
| Pregnancy                        | 1 (6.7)             | 1 (14.3)       | 0                  | 0.467    |
| Underlying liver cirrhosis       | 11 (73.3)           | 6 (85.7)       | 5 (62.5)           | 0.569    |
| Chronic kidney disease           | 0                   | 0              | 0                  | 1.000    |
| Disease severity                 |                     |                |                    |          |
| CTP score                        | 10.9                | 10.7±1.4       | 11.0±1.7           | 0.955    |
| MELD score                       | 38.8                | 40.6±5.8       | 37.3±8.4           | 0.397    |
| SAPS3 score                      | 62.5                | 64.0±11.1      | 61.3±10.6          | 0.779    |
| APACHE II score                  | 16.5                | 18.4±7.4       | 14.8±7.1           | 0.281    |
| Support modality                 |                     |                |                    |          |
| CRRT                             | 12 (80)             | 6 (85.7)       | 6 (75.0)           | 0.779    |
| Mechanical ventilation           | 3 (20)              | 2 (28.6)       | 1 (12.5)           | 0.613    |
| Vasopressor                      | 6 (40)              | 4 (57.1)       | 2 (25.0)           | 0.336    |
| Laboratory parameter             |                     |                |                    |          |
| AFP (ng/ml)                      | 39.0                | 50.5±121.9     | 29.0±42.2          | 0.779    |
| AST (IU/l)                       | 466.3               | 332.3±683.9    | 1048.0±1877.0      | 0.121    |
| ALT (IU/l)                       | 626.1               | 321.1±722.9    | 893.0±1359.5       | 0.152    |
| Test                          | Mean   | SD     | Median  | P-value |
|-------------------------------|--------|--------|---------|---------|
| Total bilirubin (mg/dl)       | 29.9   | 29.3±12.4 | 30.5±14.9 | 0.867   |
| Direct bilirubin (mg/dl)      | 18.1   | 14.6±5.8 | 21.1±10.9 | 0.189   |
| Albumin (g/dl)                | 3.3    | 3.3±0.3 | 3.2±0.3 | 0.336   |
| Creatinine (mg/dl)            | 2.0    | 1.8±0.4 | 2.2±1.6 | 0.694   |
| Ammonia (µmol/l)              | 81.8   | 71.5±26.7 | 90.7±33.8 | 0.232   |
| LD (IU/l)                     | 1645.6 | 1504.3±1339.1 | 1769.3±2122.5 | 0.867   |
| Hemoglobin (g/dl)             | 9.2    | 8.2±0.2 | 10.0±1.6 | 0.014*  |
| Platelet (10^3/µl)            | 68.4   | 71.0±53.1 | 66.1±42.9 | 0.867   |
| PT-INR (INR)                  | 2.3    | 2.4±0.7 | 2.3±4 | 0.694   |
| aPTT (sec)                    | 47.3   | 46.3±7.9 | 48.2±13.6 | 0.779   |
| Fibrinogen (mg/dl)            | 143.9  | 129.0±59.0 | 157.0±56.6 | 0.281   |
| FDP (mg/ml)                   | 68.9   | 78.0±545.1 | 60.9±60.1 | 0.536   |
| Anti-thrombin III (%)         | 25.6   | 26.9±14.3 | 24.5±8.7 | 0.779   |
| D-dimer (mg/l FEU)            | 15.0   | 16.4±13.4 | 13.8±18.7 | 0.336   |
| Factor II (%)                 | 36.1   | 36.8±6.9 | 35.6±7.5 | 1.000   |
| Factor V (%)                  | 29.6   | 16.7±9.3 | 37.4±18.4 | 0.143   |
| Factor VII (%)                | 21.0   | 19.3±2.5 | 22.0±7.0 | 0.393   |
| Factor X (%)                  | 44.3   | 43.3±6.6 | 45.2±19.3 | 0.905   |

*Values are presented as mean±standard deviation or number (%). *P<0.05

CTP: Child-Turcotte-Pugh; MELD: Model For End-Stage Liver Disease; SAPS: Simplified Acute Physiology Score; APACHE: Acute Physiology and Chronic Health Evaluation; CRRT: continuous renal replacement therapy; AST: aspartate transaminase; ALT: alanine aminotransferase; LD: lactate dehydrogenase; PT-INR: international normalized ratio of prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation product
Table 2. Changes in values before and after MARS (n=36)

