Afebrile Bacteremia in Adult Emergency Department Patients with Liver Cirrhosis：Clinical Characteristics and Outcomes

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Abstract

Background: Cirrhotic patients with bacteremia are at an increased risk of organ failure and mortality. In addition, they can develop serious infection without fever because of their impaired immune response. Our study aimed to investigate the clinical characteristics, and outcomes in afebrile bacteremic patients with liver cirrhosis. Methods: A single-center, retrospective cohort study was performed on adult patients who visited the emergency department from January 2015 to December 2018. All patients with bacteremia and a diagnosis of liver cirrhosis were enrolled and classified as either afebrile or febrile. We compared the clinical characteristics, laboratory results, microbiological data and outcomes between the two groups.

Results In total, 113 bacteremic patient with liver cirrhosis (afebrile: 60 patients and, febrile: 53) were included in the study. Compared with the febrile group, patients in the afebrile group showed a significantly higher rate of inappropriate antimicrobial agent administration (43.3% vs. 18.9%, p= 0.01). They were also at an increased risk of 30-day mortality (40% vs. 18.9%, p= 0.02), intensive care unit transfer (38.3% vs. 20.8%, p=0.04) and endotracheal intubation (28.3% vs. 11.3%, p=0.03).

Conclusions In bacteremic patients with liver cirrhosis, a significantly higher rate of inappropriate antimicrobial agent administration, higher risk of intensive care unit transfer, endotracheal intubation and 30-day mortality were observed in the afebrile group than in the febrile group. Clinicians should perform prudent evaluation in cirrhotic patients and carefully monitor for possible sings of serious infection even in the absence of fever.

Background

Patients with liver cirrhosis are prone to develop infection because of their cirrhosis-associated immune dysfunction, increased intestinal mucosa permeability and decreased hepatic bacteria filtration(1). Among these, bacteremia, which is the presence of bacteria circulating in the bloodstream, is a serious and systemic infectious disease requiring aggressive treatment and investigation(2). Compared to non-cirrhotic patients, bacteremia in cirrhotic patients shows drastically high mortality and morbidity risk and prolonged hospitalization (3–5).

Fever is a common presentation in patients with infectious disease, together with altered mental status and hypotension, which may help clinicians to diagnose bacteremia(6). Clinicians frequently rely on the presence of fever to initiate infection workup(7); however, fever is a complex and non-specific host defense response against infection, and not an indispensable component of the bacteremic syndrome(8). Afebrile bacteremic patients often have atypical clinical manifestations, such as lethargy or confusion(9), leading to decreased survival and poorer prognosis(10).

Previous studies regarding bacteremia in cirrhotic patients mainly focused on the severity of cirrhosis, bacteriology, source of infection, and presence of drug-resistant organisms. None of them addressed the issue of body temperature, which could influence the decision of treatment initiation (11–13). Our study

aimed to investigate the prevalence, clinical characteristics, and prognosis in afebrile bacteremic patients with liver cirrhosis.

Methods

Study design

A retrospective cohort study was conducted at a tertiary referral medical center with approximately 60,000 emergency department (ED) visits per year. We enrolled all adult patients (age ≥18 years) who visited the ED from January 1, 2015 to December 31, 2018 and fulfilled both criteria for further analysis: ED diagnostic code for liver cirrhosis (ICD10: K74.3, K74.4, K74.5, K74.60, K74.69, K71.7, K70.30, K70.31, K71.7); and positive blood culture results in ED. Patients with fungemia, contaminated blood samples, transferred from other medical facilities were excluded. The collection of blood culture in the ED course may not be performed at the first time; however, if patients present with unusual clinical manifestations (e.g. hypotension, leukocytosis, malaise, anorexia or deterioration of liver function such as jaundice, coagulopathy, hepatic encephalopathy…etc.) in the subsequent ED course, physicians would collect blood samples from the patients for microbial culture and commence antimicrobial therapy accordingly. True bacteremia was defined as blood culture of ≥2 sets collected from separate sites yielding same bacteria; or 1 set of blood culture yielding pathogen corresponding to the patient's clinical manifestations .The study was approved by the local Institutional Review Board (EMRP-108-003), and the requirement of informed consent was waived due to the retrospective observational nature of the study.

