Journal of Clinical and Translational Hepatology **2021** vol. 9(5) | 626–634
DOI: 10.14218/JCTH.2020.00179

Original Article

Clinical Course and Outcome Patterns of Acute-on-chronic Liver Failure: A Multicenter Retrospective Cohort Study

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Received: 23 December 2020 | **Revised:** 5 March 2021 | **Accepted:** 23 March 2021 | **Published:** 16 April 2021

Abstract

Background and Aims: Acute-on-chronic liver failure (ACLF) is acute decompensation of liver function in the setting of chronic liver disease, and characterized by high short-term mortality. In this study, we sought to investigate the clinical course of patients at specific time points, and to propose dynamic prognostic criteria. ***Methods:*** We assessed the clinical course of 453 patients with ACLF during a 12-week follow-up period in this retrospective multicenter study. The clinical course of patients was defined as disease recovery, improvement, worsening or steady patterns based on the variation tendency in prothrombin activity (PTA) and total bilirubin (TB) at different time points. ***Results:*** Resolution of PTA was observed in 231 patients (51%) at 12 weeks after the diagnosis of ACLF. Among the remaining patients, 66 (14.6%) showed improvement and 156 (34.4%) showed a steady or worsening course. In patients with resolved PTA, the clinical course of TB exhibited resolved pattern in 95.2%, improved in 3.9%, and steady or worse in 0.8%. Correspondingly, in patients with improved PTA, these values for TB were 28.8%, 27.3%, and 43.9%, respectively. In patients with steady or worsening PTA, these values for TB were 5.7%, 32.3%, and 65.6%, respectively. Dynamic prognostic criteria were developed by combining the clinical course of PTA/TB and the clinical outcomes at 4 and 12 weeks after diagnosis in ACLF patients. ***Conclusions:*** We propose the following dynamic prognostic criteria: rapid progression, slow progression, rapid recovery, slow recovery, and slow persistence, which lay the foundation for precise prediction of prognosis and the improvement of ACLF therapy.

Citation of this article: Xu MM, Kong M, Yu PF, Cao YY, Liu F, Zhu B, *et al*. Clinical course and outcome patterns of acute-on-chronic liver failure: a multicenter retrospective cohort study. J Clin Transl Hepatol 2021;9(5):626–634. doi: 10.14218/JCTH.2020.00179.

Introduction

Acute-on-chronic liver failure (ACLF) represents acute decompensation of liver function in the setting of chronic liver disease, and is characterized by high short-term mortality.[1] In view of the different etiological compositions of chronic liver disease in Eastern and Western countries, the definition and diagnostic criteria of ACLF are also diverse. The European definition of ACLF was proposed by the Chronic Liver Failure ACLF in Cirrhosis (referred to as CANONIC) study,[2] which means acute decompensation of cirrhosis associated with organ/system failure(s) (including extrahepatic organ failure), and the severity of ACLF is graded according to the number of organ/system failures.

The dynamic clinical course of ACLF can be divided into disease resolution, improvement, worsening, and steady or fluctuating course,[3] which is evaluated by the variation in ACLF grades at different time points. In Eastern countries, ACLF is defined as acute decompensation in the setting of chronic liver disease or compensated rather than decompensated cirrhosis by the Asian Pacific Association for the Study of the Liver (commonly known as APASL).[4] This definition only includes hepatic failure, and extrahepatic insults are considered as complications of this syndrome. Furthermore, ACLF under this definition is considered reversible, defined as improvement in coagulation and jaundice, and without hepatic encephalopathy, but its clinical course pat-

Keywords: Acute-on-chronic liver failure; Clinical course; Outcome patterns; Retrospective cohort study.

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; APASL, Asian Pacific Association for the Study of the Liver; CANONIC, Chronic Liver Failure Acute-on-Chronic Liver Failure in Cirrhosis; WGO, World Gastroenterology Organization; CTP, Child-Turcotte-Pugh; d3-7 ACLF, third and seventh day after ACLF diagnosis; GIB, gastrointestinal hemorrhage; LT, liver transplantation; MELD, model for end-stage liver disease; PTA, prothrombin activity; TB, total bilirubin.

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tern has not been determined.

Although definitions and diagnostic criteria of ACLF differ, it is generally accepted that ACLF has a dynamically changing course, with high mortality, and requires organ support therapy or liver transplantation (LT). Timely and dynamic assessment on clinical course of ACLF patients is essential to avoid futile treatment and to reasonably choose LT. Many prognostic models have been proposed for evaluating the outcomes of ACLF patients, but they are not universally accepted. Specially, most of the models belong to a single time-point assessment based on short-term mortality.[5–7] In recent years, although the application of dynamic scoring models to assess the prognosis of ACLF patients has aroused extensive attention,[8–10] a single time-point outcome (death or LT) is still utilized as a prognostic variable. As is known, the clinical outcome of liver failure exhibits a dynamic pattern whether the final outcome is recovery or death, and it can be divided into rapid and slow processes. Thus, accurate assessment of prognosis will contribute to the improvement in ACLF management.

