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Original Article

Liver transplantation for hepatitis B-related acute-on-chronic liver failure patients

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Abstract: Aims: This study aimed to investigate the impact of perioperative cytokines, clinical variables and scoring systems on the short-term outcomes of liver transplantation (LT) in hepatitis B-related acute-on-chronic liver failure (HB-ACLF) patients. Methods: Plasma were prospectively collected immediately before LT and on the 1st, 3rd, 5th, 7th day after LT in HB-ACLF patients. The serum levels of twenty-seven cytokines were determined by Bio-Plex Pro™ Human Cytokine Assay. Pretransplant cytokines and their dynamic changes perioperatively, twenty clinical variables and four scoring systems were analyzed to confirm the correlation with post-LT outcomes. Results: It showed significantly differences in the dynamic change of G-CSF levels for HB-ACLF patients with complications and those without complications (P=0.037). Pretransplant infection was an independent risk factor for overall complications after LT. The logistic analysis indicated that both CLIF organ failure score and G-CSF were predictors of post-LT complications. The discriminatory power of G-CSF combined with CLIF organ failure score [AUC=0.812, 95% CI (0.663-0.962)] was better than that of either [AUC=0.738, 95% CI (0.578-0.898); AUC=0.665, 95% CI (0.471-0.859), respectively]. Conclusions: G-CSF combined with CLIF organ failure score can better predict the short-term outcomes of liver transplantation in HB-ACLF patients.

Keywords: Hepatitis B-related acute-on-chronic liver failure, liver transplantation, cytokines, CLIF-organ failure score, granulocyte colony-stimulating factor, pretransplant infection

Introduction

Acute-on-chronic liver failure (ACLF) is a complicated clinical syndrome with high risk of mortality. Interestingly, there is still incomplete agreement regarding its exact definition in the Eastern and Western hemispheres [1-3] and it is unclear whether the term means the same in both parts of the world [4]. The differences in definition largely reflect the differences in underlying etiologies of acute deterioration of liver disease between the East and the West. Alcoholic cirrhosis constitutes 50-70% of all the underlying liver diseases of ACLF in the western countries, whereas hepatitis-related cirrhosis constitutes about 10-15% of all the cases. However, in most of the Asian countries, hepatitis B constitutes 70% and alcohol only about 15% of all the etiologies of ACLF [2].

Liver transplantation remains the most effective treatment option that can salvage patients with ACLF. It has been a good indication for liver transplantation [5] and the outcomes have been satisfactory as good as other indications for LT [6-11]. However, the shortage of organs is the central problem of liver transplantation, leading to increasing waiting time and risk of dropout or death while waiting [6]. Therefore, identification of pretransplant clinical factors that could predict outcome becomes important in order to facilitate a fair and objective prioritization for organ allocation among other conditions, as well as to minimize the risk of post-transplant morbidity and mortality [12].

Pathophysiology of ACLF involves liver injury, which triggers an inappropriate and widespread activation of the inflammatory cytokine pathways leading to a systemic inflammatory response (SIRS), single organ dysfunction and ultimately progressing to multi-organ dysfunction syndrome (MODS). SIRS frequently occurs

Table 1. Clinical data for ACLF patients before LT

Age (yrs.)	45.51±11.57
Male/female	33/4
Tbil (μmol/L)	498.9 (106-792)
Serum creatinine (mmol/L)	64.5 (41-168.7)
INR	2.60±0.91
PTA (%)	31.4±11.1
Serum sodium (mmol/L)	134.7 (120.0-236.2)
Child-Pugh score	12 (9-14)
Child classification	B (2, 5.4%)
	C (35, 94.6%)
MELD score	27.60±5.91
CLIF-SOFA score	9 (6-16)
CLIF-organ failure score	8 (5-13)
SOFA score	7 (5-13)
Hepatic encephalopathy	Grade 0 (17, 45.9%)
	Grade 1 (10, 27%)
	Grade 2 (5, 13.5%)
	Grade 3 (1, 2.7%)
	Grade 4 (4, 10.8%)
Infection	12 (32.4%)
Ascites	36 (97.3%)
HRS	2 (5.4%)
Intubation	2 (5.4%)
ALSS	17 (45.9%)
CRRT	1 (2.7%)

