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Prognostic factors and treatment effect of standard-volume plasma exchange for acute and acute-on-chronic liver failure: A single-center retrospective study

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ABSTRACT

Patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) have a high risk of mortality. Few studies have reported prognostic factors for patients receiving plasma exchange (PE) for liver support. We conducted a retrospective analysis using data of 55 patients with severe ACLF (n = 45) and ALF (n = 10) who received standard-volume PE (1–1.5 plasma volume) in the ICU. Hepatitis B virus infection accounts for the majority of ACLF (87%) and ALF (50%) patients. PE significantly improved the levels of total bilirubin, prothrombin time and liver enzymes ($P < 0.05$). Thirteen ACLF patients (29%) and one ALF patient (10%) underwent liver transplantation. Two ALF patients (20%) recovered spontaneously without transplantation. The overall in-hospital survival rates for ACLF and ALF patients were 24% and 30%, and the transplant-free survival rates were 0% and 20%, respectively. For the 14 transplanted patients, the one-year survival rate was 86%. Multivariate analysis showed that pre-PE hemoglobin ($P = 0.008$), post-PE hemoglobin ($P = 0.039$), and post-PE CLIF-C ACLF scores ($P = 0.061$) were independent predictors of survival in ACLF. The post-PE CLIF-C ACLF scores ≥59 were a discriminator predicting the in-hospital mortality (area under the curve = 0.719, $P = 0.030$). Cumulative survival rates differed significantly between patients with CLIF-C ACLF scores ≤ 58 and those with CLIF-C ACLF scores ≥ 59 after PE ($P < 0.05$). The findings suggest that PE is mainly a bridge for liver transplantation and spontaneous recovery is exceptional even in patients treated with PE. A higher improvement in the post-PE CLIF-C ACLF score is associated with a superior in-hospital survival rate.

1. Introduction

Extracorporeal detoxification for critically ill patients with liver failure admitted to the intensive care unit (ICU) is an important treatment modality for supporting the failing liver until spontaneous recovery or liver transplantation [1]. The most common causes of acute liver failure (ALF) in Western countries are acetaminophen and alcohol-induced liver injury, whereas hepatitis virus infections, especially acute hepatitis B flare-up, are the predominant causes of liver failure in East Asia [2–4]. The accumulation of various metabolites and the induction of cytokine burst in ALF lead to hepatic encephalopathy (HE), coagulopathy, progressive jaundice, and multiorgan failure [5–9]. Higher spontaneous recovery rates for ALF are reported for patients with acetaminophen ingestion, hepatitis A, and acute fatty liver of pregnancy, whereas lower recovery rates have been associated with hepatitis B, non-acetaminophen drug-induced liver injury, and unknown etiologies [10]. Acute-on-chronic liver failure (ACLF) occurs in patients with chronic liver disease is at high risk of in-hospital death [11]. In patients with severe ACLF, the mortality is higher than 50% during the waiting time for liver transplantation [12], and these patients have a short “transplantation window” due to the deterioration of multiorgan failure [13].

The management of ALF patients is based on hemodynamic, neuroprotective, and renal support systems with various medical treatments [14]. Liver transplantation is the only curative treatment but the availability of donor livers limits this opportunity for many. Artificial liver support system such as the molecular adsorbent recirculating system (MARS) and plasma exchange (PE) have been shown to stabilize

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clinical conditions relating to liver failure through the removal of accumulating toxic mediator [15]. Although the use of MARS in patients with liver failure leads to a significant decrease in the levels of serum creatinine and total bilirubin, short-term transplant-free survival is not affected [16]. A recent randomized control study demonstrated that high-volume PE (8–12 L per day) improves the transplant-free survival of patients with ALF by reducing activation of innate immunity and the severity of multiorgan dysfunction [17]. However, the current recommended exchange volume for ALF is 1–1.5 total plasma volume according to the American Society for Apheresis guidelines [10,18], and few studies to date have evaluated the effects of "standard-volume" PE in supporting patients with ALF and ACLF [19–22].

Various prognostic scores have been used to predict the survival of patients with liver failure and evaluate their need for liver transplantation [3]. For example, the Model for End-Stage Liver Disease (MELD) scale, which delivers a liver-specific prognostic score, has been widely used for transplantation candidate selection [23,24]. Other prognostic scores, such as the Chronic Liver Failure-Consortium (CLIF-C) ACLF score, have been used to monitor multiorgan failure and predict ICU survival [14,25–27]. However, few studies have focused on changes in these prognostic scores after administration of PE [17], and it has not yet been adequately determined whether such changes can predict survival.

In this study, we performed a retrospective analysis and reported our experience of using standard-volume PE in treating patients with ALF or ACLF in an ICU between 2009 and 2015. We also sought to identify prognostic factors determining the in-hospital survival of these patients and examined changes in MELD and CLIF-C ACLF scores after PE.

