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# Association between early antibiotic treatment after admission and mortality of acute-on-chronic liver failure patients with bacterial infection: A multicenter retrospective study

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**ABSTRACT**

Bacterial infection is a significant risk factor in the onset and development of acute-on-chronic liver failure (ACLF). Although early broad-spectrum antibiotic treatment is recommended, the optimal time to initiate antibiotic therapy remains unclear. This study aimed to investigate the relationship between the timing of antibiotic treatment and the prognosis of ACLF patients with bacterial infection. Patients with ACLF and bacterial infections upon admission were retrospectively evaluated. The predictors of 28-day mortality were identified using univariate, least absolute shrinkage and selection operator regression analysis, and multivariate logistic regression analyses. The "survminer" R package was used to categorize patients into two groups based on a 6-h threshold: early antibiotic administration (<6 h of admission) and later antibiotic administration (≥6 h after admission). A total of 295 patients were evaluated. The lungs were the most common site of infection (61.7% of patients had lung infections), followed by the peritoneum (25.4% of patients had spontaneous bacterial peritonitis). The time to first antibiotic administration was an independent predictor of 28-day mortality, and the odds of mortality increased by 2% for each hourly delay in antibiotic administration after admission. In Kaplan-Meier survival analysis, both 28-day and 90-day mortality rates were significantly lower in the early antibiotic group than in the later antibiotic group (both $p < 0.0001$). In conclusion, early antibiotic treatment is an independent predictor of 28-day mortality in ACLF patients with bacterial infections. Patients who received antibiotics less than 6 hours after admission exhibited lower 28- and 90-day mortality rates.

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Acute-on-chronic liver failure; bacterial infection; early antibiotics treatment; mortality; risk factor

## Introduction

Acute-on-chronic liver failure (ACLF) is a severe form of acute decompensation in liver cirrhosis characterized by organ failure; importantly, it significantly increases the risk of short-term mortality [1,2]. Further, the presence of bacterial infections significantly exacerbates the severity and clinical course of ACLF, leading to a notably higher mortality rate in ACLF patients with bacterial infections than in patients without bacterial infections [3,4]. Compared with patients without bacterial infections, those with bacterial infections and sepsis have higher risks of developing hepatic encephalopathy, circulatory failure, and respiratory failure. Additionally, ACLF patients with bacterial infections have a higher mortality rate [3,5]. Moreover, bacterial infections can cause secondary hepatorenal syndrome, hepatic encephalopathy, and gastrointestinal bleeding, all of which further increase the mortality rate among ACLF patients [6].

Bacterial infections are key contributors to ACLF onset and progression. During the initial stages of ACLF development, pathogens stimulate the immune system, triggering the recruitment, activation, and differentiation of effector immune cells. Macrophage activation, along with the proliferation and infiltration of circulating monocytes into the liver, leads to liver injury and necrosis [7,8]. Liver necrosis triggers the massive release of inflammatory mediators, resulting in the development of a systemic inflammatory response syndrome [9]. The body subsequently initiates a compensatory anti-inflammatory response (CARS), orchestrated by a complex interplay of immune cells,

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signalling molecules, and cytokines. However, excessive or dysregulated CARS can impair both the innate and adaptive immunities, leading to immune exhaustion, immune paralysis, and extrahepatic organ failure [9–11].

Bacterial infection plays a crucial role as a trigger for ACLF, with approximately one-third of patients with ACLF presenting with an infection on admission [3,12,13]. Additionally, approximately half of those without initial infection develop bacterial infections within 4 weeks [3,12]. Early and adequate antibiotic treatment is key to managing ACLF in patients with bacterial infections [14,15]. International guidelines recommend prompt identification of patients with infection and the initiation of early and broad-spectrum antibiotic therapy, based on several clinical observational studies [1,16,17]. Studies have shown that early and adequate antibiotic treatment can improve the prognosis of patients with cirrhosis complicated by bloodstream infections [15], with early diagnosis and timely antibiotic administration significantly reducing mortality rates [18,19].

Given the more severe and complex nature of ACLF, the mortality rate in ACLF patients with infection is notably higher than that in patients with infection and cirrhosis [6]. However, although guidelines recommend the early and adequate use of broad-spectrum antibiotics, there is currently a lack of research on the optimal timing for initiating antimicrobial therapy in ACLF patients with bacterial infections. The desire to shorten the duration of antibiotic administration may also lead to increased healthcare burden and potential harm [20,21]. Therefore, determining the optimal time to initiate antibiotic therapy in ACLF patients with infection is of paramount importance, particularly in resource-constrained settings, such as emergency departments. Thus, this study aimed to investigate the relationship between the timing of initiation of antibiotic treatment and the prognosis of ACLF patients with infection.

## Patients and methods

### Study design and population

This retrospective study was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine (Reference Number: 2024–1044). The collection of patient information, as permitted by this ethics approval, will continue until 31 December 2025. The study was conducted according to the ethical guidelines of the Declaration of Helsinki. Given the retrospective nature of the study, the requirement for individual informed consent was waived.