Note: Tbil, total bilirubin; INR, international normalized ratio; PTA, prothrombin time activity; HRS, hepatorenal syndrome; ALSS, artificial liver support system; CRRT, continuous renal replacement treatment.

in patients with advanced cirrhosis and is associated with a poor outcome [13]. The transition from a stable cirrhotic condition to the burst of an acute decompensation leading to liver failure is based on an acute SIRS, mainly mediated by cytokines which are believed to play an important role in ACLF [14]. These observations provide potential biomarkers to predict the outcomes of ACLF and allow individualization of therapy. The relationship between the SIRS response and infection leads one to hypothesis that an inflammatory response may lead to immune dysregulation, which may predispose to infection that would then further aggravate a pro-inflammatory response resulting in a vicious cycle [15].

However, there were no data to demonstrate the impact of perioperative cytokines on the prognosis of ACLF patients who performed liver transplantation. The present study was focused on the predictive value of perioperative cytokines changes for the incidence of complications and short-term mortality in HB-ACLF patients following LT.

Patients and methods

From January 2010 to December 2014, four hundred and twenty-eight LTs were performed at Beijing You-An Hospital, Capital Medical University. The definition of ACLF was based on APASL consensus and the pathological diagnosis of liver explants. Plasma were prospectively collected immediately before LT and on the 1st, 3rd, 5th, 7th day after LT, then stored in -80°C. Bio-Plex Pro Human Cytokine 27-plex Assay (Bio-Rad, USA) was used for the measurement of cytokines by Luminex® 200™ System (Luminex, USA) [cytokines including interleukin-1beta (IL-1β), IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, fibroblast growth factor (FGF) basic, eotaxin, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ), interferon gamma-induced protein 10 (IP-10), monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1α), MIP-1β, platelet-derived growth factor BB (PDGF-BB), RANTES (regulated on activation, normal T cell expressed and secreted), tumor necrosis factor alpha (TNF-α) and vascular endothelial growth factor (VEGF)]. Furthermore, clinical variables and four scoring system including MELD score, SOFA score, CLIF-SOFA score and CILF-organ failure score were evaluated for the relation with post-LT complications and three-month mortality.

Inclusion criteria was as follows: (1) adult patients with age greater than eighteen years old, (2) the underlying liver diseases were hepatitis B-related, (3) patients had samples of five point-in-time plasma. Prior to the study, the protocol was approved by the Institutional Review Board of Beijing You-An Hospital, Capital Medical University according to the principles expressed in the 1975 Declaration of Helsinki, and written informed consents were obtained from all the study patients. All the liver graft were from death cardiac donor.

Table 2. Intraoprative and postoperative data for HB-ACLF patients

	ACLF
Blood loss (mL)	2500 (200-10500)
Surgery procedure	
Classical orthotropic LT	2 (5.4%)
Modified piggyback LT	35 (94.6%)
Complications	15 (40.5%)
Pulmonary infection	14 (37.8%)
Sepsis	8 (21.6%)
ARDS	9 (24.3%)
Renal dysfunction	7 (18.9%)
Acute rejection	3 (8.1%)
Gastrointestinal bleeding	1 (2.7%)
Portal thrombosis	1 (2.7%)
Intra abdominal bleeding	2 (5.4%)
Duration of intubation (h)	38 (8-1450)
CRRT	6 (16.2%)
Three-month mortality	5 (13.5%)

Statistic analysis

Correlation analysis was based on Spearman correlation coefficient. Logistic and COX regression analysis were used to define the factors related to post-LT outcomes. The discriminative power of perioperative clinical variables, MELD score, SOFA score, CLIF-SOFA score and CLIF-organ failure score were evaluated for post-LT complications and mortality using receiver operating characteristic curve analysis. The optimal cut-off value is determined according to the Youden index. All statistical analyses were performed by SPSS v. 20.0 for Windows (SPSS Inc, Chicago, IL). A p value <0.05 was considered statistically significant.

