

Plasma Exchange in Patients of Acute on Chronic Liver Failure: An Observational Study in Bangladesh

Abdullah Al Mukit¹, Mamun Al Mahtab², Md. Abdur Rahim³, Sheikh Mohammad Noor-E-Alam⁴, Dulal Chandra Das⁵, Ahmed Lutful Moben⁶, Faiz Ahmad Khondaker⁷, Md. Ashraful Alam⁸, Rokshana Begum⁹, Mohammad Ekramul Haque¹⁰, Md. Atikul Islam¹¹, Ayub Al Mamun¹², Sheikh Mohammad Fazle Akbar¹³

ABSTRACT

Background: Therapeutic plasma exchange (PLEX) removes toxins and different mediators from plasma in patients with acute-on-chronic liver failure (ACLF).

Aim: To observe the safety and outcome of PLEX in ACLF patients in Bangladesh.

Materials and methods: Twenty-eight patients with ACLF attending Bangabandhu Sheikh Mujib Medical University from September 2020 to May 2021 were enrolled in the study. The patients were given different treatment modalities and followed up for 3 months or up to death. The patients were divided into two groups, each containing 14 patients of ACLF. One group of 14 patients received standard medical therapy (SMT) for ACLF and the second group of 14 patients received SMT plus PLEX.

Results: At 90 days, a total of 13 patients (46.43%) survived, of them 8 (57.1%) belonged to PLEX group and 5 (35.7%) were from SMT group. Serum bilirubin and ALT declined significantly after 7 and 30 days but not after 90 days in PLEX group in comparison to SMT group ($p < 0.05$) but other biochemical parameters were not significantly different ($p > 0.05$) between these two groups. Significant ($p < 0.05$) improvement of MELD, MELD-Na, and AARC scores was observed in each group from baseline to subsequent first, second, and third follow-up but no significant ($p > 0.05$) difference was observed in between two groups. Binary logistic regression analysis found that bilirubin, MELD score, MELD-Na score, and AARC score were predictors of mortality.

Conclusion: The study presented here has shown that PLEX is safe in Bangladeshi in ACLF patients, but its efficacy remains to be checked in large-scale randomized trial or in combination therapy with other procedures in ACLF patients.

Keywords: Acute on chronic liver failure, Parameters of liver diseases, Plasma exchange, Survival.

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a clinical syndrome in which the patients with chronic liver diseases take a rapidly downhill course due to some acute insult that may be of diverse nature.¹ Although there remain considerable concerns and disagreement about its nomenclature, entity, and types, there is a common consensus among physicians about the severity of this pathological lesion. ACLF is characterized by rapidly progressing organ failure and high short-term mortality. ACLF is usually characterized by jaundice, increased bilirubin in the blood, hepatic encephalopathy, hepatorenal syndrome, hemodynamic instability, increased susceptibility to severe infections, and finally multiorgan failure. These scenarios are valid for almost all etiologies. Increasing numbers of organs failing or increasing grade of ACLF is a strong predictor of short-term mortality. Both hepatic and extra-hepatic organ failures, caused by unregulated systemic inflammation, seem to be the main attributor of high mortality in ACLF. Intensive care unit (ICU) mortality for ACLF ranges from 35 to 89% and in-hospital mortality ranges from 43 to 88%.² Three months mortality in ACLF can be very high like 65%, which is regarded as very high short-term mortality in hospitalized patient.³

Therapeutic options for ACLF are limited, sometimes confusing and is not completely evidence-based. In general, treatment is diverted to challenge the etiology of chronic liver diseases and also to block effects of acute insult.⁴ However, the entire mechanism of ACLF pathogenesis remains elusive and most of these events cannot

^{1-5,12}Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

⁶Department of Hepatology, Kurmitola General Hospital, Dhaka, Bangladesh

^{7,9}Department of Hepatology, Shaheed Suhrawardi Medical College, Dhaka, Bangladesh

⁸Department of Hepatology, Shaheed Tajuddin Ahmad Medical College, Gazipur, Bangladesh

¹⁰Department of Anaesthesia, Sheikh Hasina National Institute of Burn and Plastic Surgery, Dhaka, Bangladesh

¹¹Department of Hepatology, Sheikh Russel Gastro liver Institute and Hospital, Dhaka, Bangladesh

¹³Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan

Corresponding Author: Sheikh Mohammad Fazle Akbar, Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan, e-mail: sheikhmohammadfazle@gmail.com