Adult patients with liver cirrhosis admitted to The First Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang Provincial People's Hospital, or Shulan (Hangzhou) Hospital between 1 August 2016 and 1 August 2024 were evaluated. Liver failure patients were identified by systematically searching the medical record databases of these three medical centres with a diagnosis of (sub)acute liver failure or by using the International Classification of Diseases, 10th version codes K72.0 and K70.4 [22]. To identify possible eligible patients, we included those who had liver cirrhosis combined with acute deterioration, as defined by the acute development of large ascites, hepatic encephalopathy, gastrointestinal haemorrhage, bacterial infection, hepatorenal syndrome, or a combination of these conditions [4]. Cirrhosis was diagnosed based on the histology of liver biopsy or a combination of clinical, imaging and laboratory findings [4].

The inclusion criteria were liver failure patients with concurrent bacterial infections and hospitalization for at least 1 day. Patients who did not meet the ACLF diagnostic criteria, those aged <18 years, pregnant women, and those lost to follow-up within 90 days of admission were excluded. All study centres adopted the same liver transplant allocation policy. Clinical patient data upon admission and hospitalization were collected by professional investigators who were blinded to the patient outcomes.

### Definition and outcomes

ACLF was diagnosed based on the European Association for the Study of the Liver guidelines [1]. Briefly, ACLF grade 1 (ACLF-1) is characterized by the presence of renal failure or any other single-organ failure associated with renal and/or cerebral dysfunction. ACLF grades 2 and 3 (ACLF-2 and ACLF-3) are defined as the presence of 2 or 3–6 organ failures [1]. Organ failure was defined according to the Chronic Liver Failure-Sequential Organ Failure Assessment criteria [23]. Complications of ACLF referred to ascites, gastrointestinal haemorrhage, and hepatic encephalopathy [13]. Due to all patients had bacterial infections at the time of admission, bacterial infections were considered a precipitating factor (trigger) rather than a complication [3].

Bacterial infections were diagnosed based on previous research and identified as follows. Pneumonia was defined as clinical signs of infection and new infiltrates on chest radiography. Spontaneous bacterial peritonitis (SBP) was defined as a polymorphonuclear (PMN) cell count in ascites of 250 cells/mm$^3$.

Secondary bacterial peritonitis was defined as PMN count in ascites of 250 cells/mm$^3$ and evidence (abdominal computed tomography/surgery) of an intra-abdominal source of infection. Urinary tract infection was defined as abnormal urinary sediment (>10 leukocytes/field) and positive urinary culture, or uncountable leukocytes per field in negative cultures. Spontaneous bacteraemia was defined as positive blood cultures with no cause of bacteraemia. Secondary bacteraemia was defined as (1) catheter-related infection (positive blood and catheter cultures) and (2) bacteraemia occurring within 24 h after an invasive procedure. Skin and soft tissue infections (SSTI): were defined as clinical features of infection associated with swelling, erythema, heat, and tenderness of the skin. *Clostridium difficile* infection was defined as positive stool toxin in a patient with diarrhoea [3,24]. Multidrug-resistant organism (MDRO) was defined as non-susceptibility to at least one agent in three or more antimicrobial categories [25]. Septic shock was diagnosed according to the Sepsis 3.0 diagnostic criteria [26]. Broad-spectrum antibacterial drugs included second-generation to fourth-generation cephalosporins, fluoroquinolones, macrolides, and combinations of penicillin and streptomycin. Other antibiotics were classified as narrow-spectrum antibiotics [27]. The primary outcome measure of our study was 28-day mortality; the secondary outcome measure was 90-day mortality.

### Data collection

Clinical data were collected by two independent investigators from each medical centre using a standard data collection form. Bacterial infections were diagnosed by two independent investigators after reviewing clinical patient information. Any discrepancy between the two investigators was resolved by referring to another senior investigator to determine the presence of infection. Variables including age, sex, cause of cirrhosis, ACLF complications, organ failure, site of infection, and type of first antibiotic dose were recorded. The time to first antibiotic administration was recorded as the interval from admission registration (in emergency department [ED] refers to ED presentation) to the administration of the first antibiotic dose. Laboratory data on admission were also documented. Additionally, bacterial culture obtained before the first antibiotic dose and the presence of septic shock on admission were recorded.

Survival time was recorded using medical record systems and telephone follow-ups [28]. Survival status was assessed at different intervals after admission, including the first, second, third, and fourth weeks, as well as at 60 and 90 days. The telephone numbers of the patients and of at least one of their family members or friends were recorded upon admission. For patients who were initially unreachable by phone, three contact attempts were made within 1 week. Patients who refused follow-up or could not be contacted by phone and whose survival status could not be verified through the medical records system were considered lost to follow-up.