Results

Clinical data

Thirty-seven HB-ACLF patients were enrolled to the present study. The mean age was 45.51±11.57 yrs. and the ratio of male and female was 33:4, respectively. The median total bilirubin was 498.9 μmol/L (range, 106-792 μmol/L), serum creatinine was 64.5 mmol/L (range, 41-168.7 mmol/L), serum sodium was 134.7 (120.0-236.2) mmol/L and the mean INR was 2.60±0.91, respectively. Thirty-five (94.6%) patients was class C liver function according to Child classification in ACLF group. Twelve ACLF patients (32.4%) complicated with controlled pre-transplant infection. Over half (54.1%) of the patients had hepatic encephalopathy of which ten (27%) patients were grade I, 5 (13.5%) grade II, 1 (2.7%) grade III, and 4 (10.8%) grade IV. Other conditions were comprised of 12 patients with infection, 36 with ascites, 2 with HRS, 2 with intubation, 17 with ALSS and 1 with CRRT in ACLF patients (See **Table 1**).

The perioperative managements for ACLF patients have been described in our published articles [16, 17]. Surgery procedure for the majority of patients was modified piggyback liver transplantation and only two patients utilized of classical orthotropic LT. Fifteen patients (40.5%) suffered from post-LT complications, which consisted of fourteen patients with pulmonary infection, eight with sepsis, nine with ARDS, seven with renal dysfunction, three with acute rejection, two with intra abdominal bleeding, one with gastrointestinal bleeding as well as one with portal thrombosis. Three-month mortality for ACLF patients was 13.5% (see **Table 2**).

The relation of cytokines and post-LT outcomes in HB-ACLF patients

GM-CSF were excluded because of too many default values. For the ACLF patients undergoing liver transplantation, no preoperative cytokine had dramatic differences in complications group and non-complications group (all p value >0.05). Similarly, both preoperative cytokines except PDGF-BB and dynamic changes of cytokines showed no significant differences in ACLF patients between survivors and non-survivors. The levels of G-CSF were higher in non-complications than that in complications group. It showed significantly differences in the dynamic changes of G-CSF levels in ACLF patients with complications and those without complications from pre-transplant to the 1st, 3rd, 5th, 7th day following LT (P=0.037). Furthermore, the correlation analysis suggested that pretransplant PDGF-BB was significantly related with post-LT sepsis, ARDS as well as three-month mortality.

What's important, the logistic analysis indicated that both CLIF organ failure score and G-CSF were predictors of post-LT complications. Based on the analysis of the AUROC curves, the discriminatory power of G-CSF combined with CLIF organ failure score [AUC=0.812, 95% con-

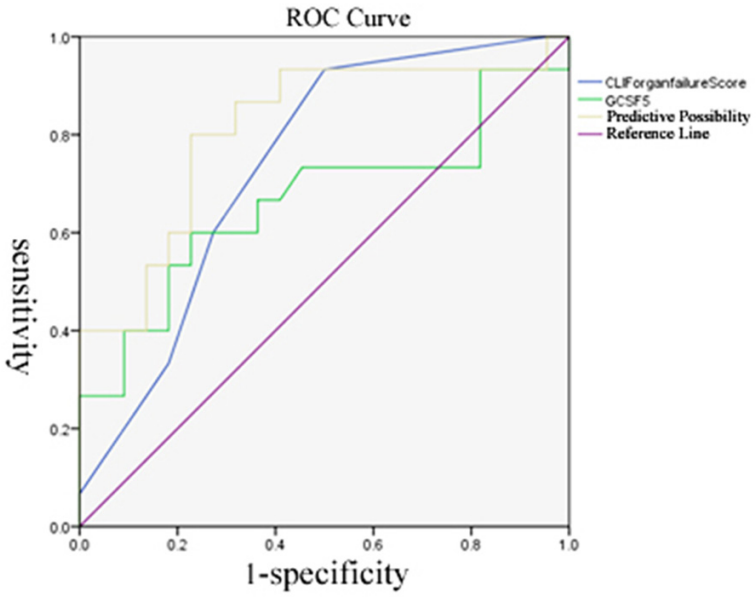

Figure 1. The predictive ability of CLIF-organ failure score and G-CSF for post-LT complications.

