Lower level of IL-28A as a predictive index of the artificial liver support system in effective treatment of patients with HBV-ACLF

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Abstract
Background: HBV-related acute-on-chronic liver failure (HBV-ACLF) is the most common type of liver failure with high mortality. Artificial liver support system (ALSS) is an important mean to reduce the mortality of HBV-ACLF but lacking index to assess its effectiveness. The cytokines are closely related to the prognosis of HBV-ACLF patients with ALSS treatment, however, which is not fully understood.

Methods: One hundred forty-two patients with HBV-ACLF and 25 healthy donors were enrolled. The cytokine profile of peripheral blood was determined in the patients before and after ALSS treatment, and their relationship with effectiveness of ALSS treatment in HBV-ACLF was analyzed.

Results: Serum IL-28A levels were markedly lower in ALSS-effective patients than those in non-effective patients pre-ALSS treatment. Similarly, serum IL-6 was significantly lower in ALSS-effective patients. Furthermore, for patients with effective treatment, serum IL-28A levels were positively related with IL-6 levels post-ALSS (r = 0.2413, p = 0.0383). The ROC curve analysis showed that serum levels of IL-28A (AUC = 0.6959 when alone or 0.8795 when combined with total bilirubin, platelet count and INR, both p < 0.0001) and IL-6 (AUC = 0.6704, p = 0.0005) were useful indices for separating effective from non-effective ALSS treatment of HBV-ACLF patients. Multivariate logistic regression analysis demonstrated that lower level of IL-28A was independently associated with higher effective rate of ALSS treatments.

Conclusions: Lower level of IL-28A is a predictive biomarker for ALSS in effective treatment of HBV-ACLF patients and IL-28A may be potential target for the treatment of HBV-ACLF.

KEYWORDS
artificial liver support system, cytokine, HBV-ACLF, IL-28A, IL-6
1 | INTRODUCTION

HBV-related acute-on-chronic liver failure (HBV-ACLF) is a life-threatening disease whose progress is closely associated with the persistence of chronic hepatitis B (CHB) and popular in the Asia-Pacific and African regions. It has become one of the great challenges of human death in the world due to its danger and rapid progress after its onset; moreover, the death rate of ACLF can reach 72% if the patients could not be timely and effectively treated. Although liver transplantation is an effective treatment of advanced HBV-ACLF, this mean is not always available because of the shortage of organ sources. Artificial liver support system (ALSS) is an adjuvant treatment of ACLF, which could produce conditions assisting hepatocyte regeneration by the way of temporary and partial replacement of the diseased liver function. A recent case–control matching study demonstrated that ALSS was an important means to reduce the 28-day liver transplant-free mortality of HBV-ACLF. Nevertheless, approximately 50% of HBV-ACLF patients who received ALSS still cannot benefit from it. The ineffective treatment of ALSS not only leads to a waste of social medical resources but also delays the patient with HBV-ACLF from receiving other treatments. Therefore, it is critical to explore a biomarker which could predict the outcomes of HBV-ACLF patients treated by ALSS.

Cumulative studies suggested that the innate immune and adaptive immune response be involved in the pathogenesis of HBV-ACLF. Systemic inflammation assessed by cytokines indicated there was acutely exacerbated in ACLF patients compared with that in non-ACLF patients with decompensated cirrhosis, moreover, the systemic inflammation assessed was strongly related to the severity and short-term mortality of ACLF. Additionally, the prolonged expression of inflammatory cytokines is a common accompaniment to more severe viral diseases. And ALSS had a satisfactory therapeutic effect on cytokine storm and inflammation of COVID-19 patients by means of peripheral plasma exchange, hemofiltration. Therefore, profiling cytokines would be a useful way in evaluating the treatment effectiveness of ALSS of patients with HBV-ACLF.

Interleukin-28A (IL-28A) as a member of type III interferon is of antiviral and anti-inflammatory potential. While interleukin-6 (IL-6) is a pro-inflammatory cytokine and sustained high level in the serum of patients with HBV-ACLF and is independently associated with the risk of mortality in patients with HBV-ACLF. Both the two inflammatory-related cytokines are proved to be key regulators of liver injury. However, to date, little is known about the kinetic profile and diagnostic value of serum IL-28A and IL-6 levels in patients with HBV-ACLF during ALSS treatment. In the present study, we dynamically measured the levels of serum IL-28A, IL-6, and other multiple cytokines, including interleukin-4 (IL-4), IL-8, IL-18, CD40 ligand (CD40L), CC chemokine ligand-2 (CCL2), CCL4, CCL20, chemokine C-X-C ligand-10 (CXCL-10), tumor necrosis factor-α (TNF-α), transforming growth factor-beta 1 (TGFβ1), and TGFβ2 in HBV-ACLF patients before and after ALSS treatment and analyzed the relationship between the cytokines and clinical variables, moreover, explored the biomarkers that could be used to predict the prognosis of ALSS.

