World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2024 May 27; 16(5): 809-821

DOI: 10.4254/wjh.v16.i5.809

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Prospective Study

Characterization of acute-on-chronic liver diseases: A multicenter prospective cohort study

Yuan-Yao Zhang, Sen Luo, Hai Li, Shu-Ning Sun, Xian-Bo Wang, Xin Zheng, Yan Huang, Bei-Ling Li, Yan-Hang Gao, Zhi-Ping Qian, Feng Liu, Xiao-Bo Lu, Jun-Ping Liu, Hao-Tang Ren, Yu-Bao Zheng, Hua-Dong Yan, Guo-Hong Deng, Liang Qiao, Yan Zhang, Wen-Yi Gu, Xiao-Mei Xiang, Yi Zhou, Yi-Xin Hou, Qun Zhang, Yan Xiong, Cong-Cong Zou, Jun Chen, Ze-Bing Huang, Xiu-Hua Jiang, Ting-Ting Qi, Yuan-Yuan Chen, Na Gao, Chun-Yan Liu, Wei Yuan, Xue Mei, Jing Li, Tao Li, Rong-Jiong Zheng, Xin-Yi Zhou, Jun Zhao, Zhong-Ji Meng

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade C

P-Reviewer: Rashidi-Alavijeh J, Germany

Received: November 29, 2023
Revised: February 9, 2024
Accepted: April 9, 2024
Published online: May 27, 2024

Yuan-Yao Zhang, Sen Luo, Yuan-Yuan Chen, Zhong-Ji Meng, Department of Infectious Disease, Institute of Biomedical Research, Regulatory Mechanism and Targeted Therapy for Liver Cancer Shiyan Key Laboratory, Hubei provincial Clinical Research Center for Precise Diagnosis and Treatment of Liver Cancer, Taihe Hospital, Hubei University of Medicine, Shiyan 442000, Hubei Province, China

Hai Li, Yan Zhang, Wen-Yi Gu, Department of Gastroenterology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200120, China

Shu-Ning Sun, Guo-Hong Deng, Xiao-Mei Xiang, Yi Zhou, Department of Infectious Diseases, Southwest Hospital, The Third Military Medical University (Army Medical University), Chongqing 400000, China

Xian-Bo Wang, Yi-Xin Hou, Qun Zhang, Center of Integrative Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing 100020, China

Xin Zheng, Yan Xiong, Cong-Cong Zou, Department of Infectious Diseases, Institute of Infection and Immunology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430020, Hubei Province, China

Yan Huang, Department of Infectious Diseases, Hunan Key Laboratory of Viral Hepatitis, Xiangya Hospital, Central South University, Changsha 110051, Hunan Province, China

Bei-Ling Li, Xiu-Hua Jiang, Ting-Ting Qi, Hepatology Unit, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou 510515, Guangdong Province, China

Yan-Hang Gao, Na Gao, Chun-Yan Liu, Department of Hepatology, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Zhi-Ping Qian, Wei Yuan, Xue Mei, Department of Liver Intensive Care Unit, Shanghai Public Health Clinical Centre, Fudan University, Shanghai 200093, China

Feng Liu, Tianjin Institute of Hepatology, Nankai University Second People's Hospital, Tianjin 300192, China

Xiao-Bo Lu, Yi Zhou, Rong-Jiong Zheng, Xin-Yi Zhou, Infectious Disease Center, The First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, Xinjiang Uygur Autonomous Region, China

Jun-Ping Liu, Jing Li, Tao Li, Department of Infectious Diseases and Hepatology, The Second Hospital of Shandong University, Jinan 250000, Shandong Province, China

Hao-Tang Ren, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Disease, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310000, Zhejiang Province, China

Yu-Bao Zheng, Department of Infectious Diseases, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510630, Guangdong Province, China

Hua-Dong Yan, Department of Infectious Diseases, Ningbo No. 2 Hospital, University of Chinese Academy of Sciences, Ningbo 315153, Zhejiang Province, China

Liang Qiao, Department of Gastroenterology, The 455th Hospital of Chinese People's Liberation Army, Shanghai 200052, China

Jun Chen, Ze-Bing Huang, Department of Infectious Diseases, Hunan Key Laboratory of Viral Hepatitis, Nation Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Jun Zhao, School of Public Health, Hubei University of Medicine, Shiyan 442000, Hubei Province, China

Corresponding author: Zhong-Ji Meng, MD, Chief Doctor, Full Professor, Research Scientist, Department of Infectious Disease, Taihe Hospital, Hubei University of Medicine, No. 32 South Renmin Road, Shiyan 442000, Hubei Province, China.
zhongji.meng@163.com

Abstract

BACKGROUND

Acute-on-chronic liver disease (AoCLD) accounts for the majority of patients hospitalized in the Department of Hepatology or Infectious Diseases.

AIM

To explore the characterization of AoCLD to provide theoretical guidance for the accurate diagnosis and prognosis of AoCLD.

METHODS

Patients with AoCLD from the Chinese Acute-on-Chronic Liver Failure (ACLF) study cohort were included in this study. The clinical characteristics and outcomes, and the 90-d survival rate associated with each clinical type of AoCLD were analyzed, using the Kaplan-Meier method and the log-rank test.

RESULTS

A total of 3375 patients with AoCLD were enrolled, including 1679 (49.7%) patients with liver cirrhosis acute decompensation (LC-AD), 850 (25.2%) patients with ACLF, 577 (17.1%) patients with chronic hepatitis acute exacerbation (CHAE), and 269 (8.0%) patients with liver cirrhosis active phase (LC-A). The most common cause of chronic liver disease (CLD) was HBV infection (71.4%). The most common precipitants of AoCLD was bacterial infection (22.8%). The 90-d mortality rates of each clinical subtype of AoCLD were 43.4% (232/535) for type-C ACLF, 36.0% (36/100) for type-B ACLF, 27.0% (58/215) for type-A ACLF, 9.0% (151/1679) for LC-AD, 3.0% (8/269) for LC-A, and 1.2% (7/577) for CHAE.

CONCLUSION

HBV infection is the main cause of CLD, and bacterial infection is the main precipitant of AoCLD. The most common clinical type of AoCLD is LC-AD. Early diagnosis and timely intervention are needed to reduce the mortality of patients with LC-AD or ACLF.

Key Words: Acute-on-chronic liver disease; Acute-on-chronic liver failure; Liver cirrhosis; Clinical features; Prognosis

Core Tip: This study systematically investigated the composition, clinical characteristics, and prognosis of each subtype of acute-on-chronic liver disease (AoCLD) for the first time. In China, liver cirrhosis acute decompensation (LC-AD) is the most common clinical type of AoCLD, with a high short-term mortality rate. Attention should be given to the early diagnosis and intervention of patients with LC-AD to avoid acute decompensation-acute-on-chronic liver failure (ACLF) transition. Type C ACLF patients have the highest mortality rate, requiring early liver transplantation to improve the overall survival rate of AoCLD.

Citation: Zhang YY, Luo S, Li H, Sun SN, Wang XB, Zheng X, Huang Y, Li BL, Gao YH, Qian ZP, Liu F, Lu XB, Liu JP, Ren HT, Zheng YB, Yan HD, Deng GH, Qiao L, Zhang Y, Gu WY, Xiang XM, Zhou Y, Hou YX, Zhang Q, Xiong Y, Zou CC, Chen J, Huang ZB, Jiang XH, Qi TT, Chen YY, Gao N, Liu CY, Yuan W, Mei X, Li J, Li T, Zheng RJ, Zhou XY, Zhao J, Meng ZJ. Characterization of acute-on-chronic liver diseases: A multicenter prospective cohort study. *World J Hepatol* 2024; 16(5): 809-821
URL: https://www.wjgnet.com/1948-5182/full/v16/i5/809.htm
DOI: https://dx.doi.org/10.4254/wjh.v16.i5.809

INTRODUCTION

Chronic liver disease (CLD) includes liver cirrhosis (LC) and noncirrhotic chronic liver diseases (NC-CLDs), such as chronic viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver diseases[1]. According to the latest global disease burden data, disability-adjusted life years caused by CLD accounted for 1.8% of the global burden in 2019[2], and CLD burden as well as challenges related to this disease are increasing worldwide[3,4]. Hepatitis virus variation, overlapping virus and/or bacterial infection, alcohol, drugs and other factors aggravate inflammation and/or fibrosis of the liver, even leading to LC acute decompensation (LC-AD) or liver failure[5,6]. This acute liver injury (ALI) or decompensation of liver function in CLD patients is collectively referred to as acute-on-CLD (AoCLD)[7].