### Statistical analysis

In the univariate analysis, normally distributed continuous variables were analysed using Student's t-test and expressed as the mean ± standard deviation, whereas non-normally distributed were analysed using nonparametric tests and expressed as the median ± quartile. Meanwhile, categorical variables were analysed using the $\chi 2$ test and Fisher's exact test. Significant variables in the univariate analysis and potential prognostic variables, as well as the cause of cirrhosis, were included in the least absolute shrinkage and selection operator (LASSO) regression analysis to determine the predictors of 28-day mortality. LASSO was performed using the "glmnet" package in the R software [29]. The appropriate time to start antibiotic treatment was established using the "surv_cutpoint" function from the "survminer" R package. Briefly, this function systematically examines all possible thresholds of a continuous variable and selects the value that best stratifies patients based on survival outcomes. This approach has been widely used in survival analysis to identify clinical cut-off values [30,31]. The patients were then divided into two groups according to the timing of their first antibiotic dose: early antibiotic treatment group and later antibiotic treatment group. Kaplan-Meier survival curves were generated using the "survival" and "survminer" R packages and compared between groups using the log-rank test. Risks were expressed as hazard ratios (HRs) with their 95% confidence intervals (CIs), which were calculated using the "survival" R packages. Potential variables influencing outcomes were included in the multivariate logistic regression model for further analysis and adjustment for confounding factors.

All statistical analyses were conducted using SPSS Software (IBM Corp., Armonk, NY, USA), GraphPad Prism Software (GraphPad Software Inc., CA, USA), and R software (version 4.2.2). $p < 0.05$ was considered significant.

## Results

### Patient characteristics

Among the 748 patients initially evaluated, 453 were excluded due to failure to meet the diagnostic criteria for ACLF ($n = 445$), pregnancy ($n = 1$), age <18 years ($n = 1$), and loss to follow-up ($n = 6$). Ultimately, 295 patients were included in the analysis (Figure 1). The patient characteristics were shown in Table 1. Among the 295 patients, 112 died and 183 survived within 28 days. Pulmonary infection was the most common infection (61.7%), followed by spontaneous bacterial peritonitis (25.4%). Hepatitis B virus (HBV) infection was the leading cause of cirrhosis, with 132 (72.1%) of the survivors and 87 (77.7%) of the nonsurvivors having HBV infection. Univariate analysis revealed that compared with survivors, nonsurvivors were older (56 years vs. 53 years, $p = 0.042$) and had a higher prevalence of organ failure (coagulation failure: 44.6% vs. 29%, $p = 0.006$; circulatory failure: 16.8% vs. 7.1%, $p = 0.015$). Furthermore, the incidence of septic shock was higher among nonsurvivors (8.9% vs. 2.2%, $p = 0.008$). Figure 2 showed the time from admission to the first antibiotic administration. The median time to first antibiotic administration was shorter among survivors than among nonsurvivors (5.4 h vs 8.6 h, $p < 0.001$). The pathogens and antibiotic usage were presented in Supplementary Table S1. Appropriate antibiotic use, MDRO occurrence, and renal failure during hospitalization were shown in the Supplementary Material.

### Risk factors for 28-day mortality

LASSO regression analysis showed that age, circulatory failure, total bilirubin level, leukocyte count, hepatic encephalopathy, time to first antibiotic administration, and international normalized ratio (INR) were independent predictors of 28-day mortality (Figure 3). To further clarify the impact of each variable on patient prognosis, these factors were subsequently incorporated into a multivariate logistic regression analysis (Table 2). The results revealed that each 1-hour delay in antibiotic administration after admission was associated with a 2% increase in the odds of mortality (Table 2). Additionally, subsequent antibiotic administration was found to be an independent predictor of transplant-free mortality in ACLF patients and bacterial infections (Supplementary Table S2).

