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# Population-representative Incidence of Acute-On-Chronic Liver Failure

## *A Prospective Cross-Sectional Study*

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**Background:** Acute-on-chronic liver failure (ACLF) is a major cause of hepatic death in the world, but no population-based studies have evaluated the incidence of ACLF. This study was conducted to determine the incidence and short-term outcomes of ACLF in a region of Eastern China.

**Methods:** In this prospective cross-sectional study, we collected data from public hospitals in Nantong city between January 1, 2005, and December 31, 2014. All hospitals with admission potential for ACLF patients were included. The primary outcome was ACLF defined as severe jaundice and coagulopathy with underlying chronic liver disease, according to diagnostic and laboratory criteria suggested by Chinese Society for Hepatology (CSH).

**Results:** During the 10-year period, a consecutive sample of 1934 ACLF patients was included in this study. The overall ACLF incidence rate over the 10-year period was 2.53 (95% confidence interval, 2.16-2.91) per 100,000 population per year, decreasing from 3.35 in 2005 to 2.06 in 2014. Chronic hepatitis B virus (HBV) infection was the leading cause of chronic liver disease and HBV reactivation was the most common cause of acute hepatic event. The 28-day mortality for the ACLF patients had a clear decline during the study period, form 50.39% in 2005 to 35.44% in 2014.

**Conclusions:** In the Eastern China population, the incidence of ACLF is decreasing and the prognosis improving. Short-term mortality was associated with the presence of cirrhosis and growing age. While ACLF remains a life-threatening disorder, our findings suggest that nationwide and long-term cohorts should be conducted for the natural history of ACLF.

**Key Words:** acute-on-chronic liver failure, incidence, mortality

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Liver failure (LF) is a common medical ailment with varied etiology and severe deterioration of liver function which results in altered coagulopathy and mentation. LF can present as acute liver failure (ALF), acute-on-chronic liver failure (ACLF), or chronic liver failure (CLIF) and all carry high morbidity and mortality. ALF, which often affects young persons without any preexisting liver disease, is a rare disorder with approximately 1600 cases per year or 5.5 cases per million population per year in the United States.[1] Before liver transplantation (LT), most studies suggested as high as 85% mortality.[2] CLIF or decompensated cirrhosis is an end-stage liver disease, with a median time from diagnosis to death of 10 years, high morbidity, and frequent hospitalizations.[3]

ACLF was proposed in 1995 as an acute deterioration of known or unknown chronic liver diseases (CLDs).[4] Before the Chinese Society for Hepatology (CSH) proposed and updated the diagnostic and treatment guidelines for ACLF formally in 2006 and 2012, respectively,[5,6] it had been called severe chronic hepatitis in China.[7] The definition of ACLF by CSH is "an acute decompensation (AD) in liver function in patients with previously diagnosed or undiagnosed chronic liver disease (CLD), manifesting within 4 weeks as severe jaundice (serum total bilirubin, TBil $\geq$ 10 mg/mL) and coagulopathy (prothrombin activity, PTA $\leq$ 40%), complicated by ascites and/or hepatic encephalopathy (HE)." This definition is close to that proposed by Asian Pacific Association for the Study of the Liver (APASL) in 2009, except the cutoff value of jaundice (TBil level $>$ 5 mg/mL).[8] There have been a growing interest in ACLF which presents many challenging opportunities in both clinical and basic research. However, our current understanding of the scale of the problem in China is based on retrospective and hospital-based studies. Although ACLF is becoming a public health issue, its incidence remains unclear.

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The aim of this prospective cross-sectional study was to report valid and precise data on incidence, etiology, and short-term outcomes of ACLF within a cooperated health care system which approximates the population for a geographically defined region of Eastern China (population representative).

## PATIENTS AND METHODS

### Study Design and Data Source

This was a prospective cross-sectional study in which ACLF patients were recruited from 6 local public hospitals during the period from January 1, 2005 to December 31, 2014. The international classification of diseases the 10th edition (ICD-10) system has been adopted and the code for ACLF is K72.005. Demographic information include personal identification such as sex and birth date, demographical details, diagnoses, admission type, length of stay, and hospital charges. The institutional review boards of these hospitals approved this study. Written informed consents for collection of their data were obtained from all patients (or in some instances, their closest relatives).

