Point by point responses to reviewers:

Reviewer #1, ID 02546652:

The paper is interesting but needs some major revision.

1. *METHODS: how was vital status assessed after discharge?*

We have provided the information in the updated method section "Vital status and liver transplantation information in patients discharged alive were collected *via* hospital information system or telephone contact." (Patients & Methods, line 9-11 on page 5).

2. *METHODS, multivariate analysis for in-hospital mortality: why was a competing risk model adopted? Which are the competing risks? To my opinion, it would be better to adopt a simple Cox regression analysis without competing risks.*

To explain this point, we have added the following sentences, it now reads: "The proportional sub-distribution hazards regression model proposed by Fine and Gray[9] was used to identify risk factors for mortality in a competing risk framework where liver transplantation was considered as a competing event of death. The standard Cox model was not applied in the current study, because Cox model doesn't cover the competing effect of liver transplantation on death and therefore result in upwards biased estimates.[10]" (Patients & Methods, line 1-4 on page 8)

3. *RESULTS, Please change Table 1 reporting separate columns for the overall study populations, and for subjects with / without BI*

The table 1 is being modified accordingly. (Table 1, on page 25-26)

4. *DISCUSSION, preventive strategies: possibly some comment for the prevention of hospital acquired infections should added*

We have added the following sentences to address this point, it now reads: "Moreover, in the hospital, a well-functional environment and equipment as well as effective program for infection prevention and control and water, sanitation and hygiene should be enhanced because it minimizes the spread the organism, particularly those resistant to multi-antibiotics and reduces hospital acquired infection by at least 30%.[25]" (Discussion, line 22 on page 14 and line 1-4 on page 15)

5. *DISCUSSION, study limits: authors report the absence of data on the resistance profile as a study limit. However, authors should expand this point: the main limit is the lack of data on the microbial etiology (a proportion of the so-called BI based on a clinical judgement might be of viral or other etiology; please comment on this limit)*

To address this point, we have added the following sentences, it now reads: "Some of the patients was classified as BI based on clinical judgement without microbiology evidence. Although we strictly adhere to the well-established diagnostic criteria[7], this could still be a source of potential investigator bias." (Discussion, line 10-13 on page 15)

6. *Lastly, I'm not a native English speaker, but the manuscript needs to be copyedited for a number of language /typographical errors and unclear sentences, e.g.: Page 2, Abstract, Conclusion: what does "particularly in the ACLF patients co-existed with pneumonia" mean? Methods, page 6, endpoint 3: "survival in patients discharged alive" (REMOVE WHO) Methods, page 6, endpoint 4: "in patients WITHOUT ACLF" 5) Discussion, page 10, second line from the bottom: "A total of 913 patients WERE discharged alive…"*

   Agree. We have corrected the abovementioned mistakes and proofreading of the manuscript. All the changes were highlighted in red color.

Reviewer #2, ID 02540325:

1. *It is stated that "Our data confirms that the high risk of developing BI in cirrhosis is independent of the etiology of cirrhosis" How can it be done when the study is carried in HBV related cirrhosis only.*

We have modified the discussion section, it now reads: "Our data demonstrated that patients with HBV-related cirrhosis were also at high risk of developing BI, suggesting that the susceptibility of cirrhosis to BI were mainly due to the increased bacterial translocation[17] and the immuno-compromised state of cirrhosis which reduces their ability to fight against infection.[18]" (Discussion, line 16-20 on page 12)

2. *It is also concluded that "BI significantly reduced the liver transplantation rate, especially in patients admitted with ACLF" Is it justifiable?*

We have modified the discussion section, "Second, BI was associated with a significant reduction of liver transplantation rate, especially in patients admitted with ACLF" (Discussion, line 15-16 on page 13)

Minor:

1. *How can be every infiltrate in the lung be taken as bacterial infection? They can also have viral or even fungal pneumonia.*

Agree. We acknowledged this as a limitation of our study and modified our discussion section, "Due to the lack of systemic assessment of respirovirus, we were not able to exclude the possibility that some pneumonia we defined in this study are viral related." (Discussion, line 8-10 on page 15)

2. *Low TLC below 4000 can't be taken as sign of infection. Patient with LC can have hypersplenism and because of this they can have TLC < 4000.*

Agree. We acknowledged this as a limitation of our study and modified our discussion section, "Leukopenia due to the cirrhosis associated hypersplenism would also introduce false positive sign of infection[2] that was not accounted for in the diagnostic criteria we used in the current study." (Discussion, line 13-15 on page 15)

3. *37% patients were HBeAg positive and only 24% were on antiviral treatment. What can be the reason?*