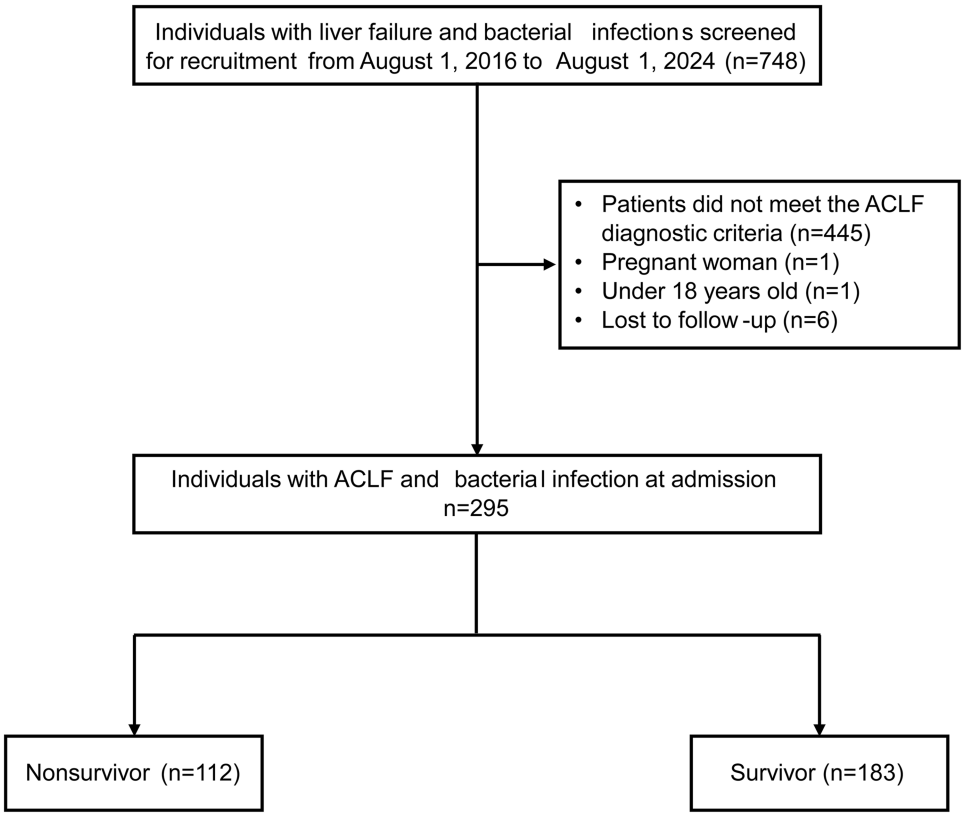


**Figure 1.** Patient selection flowchart.

**Table 1.** Clinical characteristics of ACLF patients with bacterial infections on admission.

| | Survivors ($n = 183$) | Nonsurvivors ($n = 112$) | $P$ value |
|---|---|---|---|
| Age (years) | 53 (40–66) | 56 (44–67) | 0.042 |
| Male, n | 143 (78.1%) | 84 (75%) | 0.534 |
| Cause of cirrhosis, n | | | |
| HBV | 132 (72.1%) | 87 (77.7%) | |
| HBV plus alcoholic | 6 (3.3%) | 5 (4.5%) | |
| Alcoholic | 19 (10.4%) | 8 (7.1%) | |
| Other | 26 (14.2%) | 12 (10.7%) | |
| Complications at admission, n | | | |
| Ascites | 111 (60.7%) | 77 (68.8%) | 0.161 |
| Hepatic encephalopathy | 105 (57.4%) | 73 (65.2%) | 0.184 |
| Gastrointestinal haemorrhage | 15 (8.2%) | 13 (11.6%) | 0.332 |
| Organ failures, n | | | |
| Liver | 150 (82%) | 101 (90.2%) | 0.055 |
| Kidney | 42 (23%) | 26 (23.2%) | 0.985 |
| Cerebral | 3 (2.7%) | 3 (1.6%) | 0.539 |
| Coagulation | 53 (29%) | 50 (44.6%) | 0.006 |
| Circulatory | 13 (7.1%) | 18 (16.8%) | 0.015 |
| ACLF-1 | 101 (55.2%) | 35 (31.3%) | <0.001 |
| ACLF-2 | 78 (42.6%) | 66 (58.9%) | 0.007 |
| ACLF-3 | 4 (2.2%) | 12 (10.7%) | 0.002 |
| Types of infections, n | | | |
| Pneumonia | 106 (57.9%) | 76 (67.9%) | 0.089 |
| Spontaneous bacterial peritonitis | 50 (27.3%) | 25 (22.5%) | 0.338 |
| Secondary bacterial peritonitis | 28 (15.3%) | 9 (8%) | 0.067 |
| Urinary infections | 10 (5.5%) | 9 (8%) | 0.383 |
| Bacteremia | 4 (2.2%) | 3 (2.7%) | 1 |
| SSTI | 4 (2.2%) | 3 (2.7%) | 1 |
| *Clostridium difficile* | 0 (0%) | 1 (0.9%) | 0.38 |
| Other | 6 (3.3%) | 4 (3.6%) | 1 |
| Septic shock, n | 4 (2.2%) | 10 (8.9%) | 0.008 |
| Broad-spectrum antibiotics, n | 182 (99.5%) | 110 (98.2%) | 0.303 |
| Time to first antibiotic use (h) | 5.4 [3.2–14.5] | 8.6 [6.0–23.4] | <0.001 |
| Vital signs | | | |
| T (°C) | 36.8 [36.5–37.1] | 36.7 [36.2–37.1] | 0.251 |
| HR (/min) | 88 (72–103) | 90 (75–104) | 0.33 |
| MAP (mmHg) | 88 (73–104) | 86 (70–102) | 0.284 |
| R (/min) | 19 [18–20] | 19 [18–20] | 0.485 |
| Laboratory data | | | |
| Leukocyte count ($10^9$/L) | 8 [5.8–11.9] | 9.5 [6.3–14.0] | 0.096 |
| Neutrophil ($10^9$/L) | 6.0 [4.1–9.7] | 7.4 [4.5–11.3] | 0.06 |
| CRP (mg/L) | 17.6 [10.7–30.8] | 17.0 [11.0–33.5] | 0.888 |
| Hemoglobin (g/L) | 116 [97–134] | 123 [100–139] | 0.102 |
| Total bilirubin (mg/dL) | 19 (10–28) | 22 (13–32) | 0.002 |
| ALT (U/L) | 179 [64–483] | 187 [73.25–574] | 0.75 |
| AST (U/L) | 181 [79–428] | 182 [98.5–407.5] | 0.522 |
| INR | 1.91 [1.54–2.57] | 2.34 [1.85–2.94] | <0.001 |
| Creatinine (mg/dL) | 0.83 [0.62–1.87] | 0.84 [0.67–1.94] | 0.492 |

Continuous variables were analysed using Student's t-test and non-parametric tests, and were expressed as median [interquartile spacing] or mean (mean ± standard deviation). Categorical variables were analysed using the $\chi 2$ test and Fisher's exact test, and were expressed as numbers (percentages).