To evaluate the clinical course of ACLF patients more precisely, we formulated new dynamic prognostic criteria based on the dynamic alterations in key clinical indicators and outcomes, and analyzed the potential predictors of clinical course. The patients in our study were from an Asian population, the main cause was hepatitis B virus infection, and the main clinical manifestation was intrahepatic injury,[4,11] so liver function (total bilirubin) and coagulation index [prothrombin activity (PTA) or international normalized ratio] were used to evaluate the progression of ACLF. These new prognostic criteria will help develop a more practical predictive scoring model, determine the factors potentially influencing progression, and lay the foundation for making appropriate treatment strategies (intensive care unit treatment, organ support treatment, liver transplantation treatment, or hospice care treatment).

Methods

Patients

In this observational study, we retrospectively collected the data of ACLF patients from the Department of Hepatology in three hospitals in China. The patients included had been admitted to the Tianjin Third Central Hospital and the Fifth Medical Center of PLA General Hospital between November 1, 2012 and June 30, 2019, and to Beijing You'an Hospital Affiliated to Capital Medical University between January 1, 2015 and June 30, 2019.

The diagnosis of ACLF was made according to the APASL recommendations, as follows:[4] an acute hepatic insult that occurs in patients with chronic liver disease, manifested by jaundice (serum total bilirubin [TB] ≥5 mg/dL) and coagulation dysfunction (PTA≤40%), and complicated within 4 weeks by ascites and/or encephalopathy. Patients were divided into three types according to the severity of chronic liver diseases, as follows: type-A for patients without cirrhosis, type-B for patients with well-compensated cirrhosis, and type-C for patients with previous decompensated cirrhosis.[12–15]

All patient data were retrieved from electronic medical records. All treatments that were performed, mainly including etiological and comprehensive treatment, complied with the guidelines for ACLF, which is accredited by the Chinese Medical Association.[13]

The study procedures conformed to the ethical guidelines of the Declaration of Helsinki, and were approved by the ethics committees of Beijing You'an Hospital Affiliated to Capital Medical University, the Tianjin Third Central Hospital, and the Fifth Medical Center of PLA General Hospital. Due to the retrospective nature of this study, informed consent was waived.

Data collection

We collected information on patients who met ACLF diagnostic criteria during in-hospital stay and at 12-week post-discharge follow-up visit. This information included demographic data, complications, and laboratory measurements (e.g., TB, PTA, international normalized ratio). The outcome information, such as LT or death after enrollment, was also collected.

Exclusion criteria included: a) liver cancer or other malignant tumors; b) severe underlying diseases, such as severe chronic obstructive pulmonary disease with respiratory failure, severe coronary heart disease with heart failure, diabetes mellitus with severe complications; and c) chronic kidney disease and renal failure. In addition, we also excluded patients whose bilirubin and coagulation indicators were missing. The specific screening flowchart is detailed in Figure 1.

Definitions of clinical course pattern in ACLF patients

The clinical course pattern of ACLF patients was determined according to the variation tendency of PTA/TB, which was assessed at diagnosis, during the 12-week follow-up period, until death or LT. ACLF was diagnosed at admission or after admission. The variation tendency of PTA/TB (Fig. 2) was defined as resolution, improvement, and steady or worsening, respectively. Resolution of PTA was considered when PTA was increased to >40%, and TB resolution was defined as a 50% decrease in TB from its peak. Improvement indicated a decrease in TB and an increase in PTA, but it did not meet resolution. Steady course referred to the absence of variation in PTA/TB during follow-up. Worsening course indicated an increase in TB and a decrease in PTA. In assessing the variation tendency of PTA and TB, we excluded the effects of artificial liver therapy and blood transfusion on the transient variation of these two indicators.

Dynamic stratification criteria for clinical outcome

The stratification criteria for dynamic prognosis were developed by the combination of clinical course pattern and final outcome of ACLF patients. Clinical course pattern was assessed at 12 weeks after diagnosis, or before death or LT. The 12-week ACLF outcomes were divided into three categories: recovery, death (including LT), and still in a state of liver failure (persistence). The time course of outcomes was designated as rapid or slow recovery, progression, or persistence in accordance with the variation tendency in PTA/TB at 4 weeks and 12 weeks after diagnosis, respectively.