According to the degree of ALI, AoCLD can be characterized as acute-on-chronic liver failure (ACLF) and non-ACLF [8]. According to the basic state of CLD, ACLF can be divided into three clinical types: Type A (based on chronic hepatitis), type B (based on compensated cirrhosis), and type C (based on decompensated cirrhosis)[8,9]. Non-ACLF can be further divided into chronic hepatitis with acute exacerbation (CHAE), LC active phase (LC-A), and LC-AD[8]. Studies have shown that a certain of non-ACLF AoCLDs may rapidly progress to ACLF in the absence of timely diagnosis and intervention at the initial stage of the disease, and these patients are defined as having pre-liver failure[10]. At present, most studies focus on the clinical characteristics, predictive models and prognostic factors of ACLF[11], while few studies elucidate the characteristics of non-ACLF AoCLD systematically.

This study was based on a multicenter prospective cohort of LC and NC-CLD patients, and the aim was to analyze the composition, clinical characteristics and prognosis of each clinical type of AoCLD to provide information for the accurate clinical classification of AoCLD. Rapid identification of patients with a high risk of death and administering appropriate clinical interventions for the reasonable allocation of medical resources will be helpful in reducing the short-term mortality of AoCLD patients.

MATERIALS AND METHODS

Patients

The patients included in this study were from two prospective, multicenter cohorts of CLD patients with acute exacerbation enrolled in the Chinese ACLF (CATCH-LIFE) study (NCT02457637, NCT03641872)[7]. This study was approved by the Ethics Committee of Renji Hospital (the leading center of the CATCH-LIFE study), School of Medicine, Shanghai Jiao Tong University, Shanghai, China. Signed informed consent was obtained from all patients.

The diagnostic criteria for AoCLD and its subtypes are as follows: AoCLD refers to the occurrence of ALI or AD in CLD patients under the action of various precipitants, manifested as abnormal liver function within one week or AD within one month or progression to liver failure[7]. ACLF refers to acute liver failure in patients with CLD (with or without LC), which is characterized by jaundice [total bilirubin (TB) 10 times higher than the upper limit of normal value (ULN) or daily rises ≥ 17.1 μmol/L], bleeding tendency [prothrombin activity ≤ 40% or international normalized ratio (INR) ≥ 1.5], accompanied by one or more extrahepatic organ failures, and increased mortality within 28 d and 3 months after onset[8]. According to the latest view of the World Gastroenterology Organization (WGO), ACLF can be classified into three clinical types based on the basic status of CLD: Type A (based on chronic hepatitis), type B (based on compensated cirrhosis), and type C (based on decompensated cirrhosis)[9]. LC-A refers to a state in which liver fibrosis and inflammation coexist, accompanied by elevated alanine aminotransferase (ALT) level, elevated TB level, and decreased albumin (ALB) level[8]. LC-AD refers to the presence of acute gastrointestinal bleeding, hepatic encephalopathy (HE), obvious ascites, jaundice (TB > 5 mg/dL), or any combination of these symptoms in patients with LC within one month[8]. CHAE refers to intermittent elevation in transaminase exceeding 5 times the ULN or twice the baseline level in NC-CLD patients[8].

Among the CATCH-LIFE cohort, patients who received liver transplantation within 90 d after admission, NC-CLD patients with FIB-4 score < 1.45 or loss of FIB-4 value, patients with unclear decompensation history of cirrhosis, and patients who did not meet any of the diagnostic criteria for clinical classification of AoCLD were not included in this study.

Data collection

The clinical and laboratory information were retrieved from the CATCH-LIFE study database, including demographic data (age, sex), etiology of basic liver disease (HBV related, alcohol related, or other), and predisposing factors (HBV reactivation, infection, alcoholism, surgery, overwork, *etc*.). The experimental data on admission included white blood cell count, hemoglobin (HGB), platelet (PLT) count, ALB, TB, ALT, aspartate aminotransferase (AST), prothrombin time (PT), INR, alkaline phosphatase, γ-glutamyl transferase (GGT), blood urea nitrogen (BUN), and creatinine; ascites, gastrointestinal bleeding, HE, bacterial infection and other complications were recorded and analyzed. FIB-4 was calculated according to the formula FIB-4 = [age (year) × AST (U/L)]/[PLT (10^9/L) × ALT, (U/L) 1/2][12]. Scores of the model for end-stage liver disease (MELD) were calculated according to the formula: R = 9.57 × ln [Cr (mg/dL)] + 3.78 × ln [TB (mg/dL)] + 11.2 × ln (INR) + 6.43 × Etiology (taking 0 for alcoholic and cholestatic liver disease and taking 1 for other causes)[13].

Statistical analysis

Patient demographic and clinical characteristics are summarized as frequency counts and percentages or medians and interquartile ranges, as appropriate. The differences in demographic and clinical characteristics between groups were examined using Fisher's exact tests or rank sum tests where appropriate. The 28-d and 90-d survival of each clinical type of AoCLD was analyzed using the Kaplan-Meier method, and the survival rates were compared using log-rank tests. For biochemical indicators with less than 10% missing values, the multiple imputation method was used to fill in the missing values. A P value < 0.05 was considered statistically significant. All statistical analyses and visualization were carried out using R statistical software (version R 4.0, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

RESULTS

Acute decompensation of LC is the most common clinical type of AoCLD

Of the 3970 patients in the CATCH-LIFE study cohort, 595 patients were excluded, of which 246 patients received liver transplantation within 90 d of follow-up, 180 NC-CLD patients had an FIB-4 < 1.45, 9 NC-CLD patients with a missing value for FIB-4 score, 20 LC patients had an unclear history of decompensation, and 140 patients did not meet the criteria for the diagnosis of AoCLD. Finally, 3375 patients with AoCLD were included in the present study (Figure 1).

Among the 3375 AoCLD patients, 1679 (49.7%) had LC-AD, 850 (25.2%) had ACLF (including 535 with type C, 215 with type A, and 100 with type B), 577 (17.1%) had CHAE, and 269 (8.0%) had LC-A (Figure 2).

HBV infection is the main cause of CLD

In all 3375 patients with AoCLD, the top 5 causes were HBV infection (2409 patients, 71.4%), ALD (649 patients, 19.2%), autoimmune liver disease (AILD) (308 patients, 9.1%), HCV infection (126 patients, 3.7%), and MAFLD (104 patients, 3.1%). The top 2 etiologies of LC patients and NC-CLD patients were similar, except that a higher proportion of HBV infection (87.2% *vs* 66.5%, P < 0.001) and a lower proportion of ALD (12.6% *vs* 21.3%, P < 0.001) were found in NC-CLD patients than in LC patients (Table 1). In LC patients, AILD (10.4%) ranks the third etiology, followed by Cryptogenic (6.2%), and HCV infection (4.5%). While in NC-CLD patients, MAFLD (8.7%) ranks the third etiology, followed by AILD (4.9%), and DILD (3.2%; Table 1).

Bacterial infection is the main precipitant of AoCLD

In all AoCLD patients, except 925 (27.4%) patients without a clear precipitant, bacterial infection (771 patients, 22.8%) was the most common precipitant, followed by HBV reactivation (378 patients, 11.2%), alcoholism (327 patients, 9.7%), drug-induced liver injury (230 patients, 6.8%), excessive exertion (138 patients, 4.1%), overlapping viral infection (94 patients, 2.8%), portal vein thrombosis (66 patients, 1.96%), and operation (40 patients, 1.19%; Table 2). This trend is basically consistent for the subtypes of AoCLD, except that the main precipitant of CHAE was HBV reactivation (25.8%).

The clinical characteristics of AoCLD are associated with the basic liver disease status and the severity of ALI

Compared with non-ACLF AoCLD patients, ACLF patients showed higher levels of TB (20.1 mg/dL *vs* 2.53 mg/dL, P < 0.001) and INR (2.13 *vs* 1.32, P < 0.001; Table 2). The levels of TB (20.7 mg/dL *vs* 19.2 mg/dL, P < 0.05) and INR (2.21 *vs* 2.05, P < 0.05) were significantly higher in patients with type C ACLF than in patients with type A ACLF (Table 3).

In both non-ACLF and ACLF patients, the levels of ALT, AST, HGB, PLT, and ALB showed a decreasing trend (P < 0.001) with underlying liver disease, namely, chronic hepatitis (CHAE, type A ACLF), compensated cirrhosis (LC-A, type B ACLF), and decompensated cirrhosis (LC-AD, type C ACLF; Tables 2 and 3). In non-ACLF patients, significantly higher incidences of ascites, HE, and gastrointestinal bleeding were found in LC-AD patients than in CHAE and LC-A patients (P < 0.001; Table 3). Similarly, in patients with ACLF, significantly higher incidences of ascites, HE, and gastrointestinal bleeding were found in type C ACLF than in type A and type B ACLF patients (P < 0.001; Table 3).