HBV: hepatitis B virus, SSTI: skin and soft tissue infections, ACLF: acute-on-chronic liver failure, CRP: C-reactive protein, INR: international normalized ratio, ALT: alanine aminotransferase, AST: aspartate aminotransferase, h: hour; T: temperature, HR: heart rate, R: respiration, MAP: mean arterial pressure.

### *Appropriate time to start antibiotic therapy*

Multivariate analysis demonstrated that later antibiotic administration was a risk factor for 28-day mortality. However, the early use of antibiotics can also increase the medical burden and is potential harmful [21,32]. The adverse effects of early antibiotic use might arise from patients receiving unnecessary and inappropriate antibiotic treatment, as shortening the time to antibiotic administration reduces the time for clinicians to evaluate the patient's condition. Unnecessary and inappropriate antibiotic use may lead to adverse side effects and bacterial resistance [14]. Therefore, identifying the appropriate timing for antibiotic administration is essential. In this study, the appropriate cut-off value for the time of antibiotic administration was 5.6 h (Figure 4). Similarly, the optimal cut-off value for transplant-free mortality was also found to be 5.6 h (Supplementary Figure S1). Considering clinical practicality, we chose 6 h as the cut-off value. Based on this cut-off value, 129 patients were classified into the early antibiotic treatment group, while 166 patients were classified into the later antibiotic treatment group.

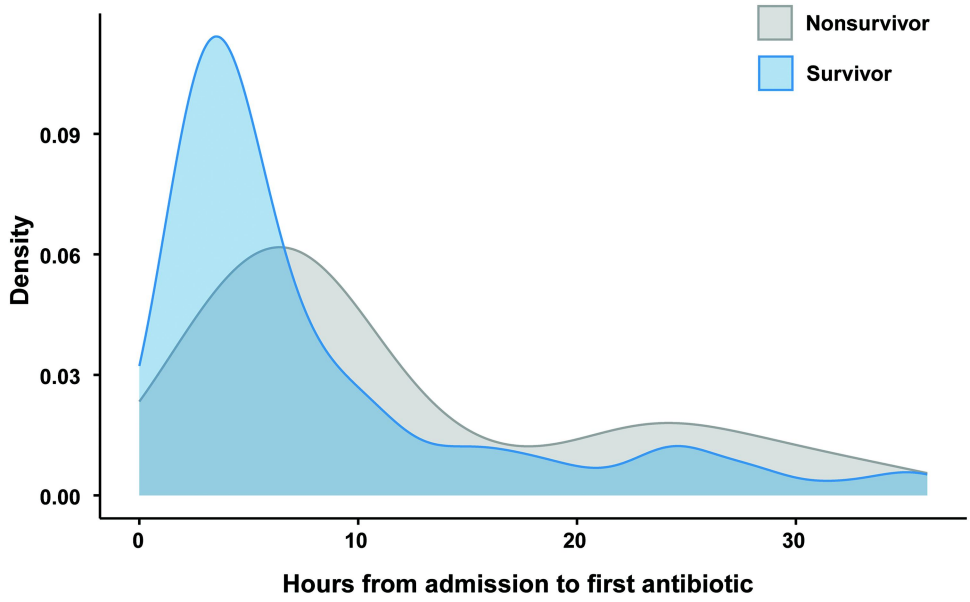


**Figure 2.** Time to first antibiotic administration after admission.

Density plot depicting the time from admission to first antibiotic administration. The distribution of survivors and nonsurvivors was represented by blue and grey lines, respectively. The median [quartile] time to first antibiotic administration was significantly lower in survivors than in nonsurvivors (5.4 [3.2–14.5] h vs 8.6 [6.0–23.4] h, $P < 0.001$).