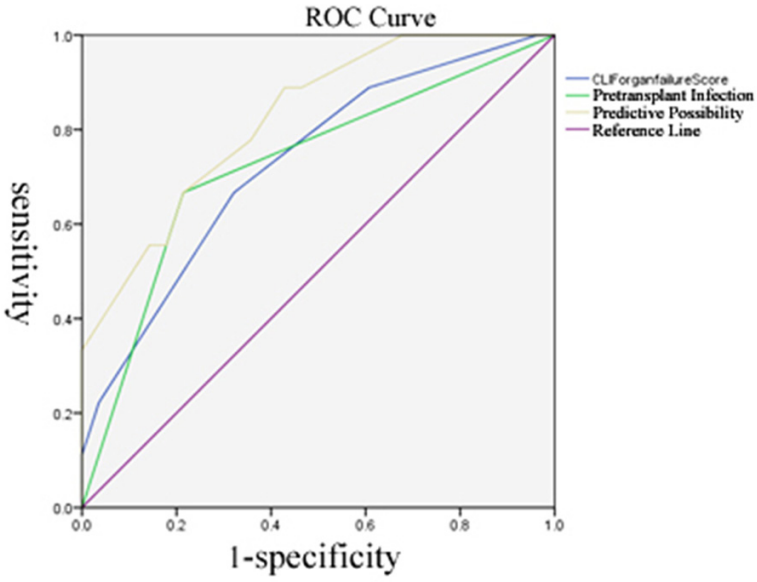

Figure 2. The predictive ability of CLIF-organ failure score and pretransplant infection for post-LT ARDS.

fidence index (CI) 0.663-0.962] was better than that of either (AUC=0.738, 95% CI 0.578-0.898; AUC=0.665, 95% CI 0.471-0.859, respectively) (**Figure 1**).

The prognosis analysis of clinical variables in HB-ACLF patients on post-LT outcomes

The correlation analysis indicated that pre-transplant infection was an important risk factor on postoperative complications, which was remarkably correlated with pulmonary infection, sepsis and ARDS after LT. Furthermore, post-LT renal dysfunction was relevant with pre-transplant MELD score, CLIF SOFA score, HRS. The further logistic analysis disclosed that pre-transplant infection was independent risk factor of post-LT pulmonary infection and sepsis, the AUC of which was 0.814 (95% CI, 0.655-0.972) and 0.931 (95% CI, 0.849-1).

For survivors and non-survivors, it showed significant differences in pre-transplant infection (P=0.00), PTA (P=0.021) and CLIF organ failure score (P=0.043). The correlation analysis indicated that pre-transplant infection, CLIF organ failure score was positively associated with survival and conversely, PTA had negative relation with survival. However, the logistic analysis suggested that pre-transplant infection, PTA and CLIF organ failure score had no predictive ability for post-LT mortality. Considering only five non-survivors, pretransplant infection, PTA and CLIF organ failure score might have the ability to predict the three-month mortality.

The predictive ability of scoring system for post-LT outcomes in HB-ACLF patients

As to four scoring systems, MELD score, SOFA score and CLIF SOFA score can not predict the incidence of post-LT complications, but CLIF organ failure score had significant differences in complications and non-complications groups (P=0.013). Also, preoperative CLIF-organ-failure score and infection can predict the occurrence of post-LT ARDS. The predictive value of the combination of preoperative CLIF-organ-failure score and infection for post-LT ARDS (AUC=0.823) was

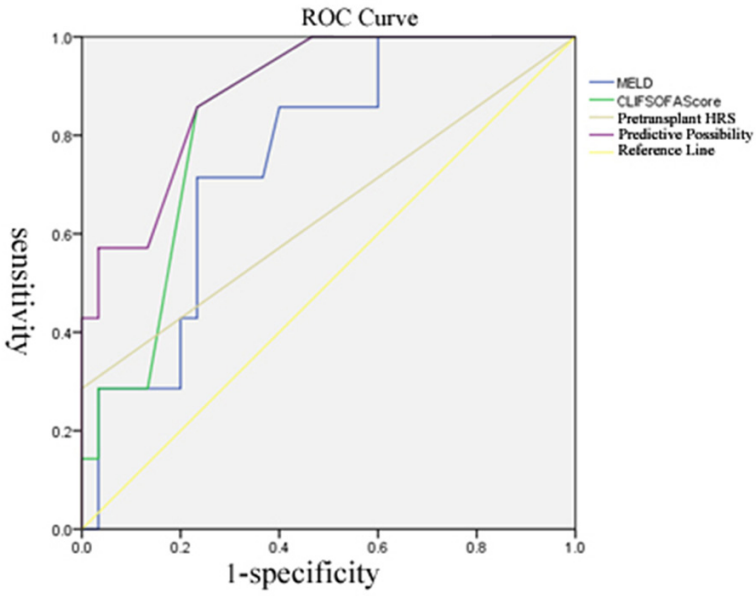

Figure 3. The AUC of preoperative MELD score, CLIF-SOFA score and HRS for post-LT renal dysfunction.