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be explained by etiology of chronic liver diseases and acute insults. However, it is accepted that the ultimate curative treatment of ACLF is mainly liver transplantation and intermediary management strategies are focused on buying time for progressing to liver transplantation. This management of in-between time may be provided by artificial liver support systems (ALSS) in ACLF.^{5,6} As of today, several ALSS have been developed and employed in ACLF patients and among these include plasma exchange (PLEX), molecular adsorbent recirculating system (MARS), and some other methods. Considering various factors, PLEX is one of the common therapeutic approaches that can be widely applied in many countries of the world.⁵⁻⁷

The scopes and limitations of PLEX have been shown with diverse outcomes. Chen et al. have reported that in a cohort of 250 ACLF patients with 661 rounds of PLEX, it positively modulated the clinical features of ACLF. However, several variables such as age ($p = 0.000$), levels of total bilirubin (TB, $p = 0.000$), direct bilirubin ($p = 0.000$), total triglycerides ($p = 0.000$), low-density lipoprotein ($p = 0.022$), Na+ ($p = 0.014$), Cl ($p = 0.038$), creatinine (Cr, $p = 0.007$), fibrinogen ($p = 0.000$), prothrombin time (PT, $p = 0.000$), white blood cell ($p = 0.000$), platelet ($p = 0.003$), and MELD score ($p = 0.000$) were significantly related to prognosis. Multivariate logistic regression analysis showed that age, disease stage, total bilirubin, creatinine, and prothrombin time were independent risk factors of mortality among HBV-ACLF patients.⁵ In another study that is prospective in nature also revealed that PLEX-based ALSS improved short-term (28/90 days and 1-year) outcomes in patients with HBV-ACLF, especially in MELD grade III patients. Optimization of PLEX-based ALSS may improve prognosis or even save lives among HBV-ACLF patients. In this study, a total of 524 ACLF patients were enrolled and divided into two, one group containing 358 patients receiving standard treatment and other 166 patients received PLEX.⁶ When considerable optimism was developed due to these reports, study from India found that PLEX did not influence mortality rate of ACLF patients.⁸ Apart from HBV-ACLF that are common in China, Indian investigators reported the importance of low-volume PLEX and low-dose steroid in elongating survival over 1 year in alcohol-related ACLF. The diverse outcome of PLEX in ACLF patients is understandable if the heterogeneity of patients and etiological diversities of ACLF along with social and economic conditions of different countries are properly considered.

Bangladesh, a country of 160 million people, harbors millions of patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Also, acute insults for induction of ACLF are commonly encountered in this country.⁹⁻¹² Although there is no proper statistics about the incidence of ACLF in Bangladesh, conservative estimates indicate that these may be several hundreds to thousands of ACLF in Bangladesh per year. The tertiary medical facilities usually encounter several ACLF patients over the year. However, the facility for liver transplantation is not present in Bangladesh. Only some patients may travel to India to have a liver transplantation, although it is very complicated and mostly out of reach to normal ACLF patients in the country. In this pretext, the study presented here has been accomplished to assess a management strategy for ACLF patients. This observational study has been done with limited number of patients with ACLF in Bangladesh to assess the utility of PLEX, if any, in Bangladesh. The outcome of this study would provide insights about scope and limitation of PLEX for management strategy of ACLF patients in other developing countries.

MATERIALS AND METHODS

The study was an observational one conducted at the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University,

Dhaka, Bangladesh. ACLF was diagnosed as per the criteria of The Asian Pacific Association for the Study of the Liver (APASL).³ The levels of serum bilirubin were more than 5 mg/dL in all patients. The enrollment of patients was done from September 2020 to May 2021. All patients were adult above the age of 18 years. At the entry, the patients were evaluated with history of present and past illness, physical examination, hematological, serological and biochemical investigations like complete blood counts, liver function tests, prothrombin time, renal function tests, ferritin, lactate, ultrasonography (USG), and endoscopy of upper gastrointestinal tract. A total of 28 patients with ACLF were selected for final analysis. Of these, 14 received PLEX in addition to standard medical treatment (SMT) (PLEX group). The remaining 14 patients received only SMT (SMT-Group). It was also observed that 10 (71.4%) patients had HBV and 3 (21.5%) patients had NASH as chronic cause of ACLF in PLEX group. On the other hand, 11 (78.6%) patients had HBV and 2 (14.3%) patients had NASH as a chronic cause of ACLF in SMT Group. Regarding etiology of acute insult in ACLF patients, eight (57.1%) patients had DILI and two (14.3%) patients had HBV as acute cause of ACLF in PLEX group. On the other hand, seven (50.0%) patients had HBV and two (14.3%) patients had HEV as the cause of acute insult of ACLF in SMT Group.

