

Figure 1. Serum levels of sCD154 in patients with acute liver injury. (a) The serum levels of sCD154 in FHF patients were significantly higher than those in AH patients and the controls. (b) Among the patients with FH, the serum levels of sCD154 in deceased patients were significantly higher than those in surviving patients and the controls. All data are expressed as mean±standard deviation. FHF, fulminant hepatic failure; AH, acute hepatitis; NS, not significant; sCD154, soluble CD154.

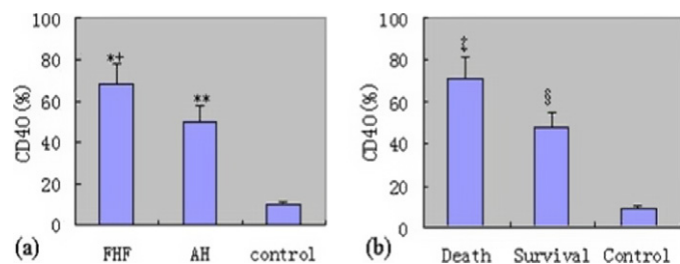


Figure 2. The percentage of CD40 expression on monocytes in patients with acute liver injury. (a) CD40 expression on monocytes in FHF patients and AH patients, * $P < 0.001$ and ** $P < 0.001$ compared with healthy controls, * $P > 0.05$ compared with AH patients. (b) Among the patients with FHF, CD40 expression on monocytes in deceased patients and the surviving patients, † $P < 0.05$ compared with the surviving patients, § $P < 0.01$ compared with the controls. All data are expressed as mean±standard deviation. FHF, fulminant hepatic failure; AH, acute hepatitis.

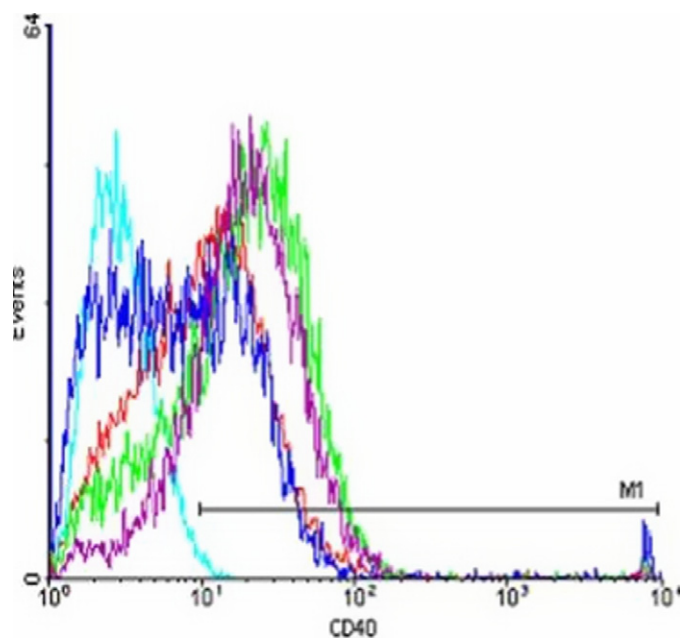


Figure 3. CD40 expression on monocytes in patients with FHF and AH, and the healthy controls.

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CIRCULATING ANGIOPOIETIN-2 CORRELATES WITH DISTANT ORGAN INJURY AND OUTCOME IN PATIENTS WITH ACUTE LIVER FAILURE

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Background: Endothelial activation leading to systemic vascular barrier breakdown may play a key role in the pathogenesis of distant organ injury after acute liver failure (ALF). Angiopoietin-2 (Ang-2), a circulating antagonistic ligand of the endothelial specific Tie2 receptor, is rapidly released from Weibel-Palade bodies and has been identified as a non-redundant gatekeeper of endothelial activation. Here, we examine whether the release of circulating Ang-2 correlates with the extent of distant organ injury and outcome in patients with ALF.

Methods: Ang-2 levels on admission were measured by immunoradiometric assay (IRMA) in sera from 20 healthy controls and 30 patients with ALF treated between 2001 and 2009, respectively. Transplant-free recovery (death or liver transplantation) after 28 days was the primary outcome studied.