Table 1 Etiological characteristics of 3375 acute-on-chronic liver disease patients, *n* (%)

Characteristic	Overall (*n* = 3375)	Noncirrhosis (*n* = 792)	Cirrhosis (*n* = 2853)	*P* value
Demographics				
Sex, male	2489 (73.7)	606 (76.5)	1883 (72.9)	0.048
Age, yr (mean ± SD)	49.65 ± 12.14	42.51 ± 11.65	51.84 ± 11.43	< 0.001
Etiology				
HBV	2409 (71.4)	691 (87.2)	1718 (66.5)	< 0.001
HCV	126 (3.7)	11 (1.4)	115 (4.5)	< 0.001
ALD	649 (19.2)	100 (12.6)	549 (21.3)	< 0.001
AILD	308 (9.1)	39 (4.9)	269 (10.4)	< 0.001
MAFLD	104 (3.1)	69 (8.7)	35 (1.4)	< 0.001
DILD	58 (1.7)	25 (3.2)	33 (1.3)	0.001
MLD	7 (0.2)	2 (0.3)	5 (0.2)	1
Schistosomiasis	49 (1.5)	4 (0.5)	45 (1.7)	0.017
Cryptogenic	169 (5.0)	10 (1.3)	159 (6.2)	< 0.001

HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALD: Alcohol-associated liver disease; MAFLD: Metabolic-associated fatty liver disease; DILD: Drug-induced liver disease; AILD: Autoimmune liver disease; MLD: Metabolic liver disease.

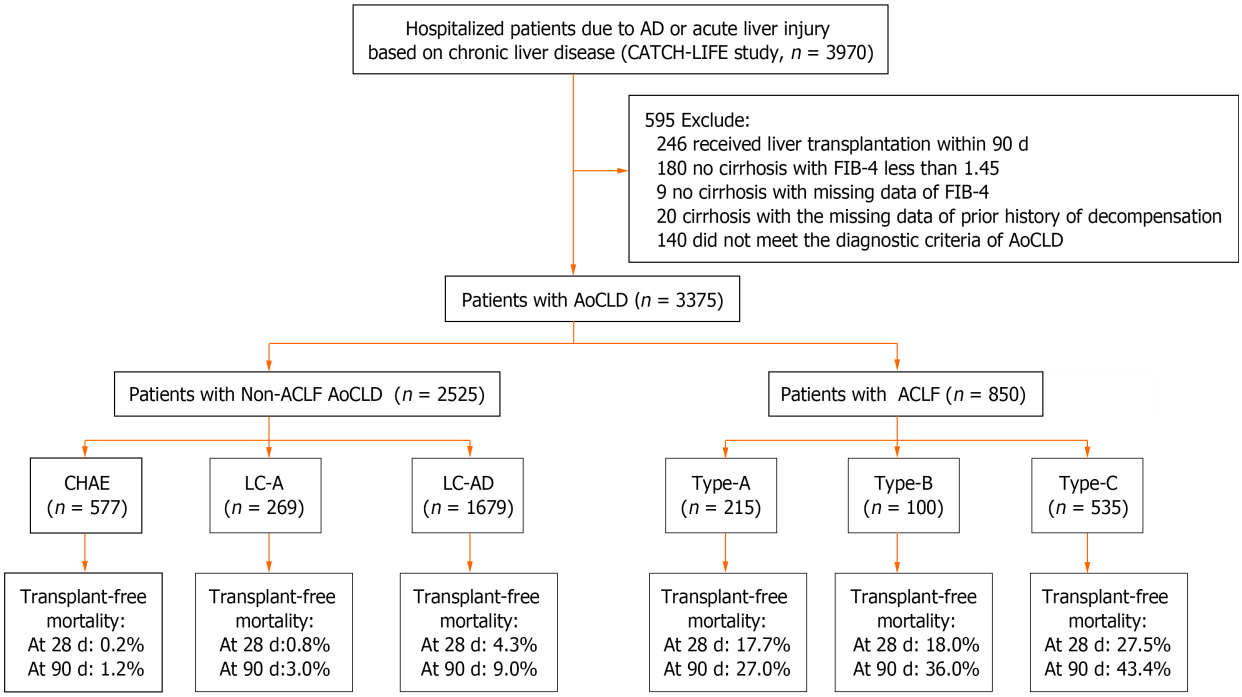

Figure 1 Flow chart of patient enrollment. AoCLD: Acute-on-chronic liver disease; CHAE: Chronic hepatitis with acute exacerbation; LC-A: Liver cirrhosis active phase; LC-AD: Liver cirrhosis acute decompensation; ACLF: Acute-on-chronic liver failure; LT: Liver transplantation; CATCH-LIEF: Chinese Acute-on-Chronic Liver Failure study; AD: Acute decompensation.

Patients with type C ACLF exhibited the highest 28-d and 90-d liver transplantation-free mortality

In this study of 3375 patients with AoCLD, the cumulative liver transplantation (LT)-free mortality at 28 and 90 d was 8.2% (278/3375) and 14.6% (492/3375), respectively. The 28-d LT-free mortalities for each clinical subtype of AoCLD were 24.0% (203/850) for ACLF, 4.3% (72/1679) for LC-AD, 0.7% (2/269) for LC-A, and 0.2% (1/577) for CHAE (Table 3). For each subtype of ACLF, the 28-d LT-free mortalities were 27.5% (147/535) for type C, 18.0% (18/100) for type B, and 17.7% (38/215) for type A (Table 3). The 90-d LT-free mortalities for each clinical subtype of AoCLD were 38.4% (326/850) for ACLF, 9.0% (151/1679) for LC-AD, 3.0% (8/269) for LC-A, and 1.2% (7/577) for CHAE (Table 2). The 90-d LT-free mortalities of each subtype of ACLF were 43.4% (232/535) for type C, 36.0% (36/100) for type B, and 27.0% (58/215) for

Table 2 Clinical characteristics of acute-on-chronic liver disease patients, *n* (%)