### Ascertainment of ACLF

A definite diagnosis of ACLF (or chronic severe hepatitis before 2006), based on Chinese guidelines,[5,7] was defined as follows: (i) presence of previously diagnosed or undiagnosed CLD; (ii) both severe jaundice (TBil $\geq$ 10 mg/mL) and coagulopathy (PTA $\leq$ 40%) within 4 weeks from symptom onset; (iii) complicated by ascites and/or HE.

Diagnosis of CLD was made mainly through known history of chronic hepatitis or cirrhosis. Patients with CLD were identified based on their medical records of liver function tests, hepatitis virus markers, results of imaging, or liver biopsy. For those without a definite etiology of CLD, the presence of stigmata of liver disease on physical examination, low platelets, history of abnormal liver function tests in previous reports may support the presence of CLD.

Exclusion criteria: ALF; CLIF; coexistent hepatocellular carcinoma (HCC); extrahepatic cholestasis; coma of nonhepatic origin; and patients who have undergone major surgery (for example liver resection) or have unsolved surgical problems.

### Etiological Investigation

The etiology of the underlying CLD was ascertained by medical history as well as supporting clinical and laboratory information. Patients were enquired whether they had one or more of the following diagnoses before the admission: chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (carrier, hepatitis, or cirrhosis), alcoholic liver diseases (ALDs), and autoimmune liver diseases (AILDs). Chronic hepatitis B (CHB) or chronic hepatitis C (CHC) were diagnosed according to the guidelines.[9,10] Noninvasive evaluation of steatosis and cirrhosis was performed with ultrasound, computed tomography scan, or transient elastography FibroTouch (Wuxi Hisky Medical Technology, Beijing, China). The diagnosis of ALDs were made by documentation of alcohol excess and evidence of liver dysfunction.[11] As the vast majority of patients with nonalcoholic fatty liver disease (NAFLD) have benign disease and steatosis may be coincident with other liver diseases, NAFLD was not specified. Instead, cryptogenic CLD, in the setting of ACLF here, may include some NAFLD cases, as previous reports.[12,13]

The causes of acute hepatic insult were classified as: (i) spontaneous viral reactivation in patients with chronic HBV or HCV infection; (ii) superinfection with other hepatitis viruses in addition to chronic HBV or HCV; (iii) active alcoholic consumption (AAC); (iv) drug-induced liver injury (DILI); and (v) undefined causes. The serology and nucleic acid testing were required to find out viral etiology. HBV or HCV reactivation was defined as the HBV DNA or HCV RNA $> 10^3$ copies/mL. Infection with other viruses such as hepatitis E virus (HEV), hepatitis A virus (HAV), or hepatitis D virus (HDV) was confirmed by serologic tests. AAC was defined as a history of alcohol consumption within 28 days of admission, exceeding 30 g/d for men and 20 g/d for women.[14] Diagnosis of DILI was made by careful history taking and thorough exclusion of other potential etiologies.[15]

### Follow-up and Outcomes

Follow-up began on the ACLF diagnosis date. Patients were followed from the diagnosis date until discharge. The short-term outcome of those who had a hospitalization $<$ 28 days was surveyed through phone with the patients or their close relatives 1 month after the diagnosis date.

### Statistical Analysis

Local databases of Nantong, a city of Eastern China with approximately 7.7 million inhabitants, were used to analyze epidemiological trends of patients diagnosed with ACLF between January 2005 and December 2014. Incidence rates of ACLF was determined by dividing the number of Nantong population with confirmed events by the total population of the study period. Data on sex and age distribution were obtained from the Nantong Bureau of Statistics which compiled the population data. The incidence of ACLF was calculated on the basis of the ACLF patients' sex and age and standardized with the local sex and age distribution. Rate ratios (RRs) and 95% confidence intervals (95% CIs) were used to describe associations between potential risk factors and short-term mortality. Poisson multivariate regression was performed to estimate multiplicative RRs associated with each factor. Data were analyzed using Stata 13 (Stata Corporation, TX).