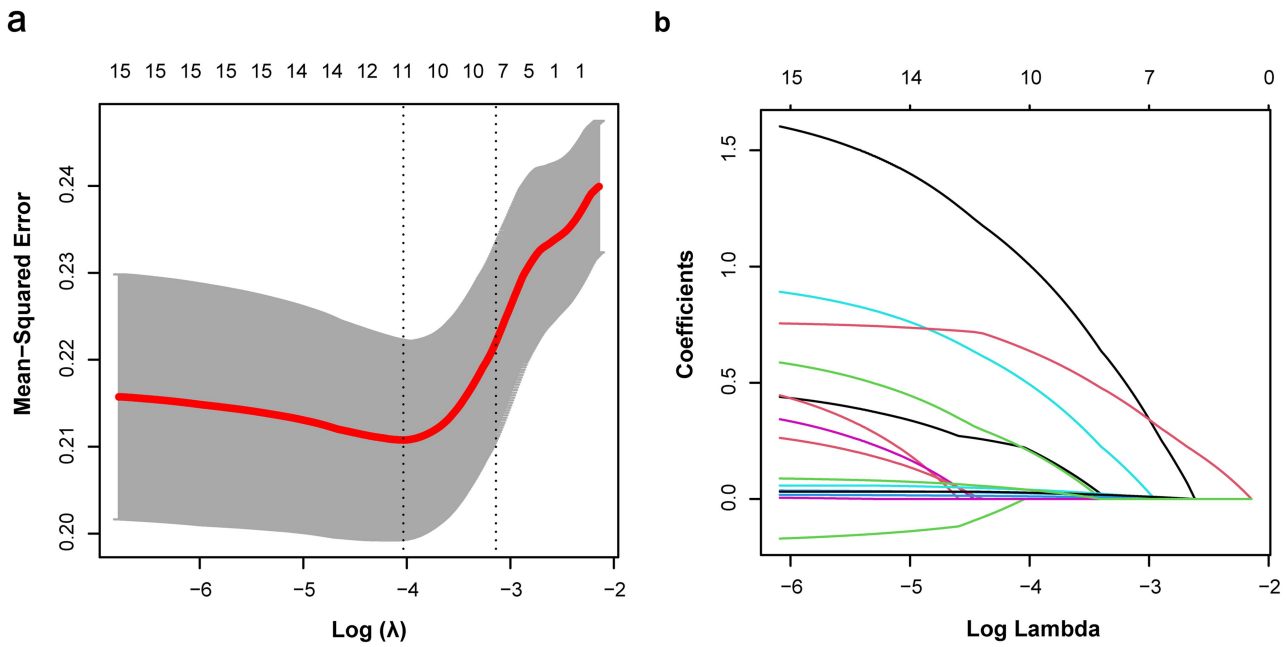


**Figure 3.** Variable selection through LASSO regression analysis.

(a)The tuning parameter (λ) for the LASSO regression analysis was selected using a 10-fold cross-validation method, based on the minimum criteria. This method identified 7 variables with nonzero coefficients at the optimal lambda value. (b) Variables of LASSO coefficients for clinical features.

### *Improved survival outcomes with early antibiotic treatment*

Survival analysis revealed significantly higher risk of both 28-day (hazard ratio [HR]: 2.88; 95% confidence interval [CI]: 1.87–4.44); $p < 0.001$) and 90-day (HR: 1.98; 95% CI: 1.45–2.69; $p < 0.001$) mortalities in the later antibiotic treatment group (Figure 5). Similar results were observed for transplant-free mortality (Supplementary Figure S2). Comparison of clinical characteristics between the early and later antibiotic

**Table 2.** Multivariate logistic regression analysis.

| | β coefficient | OR | 95% CI | *P* value |
|---|---|---|---|---|
| Age (years) | 0.04 | 1.04 | 1.01–1,06 | 0.002 |
| Total bilirubin (mg/dL) | 0.04 | 1.05 | 1.01–1.08 | 0.006 |
| INR | 0.85 | 2.33 | 1.65–3.29 | <0.001 |
| Circulatory failure | 1.4 | 4.07 | 1.73–9.57 | 0.001 |
| Time to first antibiotics (h) | 0.02 | 1.02 | 1.01–1.03 | 0.007 |
| Leukocyte count ($10^9$/L) | 0.07 | 1.07 | 1.03–1.12 | 0.003 |
| Hepatic encephalopathy | 0.68 | 1.97 | 1.12–3.48 | 0.019 |

OR: odds ratio, 95% CI: 95% confidence interval, INR: international normalized ratio, h: hour.