Characteristic	Overall (*n* = 3375)	ACLF (*n* = 850)	non-ACLF			
			Overall (*n* = 2525)	CHAE (*n* = 577)	LC-A (*n* = 269)	LC-AD (*n* = 1679)
Demographics						
Sex, male	2489 (73.7)	702 (82.6)	1787 (70.8)[a]	431 (74.7)	174 (64.7)[b]	1182 (70.4)
Age, yr [median (IQR)]	49.3 (41.6, 58.5)	47.5 (40.0, 55.1)	51.0 (42.7, 59.8)[a]	42.2 (33.0, 50.0)	50.2 (43.8, 56.3)[b]	53.0 (45.5, 61.4)[c,d]
Precipitating events						
Bacterial infection	771 (22.8)	311 (36.6)	460 (18.2)[a]	31 (5.4)	41 (15.2)[b]	388 (23.1)[c,d]
HBV reactivation	378 (11.2)	122 (14.4)	256 (10.1)[a]	149 (25.8)	25 (9.29)[b]	82 (4.9)[c,d]
Alcohol intake	327 (9.7)	99 (11.6)	228 (9.0)[a]	45 (7.8)	22 (8.18)	161 (9.6)
Superimposed hepatitis viruses	94 (2.8)	46 (5.4)	48 (1.9)[a]	18 (3.1)	1 (0.37)	29 (1.7)
Portal vein thrombosis	66 (2.0)	6 (0.7)	60 (2.4)[a]	0 (0.0)	1 (0.37)	59 (3.5)[c,d]
Surgery	40 (1.2)	5 (0.6)	35 (1.4)	1 (0.2)	2 (0.74)	32 (1.9)[d]
Drug use	230 (6.8)	94 (11.1)	136 (5.4)[a]	55 (9.5)	12 (4.46)	69 (4.1)[d]
Physiological exhaustion	138 (4.1)	56 (6.6)	82 (3.3)[a]	28 (4.9)	10 (3.72)	44 (2.6)[d]
Undefined	925 (27.4)	164 (19.3)	761 (30.1)[a]	181 (31.4)	86 (32.0)	494 (29.4)
Complications						
HE						
Non-overt HE	3080 (91.3)	726 (85.4)	2354 (93.2)	570 (98.8)	265 (98.5)	1519 (90.5)
Grade I-II	233 (6.90)	94 (11.1)	139 (5.50)[a]	7 (1.21)	3 (1.12)[b]	129 (7.68)[c,d]
Grade III-IV	62 (1.84)	30 (3.53)	32 (1.27)[a]	0 (0.00)	1 (0.37)[b]	31 (1.85)[c,d]
Gastrointestinal bleeding	520 (15.4)	38 (4.47)	482 (19.1)[a]	0 (0.00)	0 (0.00)	482 (28.7)[c,d]
Ascites	1662 (49.2)	515 (60.6)	1147 (45.4)[a]	24 (4.16)	6 (2.23)	1117 (66.5)[c,d]
Biochemical indicators, [median (IQR)]						
WBC (× 10^9/L)	4.91 (3.57, 6.90)	6.61 (4.75, 9.01)	4.49 (3.23, 6.12)[a]	4.90 (4.08, 6.09)	4.09 (3.11, 5.48)[b]	4.35 (2.95, 6.26)[c,d]
HGB (g/L)	117 (95.0, 135)	120 (104, 135)	116 (92.0, 135)[a]	140 (130, 153)	122 (108, 137)[b]	104 (83.0, 122)[c,d]
PLT (×10^9/L)	89.0 (56.0, 137)	91.0 (62.0, 129)	89.0 (55.0, 140)	143 (114, 179)	85.0 (59.8, 132)[b]	72.0 (48.0, 111)[c,d]
PT (s)	13.9 (1.69, 18.4)	20.6 (2.57, 26.8)	13.2 (1.45, 16.3)[a]	11.8 (1.29, 14.4)	1.90 (1.21, 14.8)	14.2 (1.58, 17.0)[c,d]
INR	1.44 (1.21, 1.82)	2.13 (1.77, 2.65)	1.32 (1.15, 1.52)[a]	1.17 (1.05, 1.34)	1.23 (1.10, 1.46)[b]	1.38 (1.22, 1.59)[c,d]
ALT (IU/mL)	89.0 (32.0, 448)	209 (73.7, 611)	62.3 (27.0, 359)[a]	723 (416, 1137)	89.6 (39.8, 252)[b]	38.2 (22.4, 80.4)[c,d]
AST (IU/mL)	114 (47.1, 313)	198 (105, 451)	84.0 (39.2, 258)[a]	432 (256, 748)	102 (51.8, 212)[b]	54.0 (31.0, 106)[c,d]
AKP (IU/L)	127 (92.0, 172)	148 (117, 190)	119 (84.7, 164)[a]	130 (103, 168)	127 (92.0, 168)	112 (77.0, 161)[c,d]
GGT (IU/L)	78.8 (38.0, 152)	78.0 (48.6, 127)	79.0 (33.8, 161)[a]	151 (97.3, 231)	106 (41.0, 190)[b]	54.3 (25.0, 117)[c,d]
TB (mg/dL)	4.33 (1.68, 13.7)	20.1 (14.1, 27.4)	2.53 (1.33, 5.96)	3.37 (1.71, 8.38)	2.17 (1.34, 3.34)[b]	2.44 (1.23, 5.85)[c,d]
ALB (g/L)	31.7 (27.5, 36.0)	30.7 (27.3, 33.8)	32.1 (27.6, 36.8)[a]	38.2 (34.1, 41.5)	33.5 (29.0, 37.4)[b]	30.2 (26.3, 34.0)[c,d]
CRE (mg/L)	0.77 (0.64, 0.94)	0.81 (0.65, 1.08)	0.76 (0.64, 0.91)[a]	0.76 (0.64, 0.86)	0.75 (0.61, 0.92)	0.77 (0.64, 0.93)[d]
BUN (mmol/L)	4.60 (3.50, 6.60)	4.40 (3.28, 6.60)	4.68 (3.60, 6.60)[a]	3.90 (3.12, 4.70)	4.39 (3.70, 5.47)[b]	5.30 (3.85, 7.51)[c,d]
Na (mmol/L)	138 (135, 141)	136 (133, 139)	139 (136, 141)[a]	139 (137, 141)	140 (137, 142)	138 (136, 141)[c,d]
MELD score [median (IQR)]	11.5 (5.92, 18.2)	21.9 (18.5, 25.9)	8.75 (4.60, 13.0)[a]	7.79 (3.81, 12.1)	6.56 (3.55, 9.58)[b]	9.50 (5.09, 13.7)[c,d]
Mortality (LT free)						
28-d	278 (8.24)	203 (23.9)	75 (2.97)[a]	1 (0.17)	2 (0.74)	72 (4.29)[c,d]

90-d	492 (14.6)	326 (38.4)	166 (6.57)[a]	7 (1.21)	8 (2.97)	151 (8.99)[c,d]

[a]$P < 0.05$ acute-on-chronic liver failure (ACLF) *vs* non-ACLF.
[b]$P < 0.05$ chronic hepatitis with acute exacerbation (CHAE) *vs* liver cirrhosis active phase (LC-A).
[c]$P < 0.05$ LC-A *vs* liver cirrhosis acute decompensation (LC-AD).
[d]$P < 0.05$ CHAE *vs* LC-AD.
AoCLD: Acute-on-chronic liver disease; CHAE: Chronic hepatitis with acute exacerbation; LC-A: Liver cirrhosis active phase; LC-AD: Liver cirrhosis acute decompensation; ACLF: Acute-on-chronic liver failure; ALD: Alcohol-associated liver disease; MAFLD: Metabolic-associated fatty liver disease; DILI: Drug-induced liver injury; AILD: Autoimmune liver disease; MLD: Metabolic liver disease. LT: Liver transplantation; HE: Hepatic encephalopathy; IQR: Interquartile ranges; HGB: Hemoglobin; PLT: Platelet; PT: Prothrombin time; INR: International normalized ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AKP: Anterior Knee Pain; TB: Total bilirubin; ALB: Albumin; CRE: Creatinine; BUN: Blood urea nitrogen; MELD: Model for end-stage liver disease; WBC: White blood cell; GGT: γ-glutamyl transferase.

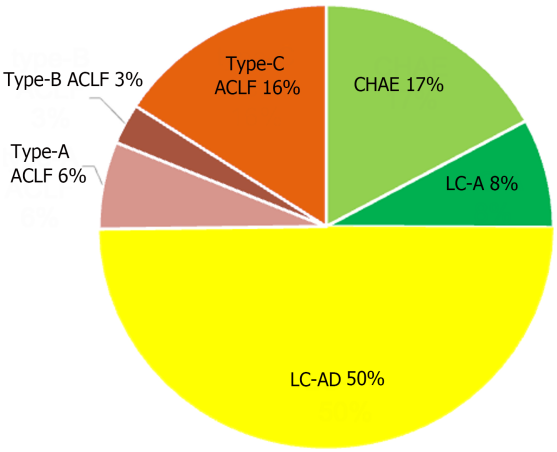

Figure 2 Constitution of clinical types of acute-on-chronic liver disease. CHAE: Chronic hepatitis with acute exacerbation; LC-A: Liver cirrhosis active phase; LC-AD: Liver cirrhosis acute decompensation; ACLF: Acute-on-chronic liver failure.

type A (Table 3).

The survival curves showed that the 28-d and 90-d survival rates were higher in non-ACLF patients than in ACLF patients ($P < 0.001$; Figure 3A and B). In non-ACLF patients, LC-A patients showed similar 28-d and 90-d survival rates to CHAE patients ($P > 0.05$), which were significantly higher than those of LC-AD patients ($P < 0.05$) (Figure 3C and D). In patients with ACLF, the 28-d and 90-d survival rates were similar in patients with type A and type B ACLF ($P > 0.05$) but significantly higher than those in patients with type C ACLF ($P < 0.05$; Figure 3E and F).

DISCUSSION

The main findings of the present study are as follows: HBV infection is the main cause of CLD, and bacterial infection is the main precipitant of AoCLD. The most common clinical type of AoCLD is LC-AD, followed by ACLF, CHAE, and LC-A. The patients with CHAE or type A ACLF presented a profile of significant elevation in serum ALT and TB, while LC-AD and type C ACLF patients were characterized by the occurrence of various complications. Patients with LC-A or type B ACLF presented less elevation in serum ALT and TB than patients with CHAE or type A ACLF and fewer complications than LC-AD and type C ACLF patients. In all subtypes of AoCLD patients, the 90-d LT-free mortality of ACLF was more than 27.0%, while in non-ACLF, the 90-d LT-free mortalities were less than 5% in LC-A and CHAE and approximately 9.0% in LC-AD. Notably, LC-AD accounts for approximately 50% of all AoCLD patients, with a 90-d LT-free mortality of nearly 10%; thus, extensive attention should be given to LC-AD patients in the clinical setting.

In terms of the causes of CLD, the results from the present study were consistent with the epidemiological data of CLD in China[14]. HBV infection is the absolute dominant cause (> 71% of cases), far higher than other causes. On the other hand, with the improvement of living standards of Chinese residents, the incidence of ALD has gradually increased[15]. In the present study, ALD was the second leading cause of CLD, especially in LC patients, in whom 21% of cases were caused by ALD. AILD is the third leading cause of CLD, accounting for approximately 10% of cases in general. Recent findings indicated that the prevalence of AILD is increasing in the Asia-Pacific region[16,17]. Therefore, more attention should be given to the prevention and treatment of ALD and AILD, in addition to the control of chronic HBV infection.