2 | MATERIALS AND METHODS

2.1 | Subjects

From December 2018 to July 2019, we enrolled 142 patients who had been treated in the First Affiliated Hospital, Zhejiang University School of Medicine since they had suffered from HBV-ACLF; additionally, 25 healthy donors (HD) were also enrolled from the physical examination center of this hospital as control group. HBV-ACLF was diagnosed following the criteria of the Chinese Group on the Study of Severe Hepatitis B (COSSH). Patients with the following situations were excluded from the study: age less than 18 or more than 80 years, suffering from hepatocellular carcinoma or any other type of cancer, having experience in organ transplantation, with human immunodeficiency virus or other virus infection, usage of immunosuppressant.

All the enrolled subjects received 2–3 courses ALSS treatment (plasma exchange combined with hemofiltration) during their hospitalization. The therapeutic effects of 90days after the patients natively subjected to ALSS admission was obtained by electronic medical records or follow-up by telephone. HBV-ACLF patients with ALSS treatment were classified as effective and non-effective ALSS treatment group who died or underwent liver transplantation after ALSS treatment. The patients who had survived within 90days after admission were classified as effective ALSS treatment group. The study protocol conformed to the principles of the Declaration of Helsinki and its approval number from the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine was 2017(674).

2.2 | Data and sample collection

Morning blood samples were obtained from the HBV-ACLF patients before the time when the patient received the first ALSS treatment and after the patients received the last ALSS treatment. The blood samples were left standing at room temperature for 30min before they were centrifuged at 1000 × g for 15 min. The isolated serum was aliquoted and stored in −80°C for standby. Clinical biochemical indices and blood routine parameters were obtained through electronic medical records in our affiliation before ALSS treatment. Further, clinical parameters including age, sex, body mass index (BMI), hospitalization days, C-reactive protein, procalcitonin, erythrocyte sedimentation rate (ESR), alpha fetoprotein (AFP), endotoxin, HBV DNA load, and plasma ammonia were also recorded.

2.3 | Cytokines measurement

The levels of cytokines (IL-28A, IL-6, IL-4, IL-8, IL-18, CD40L, CCL2, CCL4, CCL20, CXCL-10, TNF-α, TGFβ1, and TGFβ2) were measured in a Lumine 200 System (Merck, Germany) using a Human multicytokine detection kit (R&D Systems, cat.no.LXSAHM-27 and FCSTM17-03). Cytokine determined and analyzed was performed in accordance with the manufacturer’s guideline.
2.4 | Statistical analysis

Continuous variables were expressed as means±standard deviations (SD) or medians±interquartile ranges (IQR), according to the data were normal or non-normal distribution, alternatively. Comparison of non-normal distribution data used the Mann–Whitney non-parametric U test (two groups) or the Kruskal–Wallis test (more than two groups). Categorical data were presented as frequency (percentage) and evaluated using a chi-squared test or Fisher’s exact test, as appropriate. Spearman correlation analysis was performed to identify correlation between IL-28A, IL-6 levels, and other clinical parameters. Multivariate analyses were performed to explore the association of clinical variables with effectiveness of ALSS treatment of HBV-ACLF patients. The predictive value of IL-28A and IL-6 levels of pretreatment was measured using receiver operating characteristics (ROC) analysis. All statistical analyses were two-tailed and carried out using SPSS version 24.0 (IBM Corp., Armonk, NY) and GraphPad Prism 9.0 (San Diego, CA, USA). Statistical significance was set up as a value of p<0.05.

3 | RESULTS

3.1 | Baseline characteristics of the subject enrolled

The demographic and clinical characteristics of the enrolled HBV-ACLF patients were presented in Table 1. The majority enrolled patients were male (119/142, 83.8%), and their average age was 48±13 years. All the HBV-ACLF patients subjected to 2–3 courses of ALSS treatment, finally, 81 survived subjects without liver transplant were classified as ALSS treatment effective group, while 61 subjects who had died or received liver transplant were classified as ALSS treatment non-effective group. In addition, there were no significant differences in age, sex, BMI, hospitalization days and AST, total protein, C-reactive protein, procalcitonin, AFP, endotoxin, blood ammonia, HBV DNA load in serum between the effective, and non-effective group. Compared with the effective group, non-effective group had higher baseline levels of ALT (p = 0.031), total bilirubin (p = 0.003), white blood cell count (p = 0.012), neutrophils percentage (p = 0.012), creatinine (p = 0.039), and blood urea nitrogen (p = 0.002) but lower levels of albumin (p = 0.020), lymphocytes percentage (p = 0.013), platelet count (p = 0.002), and erythrocyte sedimentation rate (p = 0.022).