We described this in the discussion section, "It further highlighted the barriers for care engagement in these patients, which were rather complicated, including absence of clinical signs and symptoms, fear of stigmatization, preference to traditional herbal medicine, inadequate HBV education from the health-care system.[14]" (Discussion, line 11-14 on page 12)

Reviewer #3, ID 03024603:

1. *The term bacterial infection is very broad. It is not clear if the type of bacteria was identified in all cases diagnosed as having bacterial infection or not, this should be clarified.*

Agree. We provided detailed this information in the result section, "Among these 360 patients, 99 patients had documented bacteria isolation (27.5%), of which, 56 were Gram negative (56/99, 56.6%)." (Results, line 12-13 on page 9)

2. *It is not clear also if any of the study participants were receiving prophylactic quinolones for SBP or not, this should be clarified*

We clarified this information in the methods section, "Previous antibiotics including quinolones or rifaximin for the prophylaxis of SBP or HE was also not available in the patient's records during the study period." (Patients & Methods, line 11-13 on page 5)

We updated our discussion according to this comment, "It is also not clear whether the prior antibiotics including quinolones or rifaximin for the prophylaxis of SBP or HE play a role in the development of BI and affecting the survival. Future studies are warranted." (Discussion, line 5-8 on page 14)

3. *Indeed the type of bacterial infection is important to know, bacterial infections are broad including form mild to virulent bacteria and the outcome of the results did not clarify the type of bacterial infection, is the outcome is the same in any type of bacterial infection in this study?*

Agree. We acknowledged this as an important area of research in the future and discussed as follows: "In this study, we analyzed the impact of the source of acquisition and site of infection on the clinical outcome but the type of bacteria according to the virulence or the susceptibility to the antibiotics are the two topics not addressed in the current study." (Discussion, line 1-4 on page 14)

4. *It is not clear why the authors included only HBV+ve patients and excluded HCV+ve patients. This should be explained.*

We explained this in the manuscript as follows, "HCV+ve is beyond scope of the current study, which will be investigated in future." (Discussion, line 4 on page 14)

Reviewer #4, ID: 02942549:

1) You have not mentioned any data about prior use of antibiotics (before the admission to the hospital). How many patients were in prophylactic treatment with norfloxacin or rifaximin because of a prior episode of SBP or because of symptoms of hepatic encepalopathy respectively? Prior administration of antibiotics had any effect on the survival of patients and how?

We clarified this information in the methods section, "Previous antibiotics including quinolones or rifaximin for the prophylaxis of SBP or HE was not available in the patient's chart during the study period." (Patients & Methods, line 11-13 on page 5)

We have also updated our discussion according to this comment, "It is also not clear in our current study whether the previous antibiotics including quinolones or rifaximin for the prophylaxis of SBP or HE play a role in the development of BI and affecting the survival." (Discussion, line 5-8 on page 14)

2) Please mention the causes of death in your groups of patients and the possible differences regarding the aetiology of death among your groups of patients

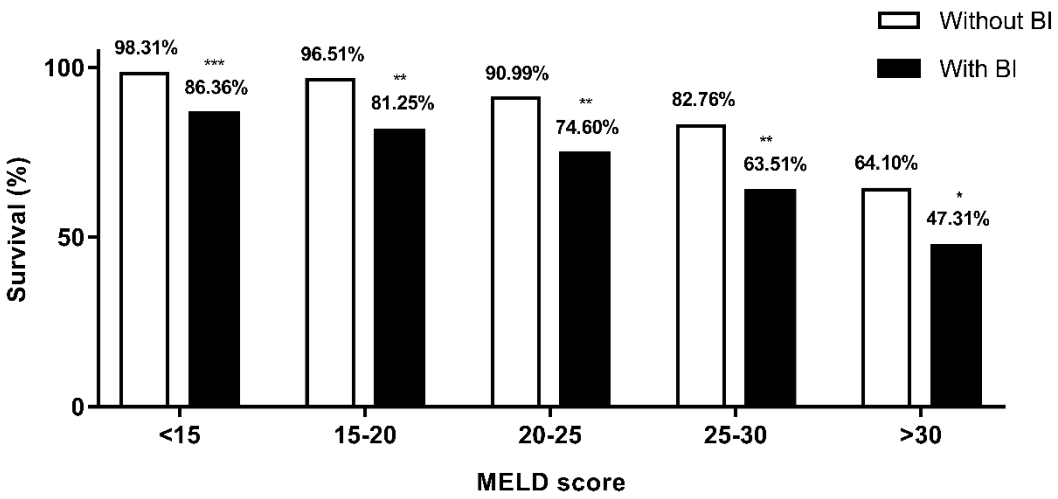
We provided the related information in the results section, as follows, "One hundred and eighty patients died while hospitalization and the overall in-hospital survival rate was 85.95%. The most common cause for death is multiple organ failure without shock (56.7%), followed by septic shock (13.3%), hypovolemic shock (10.6%) and other reasons (8.3%)." (Results, line 21-22 on page 9 and line 1-2 on page 10)