In terms of the precipitant of AoCLD, this study found that bacterial infection and HBV reactivation contributed to one-third of cases. Other precipitants, such as alcohol and drug abuse, participated in the occurrence and development of AoCLD independently or synergistically with other precipitants. These results are consistent with those reported previously[18-20]. In particular, bacterial infection accounts for over 40% of the AD-ACLF transition (transition of acute

Table 3 Characteristics of subtypes of acute-on-chronic liver failure, *n* (%)

Characteristic	Type A (*n* = 215)	Type B (*n* = 100)	Type C (*n* = 535)
Demographics			
Sex, male	175 (81.4)	87 (87.0)	440 (82.2)
Age, yr [median (IQR)]	42.0 (34.0, 49.9)	46.9 (39.7, 54.2)[a]	49.2 (43.0, 57.0)[b,c]
Precipitating events			
HBV reactivation	33 (15.3)	11 (11.0)	78 (14.6)
Bacterial infection	54 (25.1)	34 (34.0)	223 (41.7)[b]
Alcohol intake	21 (9.77)	8 (8.00)	70 (13.1)
Superimposed hepatitis viruses	13 (6.05)	9 (9.00)	24 (4.49)
Portal vein thrombosis	0 (0.00)	2 (2.00)	4 (0.75)
Surgery	2 (0.93)	0 (0.00)	3 (0.56)
Drug use	29 (13.5)	6 (6.00)	59 (11.0)
Physiological exhaustion	19 (8.84)	7 (7.00)	30 (5.61)
Undefined	55 (25.6)	34 (34.0)	75 (14.0)[b,c]
Complications			
Hepatic encephalopathy			
Non-overt HE	186 (86.5)	96 (96.0)	444 (83.0)
Grade I-II	20 (9.30)	3 (3.00)	71 (13.3)[b]
Grade III-IV	9 (4.19)	1 (1.00)	20 (3.74)[b]
Gastrointestinal bleeding	0 (0.00)	0 (0.00)	38 (7.10)[b,c]
Ascites	69 (32.1)	10 (10.0)[a]	436 (81.5)[b,c]
Biochemical indicators [median (IQR)]			
WBC ($\times 10^9$/L)	6.84 (5.27, 8.88)	6.23 (4.58, 8.67)	6.66 (4.64, 9.16)
HGB (g/L)	131 (118, 144)	126 (108, 136)[a]	116 (98.0, 130)[b,c]
PLT ($\times 10^9$/L)	121 (91.0, 154)	89.0 (62.0, 130)[a]	80.0 (52.5, 116)[b,c]
PT (s)	20.2 (2.35, 26.5)	22.5 (19.0, 27.6)[a]	20.2 (2.52, 26.6)[b]
INR	2.05 (1.72, 2.48)	2.08 (1.76, 2.50)	2.21 (1.81, 2.75)[c]
ALT (IU/mL)	531 (200, 1131)	231 (90.7, 607)[a]	133 (53.2, 388)[b,c]
AST (IU/mL)	318 (170, 743)	230 (121, 482)[a]	170 (91.0, 342)[b,c]
AKP (IU/L)	152 (124, 198)	155 (120, 198)	146 (113, 186)
GGT (IU/L)	88.0 (57.0, 141)	82.0 (54.0, 132)	72.0 (43.0, 118)[c]
TB (mg/dL)	19.2 (13.7, 25.8)	20.3 (14.2, 25.5)	20.7 (14.2, 28.5)[c]
ALB (g/L)	32.1 (29.5, 35.2)	31.4 (28.4, 33.9)[a]	29.9 (26.8, 33.1)[b,c]
CRE (mg/L)	0.77 (0.61, 0.94)	0.75 (0.61, 0.94)	0.86 (0.68, 1.13)[b,c]
BUN (mmol/L)	3.51 (2.87, 4.55)	3.92 (2.94, 6.05)[a]	5.00 (3.65, 8.11)[b,c]
Na (mmol/L)	137 (135, 140)	137 (133, 140)	136 (131, 138)[b,c]
MELD score [median (IQR)]	19.9 (17.4, 24.1)	20.7 (17.9, 25.4)	22.6 (19.3, 26.8)[b,c]
Mortality (LT free)			
28-d	38 (17.7)	18 (18.0)	147 (27.5)[b,c]
90-d	58 (27.0)	36 (36.0)	232 (43.4)[b,c]

[a]$P < 0.05$, type A *vs* type B acute-on-chronic liver failure (ACLF).

[b]*P* < 0.05, type B *vs* type C ACLF.
[c]*P* < 0.05, type A *vs* type C ACLF.
AoCLD: Acute-on-chronic liver disease; CHAE: Chronic hepatitis with acute exacerbation; LC-A: Liver cirrhosis active phase; LC-AD: Liver cirrhosis acute decompensation; ACLF: Acute-on-chronic liver failure; ALD: Alcohol-associated liver disease; MAFLD: Metabolic-associated fatty liver disease; DILI: Drug-induced liver injury; AILD: Autoimmune liver disease; MLD: Metabolic liver disease. LT: Liver transplantation; HE: Hepatic encephalopathy; IQR: Interquartile ranges; HGB: Hemoglobin; PLT: Platelet; PT: Prothrombin time; INR: International normalized ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AKP: Anterior Knee Pain; TB: Total bilirubin; ALB: Albumin; CRE: Creatinine; BUN: Blood urea nitrogen; MELD: Model for end-stage liver disease; WBC: White blood cell; GGT: γ-glutamyl transferase.

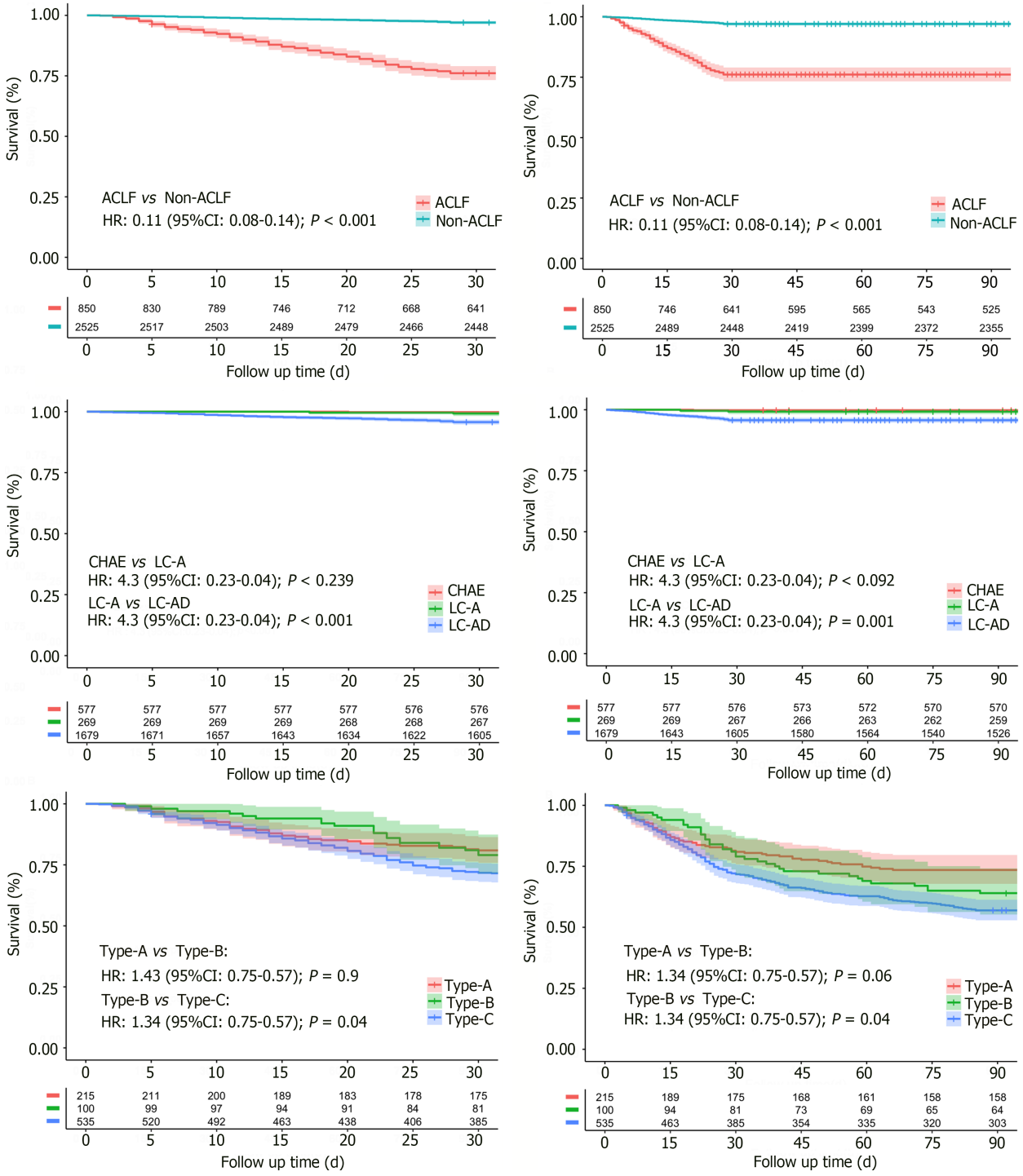

Figure 3 The 28-d and 90-d survival curves of each clinical subtype of acute-on-chronic liver disease. A and B: 28-d (A) and 90-d (B) survival curves of non-acute-on-chronic liver failure (ACLF) and ACLF; C and D: 28-d (C) and 90-d (D) survival curves of each clinical type of non-ACLF; E and F: 28-d (E) and 90-d (F) survival curves of each clinical type of ACLF. CHAE: Chronic hepatitis with acute exacerbation; LC-A: Liver cirrhosis active phase; LC-AD: Liver cirrhosis acute decompensation; ACLF: Acute-on-chronic liver failure; HR: Hazard ratio.