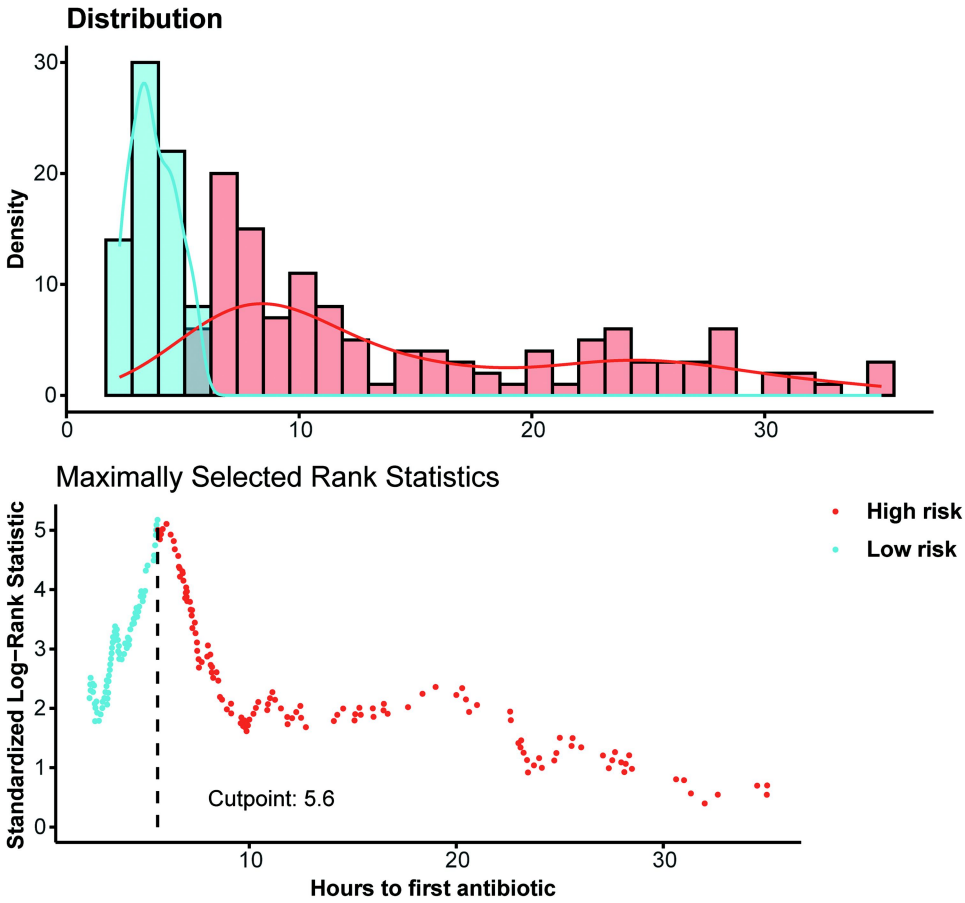


**Figure 4.** Cutoff value for the optimal timing of antibiotic administration.

treatment groups showed no significant differences in the types of infections, ACLF grades, or complications (Supplementary Table S3). The causative pathogen and antibiotic usage by group were shown in Supplementary Table S4.

## Discussion

This study evaluated a multicenter cohort of ACLF patients with bacterial infections to explore the relationship between the time to start antibiotic therapy and short-term mortality. The results indicated that the odds of mortality increased by 2% per hour of delay in antibiotic administration from the time of admission. Additionally, patients who received antibiotics less than 6 h of admission had significantly better survival rates compared to those who received antibiotics later. The 28- and 90-day mortality rates were 38% and 61%, respectively. Pulmonary infection was the most common type of infection (61.7%), followed by SBP (25.4%). Broad-spectrum antibiotics were administered to 99% of the patients.

Age, circulatory failure, total bilirubin, leukocyte count, hepatic encephalopathy, time to first antibiotic administration, and INR were independently associated with patient prognosis and predicted mortality. Among these factors, total bilirubin, INR, and hepatic encephalopathy indicated the overall severity of liver

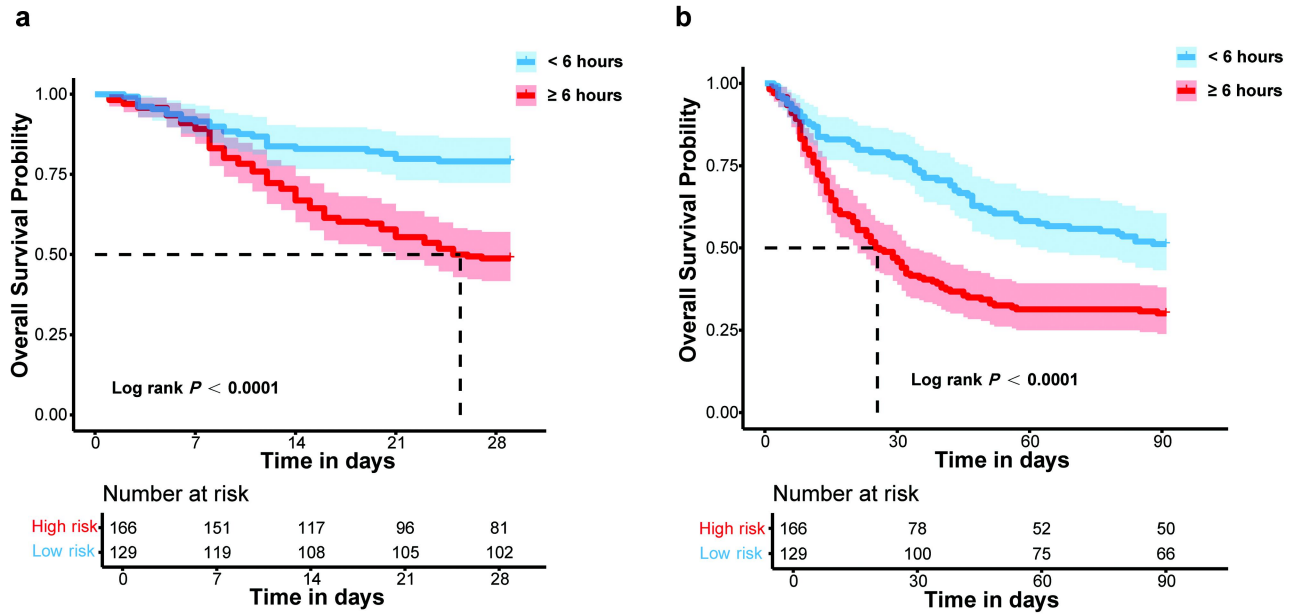


**Figure 5.** Survival curves.

(a) Survival curves for 28-day mortality. (b) Survival curves for 90-day mortality.

failure, while circulatory failure reflected organ failure. The leukocyte count reflected the severity of the infection. Our findings are consistent with those of another study that reported high mortality rates among patients with ACLF with infections, with 28- and 90-day mortality rates of 38% and 61%, respectively [3]. That study also identified infection, total bilirubin and creatinine levels, and the appropriateness of empirical antibiotic use as independent predictors of death [3].