Data collection and definitions

We collected data on demographic characteristics, initial ED vital signs, pre-existing co-morbidities, laboratory results, microbiological data, source of bacteremia, and initial use of antimicrobial agents from the manual chart review and electronic medical records of all eligible patients. We used the quick Sepsis Related Organ Failure Assessment (qSOFA) (positive if at least 2 of these criteria were met: altered mental status, respiratory rate ≥ 22 breaths/min, systolic blood pressure ≤ 100mmHg) and the Systemic Inflammatory Response Syndrome (SIRS) (positive if at least 2 of these criteria were met: body temperature <36°C or >38°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, white blood cells $<0.4 \times 10^9$/L or $>1.2 \times 10^9$/ L or bandemia ≥10%) scores for infection severity stratification in the bacteremic patients(14). We also stratified cirrhotic patients according to the etiology of cirrhosis (alcoholic, viral hepatitis, or others) and severity (chronic liver failure-sequential organ failure assessment [CLIF-SOFA] scores, Child-Pugh scores and, model of end-stage liver disease [MELD] scores)(15,16). The source of bacteremia was classified as respiratory tract infection, urinary tract infection, spontaneous bacterial peritonitis, skin or soft tissue infection, biliary tract infection, and primary bacteremia. The initial antimicrobial therapy was considered "appropriate" if they met both these criteria: antimicrobial regimen administrated within 24 hours after blood sample collection (17,18), and the pathogen was susceptible to the antimicrobial agent based on an in vitro susceptibility test. If these criteria were unfulfilled, the therapy was considered "inappropriate".

Outcomes measurement

All eligible patients of this study were divided into febrile and afebrile groups for primary and secondary outcomes measurement. The afebrile state was defined as temperature < 38°C in the tympanic membrane during the patient's ED course. The primary outcome in this study was 30-day mortality rate, while the secondary outcomes included rate of intensive care unit (ICU) transfer, endotracheal intubation (i.e. respiratory failure), shock (defined as need of vasopressors to maintain hemodynamic stability despite adequate fluid administration during ED stay), and renal replacement therapy administrated within hospital stay (i.e. renal failure).

Statistical analysis

The characteristics of the afebrile and febrile bacteremic patients with liver cirrhosis were recorded and compared. Data were presented as mean with standard deviation or medians with interquartile range for continuous variables, and numbers (%) for categorical variables. Two-sample t-test and Chi-square test were used to compare the continuous and categorical variables, respectively. Mann-Whitney test was used for continuous variables if data were not normally distributed. The 30-day survival curves of the study groups were created using the Kaplan-Meier survival analysis, and the means were compared using the log-rank test. A two-tailed *p*-value < 0.05 was considered statistically significant. All the statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 software (SPSS Inc, Chicago, IL, USA).

Results

From January 1, 2015 to December 31, 2018, we identified 2362 adult ED cirrhotic patients, of which 1823 had hospital admission. The most common reason of admission was infectious disease (52.6%), followed by gastrointestinal bleeding (27.3%). Blood cultures were drawn in 937 cirrhotic patients, of which 169 had positive blood culture results. After excluding patients with contaminated blood samples (N= 15), insufficient laboratory data (N= 18), and inter-facility transfer (N= 23), 113 bacteremic patients with liver cirrhosis (afebrile: N= 60; febrile: N=53) were finally enrolled for further analysis.

Demographics and clinical characteristics

As shown in Table 1, there were no statistically significant differences in the demographic variables (age, sex) between the afebrile and febrile groups. Furthermore, there were no underlying pre-existing comorbidities significantly associated with afebrile bacteremia. Regarding laboratory results, there were no significant differences between the afebrile and febrile groups, except for lower hemoglobin level in the afebrile group (9.7±2.4 vs. 10.6±2.2 g/dL, *p*=0.03). The afebrile and febrile groups did not differ in proportion with respect to etiology or severity of cirrhosis, although more than half of the patients in both groups belonged to Child's C classification (66.7% vs. 60.4%, respectively, *p*=0.49), indicating poor liver

function performance. In the sepsis scoring system, a significantly lower proportion of the afebrile group fulfilled the SIRS criteria (53.3% vs. 94.3%, $p<0.001$), while both groups showed non-significantly different distribution in the qSOFA scoring system (Table 1).