| Variable                  | Change before MARS | Change after MARS | P-value |
|---------------------------|--------------------|-------------------|---------|
| **Chemistry profiles**    |                    |                   |         |
| AST (IU/l)                | -238.5±808.5       | -250.1±717.0      | 0.935   |
| ALT (IU/l)                | -129.7±220.1       | -122.9±220.7      | 0.870   |
| Total bilirubin (mg/dl)   | 0.2±2.1            | -4.7±4.3          | 0.001*  |
| Direct bilirubin (mg/dl)  | 1.4±3.6            | -4.3±5.1          | <0.001* |
| Albumin (g/dl)            | -0.1±0.2           | 0.0±0.2           | 0.642   |
| Creatinine (mg/dl)        | -0.2±0.4           | -0.6±0.4          | <0.001* |
| Ammonia (µmol/l)          | -1.0±9.2           | -1.4±17.3         | 0.935   |
| LD (IU/l)                 | -1076.5±4637.3     | -408.5±1284.0     | 0.902   |
| **Complete blood count**  |                    |                   |         |
| Hemoglobin (g/dl)         | -0.3±0.5           | -0.6±0.8          | 0.305   |
| Platelet (103/µl)         | -5.7±24.0          | -17.5±32.3        | 0.317   |
| **Coagulation profiles**  |                    |                   |         |
| PT-INR (INR)              | 0.0±0.2            | 1.9±5.6           | 0.048*  |
| aPTT (sec)                | 1.7±0              | 33.7±90.1         | 0.014*  |
| Fibrinogen (mg/dl)        | 4.7±24.5           | -47.4±85.7        | 0.021*  |
| FDP (mg/ml)               | -5.2±20.8          | 125.5±124.2       | 0.003*  |
| Anti-thrombin III (%)     | 2.9±7.2            | 0.8±7.7           | 0.645   |
| D-dimer (mg/l FEU)        | -2.1±4.9           | 53.5±51.3         | 0.001*  |
| **Inflammatory markers**  |                    |                   |         |
| ESR (mm/hr)               | 1.2±4.1            | -3.3±10.7         | 0.137   |
| hsCRP (mg/dl)             | -3.3±10.7          | -5.1±10.0         | 0.775   |
| Procalcitonin (ng/ml)     | -4.9±14.7          | -0.4±0.9          | 0.290   |

Values are presented as mean±standard deviation. *P<0.05
AST: aspartate transaminase; ALT: alanine aminotransferase; LD: lactate dehydrogenase; PT-INR: international normalized ratio of prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation product; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein
Table 3. Pre-MARS values for bleeder and non-bleeder sessions

| Variable                          | Bleeder sessions (n=12) | Non-bleeder sessions (n=24) | P-value |
|-----------------------------------|-------------------------|-----------------------------|---------|
| **Support modality**              |                         |                             |         |
| CRRT                              | 11 (91.7)               | 19 (79.2)                   | 0.562   |
| Mechanical ventilation            | 4 (33.3)                | 3 (12.5)                    | 0.072   |
| Vasopressor                       | 7 (58.3)                | 4 (12.5)                    | 0.045*  |
| **Chemistry profiles**            |                         |                             |         |
| AST (IU/l)                        | 281.5±520.8             | 558.8±1148.5                | 0.295   |
| ALT (IU/l)                        | 221.5±549.2             | 630.1±998.8                 | 0.177   |
| Total bilirubin (mg/dl)           | 33.1±11.0               | 31.6±12.7                   | 0.934   |
| Direct bilirubin (mg/dl)          | 15.8±5.2                | 20.3±8.2                    | 0.093   |
| Albumin (g/dl)                    | 3.4±0.2                 | 3.3±0.4                     | 0.311   |
| Creatinine (mg/dl)                | 1.5±0.5                 | 2.0±1.1                     | 0.177   |
| Ammonia (µmol/l)                  | 74.0±24.7               | 85.0±33.6                   | 0.322   |
| LD (IU/l)                         | 1478.0±1085.0           | 1277.8±1267.3               | 0.585   |
| **Complete blood count**          |                         |                             |         |
| Hemoglobin (g/dl)                 | 8.3±0.2                 | 9.5±1.3                     | 0.001*  |
| Platelet (103/µl)                 | 77.7±41.7               | 76.7±32.2                   | 0.937   |
| **Coagulation profiles**          |                         |                             |         |
| PT-INR (INR)                      | 2.4±0.6                 | 2.1±0.4                     | 0.070   |
| aPTT (sec)                        | 45.3±6.3                | 49.0±17.8                   | 0.679   |
| Fibrinogen (mg/dl)                | 141.8±50.7              | 162.4±65.9                  | 0.344   |
| FDP (mg/ml)                       | 140.7±115.1             | 102.9±108.1                 | 0.212   |
| Anti-thrombin III (%)             | 31.8±16.3               | 28.6±11.5                   | 0.504   |
| D-dimer (mg/l FEU)                | 43.7±50.0               | 33.4±45.9                   | 0.183   |
Coagulation factors