2. Materials and methods

2.1. Study design and patients

This was a retrospective cohort study based on data obtained from the prospective registry of plasmapheresis for various diseases at Chang Gung Memorial Hospital-Linkou (CGMHL), a 3406-bed tertiary-teaching medical center. We identified 55 patients with ALF or ACLF who received PE treatment in the liver ICU between August 2009 and December 2015. We excluded patients who received plasmapheresis for ABO-incompatible liver transplantation or acute and chronic antibody-mediated rejection after liver transplantation. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taoyuan, Taiwan (IRB NO: 102-0793B).

ALF is defined as severe liver injury occurring in a patient with no preexisting liver disease and with an illness duration of up to 4 weeks, which leads to a coagulation abnormality with an international normalized ratio (INR) of prothrombin time (PT) $\geq$ 1.5 and any degree of mental alteration (encephalopathy) [28]. ACLF is an acute hepatic insult that manifests as jaundice (serum bilirubin $\geq$ 5 mg/dl and coagulopathy (INR $\geq$ 1.5), which is complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease or cirrhosis [1]. All patients received standard medical therapy for the complications associated with liver failure, and etiology-specific therapies such as entecavir, tenofovir, and lamivudine for HBV infection according to international guidelines [29,30]. The indication for liver transplantation was evaluated by transplant surgeons according to standard criteria [31,32]. Uncontrolled sepsis, uncontrolled extrahepatic malignancy, severe mental impairment, drug abuser, and non-compliance patients were excluded from liver transplantation.

2.2. PE procedure

PE was performed daily or every other day, using an automated hollow-fiber membrane plasmapheresis machine (INFOMED HF-440, Informed, Geneva, Switzerland) with an LF030 plasma separator. The processed plasma volume was approximately 3000 ml for each session (1–1.5 total plasma volume); the blood flow rate was 100 mL/min; and the PE rate was 25–30 mL/min, with an equivalent volume of replacement fluid using fresh frozen plasma. The duration of PE is approximately 100 min. The procedure was performed through an uncuffed double-lumen dialysis catheter placed in the common femoral vein. Anticoagulants such as heparin were not used for PE due to the existence of coagulopathy in liver failure patients. A course of five PE sessions was first initiated and the need of additional PE was determined by ICU physicians based on the clinical response of HE grades, the levels of total bilirubin, and INR of PT [10,33]. PE was discontinued if the patient showed sustained clinical improvement, received liver transplantation, refused further therapy, had no clinical response, or the hemodynamic status became unstable for the implementation of the procedure [34,35].

2.3. Data collection and definitions used in scoring system

The demographic characteristics, laboratory parameters, etiologies of liver failure, and outcomes were collected by reviewing electronic medical records. Changes in laboratory parameters before and after administration of PE were compared; these included albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, INR of PT, creatinine, hemoglobin, white blood cell (WBC) count, platelet count, MELD scores, and CLIF-C ACLF scores. A standard protocol was used for collecting the laboratory data both before and after PE. The MELD score was calculated according to the Malinchoc formula: (0.957 ln[creatinine] + 0.378 ln[bilirubin] + 1.120 ln[INR of prothrombin] + 0.643) $\times$ 10 [24]. The CLIF-C ACLF score was determined according to previously published criteria [26].

2.4. Statistical analyses

Continuous variables were expressed as mean $\pm$ standard deviation or median and range according to the test for normal distribution by using the Kolmogorov–Smirnov test. Normally distributed variables were compared using the unpaired two-tailed Student's t-test, and nonnormally distributed variables were compared using the Mann–Whitney U test. Categorical data were expressed as percentages and tested using the chi-square test. The predictors of in-hospital survival were first evaluated using univariate logistic regression analysis. Potentially relevant variables were then included in a multiple logistic regression model based on the forward elimination of data. Cumulative survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. Discrimination in predicting in-hospital mortality was assessed by the area under the receiver operating characteristic (AUROC) curve through the nonparametric method. Youden's index was used to decide the cutoff value. All analyses were performed using SPSS for Windows version 22.0 (IBM Corp., Armonk, NY, USA). A *P*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

We identified 55 patients who received therapeutic PE for liver failure between August 2009 and December 2015 (Table 1). In ACLF group (n = 45), the mean patient age was 53 years, and 35 patients (77.8%) were male. The average MELD score on ICU day 1 was 37 $\pm$ 7 and the CLIF-C ACLF score was 58 $\pm$ 9 in ACLF patients. In ALF group (n = 10), the mean age of patients was 50 years and 50.0% of them were male. The average MELD score on ICU day 1 was 30 $\pm$ 5 in ALF patients. ALCF patients received a median of four PE sessions (range 1–9) and ALF patients underwent a median of five PE sessions (range