Statistical analysis

Continuous variables were presented as mean±standard deviation or median (interquartile range), and categorical variables as *n* (%). Dynamic prognostic stratification criteria were formulated according to the distribution of 12-week outcomes under different clinical course patterns of PTA/TB. Univariate analyses using Chi-square, one-way analyses of variance or Kruskal-Wallis test were performed to assess the association between patients' characteristics and dynamic stratification criteria of clinical outcome. A two-

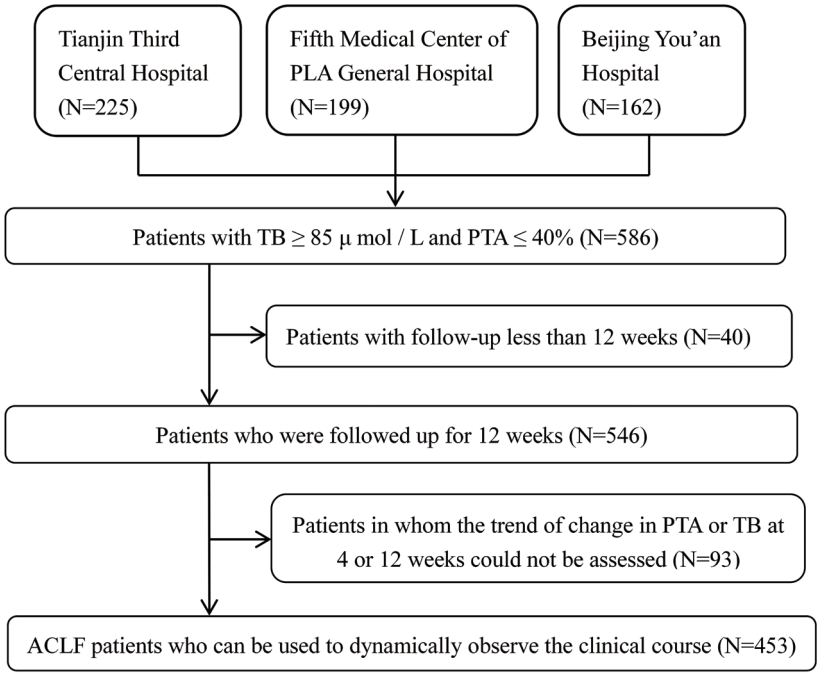

Fig. 1. Flowchart of patient enrollment. Patients whose variation tendency in PTA or TB at 4 or 12 weeks could not be assessed (*n*=93). ACLF patients whose clinical course can be dynamically observed (*n*=453). ACLF, acute-on-chronic liver failure; PTA, prothrombin activity; TB, total bilirubin.

sided *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Patient summary

Demographic and clinical characteristics of the patients are shown in Table 1. Four hundred and fifty-three patients were enrolled into the study. The mean age of patients was 48.3±11.5 years, and male patients accounted for 75.9%. The etiologies were as follows: hepatitis B virus (*n*=290, 64.0%), alcohol (*n*=67, 14.8%), hepatitis B virus+alcohol (*n*=47, 10.4%), and other (*n*=49, 10.8%). The World Gastroenterology Organization (WGO) type of all enrolled patients included type A in 144 (31.8%), type B in 146 (32.2%) and type C in 163 (36.0%). The occurrence rate of complications in these patients was 70.6% for ascites, 87.4% for bacterial infection, 12.1% for fungal infection, 7.3% for gastrointestinal hemorrhage (referred to here as GIB), 18.5% for hepatic encephalopathy, and 28.9% for acute kidney injury (AKI). Overall, the 4-week and 12-week LT-free survival rate in this study was 74.4% and 57.6%, respectively.

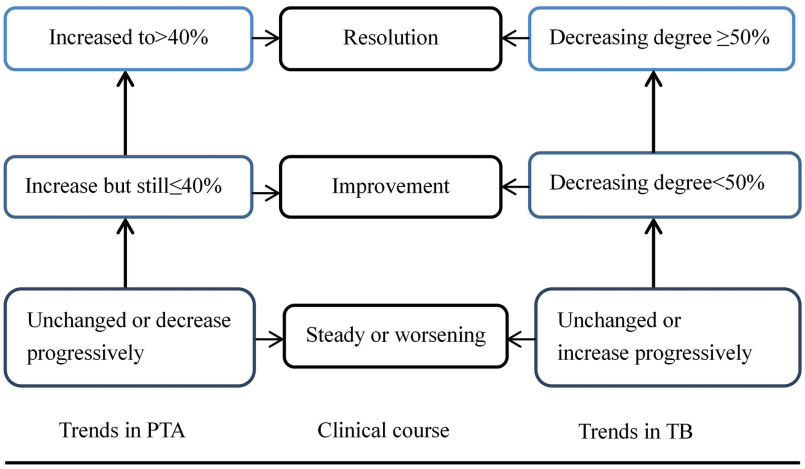

Fig. 2. Clinical course of ACLF patients assessed by variation tendency in PTA and TB. If international normalized ratio ≥1.5 is taken as the criterion of coagulation abnormality in the diagnosis of ACLF, INR and PTA show the opposite trend and can be used to evaluate the clinical process. ACLF, acute-on-chronic liver failure; PTA, prothrombin activity; TB, total bilirubin.