## RESULTS

### Study Patients

During the 2005 to 2014 period, the Nantong ACLF Study Group enrolled 2664 patients with diagnosis suggestive of chronic severe hepatitis or ACLF from 6 public hospitals. Of these, 117 patients, lacking preexisting liver disease based on medical records and serologic/virologic laboratory tests, were excluded as ALF. Another 409 patients were confirmed to have CLIF. Besides, 63 were excluded due to coexisting HCC, 58 due to extrahepatic cholestasis, 19 due to coma of nonhepatic origin, 35 due to major surgeries, and 29 due to incomplete data (Fig. 1)

Of the 1934 confirmed ACLF patients, 75% of cases were men and the average age was 48 years (range, 17 to 89 y). There were no children patients aged less than or equal to 16 years. Among these patients, 1190 (61.5%) had preexisting cirrhosis at ACLF diagnosis. Complications of

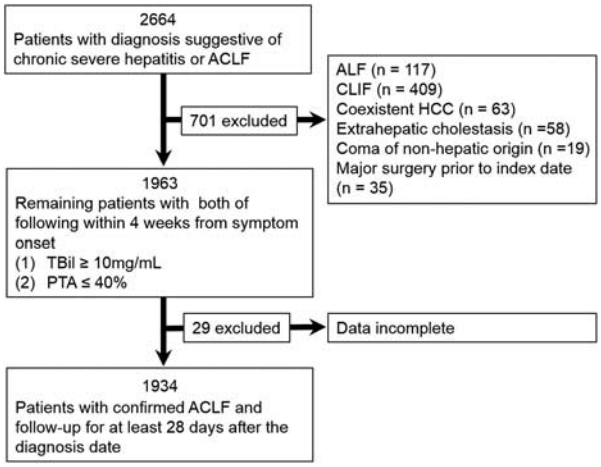


**FIGURE 1.** Flow chart of study patients. ACLF indicates acute-on-chronic liver failure; ALF, acute liver failure; CLIF, chronic liver failure; HCC, hepatocellular carcinoma; PTA, prothrombin activity; TBiL, total bilirubin.

**TABLE 1.** Demographic, Clinical, and Laboratory Features of the Study Patients

| Characteristics | Value |
|---|---|
| Male/female | 1451 (75.0%)/483 (25.0%) |
| Age (y) | 49.2 ± 11.7 (48; 17-89) |
| TBil (mg/dL) | 19.3 ± 8.9 |
| PTA(%) | 28.1 ± 17.4 |
| Preexisting cirrhosis | 1190 (61.5%) |
| Ascites | 1534 (79.3%) |
| SBP | 1199 (62.0%) |
| HE | 611 (31.6%) |
| HRS | 357 (18.5%) |
| UGIB | 188 (9.7%) |
| ALSS treatment | 1029 (53.2%) |
| Liver transplantation | 9 (0.47%) |
| Early NA treatment for HBV-ACLF | 922/1760 (52.4%) |

Values are expressed as mean ± SD, median (range), or n (%).
ALSS indicates artificial liver support system; HBV, hepatitis B virus; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; NUC, nucleos(t)ide analogues; PTA, prothrombin activity; SBP, bacterial peritonitis; TBil, total bilirubin; UGIB, upper gastrointestinal bleeding.

the progressive liver disease included spontaneous bacterial peritonitis (SBP, 1199, 62.0%), hepatic encephalopathy (611, 31.6%), hepatorenal syndrome (HRS, 357, 18.5%), and upper gastrointestinal bleeding (UGIB, 188, 9.7%). The deaths resulted from one or more of the complications in the first 28 days (Table 1).

Among all 1934 ACLF patients, 1029 (53.2%) received artificial liver support system (ALSS) treatment. The use of ALSS increased gradually, from 27.5% (71/258) in 2005 to 58.9% (93/158) in 2014. For 1760 patients with ACLF secondary to HBV infection (HBV-ACLF), 922 (52.4%) had early antiviral treatment with nucleos(t)ide analogs (NA) initiated in the first week postadmission and sustained for to the end of follow-up or till death. Early NUC treatment for HBV-ACLF patients increased from 9.1% (22/243) in 2005 to 59.9% (82/137) in 2014. LT for ACLF has not been highly utilized in China due to the extremely limited organ sources. The referral to the transplant center of Nantong Third People's Hospital was recommended for the other 5 hospitals. Eighty-four (4.34%) patients had been referred for LT evaluation, but only 9 (0.47%) patients received transplantation within the 28-day period of follow-up (Table 1).