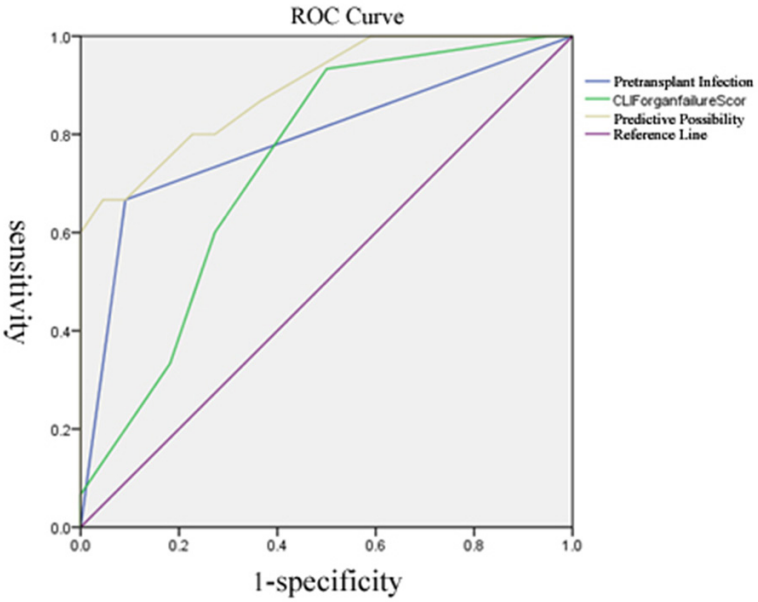

Figure 4. The predictive ability of CLIF-ogran failure score and pretransplant infection for the incidence of overall complications after LT.

better than that of either one (AUC=0.728; ACU=0.726, respectively) (**Figure 2**). Similarly, the AUC of preoperative MELD score, CLIF-SOFA score and HRS for post-LT renal dysfunction was 0.893 (range, 0.776-1) greater than any single one (**Figure 3**). Overall, pre-transplant infection and CLIF-organ-failure score could better predict the incidence of total post-LT complications (AUC=0.892, 95% CI 0.788-0.997) (**Figure 4**).

Discussion

In China, ACLF is the most common type of liver failure and the major etiology of ACLF is hepatitis B-associated liver diseases [18]. The majority of studies using nucleoside analog therapy, bioartificial liver support systems and stem cell transplantation have not shown a significant improvement in long-term survival [19-21]. So far, liver transplantation is still the only one available therapeutic option for such patients. Our data showed all the HB-ACLF patients had the severe clinical conditions preoperatively as reflected by hyperbilirubinemia, prolonged prothrombin time/INR, high MELD scores and CTP scores, and complicated with infection, hepatic encephalopathy, ascites, HRS and dysfunction or failure of one or more organs. In view of the severity of disease of these patients, all ACLF patients were admitted to SICU for supportive treatment as a bridge to LT as described in our published articles [16, 17]. Although with higher percentage of postoperative pulmonary infection, sepsis, ARDS, acute rejection, gastrointestinal bleeding, portal thrombosis and intra abdominal bleeding, the overall incidence of complications and three-month mortality were similar to other indications which suggested that liver transplantation should be a good indication for HB-ACLF patients.