Microbiological data, source of infection, and antimicrobial therapy

Both groups presented predominantly gram-negative pathogen infection, followed by gram-positive strains (Table 2). The distribution of causative microorganisms was similar in both groups. The most common pathogens were *Escherichia coli*, followed by *Klebsiella pneumoniae* and *Staphylococcus aureus*. Regarding the source of infection, spontaneous bacterial peritonitis was the most common type of infection, followed by primary bacteremia and urinary tract infection, although all of them showed non-significantly different distribution in both groups (Table 2). It is noteworthy that compared with the febrile bacteremic patient group, the rate of inappropriate antimicrobial therapy was drastically higher in the afebrile group (43.3% vs. 18.9%, $p= 0.01$) (Table 2) , and three of them (5%) received *no* antimicrobial therapy during the entire ED course.

Outcomes

The overall 30-day morality rate of our study cohort was 30% (34/113). The afebrile group showed significantly higher 30-day mortality rate than the febrile group (40% vs. 18.9%, $p= 0.02$). The afebrile bacteremic patient group also had a higher rate of ICU transfer (38.3% vs. 20.8%, $p=0.04$) and endotracheal intubation (28.3% vs. 11.3%, $p=0.03$) (Table 3). There were no significant differences in septic shock development and renal replacement therapy administered between both groups. The Kaplan-Meier survival curves for 30-day survival comparing both groups are shown in Figure 1. The 30-day cumulative survival probabilities in the afebrile and febrile groups were 60% and 81.1%, respectively (log-rank $p= 0.01$).

Discussion

In this ED-based single-center retrospective study, we investigated the prevalence, clinical characteristics and outcomes in afebrile bacteremic patients with liver cirrhosis. We demonstrated that although baseline characteristics were similar between the afebrile and febrile groups in our study cohort, delayed and improper selection of antimicrobial agents occurred more frequently in the afebrile group, and were at an increased risk of organ failure, including higher rate of ICU transfer and endotracheal intubation, further associated with higher mortality rate.

Previous studies considered afebrile bacteremia as a unique phenomenon in the elderly (9,19) and immunocompromised patients(20). These were not seen in our patients probably due to their cirrhotic condition, which already caused dysregulated immune response and absence of typical clinical manifestations compared with the general population(1). Cirrhotic patients presented bacteremia more easily than other comorbidities because of gut bacteria overgrowth and local immune defenses dysfunction(1), further precipitated by polymorphonuclear leukocyte dysfunction and complement

deficiency, leading to substantially high mortality rate (range 26–59%) (4,21). Interestingly, cirrhosis itself had been recognized as a potential risk factor of afebrile bacteremia, further strengthening the distinct disease entity and treatment complexity(10).

Our cirrhotic patients were younger and predominantly male, and half of them had cirrhosis attributed to alcoholism, which was different from a recent epidemiological research on liver cirrhosis (22). Although the prognosis and survival of patients between alcoholic and non-alcoholic cirrhotic patients were similar in previous studies (23,24), alcoholic cirrhotic patients tended to have bacterial infections, less incidence of hepatocellular carcinoma formation, and more mortality events attributed to infectious disease(24,25). Previous systemic reviews demonstrated that in hospitalized patients with decompensated cirrhosis related acute illness, median survival is < 6 months with Child-Pugh score ≥ 10 or MELD score ≥ 18, which was seen in majority of our cirrhotic patients(26). These could explained why our sicker patient cohort was more susceptible to acute illness, especially infection events, resulting in worse outcome compared with other comorbidities(21).

It is not surprising that the proportion fulfilled the SIRS criteria in the afebrile group was far less than that of the febrile group because they were divided by body temperature, a determinant composed of SIRS criteria. Nevertheless, SIRS criteria exhibited poor accuracy in diagnosing cirrhotic patients with bacterial infection, including in-hospital mortality discrimination and septic shock development, ICU transfer or acute on chronic liver failure prediction(27). Cirrhotic patients may have hypersplenism, use beta-blockers, and present leukopenia and bradycardia, thus showing a lack of SIRS parameters (28,29). In concurrence with this hypothesis, more than half of our afebrile bacteremic patients presented absence of tachycardia or leukocytosis, which further lowered warning level for clinicians, thereby dismissing infectious diseases (9,10). It had been proposed that markers of organ dysfunction rather than inflammatory variables, have better prognosis impact and mortality prediction performance in cirrhotic patients with sepsis(27).

Unlike other diseases that were more likely to have bacteremia with respiratory or urinary tract origin, cirrhotic patients tended to have spontaneous bacterial peritonitis as their primary infection source, which was consistent with our results (4,12,13). The distribution of bacteremic isolates in our study cohort was similar to previous studies, predominantly presenting gram-negative pathogens including Escherichia coli and Klebsiella pneumoniae predominantly, suggesting that the gastrointestinal tract is the most common source of bacterial infection in cirrhotic patients (4,11–13,30).