## Incidence

The overall ACLF incidence rate over the 10-year period was 2.53 (95% CI, 2.16-2.91) per 100,000 population per year, decreasing from 3.34 in 2005 to 2.07 in 2014 (Fig. 1A). The incidence rate was 3-fold higher in males than females (3.83 vs. 1.25 per 100,000 population per year), and this male-to-female ratio gradually decreased from 2005 to 2014 (3.07 to 1.87; Fig. 2A). Men had an incidence peak around 35 to 39 and a smaller peak at 65 to 69 years of age. Women had 2 incidence peaks around 50 to 54 and 65 to 69 years of age (Fig. 2B).

## Etiology of CLDs

The most common cause of CLD was chronic HBV infection here, accounting for 91% (1760 cases) of all. The other causes were AILDs (58, 3%), ALDs (53, 2.74%), and chronic HCV infection (23, 1.19%). Thirty-two (1.65%) patients has been diagnosed as having cryptogenic CLD. Besides, there were a tiny percentage of patients confirmed with 2 causes: coexistence of chronic HBV infection and ALD in 5 cases, coinfection of HBV and HCV in 3 cases (Fig. 3A). During the 2005 to 2014 period, there was a gradual decrease in the proportion of cases of HBV-related CLD, and somewhat increasing rates of AILDs and ALDs (data not shown).

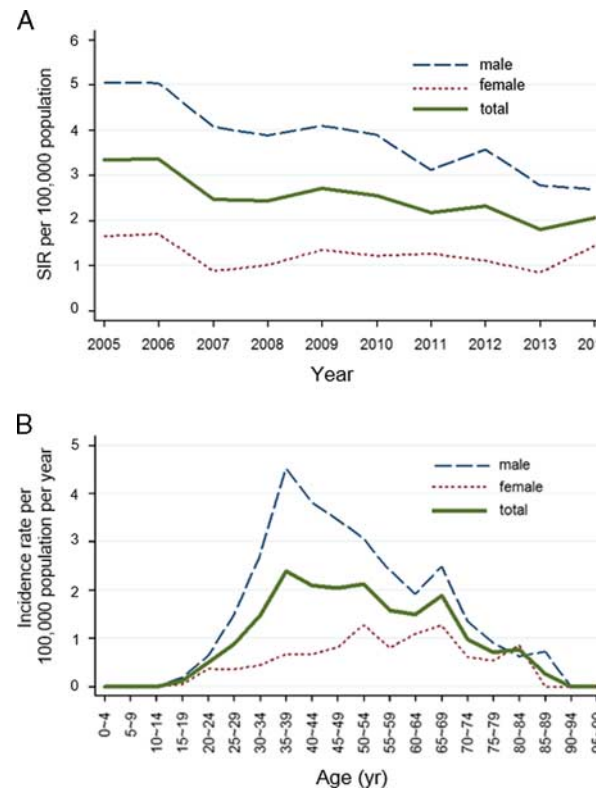


**FIGURE 2.** Incidence rates of acute-on-chronic liver failure (ACLF) in Nantong, China 2005 to 2014. A, Sex-standardized incidence rates (SIR) of ACLF. B, Age-specific and sex-specific incidence rates computed in 5-year age groups.