Results: Median age of ALF patients was 35 years, 73% were female, and 50% had encephalopathy ≥grade 3. ALF etiologies were cryptogenic (30%), acute hepatitis B (20%), acetaminophen-induced hepatotoxicity (20%), and other causes (30%). Thirty-three percent of patients survived without transplantation, 10% died without transplantation, and 57% received a transplant (overall 28-day survival 90%). Median [IQR] Ang-2 serum concentrations were increasingly higher across the following groups: healthy controls (1.5 [81.4–2.2] ng/mL), patients with transplant-free recovery (5.0 [3.0–21.0] ng/mL), and patients that reached the composite endpoint of death or transplantation (17.7 [8.4–40.2] ng/mL). Ang-2 release correlated strongly with lactate levels as a surrogate marker of liver damage ($r = 0.66$, $P < 0.001$). Moreover, Ang-2 levels were closely associated with the extent of distant organ injury as evidenced by a close correlation with pulse rate/mean arterial pressure index ($r = 0.57$, $P = 0.0012$), fraction of inspired oxygen ($r = 0.5$, $P = 0.006$), acute kidney injury ($r = 0.58$, $P < 0.001$), and Sequential Organ Failure Assessment (SOFA) score ($r = 0.49$, $P = 0.009$). Kaplan–Meier analysis demonstrated that a ROC curve-generated Ang-2 cutoff value of 7.2 ng/mL (AUC of 0.76 [95% CI 0.57 to 0.95]) predicted transplant-free recovery during 28-day follow-up (Log-rank test: $p < 0.05$).

Conclusions: A marked imbalance of the Ang-Tie system in favour of Ang-2 is present in patients with ALF. Ang-2 may be used as a readily available powerful predictor of outcome and may open new perspectives to individualize treatment in the ICU.

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SAFETY AND EFFICACY OF THE EXTRACORPOREAL LIVER ASSIST DEVICE (ELAD®) IN PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE

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Background: Patients with acute-on-chronic liver failure (ACLF) have limited treatment options, leading to significant morbidity and mortality. The Extracorporeal Liver Assist Device (ELAD) circulates patient plasma through a hollow fiber cartridge containing

metabolically active, immortalized C3A human liver cells. Prior multicenter Phase 1 and 2 studies have indicated clinical utility in patients with Acute Liver Failure, and a study demonstrated significant improvement in transplant-free survival (TFS) in Chinese patients with ACLF.

Aim: Multicenter, Phase 2, open-label, randomized, concurrent control study to evaluate the safety and efficacy of the ELAD® bioartificial liver support system in ACLF patients. Efficacy endpoints included (TFS) and overall survival (OS) at 30 and 90 days.

Methods: Adults with acute decompensation of cirrhosis, SOFA score ≥ 9 at screening, and either a MELD score of ≥ 32 , or MELD ≥ 24 and at least one of

- Encephalopathy – West Haven grade 3 or 4;
- Type-1 hepatorenal syndrome.

Subjects were randomized 2:1 to either standard medical therapy (SMT) PLUS continuous ELAD treatment (SMT+ELAD) or SMT alone.

Results: Eighteen (18) patients with ACLF were randomized to SMT+ELAD (n=14) or SMT (n=4). One patient randomized to SMT+ELAD was ineligible at baseline and never treated. Mean MELD scores were 34.3 ± 5.7 and 40.8 ± 5.1 (p=0.08), respectively. ELAD treatment ranged from 36–240 hours (mean = 122.8 ± 21.7). More patients achieved 30-day TFS in the SMT+ELAD group (23%) versus SMT (0%). There was no difference in 30-day OS (SMT+ELAD 46% vs SMT 50%). 90-day OS was improved for SMT+ELAD (39%) vs SMT (25%) as was 90-day TFS (SMT+ELAD 15% vs SMT 0%). The rate of liver transplantation was higher for SMT (75%) vs SMT+ELAD (23%). ELAD treatment was well tolerated; of 39 SAEs reported (SMT+ELAD = 32, SMT = 7), none were unexpected for an extracorporeal device. In 2 patients SAEs, thought to be possibly related to ELAD treatment, led to discontinuation of ELAD.

Conclusion: SMT+ELAD in ACLF improves TFS at 30 and 90 days and OS at 90 days, is safe and well-tolerated. A larger, sufficiently powered randomized controlled trial is currently underway to expand on the results of this Phase 2 study.