compensation to ACLF) in patients with type C ACLF. In the AD-ACLF transition, precipitants such as bacterial infection play a key role in initiating an inflammatory storm, which can directly or indirectly activate immune cells and inflammatory cytokine pathways, leading to massive or submassive necrosis of liver cells[21]. LC patients are prone to bacterial infection due to the dysfunction/decompensation of liver function, with increased intestinal permeability and bacterial translocation and compromised immunity. Bacterial infection may initiate imbalance in pro-inflammatory/anti-inflammatory systems, leading to systemic inflammatory response syndrome and multiple organ dysfunction syndrome, which further promote disease progression and significantly increase the incidence of AD-ACLF transition[22-24]. Bacterial infection has been shown to be an independent risk factor for ACLF development in AD patients within 28 d[25]. Therefore, to reduce the morbidity of AoCLD and the incidence of adverse events, attention should be given to managing the precipitants contributing to the CLD-AoCLD transition, in particular, early identification and control of bacterial infection in patients with decompensated cirrhosis.

This study revealed that individual subtypes of AoCLD display distinct clinical characteristics. CHAE and type A ACLF, which occur based on NC-CLD, show significant increases in ALT and AST (indicating active inflammation in the liver), while LC-A and type B ACLF, which occur based on compensated LC, show relatively less increase in ALT and AST levels, and LC-AD and type C ACLF, which occur based on decompensated LC, show the least increased levels of ALT and AST. From the pathophysiological view of CLD, with the gradual aggravation of basic liver disease (chronic hepatitis, compensatory cirrhosis, decompensated cirrhosis), the number of functional liver cells is decreasing, leading to gradually reduced liver reserve capacity and less transaminase production. Accordingly, less transaminase is released into the blood in the case of liver cell damage[26]. On the other hand, cirrhosis-related complications, such as ascites, variceal bleeding, HE, or nonobstructive jaundice, frequently occur in patients with LC-AD or type C ACLF, attributed to diffuse liver fibrosis with obvious portal hypertension[27]. Once a complication occurs, patients with LC-AD or type C ACLF are prone to other complications[27]. Therefore, attention should be given to the prevention and timely management of cirrhosis-related complications to improve the quality of life and life span of patients with LC.

This study also found that the levels of HGB and PLT showed a downward trend with the aggravation of basic liver disease. The reasons are as follows: In patients with LC-AD and type C ACLF, HGB levels might be reduced for various reasons, including esophageal and gastric varices rupture and bleeding, chronic malnutrition caused by portal hypertensive gastropathy, reduced EPO production, and reduction in bone marrow hematopoietic stem cells due to inflammatory stimulation[28,29]. A decrease in PLT may be caused mainly by hypersplenism and might also be associated with secondary immune dysfunction in liver failure[30], and a low level of PLT has been shown to be associated with 90-d adverse outcomes of AoCLD[31]. In contrast, with the aggravation of basic liver disease, BUN levels showed an upward trend. Patients with LC-AD or type C ACLF may experience visceral vasodilation due to portal hypertension, ascites, and hemodynamic instability, which can activate the renin-angiotensin aldosterone system, leading to renal vasoconstriction and inadequate renal perfusion and resulting in a decrease in the glomerular filtration rate and an increase in BUN and Cr[32]. Therefore, patients are prone to renal failure, electrolyte disorders, and other complications.

Whether ACLF develops from LC or NC-CLD, all three clinical types of ACLF show significant increases in bilirubin and INR. In patients with ACLF, there is a sharp decrease in the ability to metabolize bilirubin and synthesize coagulation factors due to massive necrosis of hepatocytes, which leads to elevated bilirubin, prolonged PT or increased INR[33]. Studies have shown that a rapid rise in TB or INR in the short term suggests an acute exacerbation and deterioration of the condition in CLD patients, with a high risk of developing ACLF[34,35]. Therefore, TB and INR should be strictly monitored to identify those at high risk early in patients with AoCLD.

The prognosis of patients with AoCLD varies significantly among subtypes. In non-ACLF AoCLD, with or without LC, if decompensation does not occur, the 28-d and 90-d mortality rates are very low (less than 3.0%). In contrast, all ACLF patients have relatively high short-term mortality, among which patients with type C ACLF have significantly higher 28-d and 90-d mortality than those with type A and type B ACLF. This result suggests that due to severe insufficiency of liver reserve function and the instability of portal hypertension-portal systemic circulation, ACLF occurring on the basis of decompensated LC becomes the most critical type of ACLF, with a high cumulative incidence of adverse events, which is consistent with previous reports[36]. Therefore, attention should be given to LC patients with acute decompensation or who experienced previous decompensatory events to reduce the incidence rate of type C ACLF and give priority to liver transplantation for type C ACLF patients to reduce mortality.

Our research has the following advantages. First, this was a multicenter study, with 15 research centers covering 95% of the population of China, which is representative of China's demography, ensuring the reliability of our conclusions. Second, this study used the WGO ACLF classification to compensate for the lack of type A ACLF in the EASL ACLF diagnostic criteria and type C ACLF in the APSAL ACLF diagnostic criteria. Finally, the description of the composition and clinical characteristics of each subtype of AoCLD is helpful for clinicians to classify and manage patients with the best clinical decisions.

Of course, this study also had certain limitations. First, the data of this study came from a high incidence area of HBV, so this study does not represent the characteristics of global CLD patients. Second, patients with liver diseases were diagnosed mainly based on laboratory and imaging data, without liver histologic evidence; thus, a small number of patients with NC-CLD diagnosed by imaging may have early cirrhosis, while in other patients with NC-CLDs, objective evidence of CLD may be lacking. To avoid this situation, patients with an FIB-4 < 1.45 were excluded from this study since many studies have shown that an FIB-4 < 1.45 is highly specific for excluding NC-CLD with mild or no liver fibrosis [37-39]. Finally, we excluded patients receiving liver transplantation, which may have some potential impact on the outcomes. However, in most ACLF studies, it is a common practice to use transplant-free mortality as the primary outcome to obtain the natural prognosis of patients[40].

CONCLUSION

This study systematically investigated the composition, clinical characteristics, and prognosis of each subtype of AoCLD for the first time. In China, LC-AD is the most common clinical type of AoCLD, with a high short-term mortality rate. Attention should be given to the early diagnosis and intervention of patients with LC-AD to avoid AD-ACLF transition. Type C ACLF patients have the highest mortality rate, requiring early liver transplantation to improve the overall survival rate of AoCLD.

ACKNOWLEDGEMENTS

We thank the following Chinese (Acute on) Chronic Liver Failure Consortium members and participants for their contributions to this study: Department of Gastroenterology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University—Liang Qiao, Yan Zhang, Tong-Yu Wang, Dan-dan Wu, Shan Yin, Wenyi Gu; Centre of Integrative Medicine, Beijing Ditan Hospital, Capital Medical University—Qun Zhang, Yi-Xin Hou; Department of Infectious Diseases, Southwest Hospital, Third Military Medical University (Army Medical University)—Shu-Ning Sun, Xiao-Mei Xiang; Department of Infectious Disease, Hunan Key Laboratory of Viral Hepatitis, Xiangya Hospital, Central South University—Jun Chen, Ze-Bing Huang; Department of Infectious Diseases, Institute of Infection and Immunology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology—Yan Xiong, Cong-Cong Zou; Hepatology Unit, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University—Bei-Ling LI, Xiu-Hua Jiang, Ting-Ting Qi; Department of Hepatology, The First Hospital of Jilin University—Na Gao, Chun-Yan Liu; Department of Infectious Disease, Taihe Hospital, Hubei University of Medicine—Qin Lei, Sen Luo, Yuan-Yuan Chen; Department of Infectious Disease, The First Hospital of Zhejiang University—Hao-Tang Ren; Department of Liver Intensive Care Unit, Shanghai Public Health Clinical Centre, Fudan University—Xue Mei, Jie-Fei Wang, Liu-Juan Ji; Department of Infectious Diseases and Hepatology, Second Hospital of Shandong University—Tao Li, Jing Li; Liver Disease Centre, The First Affiliated Hospital of Xinjiang Medical University—Rong-Jiong Zheng, Xin-Yi Zhou; Department of Infectious Disease, Henan Provincial People's Hospital—Hui-Ming Jin; Infectious Disease Center, The Affiliated Hospital of Logistics University of People's Armed Police Force—Hai Li, Qing Zhang, Xue-Qun Zheng; and Department of Infectious Disease, Fuzhou General Hospital of Nanjing Military Command—Shao-Yang Wang, Tao-Fa Lin.