3.2 | Comparison of cytokines between the ALSS-effective and non-effective groups

The 142 HBV-ACLF patients subjected to 2–3 courses of ALSS treatment and there were significant changes in 9 out of 13 cytokines before and after ALSS treatment. The levels of IL-8, CCL4 and CCL20 with significant reduction were found only in the effective group (Figure 1A, all p < 0.01). Moreover, the levels of IL-6 [4.36 (2.60–8.4) pg/ml to 1.68 (0.64–3.76) pg/ml, 8.99 (4.36–15.59) pg/ml to 6.00 (1.26–14.22) pg/ml, p < 0.005], IL-18 [1013.2 (624.8–1507.1) pg/ml to 622.8 (404.1-1079.2) pg/ml, 926.1 (639.5–1395.5) pg/ml to 509.1 (359.1–927.0), p < 0.05], CD40L [5700.7 (3768.2–7771.6) pg/ml to 3330.7 (1296.2–6435.7) pg/ml, 4609.1 (3211.1–6584.5) pg/ml to 1372.2 (451.0–2671.1) pg/ml, p < 0.05], CCL2 [275.6 (183.2–355.1) pg/ml to 109.9 (73.2–204.7) pg/ml, 294.9 (179.2–435.7) pg/ml to 143.6 (78.7–274.2) pg/ml, p < 0.05], TGFβ1 [1182.5 (1120.4–3676.1) pg/ml to 1234.4 (654.2–3115.5) pg/ml, 2088.9 (1166.0–3596.6) pg/ml to 841.3 (507.8–1360.4) pg/ml, p < 0.05] and TGFβ2 [49.7 (31.1–64.7) pg/ml to 31.1 (15.5–49.3) pg/ml, 58.4 (33.3–70.8) pg/ml to 35.4 (14.7–56.3) pg/ml, p < 0.05] presented significant reduction both in the effective and non-effective group (Figure 1B). However, the differences between the levels of IL-28A, TNF-α (Figure 1C), IL-4, and CXCL10 (Figure S1) before and post-ALSS were significant neither in the effective nor in the non-effective groups. And IL-28A was the only cytokine increased after ALSS treatment in serum of HBV-ACLF patients, although the difference was not statistically significant.

Additionally, at baseline, 11 out of 13 cytokines of HBV-ACLF patients were significantly different from these in HD, the detail was that serum levels of IL-6, IL-8, IL-18, CCL2, CCL20, CXCL-10, and CD40L were increased in HBV-ACLF patients, while IL-28A, IL-4, TGFβ1, and TGFβ2 were decreased (Table S1). However, no significant differences in serum levels of CCL4 or TNF-α were observed between HBV-ACLF patients and HD (Table S1). Furthermore, at baseline, the median of IL-28A levels in effective group (103.8 pg/ml) was significantly lower (p = 0.003) than that in non-effective group (182.3 pg/ml), and the median of IL-6 levels in effective group (4.36 pg/ml) was significantly lower (p = 0.001) than that in non-effective group (8.99 pg/ml) (Figure 2).

3.3 | Correlation of serum IL-28A or IL-6 levels with clinical variables

Using Spearman correlation analysis, we found that there was a significantly positive relationship between baseline IL-28A and white blood cell count, procalcitonin, blood urea nitrogen, INR, and a negative relationship between IL-28A and albumin. Simultaneously, the baseline IL-6 level was positively associated with serum ALT, total bilirubin, C-reactive protein, procalcitonin levels, and INR, but negatively correlated with serum levels of total protein and albumin (Table 2).

3.4 | Serum IL-28A level at post-ALSS positively associated with IL-6 in effective group

The Relationship between the serum IL-28A and IL-6 levels of ACLF patients with effective ALSS treatment in pre-ALSS (Figure 3A) or post-ALSS (Figure 3B), and with non-effective ALSS treatment in pre-ALSS (Figure 3C) or post-ALSS (Figure 3D) were analyzed using...
To evaluate the value for serum IL-28A or IL-6 levels to predict ALSS effectiveness, Spearman correlation analysis. Interestingly, there was only a statistically positive correlation between IL-28A and IL-6 in effective group at post-ALSS treatment ($r = 0.2413$, $p = 0.0383$, Figure 3B), but there were no significant correlation in effective group at pre-group at post-ALSS treatment ($r = 0.2413$, $p = 0.0383$, Figure 3B), but there were no significant correlation in effective group at pre-effective group.