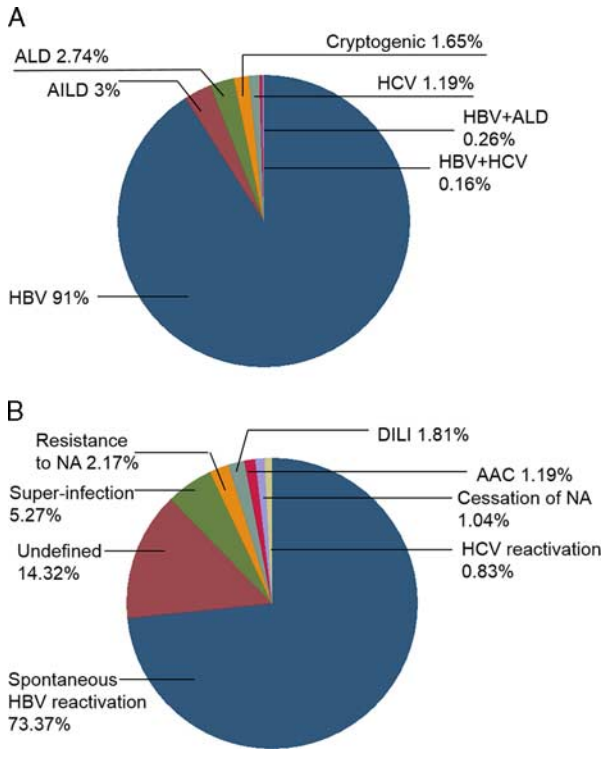


**FIGURE 3.** Etiology of chronic liver diseases (A) and profile of acute events (B) in the ACLF patients. AAC indicates active alcoholic consumption; AILD, autoimmune liver disease; ALD, alcoholic liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, nucleos(t)ide analogs.

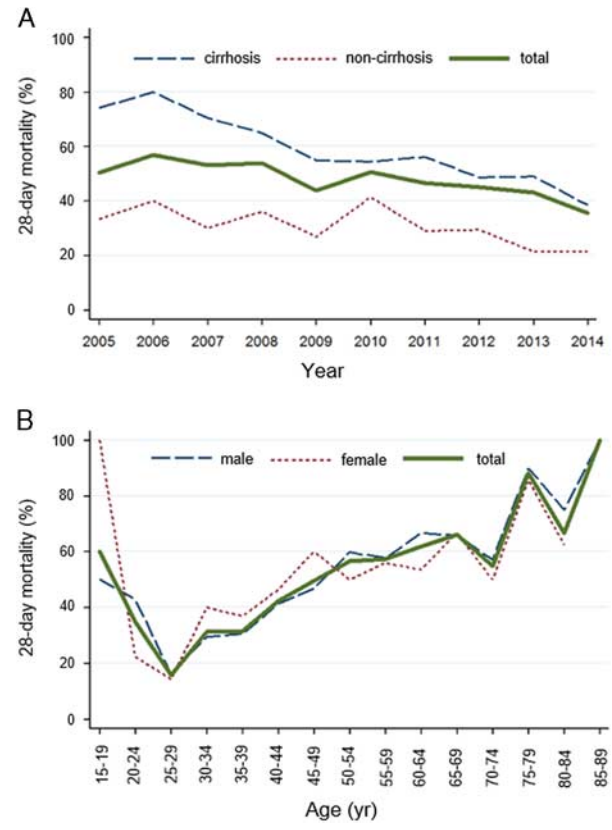


**FIGURE 4.** Short-term mortality rates of acute-on-chronic liver failure (ACLF) in Nantong, China 2005 to 2014. A, Short-term mortality rates in cirrhotic or noncirrhotic patients with ACLF. B, Age-adjusted and sex-adjusted mortality rates computed in 5-year age groups.

## Profile of Acute Events

The leading acute hepatic insult is spontaneous reactivation of HBV (1419, 73.37%). Superinfection with other viruses such as HEV (73, 3.77%), HDV (21, 1.09%), or HAV (8, 0.42%) were recognized as triggers of hepatic decompensation in patients with CHB. Emergence of HBV drug resistance to NAs or cessation of NAs were found in 42 (2.17%) and 20 (1.04%) cases, respectively. HCV reactivation occurred in 16 (0.83%) cases. Among the noninfectious etiologies, DILI (35, 1.81%) and AAC (23, 1.19%) were the major causes of acute hepatotoxicity. The drugs responsible vary by location and prevailing drug use, with herbal or traditional medications as the most common cause. For the rest 277 patients (14.32%), no acute events could be clearly defined (Fig. 3B).