The timing and selection of antibiotics treatment differed significantly between our afebrile and febrile groups, with much higher rate of inappropriate use noted in the afebrile one. Prompt and appropriate antibiotics management is a crucial element in treating patients with sepsis(31). Delayed antibiotics administration in bacteremic patients had been recognized as an independent risk factor of mortality(17,18). In cirrhotic patients, hypoalbuminemia leading to reduction of proteins binding to antimicrobial agents, and altered distribution and clearance of drugs also changed their pharmacokinetic activity, further influencing treatment effectiveness(1). Furthermore, cirrhotic bacteremic patients

presented with non-specific symptoms because they had blunted inflammatory response, which hindered localization of the primary focus causing frequent delayed and improper antibiotics administration (4,21).

The 30-day mortality in our afebrile bacteremic group was substantially high (40%), and was similar to a previous afebrile bacteremia study(10). This could be attributed to their higher proportion of inappropriate antibiotics treatment since timely and adequate antimicrobial therapy was still considered as an important prognostic factor in cirrhotic bacteremic patients, regardless of their comorbidities or infection severity(11,30,32). Another explanation for grave prognosis in the afebrile group is the consequence of their highly impaired systemic immune response to infection, predisposing serious complications and mortality, although this had not been validated by immunological assays(33).

Since more than half of our patients belonged to end-stage liver disease (ESLD), the mortality may attributed to their acute-on-chronic liver failure (ACLF), developing acute decompensation of liver cirrhosis, further associated with liver and other extra-hepatic organ failure(34). Nevertheless, bacterial infection was a common complication in cirrhotic patients and was the most common precipitating factor of ACLF(35), inducing excessive host immune system pro-inflammatory response and resulting in tissue damage even organ failure, including kidney, brain, gastrointestinal tract and coagulation system(34). In summary, the higher proportion of inappropriate treated infection in our afebrile bacteremic group could cause progression of sepsis and deterioration of liver function, both of which were related to mortality events.

It was unexpected that the rate of septic shock would not differ significantly between the two groups, probably because we only identified those needing vasoactive agents to maintain adequate hemodynamic stability during the ED course as shock condition, and not taking account of the following ICU or ordinary ward course. Therefore, we may have missed a portion of patients who developed shock later. Nevertheless, the analysis of cumulative survival probabilities and other organ failure parameters, including rate of ICU transfer and respiratory failure, all indicated a far worse prognosis in afebrile patients.

There were several limitations in our study, including its monocentric and retrospective design. First, we did not calculate the detailed amount of fluid administration in bacteremic patients, which is also important in treating patients with sepsis or septic shock(31). Second, the different epidemiological data of our study cohort may limit the extrapolation ability of these results. Third, all data obtained from the manual chart reviews and electronic medical records made recall and selection bias inevitable. Fourth, our study failed to recognize patients who did not undergo blood culture tests in the ED, but developed bacteremia subsequently. Finally, some patients may have taken anti-pyretic agents before the ED visit, which may have influenced our stratification based on body temperature. Nonetheless, we defined the afebrile state as absence of fever during the entire ED course, thus minimizing the effect of anti-pyretic use before the ED treatment.

Conclusions

In summary, afebrile bacteremic patients with liver cirrhosis is a unique, but not a minority group. They have multifactorial immune system impairment and, lack of typical manifestations of infectious disease, which results in delayed diagnosis and inappropriate antimicrobial agent use. They carry an overwhelmingly higher rate of respiratory failure and, ICU transfer, further associated with worse prognosis. Clinicians should pay more attention while treating cirrhotic patients, and not only rely on their body temperature or laboratory results. They should always keep in mind the possibility of occult severe infection when unusual clinical manifestations are presented, such as lethargy, confusion, or unexplained hypotension. Only early recognition and prompt treatment can avoid deterioration of the disease and improve their outcomes.