FOOTNOTES

Author contributions: Meng ZJ and Li H contributed to the conception and design of the study. Li H, Zheng X, Huang Y, Meng ZJ, Gao YH, Qian ZP, Liu F, Lu XB, Liu JP, Deng GH, Zheng YB, Yan HD, Qiao L, Zhang Y, Gu WY, Xiang XM, Zhou Y, Sun SN, Hou YX, Zhang Q, Xiong Y, Zou CC, Chen J, Huang ZB, Jiang XH, Qi TT, Luo S, Chen YY, Gao N, Liu CY, Yuan W, Mei X, Li J, Li T, Zheng RJ, Zhou XY, and Ren HT contributed to the acquisition, analysis, or interpretation of data; Zhang YY wrote the original draft of the manuscript; Zhang YY and Zhao J performed the statistical analysis. Meng ZJ and Li H performed critical revision of the manuscript for important intellectual content; All authors read and approved the final version of the submitted manuscript.

Supported by The National Science and Technology Major Project, No. 2018ZX10723203 and No. 2018ZX10302206; Hubei Province's Outstanding Medical Academic Leader Program, Advantage Discipline Group (Public Health) Project in Higher Education of Hubei Province, No. 2023PHXKQ1; The Foundation of Health Commission of Hubei Province, No. WJ2021F037 and No. WJ2021M051; Project of Hubei University of Medicine, No. FDFR201902 and No. YC2023047; and The Hubei Provincial Technology Innovation Project, No. 2023BCB129.

Institutional review board statement: This study was approved by the Ethics Committee of Renji Hospital (the leading center of the CATCH-LIFE study), School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

Clinical trial registration statement: This study is registered at https://clinicaltrials.gov/. The registration identification number is NCT02457637.

Informed consent statement: Signed informed consent was obtained from all patients.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

Country/Territory of origin: China

ORCID number: Yuan-Yao Zhang 0000-0002-7630-1796; Sen Luo 0000-0001-5846-6717; Hai Li 0000-0002-3645-6232; Xian-Bo Wang 0000-0002-3593-5741; Xin Zheng 0000-0001-6564-7807; Yan Huang 0000-0002-4747-3740; Bei-Ling Li 0000-0002-0633-5632; Yan-Hang Gao 0000-0002-6836-0614; Zhi-Ping Qian 0000-0003-4641-3348; Feng Liu 0000-0001-7060-3710; Xiao-Bo Lu 0000-0001-5532-7551; Yu-Bao Zheng 0000-0002-2630-2563; Hua-Dong Yan 0000-0003-2792-7490; Guo-Hong Deng 0000-0003-1263-7220; Liang Qiao 0000-0001-7082-3326; Yan Zhang 0000-0003-0159-9062; Wen-Yi Gu 0000-0002-1615-6064; Yi-Xin Hou 0000-0001-8233-7210; Qun Zhang 0000-0002-6365-0030; Yan Xiong 0000-0001-9356-4777; Cong-Cong Zou 0000-0002-9197-055X; Jun Chen 0000-0001-8320-636X; Ze-Bing Huang 0000-0003-0485-1294; Xiu-Hua Jiang 0000-0002-4646-6186; Yuan-Yuan Chen 0000-0003-3587-7711; Na Gao 0000-0002-8622-9273; Jing Li 0000-0001-5878-6964; Tao Li 0000-0002-2548-5476; Xin-Yi Zhou 0000-0001-9827-7873; Zhong-Ji Meng 0000-0003-0401-535X.

S-Editor: Li L
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **De Siervi S**, Cannito S, Turato C. Chronic Liver Disease: Latest Research in Pathogenesis, Detection and Treatment. *Int J Mol Sci* 2023; **24** [PMID: 37445809 DOI: 10.3390/ijms241310633]
2 **GBD 2019 Diseases and Injuries Collaborators**. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**: 1204-1222 [PMID: 33069326 DOI: 10.1016/S0140-6736(20)30925-9]
3 **Li M**, Wang ZQ, Zhang L, Zheng H, Zhou MG, Liu DW. Burden of viral hepatitis caused by specific aetiologies in China, 1990-2016: findings from the GBD 2016. *BMC Public Health* 2020; **20**: 1461 [PMID: 32993585 DOI: 10.1186/s12889-020-09533-4]
4 **Moon AM**, Singal AG, Tapper EB. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. *Clin Gastroenterol Hepatol* 2020; **18**: 2650-2666 [PMID: 31401364 DOI: 10.1016/j.cgh.2019.07.060]
5 **Arroyo V**, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, Fernández J, Gustot T, Caraceni P, Bernardi M; investigators from the EASL-CLIF Consortium, Grifols Chair and European Foundation for the Study of Chronic Liver Failure (EF-Clif). The systemic inflammation hypothesis: Towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. *J Hepatol* 2021; **74**: 670-685 [PMID: 33301825 DOI: 10.1016/j.jhep.2020.11.048]
6 **Moreau R**. The Pathogenesis of ACLF: The Inflammatory Response and Immune Function. *Semin Liver Dis* 2016; **36**: 133-140 [PMID: 27172355 DOI: 10.1055/s-0036-1583199]
7 **Qiao L**, Wang X, Deng G, Huang Y, Chen J, Meng Z, Zheng X, Shi Y, Qian Z, Liu F, Gao Y, Lu X, Liu J, Gu W, Zhang Y, Wang T, Wu D, Dong F, Sun X, Li H. Cohort profile: a multicentre prospective validation cohort of the Chinese Acute-on-Chronic Liver Failure (CATCH-LIFE) study. *BMJ Open* 2021; **11**: e037793 [PMID: 33419900 DOI: 10.1136/bmjopen-2020-037793]
8 **Zhang YY**, Meng ZJ. Definition and classification of acute-on-chronic liver diseases. *World J Clin Cases* 2022; **10**: 4717-4725 [PMID: 35801045 DOI: 10.12998/wjcc.v10.i15.4717]
9 **Jalan R**, Yurdaydin C, Bajaj JS, Acharya SK, Arroyo V, Lin HC, Gines P, Kim WR, Kamath PS; World Gastroenterology Organization Working Party. Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology* 2014; **147**: 4-10 [PMID: 24853409 DOI: 10.1053/j.gastro.2014.05.005]
10 **Trebicka J**, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, Giovo I, Uschner FE, Jimenez C, Mookerjee R, Gustot T, Albillos A, Bañares R, Janicko M, Steib C, Reiberger T, Acevedo J, Gatti P, Bernal W, Zeuzem S, Zipprich A, Piano S, Berg T, Bruns T, Bendtsen F, Coenraad M, Merli M, Stauber R, Zoller H, Ramos JP, Solè C, Soriano G, de Gottardi A, Gronbaek H, Saliba F, Trautwein C, Özdogan OC, Francque S, Ryder S, Nahon P, Romero-Gomez M, Van Vlierberghe H, Francoz C, Manns M, Garcia E, Tufoni M, Amoros A, Pavesi M, Sanchez C, Curto A, Pitarch C, Putignano A, Moreno E, Shawcross D, Aguilar F, Clària J, Ponzo P, Jansen C, Vitalis Z, Zaccherini G, Balogh B, Vargas V, Montagnese S, Alessandria C, Bernardi M, Ginès P, Jalan R, Moreau R, Angeli P, Arroyo V; PREDICT STUDY group of the EASL-CLIF Consortium. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. *J Hepatol* 2020; **73**: 842-854 [PMID: 32673741 DOI: 10.1016/j.jhep.2020.06.013]
11 **Verma N**, Dhiman RK, Singh V, Duseja A, Taneja S, Choudhury A, Sharma MK, Eapen CE, Devarbhavi H, Al Mahtab M, Shukla A, Hamid SS, Jafri W, Butt AS, Ning Q, Chen T, Tan SS, Lesmana LA, Lesmana CRA, Sahu MK, Hu J, Lee GH, Sood A, Midha V, Goyal O, Ghazinian H, Kim DJ, Treeprasertsuk S, Mohan Prasad VG, Dokmeci AK, Sollano JD, Shah S, Payawal DA, Rao PN, Kulkarni A, Lau GK, Duan Z, Chen Y, Yokosuka O, Abbas Z, Karim F, Chowdhury D, Prasad AS, Sarin SK; APASL ACLF Working Party. Comparative accuracy of prognostic models for short-term mortality in acute-on-chronic liver failure patients: CAP-ACLF. *Hepatol Int* 2021; **15**: 753-765 [PMID: 34173167 DOI: 10.1007/s12072-021-10175-w]
12 **Vallet-Pichard A**, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, Fontaine H, Pol S. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology* 2007; **46**: 32-36 [PMID: 17567829 DOI: 10.1002/hep.21669]
13 **Yip TC**, Lee HW, Wong VW, Wong GL, Tse YK, Lui GC, Ahn SH, Chan HL. Factors associated with improvement in MELD score after antiviral treatment in patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2020; **35**: 1610-1618 [PMID: 32032974 DOI: 10.1111/jgh.15007]
14 **Wang H**, Men P, Xiao Y, Gao P, Lv M, Yuan Q, Chen W, Bai S, Wu J. Hepatitis B infection in the general population of China: a systematic review and meta-analysis. *BMC Infect Dis* 2019; **19**: 811 [PMID: 31533643 DOI: 10.1186/s12879-019-4428-y]
15 **Li YM**, Fan JG; National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association; Fatty Liver Disease Expert Committee, Chinese Medical Doctor Association. Guidelines of prevention and treatment for alcoholic liver disease (2018, China). *J Dig Dis* 2019; **20**: 174-180 [PMID: 30450822 DOI: 10.1111/1751-2980.12687]
16 **Katsumi T**, Ueno Y. Epidemiology and surveillance of autoimmune hepatitis in Asia. *Liver Int* 2022; **42**: 2015-2022 [PMID: 34990076 DOI:

10.1111/liv.15155]
17 **Tanaka A**, Mori M, Matsumoto K, Ohira H, Tazuma S, Takikawa H. Increase trend in the prevalence and male-to-female ratio of primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis in Japan. *Hepatol Res* 2019; **49**: 881-889 [PMID: 30932290 DOI: 10.1111/hepr.13342]
18 **Gerber LH**, Weinstein AA, Mehta R, Younossi ZM. Importance of fatigue and its measurement in chronic liver disease. *World J Gastroenterol* 2019; **25**: 3669-3683 [PMID: 31391765 DOI: 10.3748/wjg.v25.i28.3669]
19 **Hernandez N**, Pontet Y, Bessone F. Translating new knowledge on drug-induced liver injury into clinical practice. *Frontline Gastroenterol* 2020; **11**: 303-310 [PMID: 32587673 DOI: 10.1136/flgastro-2018-101120]
20 **Ren T**, Mackowiak B, Lin Y, Gao Y, Niu J, Gao B. Hepatic injury and inflammation alter ethanol metabolism and drinking behavior. *Food Chem Toxicol* 2020; **136**: 111070 [PMID: 31870920 DOI: 10.1016/j.fct.2019.111070]
21 **Trebicka J**. Predisposing Factors in Acute-on-Chronic Liver Failure. *Semin Liver Dis* 2016; **36**: 167-173 [PMID: 27172359 DOI: 10.1055/s-0036-1583195]
22 **Ahluwalia V**, Wade JB, Heuman DM, Hammeke TA, Sanyal AJ, Sterling RK, Stravitz RT, Luketic V, Siddiqui MS, Puri P, Fuchs M, Lennon MJ, Kraft KA, Gilles H, White MB, Noble NA, Bajaj JS. Enhancement of functional connectivity, working memory and inhibitory control on multi-modal brain MR imaging with Rifaximin in Cirrhosis: implications for the gut-liver-brain axis. *Metab Brain Dis* 2014; **29**: 1017-1025 [PMID: 24590688 DOI: 10.1007/s11011-014-9507-6]
23 **Antoniades CG**, Wendon J, Vergani D. Paralysed monocytes in acute on chronic liver disease. *J Hepatol* 2005; **42**: 163-165 [PMID: 15664238 DOI: 10.1016/j.jhep.2004.12.005]
24 **Cai Q**, Liu W, Zhu M, Sheng J. Microbial Infections as a Trigger for Acute-on-Chronic Liver Failure: A Review. *Med Sci Monit* 2019; **25**: 4773-4783 [PMID: 31282874 DOI: 10.12659/MSM.915637]
25 **Shalimar**, Rout G, Jadaun SS, Ranjan G, Kedia S, Gunjan D, Nayak B, Acharya SK, Kumar A, Kapil A. Prevalence, predictors and impact of bacterial infection in acute on chronic liver failure patients. *Dig Liver Dis* 2018; **50**: 1225-1231 [PMID: 29910108 DOI: 10.1016/j.dld.2018.05.013]
26 **Kwo PY**, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol* 2017; **112**: 18-35 [PMID: 27995906 DOI: 10.1038/ajg.2016.517]
27 **Ginès P**, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet* 2021; **398**: 1359-1376 [PMID: 34543610 DOI: 10.1016/S0140-6736(21)01374-X]
28 **Risør LM**, Fenger M, Olsen NV, Møller S. Hepatic erythropoietin response in cirrhosis. *Scand J Clin Lab Invest* 2016; **76**: 234-239 [PMID: 26924722 DOI: 10.3109/00365513.2015.1137351]
29 **Sawada K**, Takai A, Yamada T, Araki O, Yamauchi Y, Eso Y, Takahashi K, Shindo T, Sakurai T, Ueda Y, Seno H. Hepatitis-associated Aplastic Anemia with Rapid Progression of Liver Fibrosis Due to Repeated Hepatitis. *Intern Med* 2020; **59**: 1035-1040 [PMID: 31875639 DOI: 10.2169/internalmedicine.4072-19]
30 **Francoz C**, Durand F, Kahn JA, Genyk YS, Nadim MK. Hepatorenal Syndrome. *Clin J Am Soc Nephrol* 2019; **14**: 774-781 [PMID: 30996046 DOI: 10.2215/CJN.12451018]
31 **Ouyang R**, Li H, Xia J, Wang X, Zheng X, Huang Y, Meng Z, Gao Y, Qian Z, Liu F, Lu X, Shi Y, Shang J, Liu J, Deng G, Zheng Y, Yan H, Zhang W, Qiao L, Jiang X, Wang H, Zhong G, Li B, Chen J. Lower platelet counts were associated with 90-d adverse outcomes in acute-on-chronic liver disease patients. *Ann Palliat Med* 2021; **10**: 9342-9353 [PMID: 34412498 DOI: 10.21037/apm-21-1019]
32 **Simonetto DA**, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. *BMJ* 2020; **370**: m2687 [PMID: 32928750 DOI: 10.1136/bmj.m2687]
33 **Li S**, Zhang X, Li Q, Lv B, Zhang Y, Jia J, Yue X, Lu W. Development and validation of the nomogram based on INR and eGFR for estimation of mortality in patients with acute-on-chronic hepatitis B liver failure. *BMC Gastroenterol* 2021; **21**: 474 [PMID: 34911462 DOI: 10.1186/s12876-021-02054-3]
34 **Abudeif A**, Sayed EKA, Galal GM. Characteristics and predictors of short-term mortality in decompensated cirrhotic patients with acute-on-chronic liver failure. *Clin Exp Hepatol* 2022; **8**: 300-308 [PMID: 36683875 DOI: 10.5114/ceh.2022.122332]
35 Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. Geneva: World Health Organization; 2015 Mar- [PMID: 26225396]
36 **Ferstl P**, Trebicka J. Acute Decompensation and Acute-on-Chronic Liver Failure. *Clin Liver Dis* 2021; **25**: 419-430 [PMID: 33838858 DOI: 10.1016/j.cld.2021.01.009]
37 **Dolmazashvili E**, Karchava M, Abutidze A, Sharvadze L, Tsertsvadze T. Comparative Study Of Fib-4 Index And Transient Elastography Among Patients With Chronic Hepatitis C Virus Infection In Georgia. *Georgian Med News* 2017; 81-86 [PMID: 28480856]
38 **Moini M**, Onofrio F, Hansen BE, Adeyi O, Khalili K, Patel K. Combination of FIB-4 with ultrasound surface nodularity or elastography as predictors of histologic advanced liver fibrosis in chronic liver disease. *Sci Rep* 2021; **11**: 19275 [PMID: 34588540 DOI: 10.1038/s41598-021-98776-1]
39 **O'Leary JG**, Reddy KR, Garcia-Tsao G, Biggins SW, Wong F, Fallon MB, Subramanian RM, Kamath PS, Thuluvath P, Vargas HE, Maliakkal B, Tandon P, Lai J, Thacker LR, Bajaj JS. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-d survival in hospitalized patients with cirrhosis. *Hepatology* 2018; **67**: 2367-2374 [PMID: 29315693 DOI: 10.1002/hep.29773]
40 **Mahmud N**, Kaplan DE, Taddei TH, Goldberg DS. Incidence and Mortality of Acute-on-Chronic Liver Failure Using Two Definitions in Patients with Compensated Cirrhosis. *Hepatology* 2019; **69**: 2150-2163 [PMID: 30615211 DOI: 10.1002/hep.30494]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com