## Short-term Mortality

Of the 1934 patients, 941 patients (48.66%) died during the 28-day follow-up. The short-term mortality for the ACLF patients had a clear decline during the study period, form 50.39% in 2005 to 35.44% in 2014. The mortality was markedly higher for those who had been diagnosed with cirrhosis, compared with those not (698/1189, 58.7% vs. 241/745, 32.35%; $P < 0.001$) (Fig. 4A). Both in male and female ACLF patients, the mortality rate increased with age, except that the mortality rate of 100% (2/2) for female aged 15 to 19 resulting from the small sample size (Fig. 4B).

Table 2 shows the relationship of several factors with 28-day postadmission mortality due to ACLF. The gender, elder ages (≥ 50 y), preexisting cirrhosis, the presence of ascites, SBP, HE, HRS, or UGIB; ALSS treatment revealed individual associations with short-term outcome ($P < 0.05$). When these variables were entered into Poisson regression model, elder ages (RR 1.48; 95% CI, 1.22-1.69), preexisting cirrhosis (RR 1.84; 95% CI, 1.62-2.08), the presence of ascites (RR 1.77; 95% CI, 1.57-2.15), SBP (RR 2.49; 95% CI, 2.22-3.04), HE (RR 2.66; 95% CI, 2.43-2.99), HRS (RR 3.18; 95% CI, 2.55-3.58), and UGIB (RR 1.93; 95% CI, 1.68-2.32) emerged as independent predictors for short-term mortality due to ACLF ($P < 0.05$). Intriguingly, ALSS treatment (RR 0.73; 95% CI, 0.64-0.92) was found to be associated with the favorable outcome of the patients here ($P < 0.05$).

## Economic Burden

The mean cost per ACLF hospitalization (as exchanged to US dolor) is as high as $6615 (95% CI, 6220-7010). Although the costs per ACLF hospitalization have not changed significantly over time, the total cost of ACLF hospitalizations has decreased as the number of ACLF patients has decreased from 258 cases in 2005 to 158 cases in 2014.

# DISCUSSION

In this regional population-representative study of ACLF in Eastern China 2005 to 2014, a male predominance (75%) was found. The incidence rate of ACLF for

**TABLE 2.** Prognostic Factors for 28-Day Mortality Among the Study Patients

| Variable | Death/ Exposed | Univariate RR (95% CI) | Multivariate RR (95% CI) |
|---|---|---|---|
| Male | | 0.90 (0.81-1.00) | 0.94 (0.84-1.09) |
| No | 254/483 | | |
| Yes | 687/1451 | | |
| Age (y) | | 1.58 (1.44-1.73) | 1.48 (1.22-1.69) |
| < 50 | 420/1082 | | |
| ≥ 50 | 521/852 | | |
| Preexisting cirrhosis | | 1.79 (1.59-2.00) | 1.84 (1.62-2.08) |
| No | 244/744 | | |
| Yes | 697/1190 | | |
| Ascites | | 2.08 (1.75-2.46) | 1.77 (1.57-2.15) |
| No | 105/400 | | |
| Yes | 836/1534 | | |
| SBP | | 3.01 (2.61-3.48) | 2.49 (2.22-3.04) |
| No | 159/735 | | |
| Yes | 782/1199 | | |
| HE | | 2.63 (2.41-2.86) | 2.66 (2.43-2.99) |
| No | 425/1323 | | |
| Yes | 516/611 | | |
| HRS | | 2.28 (2.12-2.44) | 3.18 (2.55-3.58) |
| No | 621/1577 | | |
| Yes | 320/357 | | |
| UGIB | | 1.71 (1.56-1.87) | 1.93 (1.68-2.32) |
| No | 795/1746 | | |
| Yes | 146/188 | | |
| ALSS treatment | | 0.64 (0.59-0.71) | 0.73 (0.64-0.92) |
| No | 543/905 | | |
| Yes | 398/1029 | | |

ALSS indicates artificial liver support system; CI, confidence interval; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; NUC, nucleos(t)ide analogues; RR, rate ratio; SBP, bacterial peritonitis; UGIB, upper gastrointestinal bleeding.

men was 3-fold higher than women and had a gradually decreasing trend during the study period. Nearly two thirds of the patients had established cirrhosis already at ACLF diagnosis. The short-term mortality rate for patients with cirrhosis was twice as high as those without, indicating cirrhosis was an adverse prognostic factor.