Our research further investigated the crucial effect of the time to first antibiotic administration in patients with ACLF. The findings provide important insights into the time to first antibiotic administration in ACLF patients with bacterial infections. First, each hour of delay in antibiotic administration after admission was associated with a 2% increase in the odds of mortality. Moreover, we identified a cut-off for the time to first antibiotic administration that best differentiated between patients who survived and those who died. Patients who received antibiotics within 6 hours of admission had significantly better survival rates compared to those who received antibiotics later. When patients were stratified into early and later antibiotic treatment groups based on a 6-h threshold, those in the later antibiotic administration group exhibited a significantly higher risk of mortality, with HR of 2.88 for 28-day mortality and 1.98 for 90-day mortality. These results underscore the critical importance of early antibiotic administration, offering a reference for clinical practice and highlighting a clearer strategy to improve outcomes in patients with ACLF and infections.

Second, hospital admission time was selected as the starting point for recording, enhancing the practicality for clinical application. Several studies had shown that early antibiotic administration reduces patient mortality and complications. In this study, the time of hospital admission was used as the reference point, and the interval between admission and the administration of the first antibiotic dose was meticulously recorded. This was the early moment when most patient care started, and the initial treatment plan was formulated, which also helped ensure the timeliness of treatment and comparability of data. This approach is consistent with routine clinical operations, rendering our findings both applicable and valuable in real-world settings.

There are several explanations for the use of antibiotics less than 6 h. First, the rapid use of antibiotics reduces the burden of pathogens on the body. Early antibiotic administration can rapidly inhibit the growth and reproduction of pathogens, reduce their load, and prevent the spread of infection [33]. Second, pathogens and their toxins trigger an immune response that leads to the release of inflammatory mediators [34]. Excessive inflammatory response may cause tissue damage, organ failure, and immune system disruption, increasing the risk of secondary infections [35]. Early use of antibiotics can reduce the release of inflammatory mediators and alleviate the inflammatory response, thus protecting tissues and organs from further damage and maintaining normal immune function [32,35]. Lastly,

uncontrolled infections can lead to severe complications, such as septic shock and multiple organ failure, which increase mortality rates [36]. Early administration of antibiotics can eliminate pathogens more effectively, improve the treatment success rate, shorten disease course, and reduce hospital stay [32].

In patients with ACLF complicated by bacterial infections, antibiotic selection is often empirical, based on the site of infection, clinical severity, and comorbidities, owing to the urgency of treatment [16]. However, very early antibiotic use reduces the time available for clinicians to assess the infectious condition, which may result in overtreatment or inappropriate antibiotic therapy [14]. Unnecessary and inappropriate antibiotic use may lead to adverse side effects and contribute to bacterial resistance [21,37]. Additionally, because some antibiotics are hepatotoxic and nephrotoxic, they may further impair the liver and kidney functions [21]. This study found no significant differences in early and later antibiotic use group with respect to appropriate antibiotic use, new renal failure, or the occurrence of MDRO during hospitalization. Early antibiotic treatment also necessitates a more accurate clinical judgement regarding the presence of infection, considering the local pathogen profiles when selecting antibiotics. Furthermore, the timely adjustment and de-escalation of antibiotic therapy are essential [21,38].

Our study had limitations. First, the retrospective design might have introduced selection and treatment decision biases to the results. Owing to the retrospective nature of the study, we cannot conclude whether subsequent antibiotic use is the cause of increased mortality and can only conclude that there is an association between them. Further prospective randomized controlled trials are needed to clarify this relationship. Second, our analysis only included 295 ACLF patients with bacterial infections because of the relatively low number of ACLF patients with bacterial infections upon admission. Similar limitations were observed in other study [4]. Third, bacterial cultures were not performed before antibiotic therapy in some patients, and some bacterial culture results were negative. The lack of bacterial culture results for some patients upon admission limited the comprehensiveness of the pathogen information for this study. An even larger cohort would be beneficial to further validate the optimal timing of antibiotic therapy.

In conclusion, this multicenter retrospective study shows that for ACLF patients with bacterial infections, each hour of delay in antibiotic administration increases the odds of mortality by 2%. Patients who receive broad-spectrum antibiotic therapy less than the first 6 h of admission have lower 28-and 90-day mortality rates. However, the current study only establishes an association between early antibiotic treatment and survival rates; causal relationships cannot be inferred owing to the retrospective study design. The findings need to be further validated through prospective cohort studies or randomized controlled trials to determine the optimal timing of antibiotic therapy.

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## Author contributions

**Xinyi Chen**: conceptualization, data curation, methodology, formal analysis, visualization and writing – original draft. **Wenyi Chen**: data curation, formal analysis and investigation. **Jiahang Zhou**: data curation, supervision and validation. **Jingyi Chen**: data curation and visualization. **Guoqiang Cao**: data curation and validation. **Chenjie Huang**: data curation and validation. **Xiaoqing Lu**: data curation and validation. **Xiaoxiao Chen**: data curation and validation. **Rui Luo**: data curation and validation. **Haijun Huang**: data curation. **Qiaoling Pan**: data curation. **Jinfeng Yang**: data curation. **Jiong Yu**: supervision. **Hongcui Cao**: conceptualization, writing – review and editing, supervision and funding acquisition.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Data availability statement

The data that support the findings of this study are openly available in https://www.scidb.cn/en/anonymous/NnpFTjdu (DOI: 10.57760/sciencedb.22804).

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