| Factor   | Mean ± Standard Deviation | Mean ± Standard Deviation | P-Value |
|----------|---------------------------|---------------------------|---------|
| Factor II (%) | 36.5±6.3 | 38.1±9.1 | 0.677 |
| Factor V (%)   | 19.2±7.4 | 38.3±18.9 | 0.033* |
| Factor VII (%)  | 21.6±4.6 | 25.3±9.4 | 0.266 |
| Factor X (%)   | 43.0±6.5 | 51.5±16.7 | 0.340 |

Values are presented as mean±standard deviation or number (%). *P<0.05

CRRT: continuous renal replacement therapy; AST: aspartate transaminase; ALT: alanine aminotransferase; LD: lactate dehydrogenase; PT-INR: international normalized ratio of prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation product
Table 4. Pre-MARS values for bleeding and non-bleeding sessions based on rate of hemoglobin decrease during MARS

| Variable                      | Bleeding sessions (n=9) | Non-bleeder sessions (n=9) | P-value |
|-------------------------------|-------------------------|---------------------------|---------|
| **Support modality**          |                         |                           |         |
| CRRT                          | 8 (88.9)                | 7 (77.8)                  | 0.730   |
| Mechanical ventilation        | 2 (22.2)                | 0                         | 0.436   |
| Vasopressor                   | 4 (44.4)                | 0                         | 0.113   |
| **Laboratory parameter**      |                         |                           |         |
| AST (IU/l)                    | 418.4±610.8             | 982.0±1769.3              | 0.436   |
| ALT (IU/l)                    | 435.0±727.0             | 1102.2±1362.8             | 0.340   |
| Total bilirubin (mg/dl)       | 30.6±11.8               | 25.2±14.5                 | 0.340   |
| Direct bilirubin (mg/dl)      | 16.7±6.7                | 17.0±10.0                 | 0.666   |
| Albumin (g/dl)                | 3.3±0.5                 | 3.4±0.5                   | 0.387   |
| Creatinine (mg/dl)            | 1.9±0.9                 | 1.6±0.7                   | 0.730   |
| Ammonia (µmol/l)              | 72.9±24.4               | 96.0±41.5                 | 0.258   |
| LD (IU/l)                     | 1316.8±1162.2           | 1844.2±1968.7             | 0.436   |
| **Complete blood count**      |                         |                           |         |
| Hemoglobin (g/dl)             | 8.5±0.4                 | 10.2±1.6                  | 0.008*  |
| Platelet (10^3/µl)            | 76.9±41.0               | 90.8±33.2                 | 0.297   |
| **Coagulation profiles**      |                         |                           |         |
| PT-INR (INR)                  | 2.3±0.5                 | 2.0±0.2                   | 0.113   |
| aPTT (sec)                    | 46.8±6.7                | 42.1±4.9                  | 0.136   |
| Fibrinogen (mg/dl)            | 159.1±107.9             | 159.8±47.0                | 0.370   |
| FDP (mg/ml)                   | 137.0±110.5             | 107.3±103.1               | 0.481   |
| Anti-thrombin III (%)         | 30.6±14.2               | 25.8±6.9                  | 0.481   |
| Coagulation factors          |  |  |  |
|-----------------------------|---|---|---|
| D-dimer (mg/l FEU)          | 40.3±54.3 | 35.7±43.3 | 0.815 |
| Factor II (%)               | 34.8±4.3 | 37.8±7.8 | 0.730 |
| Factor V (%)                | 21.6±7.9 | 45.5±20.6 | 0.032* |
| Factor VII (%)              | 24.2±3.6 | 27.0±5.9 | 0.730 |
| Factor X (%)                | 43.6±6.9 | 55.8±15.3 | 0.286 |

Values are presented as mean±standard deviation or number (%). *P<0.05

CRRT: continuous renal replacement therapy; AST: aspartate transaminase; ALT: alanine aminotransferase; LD: lactate dehydrogenase; PT-INR: international normalized ratio of prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation product
Figure 1. Sequential measurements of coagulation factors (n=22). All factors (Factor II, V, VII, and X) decreased significantly over time (P=0.042, P<0.001, P=0.006 and P=0.031, respectively). Note that factor V sharply decreased from 33.1% before MARS to 27.2% and 22.6% after MARS start and after MARS, respectively.
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