Abbreviations

ED: Emergency Department

qSOFA: quick Sepsis Related Organ Failure Assessment

SIRS: Systemic Inflammatory Response Syndrome

CLIF-SOFA: chronic liver failure-sequential organ failure assessment

MELD: model of end-stage liver disease

ICU: Intensive Care Unit

ESLD: end-stage liver disease

ACLF: acute-on-chronic liver failure

Declarations

Ethics approval and consent to participate

This observational study was approved by the Institutional Review Board of EDa hospital (EMRP-108-003), the informed consent was waived due to the retrospective observational nature of the study.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

HYC conceived and designed the study and drafted manuscript. HYC and YCH conducted data extraction and manual chart review. YCH performed data analysis and critically revised manuscript and final approval

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Tables

Table 1. Baseline characteristics of bactermic patients with liver cirrhosis (n=113)

Characteristics	Afebrile group (n=60)	Febrile group (n=53)	*p* value
Age, y, mean±SD	56.3±12.5	56.6±11.7	0.91
Male, n (%)	43 (71.7)	42 (79.2)	0.35
Laboratory results			
Hemoglobin, g/dL, mean±SD	9.7±2.4	10.6±2.2	0.03*
Leukocyte, $\times 10^9$/L, median(IQR)	10.8 (5.2-16.2)	8.6 (5.4-12.3)	0.12
Platelet, $\times 10^9$/L, median(IQR)	68.5 (43.3-114.5)	73 .(39-125.5)	0.84
INR, median(IQR)	1.5 (1.3-1.9)	1.5 (1.3-1.8)	0.7
Bilirubin, mg/dL, median(IQR)	4.2 (2.3-10.1)	5.2 (2.4-8.2)	0.7
Sodium , mmol/L, mean±SD	130±9	130±5	0.86
Creatinine, mg/dL, median(IQR)	1.5 (1-2.7)	1.3 (1.1-1.8)	0.21
eGFR, ml/min/1.73m^2, mean±SD	49±29	56±22	0.2
CRP, mg/dL, median(IQR)	2.7 (0.9-8.2)	2.1 (0.8-8.6)	0.66
Comorbidities, n (%)			
Diabetes Mellitus	21 (35)	22 (41.5)	0.48
Hypertension	22 (36.7)	20 (37.7)	0.91
Malignancy	16 (26.7)	16 (30.2)	0.68
Immunosuppressant use, n (%)	5 (8.3)	4 (7.5)	0.88
Indwelling catheter, n (%)	4 (6.7)	0 (0)	0.06
Etiology of cirrhosis, n (%)			
Alcohol	33 (55)	28 (52.8)	0.82
Viral Hepatitis	23 (38.3)	18 (34)	0.63
Other	4 (6.7)	7 (13.2)	0.24
Child-Pugh Classification, n (%)			0.5
A	4 (6.7)	2 (3.8)	
B	16 (26.7)	19 (35.8)	
C	40 (66.7)	32 (60.4)	
MELD score , mean±SD	25±7	25±7	0.62
CLIF-SOFA score, mean±SD	8±3	8±3	0.45
qSOFA score, n (%)			0.24
0	32 (53.3)	20 (37.7)	
1	18 (30)	23 (43.4)	
2	7 (11.7)	9 (17)	
3	3 (5)	1 (1.9)	
SIRS, n (%)	32 (53.3)	50 (94.3)	<0.001*

Abbreviations:

SD, standard deviation; IQR, interquartile range; INR, international normalized ratio;

eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; MELD, Model for End-Stage Liver Disease; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; qSOFA, quick Sepsis Related Organ Failure Assessment; SIRS, systemic inflammatory response syndrome

Table 2. Microbiological distribution, infection source and antibiotics use of bactermic patients with liver cirrhosis (n=113)

	Afebrile group (n=60)	Febrile group (n=53)	*p* value
Gram-positive pathogen, n (%)	21 (35)	15 (28.3)	0.45
Staphylococcus aureus	5 (8.3)	2 (3.8)	
Group B Streptococcus	3 (5)	1 (1.9)	
Viridans streptococcus	1 (1.7)	3 (5.7)	
Others	12 (20)	9 (17)	
Gram-negative pathogen, n (%)	33 (55)	34 (64.2)	0.32
Escherichia coli	13 (21.7)	14 (26.4)	
Klebsiella pneumoniae	9 (15)	8 (15.1)	
Aeromonas sobria	3 (5)	1 (1.9)	
Aeromonas hydrophila	1 (1.7)	3 (5.7)	
Others	7 (11.7)	8 (15.1)	
Polymicrobial , n (%)	6 (10)	4 (7.5)	0.65
Infection source, n (%)			
Respiratory tract infection	4 (6.7)	3 (5.7)	0.83
Urinary tract infection	8 (13.3)	8 (15.1)	0.79
Spontaneous bacterial peritonitis	20 (33.3)	18 (34)	0.94
Biliary tract infection	3 (5)	7 (13.2)	0.13
Soft tissue infection	10 (16.7)	6 (11.3)	0.42
Primary bacteremia	15 (25)	11 (20.8)	0.59
Inappropriate antibiotics use, n (%)	26 (43.3)	10 (18.9)	0.01*
Effective antibiotics[a]	37 (61.7)	43 (81.1)	0.02*
Antibiotics within 24 hours	52 (86.7)	53 (100)	0.01*