Table 1. Clinical characteristics of the patients with ACLF

Characteristics	*n*=453
Age in years, mean±SD	48.3±11.5
Male sex, *n* (%)	198 (75.9)
Underlying liver disease, *n* (%)	
Without cirrhosis	144 (31.8)
Compensated cirrhosis	146 (32.2)
Decompensated cirrhosis	163 (36.0)
Etiology of liver disease, *n* (%)	
Hepatitis B virus	290 (64.0)
Alcohol	67 (14.8)
Hepatitis B virus and alcohol	47 (10.4)
Other etiologies	49 (10.8)
Precipitating events, *n* (%)	
Reactivation of HBV	59 (13.0)
Alcohol	24 (5.3)
Bacterial infection	48 (10.6)
Drugs or poisons	34 (7.5)
Other	42 (9.3)
Unclear	246 (54.3)
Complications, *n* (%)	
Ascites	320 (70.6)
Bacterial infection	396 (87.4)
Fungal infection	55 (12.1)
Gastrointestinal hemorrhage	33 (7.3)
Hepatic encephalopathy	84 (18.5)
AKI	131 (28.9)
Laboratory data and scores, mean±SD	
Serum total bilirubin in mg/dL	17.9±9.2
Prothrombin activity, %	32.5±10.1
International normalized ratio	2.4±0.8
Serum creatinine in μmol/L	82.2±44.2
Blood sodium in mmol/L	134.2±5.1
White blood cell count as $\times 10^9$/L	8.1±6.9
Platelet count as $\times 10^9$/L	102.9±54.4
MELD score	24.6±5.7
CTP score	11.4±1.3
Survival rates, *n* (%)	
4-week LT-free survival	337 (74.4)
12-week LT-free survival	261 (57.6)

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; MELD, model for end-stage liver disease; SD, standard deviation.

Clinical course pattern and its relationship with 4-week and 12-week mortality in ACLF

At 4 weeks after ACLF diagnosis, PTA was found to be resolved in 191 patients (42.2%) (Table 2), steady or worsening in 155 (34.2%), and improved in 107 (23.6%). For 191 patients with resolved PTA, resolution pattern was most frequent (72.8%), followed by an improved pattern (23.6%) and a steady or worsening pattern (3.7%; Table 2). For 107 patients with improved PTA, TB improvement was most frequent (38.3%), followed by TB resolution (30.8%) and steady or worsening pattern (30.8%) (Table 2). For patients with steady or worsening PTA (34.2%), resolution was found in 8 (5.2%), improvement in 50 (32.3%), and a steady or worsening course in 97 (65.6%).

We also assessed the clinical course of PTA and TB at 12 weeks after ACLF diagnosis (Table 2). Overall, PTA resolution was observed in 231 patients (51%). Among the remaining patients, 66 (14.6%) showed improvement and 156 (34.4%) showed a steady or worsening course. For patients with resolved PTA, the clinical course of TB was as follows: resolution in 95.2%, improvement in 3.9%, and steady or worsening in 0.8%. For patients with improved PTA, the corresponding proportion of TB clinical course with resolution, improvement and steady or worsening pattern was 28.8%, 27.3%, and 43.9%, respectively. Similar to the 4-week data, the distribution of TB clinical course in patients with a steady or worsening PTA was resolved in 5.7%, improved in 32.3%, and steady or worsening in 65.6%.

Consistency was found in the clinical course of TB and PTA. The frequency of TB resolution was high in patients with resolved PTA and low in those with steady or worsening PTA, and vice versa (Table 2).

The 4-week and 12-week mortality rate was low in patients with resolved PTA and TB (0%), moderate in those with improved PTA and TB (14.6% and 55.6%), and high in those with steady or worsening PTA and TB (63.9% and 98%). Of note, the 12-week mortality rate was very high in those with steady or worsening PTA, regardless of TB course (Table 2).

Dynamic stratification criteria for clinical outcome

Dynamic prognostic criteria were developed by combining the clinical course of PTA/TB and the clinical outcomes of ACLF patients at 4 and 12 weeks after diagnosis. Patients were divided into three categories according to these criteria: recovery, progression, and persistence (Fig. 3). Rapid recovery was considered when both PTA and TB in ACLF patients were resolved within 4 weeks after diagnosis and the patients survived, and slow recovery was defined if both PTA and TB were resolved at 12 weeks after diagnosis. Progression could be categorized into rapid progression and slow progression, which were considered when ACLF patients had worsening PTA and TB or they did not achieve resolution and died within 4 and 12 weeks after diagnosis. Persistence was designated when ACLF patients had PTA less than 40% and/or worsened TB or the patients did not achieve resolution at 12 weeks after diagnosis. In addition, we defined the clinical course of two ACLF patients as slow persistence because they had resolved PTA and TB at 4 weeks but decreased PTA (<40%) at 12 weeks.

Clinical characteristics of ACLF patients stratified by the dynamic criteria for clinical outcome

According to dynamic prognostic criteria, 116 (25.6%) patients with ACLF were classified as rapid progression, 76 (16.8%) as slow progression, 137 (30.2%) as rapid recovery, 83 (18.3%) as slow recovery, and 41 (9.1%) as persistence (Table 3). The age of ACLF patients with recovery pattern was significantly lower than that of patients with

Table 2. Clinical course patterns in ACLF patients within 4 weeks and 12 weeks after diagnosis.