Elevated levels of multiple pro- and anti-inflammatory cytokines have been described in ACLF including TNF-α, sTNF-αR1, sTNF-αR2, IL-2, IL-2R, IL-6, IL-8, IL-10, and IFN-γ [22, 23]. Si-

milarly, IL-1β, IL-6, IL-8, IL-10 TNF-α, IFN-γ and IL-21 levels in HB-ACLF were significantly higher than in normal control group [24, 25]. Moreover, plasma IL-10 levels may provide an early predictive marker for progression to HB-ACLF [24] and IL-21 has a causal role in the development of severe liver inflammation, which is upregulated in HB-ACLF and associated with severity of liver disease [25]. Our data also indicated that the increased levels of cytokines can be found in HB-ACLF patients including IL-1β, IL-1ra, IL-6, IL-8, IL-9, IL-10, IL-15, IL-17, Eotaxin, G-CSF, IP-10, MCP-1, MIP-1α, MIP-1β and TNF-α before LT. The differences in cytokines suggested the pathophysiology of ACLF were involved with an increased inflammatory cytokine response. What's important, G-CSF and PDGF-BB might be associated with post-LT morbidity and mortality. Recent trials in humans have shown the potential of G-CSF in amelioration of liver injury and improved survival in patients with ACLF. G-CSF has multifaceted actions in these patients because it causes increased mobilization of bone marrow-derived stem cells potentiating liver regeneration, prevents sepsis by causing improvement in the neutrophil numbers and function and modulates the dysfunctional immune response in these patients [26-28]. Neutrophil dysfunction has been shown to cause sepsis and further to the development of hepatorenal syndrome and hepatic encephalopathy in patients with ACLF. So, the higher levels of G-CSF might suggest the better prognosis for HB-ACLF patients undergoing LT.

Similarly, the incidence of pre-transplantation infection was significantly higher in HB-ACFL patients which might reflect the relationship between cytokines and pretransplant infections. Although the exact pathophysiology of the development of ACLF remains to be elucidated, unregulated inflammation is thought to be a major contributing factor and SIRS should be associated with increased inflammatory cytokine response. Moreover, the study demonstrated that pretransplant infection had an important role in selecting liver transplant candidates, which was remarkably correlated with pulmonary infection, sepsis and ARDS after LT. Meanwhile, pretransplant infection might be positively related with short-term mortality. ACLF patients receiving supportive treatment while awaiting liver transplant are at high risk for bacterial infections [29] and the most common cause of post transplant mortality in these patients is sepsis, which may preclude them from LT [6]. However, pretransplant infections that have been adequately treated do not pose a significant risk for poor outcomes, including post-transplant mortality [29, 30]. On the contrary, severe sepsis not responding to treatment (uncontrolled infection/sepsis) and sepsis induced progressive organ failure should be considered a contraindication for ACLF [6]. A pretransplant bacterial infection was considered adequately treated and the affected patient was regarded as an eligible transplant recipient only when he or she fulfilled the criteria as follows: (i) disappearance of symptoms and signs suggestive of sepsis, and (ii) normalization or improvement of laboratory and/or imaging findings indicating bacterial infection [30]. Pretransplant infection which can be controlled should not be contraindication for liver transplantation in HB-ACLF patients.

An ideal scoring system to select ACLF patients for LT should examine liver specific inclusion criteria and organ system-wide exclusion criteria. Increasing studies have demonstrated that CLIF-SOFA should be the best scoring system in predict the prognosis of ACLF [31-34]. The CLIF-SOFA score assessed the six organ systems, but it also took into account some specificities of end-stage liver disease and divides ACLF into no ACLF, grade 1, grade 2 and grade 3, with higher scores indicating more severe organ impairment [3]. In liver transplant recipients, 12-week mortality figures climbed along with ACLF grades and CLIF-SOFA in predicting 12-week mortality after LT was higher than those of MELD, MELD-Na, Refit-MELD, Refit-MELD-Na and Child-Turcotte-Pugh [32]. Unexpectedly, CLIF-organ failure score system [35] as the derivations of CILF-SOFA not only can predict the occurrence of post-LT complications but also short-term mortality. However, the scoring systems including MELD score, SOFA score and CILF-SOFA score had no predictive ability of post-LT short-term complications and survival, which was consistent with our past reports [16, 17]. Interestingly, CLIF-organ score combined with other parameters such as G-CSF, pretransplant infection had more strong predictive ability of the post-LT outcomes.

In summary, the present study evaluated perioperative cytokines in HB-ACLF patients as well

as their impact on the post-LT outcomes. G-CSF combined with CLIF organ failure score can better predict the shor-term outcomes of liver transplantation in ACLF patients induced by hepatitis B-related diseases. It also suggested that G-CSF intervention therapy might be developed to improve survival of patients with ACLF.

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Disclosure of conflict of interest

None.

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