All patients gave written consent to the study. Patients with features of hepatocellular carcinoma, other malignancy, active sepsis, severe cardiac or pulmonary disease, and pregnancy were excluded from the present study.

Before PLEX treatment, blood access was established with a double-lumen catheter inserted into the patient's femoral vein. PLEX was done using MCS+ Plasmapheresis Machine (HAEMONETICS, Boston, Massachusetts, USA). Around 1–1.5 L of plasma was exchanged with fresh frozen plasma for 1–2 hours daily for consecutive 3 days. After procedure, patients were carefully followed up hourly for 6 hours and then all of them were kept on proper monitoring. Both groups were followed up for at least 90 days or up to death of the patient. Close liaison was maintained with all patients. Permanent address and phone number of all patients were recorded.

In order to have insights about the role of treatments, clinical assessment and laboratory investigations [CBC, alanine aminotransferase (ALT) aspartate aminotransferase (AST), bilirubin, prothrombin time (INR), albumin, creatinine, serum electrolyte, serum ferritin, and serum lactate] were done at day 0, 7, 30 and at days 90. Patient who expired within the study period, date, and cause of death was documented. Each patient was in close monitoring throughout the study period through either hospital visit or over phone.

Statistical Analysis

All data were analyzed by SPSS (version 21.0). Quantitative data were displayed as mean \pm standard deviation (SD). Qualitative data were analyzed by Chi-square test and quantitative data were analyzed by Student's *t*-test. Comparison between two groups in each follow-up was done by unpaired *t*-test. All quantitative and qualitative data were analyzed between survival and nonsurvival group as well. The Univariate and Binary Logistic Regression analysis was done to find out the best predictor of mortality. A statistically significant result was considered when *p*-value was less than 0.05.

RESULTS

Baseline Characteristics of the Study Population

Baseline characteristics of the study population are presented in Table 1. Pretreatment parameters were similar between PLEX group

Table 1: Comparison of baseline clinical features between patients in the PLEX and control groups

Variables	PLEX group (n = 14)	SMT group (n = 14)	p-value
Age (years)	41.7 ± 12.2	44.6 ± 9.2	0.483
Male gender	13	12	0.541
ALT (U/L)	314.1 ± 505.7	260.6 ± 208.3	0.717
AST (U/L)	349.4 ± 508.1	259.9 ± 255.5	0.561
Bilirubin (mg/dL)	23.6 ± 11.2	18.3 ± 9.1	0.181
Albumin (g/dL)	2.5 ± 0.5	2.2 ± 0.6	0.162
INR	2.3 ± 0.7	2.4 ± 1.0	0.761
Platelet count (×10 ⁹ /L)	175.9 ± 81.1	157.1 ± 121.0	0.633
S. Creatinine (mg/dL)	1.3 ± 0.8	1.5 ± 0.9	0.539
Ferritin (ng/mL)	1878.9 ± 634.8	829.6 ± 622.1	0.001
Lactate (mmol/L)	2.9 ± 2.2	2.0 ± 1.0	0.175
AARC Grade (I/II/III)	2/9/3	2/9/3	0.998
MELD score	28.6 ± 4.8	28.0 ± 5.3	0.756
MELD-Na score	30.7 ± 3.7	30.1 ± 5.3	0.731
AARC score	9.5 ± 1.6	9.2 ± 1.8	0.645

and SMT group, except serum ferritin level, which was significantly higher in PLEX group.

ALT—alanine aminotransferase (normal value: 16–63 U/L), AST—aspartate aminotransferase (normal value: <37 U/L), INR—international normalized ratio of prothrombin time, bilirubin (normal value: <1.1 mg/dL), albumin (normal value: 3.6–6.0 g/dL), platelet (normal value: 150–450 × 10⁹/L), S. Creatinine (normal value: 0.5–1.3 mg/dL), S. Ferritin (normal value: 12–300 ng/mL), lactate (normal value: 0.5–2.2 mmol/L), MELD—model for end-stage liver disease, AARC score—APASL ACLF Research Consortium score.