	Variation tendency in TB					
	4 weeks			12 weeks		
Variation tendency in PTA	Recovery (*n*=180)	Improvement (*n*=136)	Steady or worsening (*n*=137)	Recovery (*n*=248)	Improvement (*n*=72)	Steady or worsening (*n*=133)
Recovery, *n* (%)						
Prevalence	139 (72.8)	45 (23.6)	7 (3.7)	220 (95.2)	9 (3.9)	2 (0.8)
Mortality, *n*/total	0/139 (0)	1/45 (2.3)	1/7 (14.3)	0/220 (0)	2/9 (22.2)	1/2 (50)
Improvement, *n* (%)						
Prevalence	33 (30.8)	41 (38.3)	33 (30.8)	19 (28.8)	18 (27.3)	29 (43.9)
Mortality, *n*/total	0/33 (0)	6/41 (14.6)	9/33 (27.3)	0/19 (0)	10/18 (55.6)	29/29 (100)
Steady or worsening, *n* (%)						
Prevalence	8 (5.2)	50 (32.3)	97 (65.6)	9 (5.7)	45 (32.3)	102 (65.6)
Mortality, *n*/total	1/8 (12.5)	23/50 (46.0)	62/97 (63.9)	7/9 (77.8)	43/45 (95.6)	100/102 (98.0)

ACLF, acute-on-chronic liver failure; PTA, prothrombin activity; TB, total bilirubin.

progressive and persistent patterns (p=0.011). To be specific, the ages of ACLF patients with rapid and slow recovery patterns were 46.5±12 and 45.7±10.9 years, while the ages of patients with rapid progression, slow progression and persistence patterns were 50.3±11.7, 50.4±9.4 and 50.3±11.7 years, respectively.

The proportion of WGO type-C in patients with rapid and slow progression was 42.2% and 44.7%, which was significantly higher than that in patients with recovery pattern (24.1% and 31.3%, respectively), as the highest proportion of WGO type-C was 51.2% in patients with persistent pattern. Moreover, the proportion of complications (ascites, bacterial infection, fungal infection, and GIB) was significantly higher in patients with progression pattern compared to that in patients with recovery pattern; however, there was no significant difference between progression and persistence patterns (Table 3). With regard to other complications, the occurrence rate of hepatic encephalopathy was highest in patients with rapid and slow progression (34.5% and 21.1%), followed by slow persistence (19.5%), but it was low in patients with rapid and slow recovery patterns (6.6% and 13.3%). The rate of AKI was 50.9%, 35.5%, 14.6%, 21.7%, and 17.1% in patients with rapid progression, slow progression, rapid recovery, slow recovery, and persistence patterns, respectively (p=0.000).

However, outcome pattern cannot be distinguished accurately by a single complication. Thus, we classified patients into three categories according to the number of complications, namely, a: 0–1 complication, b: 2 complications, and c: 3 or more complications. The number of complications was significantly different among the five prognostic patterns. For patients with rapid progression, slow progression, slow persistence, slow recovery, and rapid recovery patterns, the percentage with 0–1 complication was 7%, 14%, 20%, 28%, and 42%, respectively (Fig. 4). Similarly, the percentage with two complications was 18%, 37%, 49%, 41%, and 42%, and the percentage with 3 or more complications was 75%, 49%, 32%, 31%, and 16%, respectively (p=0.000).

The baseline PTA in ACLF patients with rapid progression was significantly lower than that in patients with other outcome patterns; conversely, TB in these patients was remarkably higher than that in patients with other patterns. There was no significant difference in PTA and TB among the other patterns (p>0.05). Similarly, baseline model for end-stage liver disease (MELD) score and Child-Turcotte-Pugh (commonly referred to as CTP) score were notably higher in ACLF patients with rapid progression than in those with other patterns; however, they were not significantly different among the other patterns.

Discussion

This study analyzed the clinical course of ACLF patients using jaundice and coagulation function as key diagnostic indicators. We found that the death or LT rate was 42.4% at 12 weeks after diagnosis. In the remaining patients, PTA and TB were both resolved in 48.6% of patients, and liver failure was persistent in 9.1% of patients. In view of the dynamics of the ACLF process, we proposed dynamic prognostic criteria based on the different clinical outcomes at 4 and 12 weeks after ACLF diagnosis, and found that the percentage of ACLF patients who exhibit rapid progression, slow progression, rapid recovery, slow recovery, and slow persistence was 25.6%, 16.8%, 30.2%, 18.3%, and 9.1%, respectively. We then preliminarily analyzed the clinical factors potentially affecting the dynamic outcome of ACLF patients. We also observed that an increasing number of complications not only accelerated death in ACLF patients but also deferred possible recovery. However, indicators in-