and

"Patients with BI most died from multiple organ failure (50.4%) and septic shock (38.1%) whereas those without BI mostly died from multiple organ failure (67.2%), hypovolemic shock (14.9%) and other reasons (16.4%)." (Results, line 8-11 on page 10)

3) So in your study, we do not know if patients with ACLD with or without bacterial infection had the same stage and severity of ACLD. This makes the comparison between these 2 groups very difficult and the results questionable. Please express your opinion regarding this issue

We acknowledged that the ACLF is a homogeneous group and therefore perform subgroup analysis according to the presence of ACLF or not. To further address this point, we stratified these patients into 5 group according to the values of MELD score (<15, 15-20, 20-25, 25-30, >30) to see the impact of BI on survival. We described the new results in the results section as follows, "The negative impact of BI on survival was independent of disease stage as suggested by the subgroup analysis, showing that both patients with and without ACLF had significantly lower survival when BI occurs (Figure 2). It was also independent of the severity of liver disease as was shown by the stratification analysis by the MELD score (Supplementary Figure 1)." (Results, line 4-8 on page 10)



Supplementary Figure 1, Impact of bacterial infection on in-hospital overall survival according to the values of MELD score

*, p <0.05 **, p <0.01 ***, p <0.001

Abbreviation: ACLF, acute-on-chronic liver failure; BI, bacterial infection; MELD, model for end stage liver disease

Reviewer #5, ID: 00052765:

What is frequency and etiologies of bacterial infection, as well as survival rate, and rate of ACLF presentation among patients with isolated chronic HBV-related liver disease versus those with concomitant alcoholic and HBV-related liver disease?

We have re-analyzed our data accordingly, and found no significant difference between patients with isolated chronic HBV-related liver disease and those with concomitant alcoholic and HBV-related liver disease, as was shown in the Supplementary Table 1 and Supplementary Table 2.

Supplementary Table 1. BI, ACLF and overall in-hospital survival according to the presence or absence of concomitant alcoholic liver disease

Characteristic	DC with Isolated HBV (N=1091)	DC with HBV and alcoholic liver disease (N=142)	P value
Prevalence of BI, n (%)	308 (28.2)	40 (28.2)	1.00
ACLF at admission, n (%)	240 (22)	29 (20.4)	0.75
ACLF during hospitalization, n (%)	108 (9.9)	20 (14.1)	0.16
Overall In-hospital survival, n (%)	156 (14.3)	17 (12)	0.53

Abbreviation: DC, decompensated cirrhosis; BI, bacterial infection; ACLF, acute-on-chronic liver failure;

Supplementary Table 2 Characteristics of Bacterial infection according to the presence or absence of concomitant alcoholic liver disease

Characteristic	DC with Isolated HBV and BI (N=308)	DC with HBV and alcoholic liver disease and BI (N=40)	P value
Source of acquisition			
Community-acquired	60 (21.4)	7 (17.5)	0.71
Healthcare-associated	114 (37)	16 (40)	0.85
Nosocomial infection	140 (45.5)	18 (45)	1.00
Single site			
Pneumonia	107 (34.7)	16 (40)	0.51
Spontaneous bacterial peritonitis	59 (19.2)	9 (22.5)	0.62
Urinary tract infection	27 (8.8)	2 (5)	0.42
Spontaneous bacteremia	13 (4.2)	2 (5)	0.82
Skin or soft tissue infection	9 (2.9)	0	0.27
Others	17 (5.5)	0	0.13
Multi sites	26 (8.4)	3 (7.5)	0.84
Unknown site	50 (16.2)	8 (20)	0.55

Abbreviation: DC, decompensated cirrhosis; BI, bacterial infection

We added the description of the Supplementary table in the discussion section as follows, “It is also interesting to note that there was no significant difference regarding the frequency and etiologies of bacterial infection, prevalence of ACLF as well as survival rate among patients with isolated chronic HBV-related liver disease versus those with concomitant alcoholic and HBV-related liver disease (Supplementary Table 1 and Supplementary Table 2), suggesting little impact of the etiology of cirrhosis on the development of bacterial infection and associated outcome.” (Discussion, line 20-22 on page 12 and line 1-3 on page 13)