Survival after 90 days of Follow-up

In this current study it was observed that 15 patients expired within the observation period of 90 days. Of them six patients belonged to PLEX group. Among them four (66.6%) patients had variceal hemorrhage, one (16.7%) patient had hepatic encephalopathy, and one (16.7%) patient had multi organ failure. On the other hand, nine patients of the SMT-Group died within 90 days. Among them three (33.3%) patients had variceal hemorrhage, three (33.3%) patients had renal failure, one (11.1%) had septicemia, one (11.1%) had hepatic encephalopathy, and one (11.1%) patient had multi organ failure. Thus, 8 out of 14 patients (57.1%) survived at the end of 90 days follow-up in PLEX group. Thus, 5 out of 14 patients (35.7%) survived in SMT group. This difference is not statistically significant (*p* >0.05). The survival curve of the patients has been shown in Figure 1.

Baseline Predictors for Liver-related Mortality at 90 days

A comparison was made to assess the factors related to death by comparing different parameters of 13 survived patients and 15 death patients. Table 2 shows the comparison of variables at baseline for predicting death. It was observed that the levels of serum bilirubin, AST, ALT, MELD score, MELD-Na score, and AARC score were statistically significant (*p* <0.05) and other parameters were statistically not significant (*p* >0.05) between two groups. Table 3 shows binary logistic regression analysis to predict death.

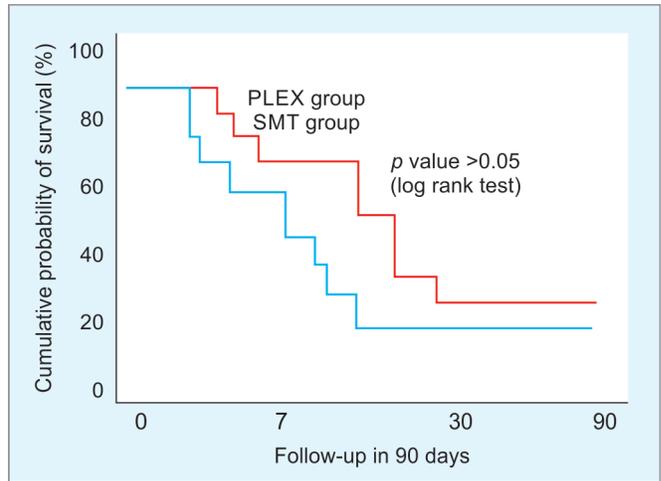


Fig. 1: Survival curve for the PLEX and SMT groups as determined by the Kaplan-Meier method

Table 2: Univariate analysis of variables at baseline for predicting death

Parameter	Survival group (n = 13)	Nonsurvival group (n = 15)	p-value
Age (in years)	41.1 ± 12.1	44.6 ± 11.2	0.434
Sex (M/F)	11/2	14/1	0.455
PLEX/ SMT	8/5	6/9	0.255
INR	2.3 ± 0.7	2.2 ± 1.0	0.765
Serum albumin	2.5 ± 0.5	2.2 ± 0.7	0.209
Serum creatinine	1.1 ± 0.3	1.6 ± 0.9	0.067
Serum ferritin (ng/mL)	1560.2 ± 873.4	1040.9 ± 648.2	0.083
Serum lactate (mmol/L)	2.7 ± 0.9	2.1 ± 0.7	0.058
Serum bilirubin (mg/dL)	8.7 ± 3.2	19.2 ± 9.2	0.001
ALT (U/L)	130.1 ± 45.7	98.8 ± 32.6	0.044
AST (U/L)	122.8 ± 62.4	182.4 ± 67.1	0.022
MELD score	17.8 ± 4.8	25.6 ± 6.2	0.001
MELD-Na score	20.4 ± 5.7	29.9 ± 4.0	0.001
AARC score	6.5 ± 0.7	9.4 ± 1.7	0.001

Table 3: Baseline predictors of mortality by binary logistic regression analysis (n = 28)

	B	SE	p-value	OR	95% CI for OR	
					Lower	Upper
Serum bilirubin	0.177	0.048	0.016 ^s	2.76	1.58	4.23
AST	0.165	0.054	0.336 ^{ns}	0.96	0.98	1.54
ALT	0.228	0.126	0.218 ^{ns}	0.77	0.54	2.13
MELD score	-0.271	0.198	0.036 ^s	1.36	1.88	4.12
MELD-Na score	-0.218	0.112	0.018 ^s	1.24	1.56	3.21
AARC score	-0.178	0.068	0.044 ^s	0.98	1.65	2.78

B, unstandardized regression weight; CI, confidence interval; Ns, not significant; OR, odds ratio; S, significant, SE, standard error

Serum bilirubin, MELD score, MELD-Na score, and AARC score were statistically significant (*p* <0.05) between two groups.