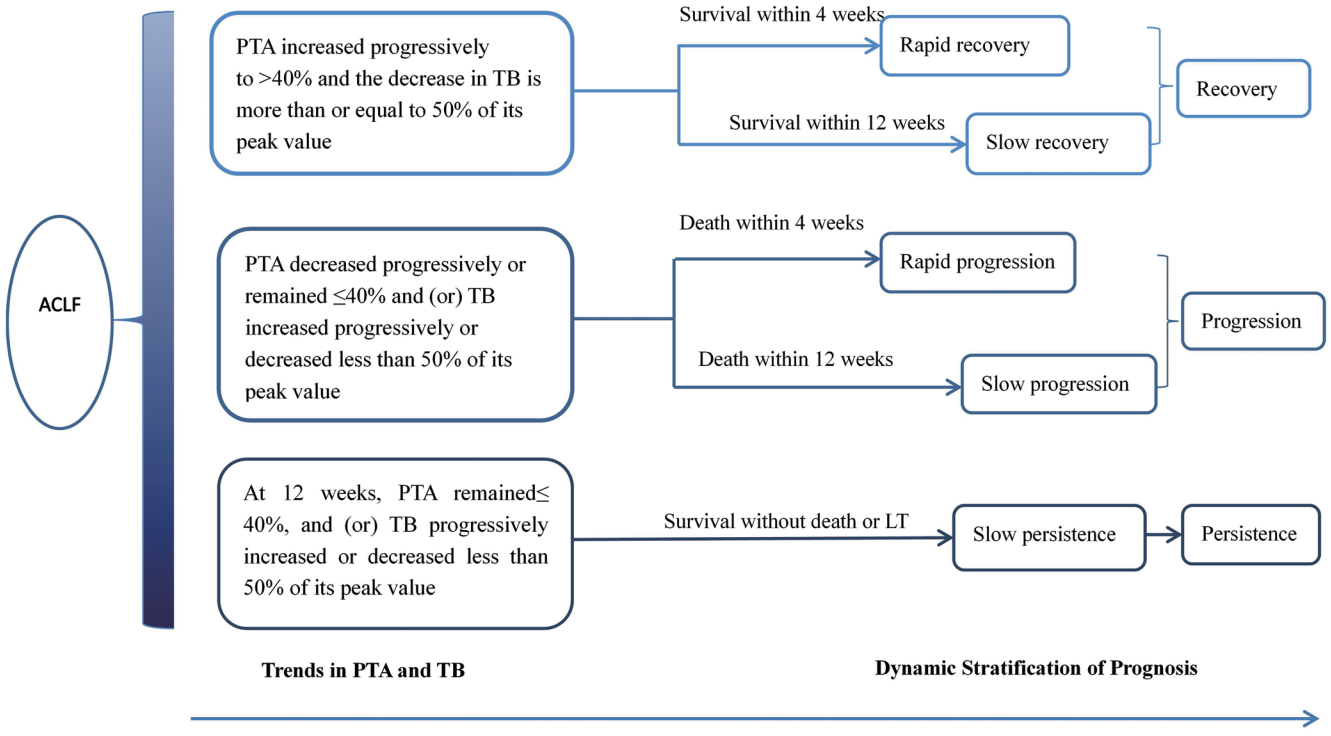

Fig. 3. Dynamic stratification criteria for clinical outcomes in ACLF patients. If INR ≥1.5 is taken as the criterion of coagulation abnormality in the diagnosis of ACLF, INR and PTA show the opposite trend and can be used to evaluate the clinical process. ACLF, acute-on-chronic liver failure; INR, international normalized ratio; PTA, prothrombin activity; TB, total bilirubin.

cluding baseline PTA, TB, MELD score and CTP score have limited power to predict dynamic prognosis.

Our findings suggest that the assessment on ACLF prognosis should be dynamically stratified in order to develop a more precise and individualized prognostic scoring model. Timely assessment of the clinical course of PTA and TB and monitoring of the complications during ACLF treatment can help to formulate subsequent treatment strategies: intensive care unit management and LT, or discontinuation due to futility.

Our data showed that the percentages of resolved PTA in ACLF patients at 4 and 12 weeks after diagnosis were 42.2% and 51.0%, respectively; for resolved TB, they were 39.7% and 54.7%, respectively and for resolved PTA and TB, they were 30.7% and 48.7%, respectively. These results are similar to those reported by APASL.[4] According to the consensus on ACLF, approximately 70% of ACLF patients who survived 90 days gradually recover, and the coagulation index returns to normal earlier than TB, which is consistent with our data. The European CANONIC study[3] used the change in ACLF grade of patients within 4 weeks after diagnosis to define the disease outcome, which showed that resolution (no-ACLF) is observed in 42.5% of patients within 4 weeks after diagnosis, arguing that the best period to define the clinical course of ACLF is between the third and seventh day after ACLF diagnosis (referred to as d3-7 ACLF). This viewpoint is based on its ability to predict 28-day and 90-day mortality. However, our study demonstrated that within 12 weeks after diagnosis, apart from survivors with a recovery pattern, 9.1% of survivors have a persistence pattern, excepting death or LT. Therefore, the predictive value of the d3-7 ACLF clinical course is limited.