To the best of our knowledge, this is the first population-representative cross-sectional study of ACLF. The established network of local public hospitals ensured that all patients with ACLF were diagnosed and included in our study. We are certain that the clinicians adhered to the established diagnostic criteria.[5–7] The incidence of ACLF in Nantong clearly decreased during the study period. As the vast majority of CLDs were HBV-related, we believe that this decline may to some extent reflect the development in prevention and treatment for HBV infection. Actually, epidemiological survey reported that HBV prevalence gradually declined in China due to hepatitis B vaccination program since 1992.[16] It is forecasted that there will be significant decreases in the number of Chinese with cirrhosis due to chronic HBV infection. Moreover, our study period parallels the development of antiviral NAs including adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil. These agents have been proved to markedly suppress HBV replication, resulting in improvement of liver function and reduced incidence of cirrhosis and HCC.[17–19]

Our finding that 61.48% of the ACLF patients had already developed cirrhosis at the time of diagnosis is in agreement with other studies.[20] It should be noted that the inclusion criteria according to CSH guidelines is close to that proposed by APASL, except the cutoff value of jaundice (TBil level > 5 mg/mL).[21] However, as in many other aspects of life and medicine, there is a sharp East-West divide with respect to the definition of ACLF. The American association for the study of liver diseases (AASLD) and European association for the study of the liver (EASL) consensus defines it as "a syndrome that defines a subgroup of cirrhotic patients who develop organ failure following hospital admission with or without an identifiable precipitating event and have increased mortality rates."[22,23]

Like others,[24] we found that cirrhosis at ACLF diagnosis was associated with markedly higher mortality. In addition, we found the mortality increased with age. Indeed, that age may be an independent prognostic factor for end-stage liver diseases is in accordance with previous studies.[25,26] Moreover, in some western trials, variceal bleeding was also regarded as an acute insult for ACLF. It has been extensively debated whether to consider infection and variceal bleeding as acute events of ACLF. The LF in patients with variceal bleeding may be mainly due to hepatic ischemia rather than direct hepatic insult.[27] While bacterial infection may play an important role in the pathogenesis and mortality in ACLF,[28] it is also a common complication in the natural history of cirrhosis.[29] Whether infection is the cause or a result of LF remains debated. Therefore, we did not include UGIB or SBP as acute insults for ACLF, in agreement with the latest APASL guidelines.[21]

The decreasing mortality for the ACLF patients observed during our study period should be noted. While the proportion of patients with cirrhosis at the time of ACLF diagnosis remained stable each year, the most likely explanation may be that clinical management has improved. In fact, the improved short-term and long-term prognosis of ACLF resulting from the use of ALSSs and anti-HBV agents have been indicated by other studies[30,31] and our own observations as well.[26,32]

Earlier studies have reported children patients with Wilson disease presenting with ACLF.[33] However, we have not identified children patients with ACLF in this study. It is partly because HBV infection, rather than inherited disorder such as Wilson disease, usually causes minimal liver damage in the childhood, perhaps during the immune-tolerance phase.[34]

Admittedly, there are some limitations of our study. First, although our results are derived from a prospectively obtained consecutive sample, the accurate information concerning the long-term prognosis of ACLF patients are lacking, due to the study design.[35] Another limitation lies in our use of the Chinese criteria for the definition of ACLF. On the one hand, the CSH criteria, with a cut-off TBil value of 10 mg/dL, provided an underestimation of the incidence of ACLF than APASL criteria which used a cut-off value of 5 mg/dL.[21] On the other hand, the fact of including patients without preexistent cirrhosis overestimated the incidence of ACLF than AASLD/EASL criteria which emphasized cirrhosis as prerequisite for the diagnosis.[22,23] Nevertheless, along with the fact that two thirds of the patients had cirrhosis at the baseline evaluation, we believe that our results are applicable to the general population of ACLF.

In summary, we showed that, in the Eastern China population, the incidence of ACLF is decreasing and the prognosis improving. Short-term mortality were clearly associated with the presence of cirrhosis and growing age.

Concerning that ACLF remains a life-threatening disorder, our findings suggest that nationwide and long-term cohorts should be conducted for the natural history of ACLF.

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