### 3.5 Predictive value of serum IL-28A and IL-6 levels in ALSS effectiveness

To evaluate the value for serum IL-28A or IL-6 levels to predict ALSS treatment effectiveness, receiver operating characteristic (ROC) curves were obtained (Figure 4). The AUC was 0.6959 for IL-28A and 0.7248 for IL-6. The optimal cut-off value for IL-28A (170.4 pg/ml) and IL-6 (7.335 pg/ml) were determined using ROC analysis.

Variables (albumin, total bilirubin, white blood cell count, neutrophils percentage, lymphocytes percentage, platelet count, creatinine, blood urea nitrogen, INR, HBV DNA, plasma ammonia, IL-6, and IL-28A) that showed significant difference between ALSS treatment effective and non-effective groups were put into multivariate analyses. The results demonstrated that total bilirubin, platelet count, INR, and IL-28A were independent predictor of the ALSS being effective in the treatment of HBV-ACLF patients (Table 3). The effective rate of ALSS treatment of HBV-ACLF patients with low IL-28A (<170.4 pg/ml) were significantly higher than that in patients with high IL-28A (>170.4 pg/ml, OR = 4.854, 95% CI: 1.690–13.945, $p = 0.003$). And the AUC of the model built by IL-28A, total bilirubin, platelet count, and INR was 0.8795 (Figure 4C).

### 4 DISCUSSION

In the present study, the effective rate of ALSS treatment of HBV-ACLF patients is of 57.0% (81/142) and the higher levels of serum IL-28A or IL-6 in non-effective group is compared with that in effective group. By establishing a ROC curve, we found that the level of IL-28A or IL-6 could be used to predict the effectiveness for ALSS treatment of HBV-ACLF patients. Multivariate logistic regression analysis showed that lower level of IL-28A was independently associated with higher effective rate of ALSS treatment of HBV-ACLF patients.

HBV-ACLF patients could demonstrate a seriously high mortality if lack of effective and timely therapies, such as liver transplantation.
ALSS is widely used to bridge patients with liver failure to liver regeneration or liver transplantation when they were waiting liver source and reported to be effective in removing toxins of patients. The 90-day survival probability of HBV-ACLF patients treated by ALSS was approximately 50.0%–60.0%, which is consistent with our result (57%). And more and more studies succeeded to demonstrate that ALSS can improve survival rate of HBV-ACLF patients. Early prediction of the treatment effect of ALSS on ACLF patients is important for clinicians to make timely and accurate therapeutic decision.

Novel models comprising four (number of complications, age, scores of the model for end-stage liver disease and type of ALSS) or five (liver cirrhosis, total bilirubin, INR, infection, and hepatic encephalopathy) variables were constructed to discriminate survival in ACLF patients treated with ALSS. The former was related to ACLF patients with HBV as prevailing etiology and the latter focused on HBV-ACLF only. Another study developed a classification and regression tree constituted of three factors (hepatic encephalopathy, prothrombin time, and total bilirubin level) to identify subgroups of patients with...

**FIGURE 1** Serum cytokine levels in ACLF patients pre- and post-ALSS analyzed. Pre-ALSS, post-ALSS represented the cytokine levels in 142 ACLF patients before, after the 2–3 courses of ALSS treatment. In all, 9 out of 13 cytokines exhibited significant changes due to ALSS treatment. (A) The levels of 6 cytokines showed significant reduction both in the effective and non-effective groups at post-ALSS. (B) The levels of 3 cytokines showed significant reduction in the effective group at post-ALSS. (C) The levels of IL-28A and TNF-α showed significant difference neither in the effective nor in the non-effective group at post-ALSS. The data were expressed as Median with interquartile range (IQR), the middle solid circle (pre-ALSS) or square (post-ALSS) in the each panel presented as median values. *p < 0.05, **p < 0.01, ***p < 0.001.
HBV-ACLF who may benefit from ALSS therapy. However, none of these studies was associated with cytokines that were related not only to the prognosis of patients with HBV-ACLF but also to the effectiveness of ALSS treatment of HBV-ACLF.