To construct a more precise and comprehensive prognostic model, we proposed the following dynamic prognostic criteria: rapid progression, slow progression, rapid recovery, slow recovery, and slow persistence. We preliminarily analyzed the clinical factors potentially affecting the dynamic outcome of ACLF patients. The results showed that baseline PTA, TB, MELD and CTP scores are obviously different between patients with rapid progression and those with other prognostic patterns, but they are not remarkably different among other prognostic patterns. Thus, the MELD score, which is currently most commonly used to allocate liver resources,[16] can rapidly identify progressive patients, but it has restricted predictive value for other prognostic patterns. Nevertheless, patients with rapid progression die within 4 weeks after onset and have more complications, they are often in the late stage of liver failure, and have poor prognosis, even after LT. Studies[17–19] have shown that ACLF-3 LT has a lower survival rate than ACLF-1, 2 and a short transplantation window. Therefore, for patients with rapid progression, treatment decisions need to be made quickly to avoid salvage LT, and for patients with slow progression, LT can be delayed. At the same time, dispensable LT should be avoided in patients with potential recovery. Therefore, new scoring criteria should be derived from the dynamic outcome model in order to reasonably allocate scarce donor livers.

In addition, dynamic prognostic classification is beneficial for identifying patients who are receiving futile treatment and to adjust treatment strategies in a timely manner. In the present study, the mortality rate of patients with non-resolution of PTA and TB within 4 and 12 weeks after ACLF diagnosis was 63.9% and 98%, respectively. For these patients, whether emergency LT or termination of futile organ support treatment, such as artificial liver therapy, needs to be performed requires further study to prove.

As reported in many previous studies, hepatic encephalopathy,[20] infection,[21] GIB[22] and AKI[23] have predictive value for death in ACLF patients. They can be used to dis-

Table 3. Clinical characteristics of ACLF patients with dynamic stratification based on different clinical outcomes

Characteristics	Rapid progression	Slow progression	Rapid recovery	Slow recovery	Slow persistence	*p*
	n=116 (25.6%)	*n*=76 (16.8%)	*n*=137 (30.2%)	*n*=83 (18.3%)	*n*=41 (9.1%)	
Age in years, mean±SD	50.3±11.7	50.4±9.4	46.5±12	45.7±10.9	50.3±11.7	0.011
Male sex, *n* (%)	94 (81.0)	61 (80.3)	104 (75.9)	68 (81.9)	30 (73.2)	0.664
Underlying liver disease, *n* (%)						0.001
Without cirrhosis	28 (24.1)	18 (23.7)	63 (46)	27 (32.5)	8 (19.5)	
Compensated cirrhosis	39 (33.6)	24 (31.6)	41 (29.9)	30 (36.1)	12 (29.3)	
Decompensated cirrhosis	49 (42.2)	34 (44.7)	33 (24.1)	26 (31.3)	21 (51.2)	
Ascites, *n* (%)	96 (82.8)	55 (72.4)	84 (61.3)	54 (65.1)	31 (75.6)	0.003
Bacterial infection, *n* (%)	108 (93.1)	70 (92.1)	106 (77.4)	74 (89.2)	38 (92.7)	0.001
Fungal infection, *n* (%)	23 (19.8)	11 (14.5)	7 (5.1)	10 (12)	4 (9.8)	0.010
GIB, *n* (%)	12 (10.3)	11 (14.5)	3 (2.2)	6 (7.2)	1 (2.4)	0.007
Hepatic encephalopathy, *n* (%)	40 (34.5)	16 (21.1)	9 (6.6)	11 (13.3)	8 (19.5)	0.000
AKI, *n* (%)	59 (50.9)	27 (35.5)	20 (14.6)	18 (21.7)	7 (17.1)	0.000
ALT in U/L, median (IQR)	150 (65–548)	169.8 (54.9–405)	257 (75.8–797.7)	181.7 (62–546.5)	85 (31–247.4)	0.008
AST in U/L, median (IQR)	189 (93.6–189)	166 (106.6–451.6)	244 (119.6–542.8)	193.1 (107.3–326.8)	115.5 (70.5–243)	0.010
ALB in g/L, mean±SD	29.2±4.7	28.0±5.7	29.1±5.4	29.4±4.8	27.4±4.9	0.165
TB in mg/dL, mean±SD	22±9.7	18.1±9.2	15.9±8.1	17.2±9.6	13.9±6.5	0.000
PTA in %, mean±SD	27.7±10.6	34.2±11.5	35.3±9.2	32.4±7.9	33.5±7.8	0.000
INR, mean±SD	2.8±1.0	2.3±0.6	2.2±0.6	2.3±0.7	2.3±0.7	0.000
Cr in μmol/L, mean±SD	91±51.1	79.4±40.1	75.9±33.2	82.3±51	83.2±46.1	0.084
Na in mmol/L, mean±SD	132.7±5.1	133.9±4.9	135.7±4.6	134.5±4.9	132.8±5.9	0.000
WBC as $\times 10^9$/L), mean±SD	7.8±3.6	7.5±4.1	8.1±8.0	8.5±4.8	9.3±14.3	0.114
PLT as $\times 10^9$/L), mean±SD	92.1±49.1	100±51.2	113.9±57.9	109.6±54.7	87.8±54.6	0.004
MELD score, mean±SD	27.8±6.2	23.8±6.0	22.7±4.7	24.3±4.6	23.4±5.6	0.044
Child-Pugh score, mean±SD	11.7±1.3	11.4±1.6	11.1±1.3	11.5±1.2	11.6±1.3	0.028

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; GIB, gastrointestinal bleeding; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelet; PTA, prothrombin activity; SD, standard deviation; TB, total bilirubin; WBC, white blood cell count.