Biochemical Response during the Follow-up

Table 4 shows kinetics of parameters during different follow-up points. These assessments were done at basal level, 7, 30, and 90 days

Table 4: Association between investigations in different follow-up among two groups

Investigations	PLEX group	SMT group	p-value
S. Bilirubin (mg/dL)			
Baseline (n = 14/14)	23.6 ± 11.2	18.3 ± 9.1	0.181 ^{ns}
At first follow-up (At 7 days) (n = 14/12)	13.1 ± 6.7	19.9 ± 8.3	0.032 ^s
At second follow-up (At 30 days) (n = 11/7)	9.1 ± 4.6	15.8 ± 6.3	0.026 ^s
At third follow-up (At 90 days) (n = 8/5)	2.5 ± 1.2	3.5 ± 1.8	0.298 ^{ns}
ALT (U/L)			
Baseline (n = 14/14)	314.1 ± 505.7	260.6 ± 208.3	0.717 ^{ns}
At first follow-up (At 7 days) (n = 14/12)	115.1 ± 48.5	151.3 ± 32.5	0.039 ^s
At second follow-up (At 30 days) (n = 11/7)	102.5 ± 32.4	138.4 ± 38.3	0.048 ^s
At third follow-up (At 90 days) (n = 8/5)	64.8 ± 47.3	89.8 ± 31.6	0.273 ^{ns}
INR			
Baseline (n = 14/14)	2.3 ± 0.7	2.4 ± 1.0	0.761 ^{ns}
At first follow-up (At 7 days) (n = 14/12)	1.7 ± 0.4	1.9 ± 0.6	0.321 ^{ns}
At second follow-up (At 30 days) (n = 11/7)	1.6 ± 0.4	1.7 ± 0.5	0.644 ^{ns}
At third follow-up (At 90 days) (n = 8/5)	1.5 ± 0.3	1.2 ± 0.4	0.149 ^{ns}
S. Creatinine (mg/dL)			
Baseline (n = 14/14)	1.3 ± 0.8	1.5 ± 1.9	0.719 ^{ns}
At first follow-up (At 7 days) (n = 14/12)	1.1 ± 0.4	0.9 ± 0.6	0.323 ^{ns}
At second follow-up (At 30 days) (n = 11/7)	1.1 ± 0.3	0.8 ± 0.2	0.033 ^s
At third follow-up (At 90 days) (n = 8/5)	1.2 ± 0.3	0.8 ± 0.2	0.023 ^s

ns, not significant; s, significant

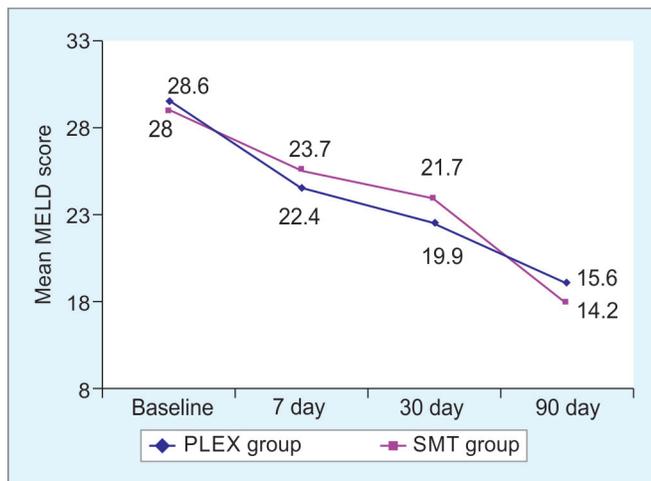


Fig. 2: Line diagram shows mean MELD score in different follow-up

after admission, where possible. It was observed that serum bilirubin and ALT were statistically significant ($p < 0.05$) between first follow-up (at 7 days) and second follow-up (At 30 days) among two groups. Serum creatinine decreased significantly in the SMT group compared to PLEX group in the second and third visit. Other parameters were statistically not significant ($p > 0.05$) between baseline and third follow-up and (at 90 days) follow-up among two groups.