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HUMAN LIVER PROGENITOR CELLS EXPRESS THE HEMATOPOIETIC STEM CELL MARKERS CD34/CD45

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Background: Despite widespread studies, the precise origin of liver progenitor cells (LPCs) which are found in the liver when hepatocyte proliferation is limited and followed by some kinds of liver injury remains controversial. Our previous research demonstrated that acute hepatic failure (AHF)-derived bone marrow stem cells (BMSCs) displayed a hepatic transcriptional profiling and early expression of hepatocyte specific genes. The purpose of this study was to profile the phenotype of LPCs in normal human liver.

Methods: Human LPCs were isolated from fresh surgical specimens of patients undergoing hepatectomies with Percoll density gradient centrifugation followed by four-step collagenase perfusion. LPCs were characterized by hematopoietic stem cell markers such as cluster domain (CD)34, CD45, CD90 and CD117 and liver progenitor cells markers such as α -fetoprotein (AFP), cytokeratin (CK)18, CK19, hepatocyte nuclear factor-1 α (HNF1 α), HNF4 α , hepatocyte growth factor receptor (c-Met) using flow cytometry and RT-PCR. Immunohistochemistry was used to characterize known oval cell with OV-6, CK18 and CK19. We also analyzed the transcriptomic profile of such cells as well as primary human hepatocytes by

Affymetrix GeneChip U133 plus 2.0 Array to demonstrate the characteristics of LPCs in normal human liver.

Results: The result of flow cytometry showed that LPCs expressed hematopoietic stem cell markers CD34, CD45, CD90 and CD117, similar to hematopoietic stem cells. RT-PCT detection showed that LPCs expressed hepatic stem cell specific markers AFP, CK18, CK19, c-Met, CD90 and CD117, as well as hepatocyte specific makers Albumin, HNF1 α , HNF4 α , glucose-6-phosphatase, Glutamine synthetase and transferrin, but negative for tyrosine aminotransferase and tryptophan 2, 3-dioxygenase. Immunohistochemistry analysis result showed that LPCs were positive for CK18 and CK19 but negative for OV-6. The microarray gene expression profile revealed that LPCs were similar to known oval cells. Moreover, LPCs shared more commonly expressed genes with AHF-derived BMSCs.

Conclusion: LPCs are a novel population of typical liver progenitors that express hematopoietic stem cell markers CD34, CD45 and can be isolated from normal liver tissue, which makes them potentially useful for future clinical therapy. These cells are likely to represent a resident progenitor population in adult human liver, even in the absence of liver failure.

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OUTCOME PREDICTION MODELS TO DETERMINE THE INDICATIONS OF LIVER TRANSPLANTATION IN PATIENTS WITH ACUTE LIVER FAILURE: DATA MINING USING DECISION TREE LEARNING AND RBF NETWORK

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Aims: In Japan, the indications for liver transplantation in patients with acute liver failure (ALF) are currently determined according to the guideline published by ALF study group of Japan in 1996 and clinical criteria described in King's College in 1989. However, a decline in the predictive accuracies of both guidelines was found when they were applied for recent patients. We established new guidelines using data mining techniques.

Methods: The subjects were 698 patients developing ALF between 1998 and 2003. All patients showed a prothrombin time (PT) of less than 40% and grade II or more severe hepatic encephalopathy. Patients who were either older than 65 years old, underwent liver transplantation or had been administered blood products before the development of hepatic encephalopathy were excluded from the study. Data on a total of 104 items were collected from 370 patients (survived: 170; died: 200) to construct decision trees and Radical Basis Function (RBF) networks. Validation of the obtained algorithms was performed using data similarly selected from 77 ALF patients seen in 2004/2005.

Results:

- Decision Tree:** ALF patients were classified into 7 categories through 5 items; serum total bilirubin, peripheral platelet counts, disease etiology, age of patients and the presence of ascites. The mortality rates were 89%, 88%, 80%, 67%, 31%, 25% and 23% in categories 1–7, respectively. The accuracy, sensitivity and specificity of the model were 79%, 78% and 81%, respectively. Similarly high values (74%, 82% and 67%, respectively) were obtained in the patients for validation.
- RBF models:** The patients were classified into 8 clusters, and predictive mortality values were calculated depending on a model in each cluster. When prognosis of patients with values greater than 0.5 was judged as “death”, the accuracy, sensitivity and specificity of the models were 71%, 75% and 67%, respectively.