Cytokine storm was first reported in graft-versus-host disease and referred to the phenomenon that immune cells in grafts attack host cells as foreign bodies. From then on, researchers gradually found that cytokine storm can also result from certain infections such as bacteria and virus. And cytokine storm produced by enhanced immune reaction against hepatitis B virus is considered to be an important incentive of ACLF derived from chronic hepatitis B. In HBV-ACLF, a variety of cytokines, such as...
IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, and IFN-γ, were of high levels in serum and could be removed by ALSS. However, we found no significant difference in TNF-α between HBV-ACLF patients and HD. And there were no obvious changes in IL-4, TNF-α in HBV-ACLF patients after ALSS. The different results may be related to the subjects in different population and different assays used to detect cytokines.

Similarly, our data showed elevated levels of serum IL-6 in patients with HBV-ACLF and decreased levels of IL-6 after ALSS treatment compared with that at before ALSS. Moreover, it was the first time to profile the level of serum IL-28A, which is a member of type III interferons (IFN-λ) and controls the inflammatory response, in HBV-ACLF patients before and after ALSS treatment. Among multitudinous cytokines detected, only IL-6 and IL-28A levels had ability to distinguish effective from non-effective ALSS treatment of HBV-ACLF patients. Interestingly, the relationship between IL-6 and IL-28A is significantly positive in effective group at post-ALSS treatment, but there was no significant correlation in effective group at pre-ALSS or in non-effective groups. This finding will contribute to predicting effectiveness of ALSS treatment of HBV-ACLF patients.

Additionally, the lower level of IL-28A or IL-6 was associated with higher effective rate of ALSS treatment of HBV-ACLF patients. Moreover, ROC curve was established to define the optimal cutoff value of IL-28A or IL-6 for distinguishing effective ALSS treatment of HBV-ACLF patients from non-effectiveness. Multivariate analysis showed that lower level of IL-28A was independently associated with higher effective rate of ALSS treatment of HBV-ACLF patients. And the AUC of the model built by IL-28A, total bilirubin, platelet count, and INR was 0.8795. Collectively, IL-28A may be a potential index of the ALSS-effective treatment of HBV-ACLF patients. As mentioned above, IL-28A is a member of type III interferons with
able to doubt that the low IL-28A level in HBV-ACLF patients is as conducive to the regeneration of hepatocytes. This may be one of the reasons why IL-28A is lower in HBV-ACLF patients who respond after ALSS treatment in serum of HBV-ACLF patients, and the raised plasmacytoid, and myeloid DCs. Once these cells are injured, serum be restrictively produced by hepatocytes, airway epithelial cells, and the generalizability of our results to other populations needs further verification.

There are some limitations in this study. First, the limited sample size of our study may cause potential bias of ability cytokines identifying effectiveness and non-effectiveness of ALSS treating HBV-ACLF patients. Second, subjects of this study are from the same center, and the generalizability of our results to other populations needs further verification.

In summary, the study presents that the changing profile of cytokines in peripheral blood of ACLF patients before and after ALSS treatment, and the lower level of IL-28A is an index of the ALSS-effective treatment of HBV-ACLF patients. Detection of serum level of IL-28A could contribute to early estimate HBV-ACLF patients who can exactly benefit from ALSS or not, and the clinician timely and accurately make therapeutic decision, although their roles in the pathogenesis of ALSS effectiveness need to be confirmed in the future.

**TABLE 3 Multivariate analyses for effectiveness of ALSS treating patients with HBV-ACLF**

| Variables                        | OR (95% CI)   | p Value |
|----------------------------------|--------------|---------|
| ALT (U/L)                        | 0.528        |         |
| Albumin (g/dl)                   | 0.677        |         |
| Total bilirubin (μmol/L)         | 0.993 (0.987–0.999) | 0.016 |
| White blood count (×10^9/L)      | 0.107        |         |
| Neutrophils percentage (%)       | 0.083        |         |
| Lymphocytes percentage (%)       | 0.084        |         |
| Platelet count (×10^9/L)         | 1.018 (1.005–1.031) | 0.005 |
| Erythrocyte sedimentation Rate (mm/h) | 0.389    |         |
| Creatinine (μmol/L)              | 0.271        |         |
| Blood Urea Nitrogen (mmol/L)     | 0.177        |         |
| INR                              | 0.050 (0.014–0.177) | <0.001 |
| IL-6 (IL-6 < 7.335 pg/ml vs. IL-6 ≥ 7.335 pg/ml) | 0.317 |         |
| IL-28A (IL-28A < 170.4 pg/ml vs. IL-28A ≥ 170.4 pg/ml) | 4.854 (1.690–13.945) | 0.003 |

**Abbreviations:** ALT, alanine aminotransferase; INR, international normalized ratio.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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