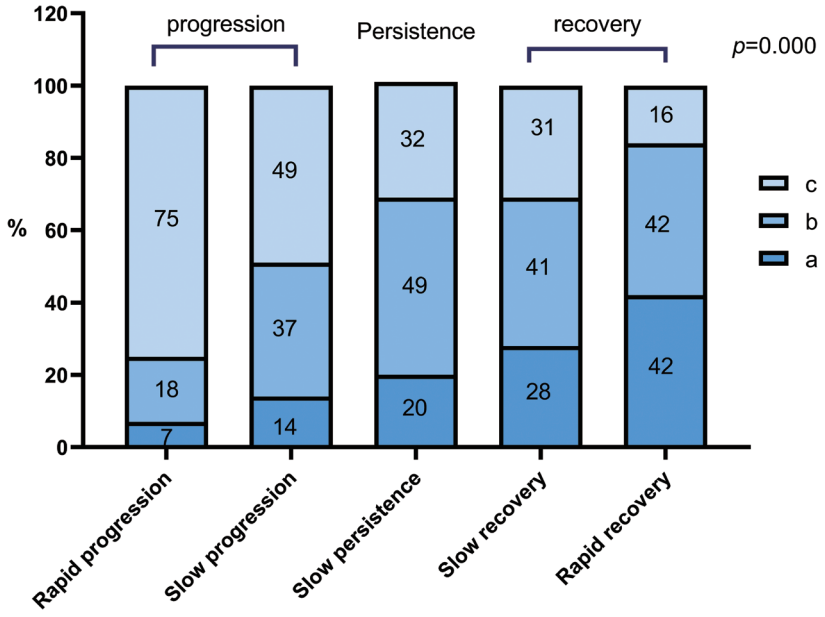

Fig. 4. Distribution of complications in ACLF patients with different clinical outcomes according to the dynamic stratification criteria. (a) 0–1 complication; (b) 2 complications; (c) 3 or more complications. ACLF, acute-on-chronic liver failure.

tinguish patients with recovery from those with progression but cannot distinguish patients with progression from those with persistence. It is well known that mortality will increase cumulatively as the number of dysfunctional or failed organs increases. Undoubtedly, these events can be utilized to predict outcomes and to calculate SOFA scores.[2] Meanwhile, a higher proportion of patients with three or more complications are observed in those with the aggravated dynamic prognostic classification, which is consistent with another study.[24] Thus, preventing complications is important to improve the dynamic outcome of ACLF patients.

There are limitations in this study. This is a retrospective cohort with insufficient information on the treatment of liver failure. Also, the impact of treatment options such as artificial liver therapy on dynamic prognosis was not analyzed. In addition, bacterial infection was judged according to the use of antibiotics, which, since it is often related to the diagnosis and treatment experience of clinicians, may have led to an overestimation of the bacterial infection rate among our patients. Moreover, ACLF patients were enrolled in this study when experiencing different disease courses, which may lead to misjudgment and ensuing uncertain results affecting the dynamic prognosis. Furthermore, multivariate analysis could not be performed in this study, due to the limited sample size. Hence, it is imperative to conduct a prospective cohort study for analyzing factors potentially affecting dynamic prognosis and developing new prognostic models.

In conclusion, we propose a more refined dynamic prognostic classification, which lays the foundation for developing a new accurate prognostic model for ACLF. Prediction of dynamic prognosis is helpful for making the optimal treatment strategy for ACLF patients and utilizing medical resources reasonably.

Funding

This study was supported by the National 13th 5-Year Plan for Hepatitis Research (Grant No. 2017ZX10203201-005 ,2017ZX10203201-007), National Key R&D Program of China (Grant No.2017YFA0103000), Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (Grant No. ZYLX201806), the National Natural Science Foundation of China (Grant No.81870429), Capital Clinic Characteristic Application Research (Grant No. Z181100001718143).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study conception and design (MMX, MK, YC, ZPD), acquisition of data (MMX, MK, PFY, YC, FL, YYC), analysis and interpretation of data (MMX, MK, YC, SLY, YZZ, WL, HBZ, BWD), drafting of the manuscript (MMX, MK), critical revision of the manuscript for important intellectual content (YC, ZPD, SJX, TH, HBZ, BWD), administrative, technical, or material support and study supervision (YC, ZPD).

Data sharing statement

No additional data are available.

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