Improvement of MELD Score during Follow-up (Fig. 2)

At baseline the mean MELD score was found to be 28.6 ± 4.8 in PLEX group and 28.0 ± 5.3 in SMT group. At first follow-up (At 7 days) the mean MELD was found to be 22.4 ± 4.2 in PLEX group and 23.7 ± 7.3 in SMT group. At second follow-up (At 30 days) mean was found to be 19.9 ± 5.8 in PLEX group and 21.7 ± 3.4 in SMT group. At third

follow-up (At 90 days) mean MELD was found to be 15.6 ± 4.6 in PLEX group and 14.2 ± 2.9 in SMT group. The difference of MELD score at different time points did not show any statistical significance. At baseline mean MELD Na score was found to be 30.7 ± 3.7 in PLEX group and 30.1 ± 5.3 in SMT group. At first follow-up (At 7 days) mean was found to be 23.6 ± 4.8 in PLEX group and 25.9 ± 6.7 in SMT group. At second follow-up (At 30 days) mean was found to be 23.1 ± 5.3 in PLEX group and 24.9 ± 4.3 in SMT group. At third follow-up (At 90 days) mean was found to be 19.3 ± 6.9 in PLEX group and 18.2 ± 3.1 in SMT group. Statistically significant ($p > 0.05$) difference was not observed between two groups as well.

DISCUSSION

The study presented here has opted to check if PLEX may be a possible treatment alternative in ACLF patients in Bangladesh. In this context, it is important to present a short note of the realities of Bangladesh in the context of treatment of ACLF. In one hand, there are millions of patients with chronic liver diseases in this country and it is expected that most of these patients are unaware of their chronic liver diseases. Also, the acute insults that may cause ACLF in patients with chronic liver diseases are abundant in Bangladesh. Thus, the unawareness of the patients regarding development of severe liver diseases like ACLF and inherent limitations of health care delivery system of this country keeps the patients with chronic liver diseases in extreme susceptibility to develop ACLF. Next, if one develops ACLF, it is unlikely that he or she would receive a curative therapy for ACLF like liver transplantation in Bangladesh. Additionally, the patients with ACLF consult the physicians and health facilities at the fag end of their life. Taken together the entire management system of ACLF patients of Bangladesh needs to be developed on the target of time-buying process so that the liver can regain its regenerative process to have a recovery. In this context SMT is applied to ACLF patients. We have previously used

other immune modulators to treat ACLF with inconclusive but inspiring outcome.^{9–12} The present study allowed us to develop insights about scope and limitations of PLEX as an alternate and additive treatment modality in Bangladesh for ACLF patients. This may also constitute a credible example for the treatment of ACLF in developing and resource-constrained countries with huge burden of patients with chronic liver diseases but limited technical advancement.

We conducted only one cycle of PLEX therapy and one group receiving SMT was kept as control. Within an observation period of 90 days, of total 28 patients, there were 15 deaths and 13 survival in this cohort. The levels of serum creatinine, bilirubin, MELD score, and AARC score were significantly lower at basal level in survival group compared to death patients. Thus, patients with less severe form ACLF seem to be benefitted by SMT or PLEX therapy. If these are analyzed on the basis of PLEX therapy group and SMT therapy group, six patients of PLEX group and nine patients of SMT groups died and these variables were not statistically significant.

Regarding the efficacy, there was no clear survival benefit of PLEX-recipients compared to those treated by SMT. As expected, PLEX therapy improved serum bilirubin level compared to SMT receiver, although this was not statistically significant. This is a normal expected outcome. However, PLEX therapy did not improve serum creatinine. But, SMT group exhibited improvement of serum creatinine, but considerable patients of SMT group died of renal failure. These facts indicate that the delicate pathological process of ACLF is yet to be fully understood. However, we remain to put any evidence-based conclusive observation as the sample size was very low.

One contribution of the study is the safety of usage of PLEX. PLEX-related adverse events were not recorded in any patient. Different parameters of liver and kidney function did not aggravate due to PLEX therapy. Although PLEX is regarded as a safe treatment modality, however, this is the first evidence-based observation about confirmation of safety of PLEX in Bangladeshi set-up.

However, there remain several opportunities to improve PLEX therapy for ACLF patients. An ongoing study would check the efficacy and safety of combination treatment of double plasma molecular adsorption system and low-volume plasma exchange for patients with ACLF.¹³ In this study, PLEX was given for one cycle. It remains to be assessed if PLEX is repeated for two or three cycles and if better outcome follows. However, uncertainty will prevail about the utility of PLEX until large-scale multicenter trials are not accomplished.¹⁴ In addition, we have accomplished a therapy targeting generation of hepatocytes by GM-CSF in ACLF patients.¹¹ There remains opportunity to combine PLEX with GM-CSF for treating ACLF.

ORCID

Mamun Al Mahtab  <https://orcid.org/0000-0003-3728-3879>

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