[a] - The isolated microorganism was sensitive to the selected antimicrobial agents based on an in vitro susceptibility test result

Table 3. Outcome analysis of bactermic patients with liver cirrhosis (n=113)

Variables, n (%)	Afebrile group (n=60)	Febrile group (n=53)	*p* value
Intensive care unit transfer	23 (38.3)	11 (20.8)	0.04*
Shock	28 (46.7)	25 (47.2)	0.96
Endotracheal intubation	17 (28.3)	6 (11.3)	0.03*
Renal replacement therapy	4 (6.7)	2 (3.8)	0.49
30-day mortality	24 (40)	10 (18.9)	0.02*

Figures

between the afebrile and febrile bacteremic patients with liver cirrhosis

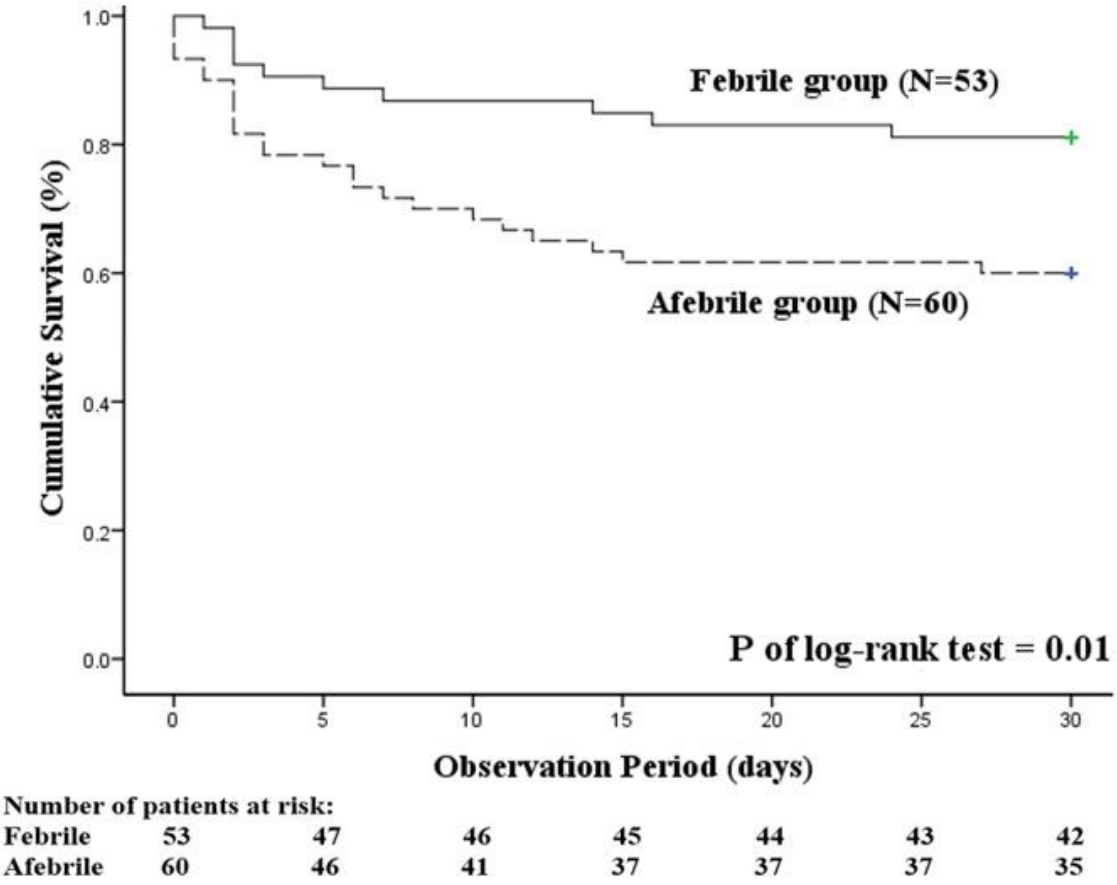

Figure 1

The Kaplan-Meier survival analysis for 30-day cumulative survival