Received: 19 July 2020 | Revised: 12 January 2021 | Accepted: 22 February 2021

DOI: 10.1111/liv.14842

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Isolated bacterial infection without decompensation has no impact on survival of compensated patients with cirrhosis

Matthias C. Reichert[1] | Christina Schneider[1] | Robin Greinert[2] | Markus Casper[1] | Frank Grünhage[1] | Andreas Wienke[3] | Alexander Zipprich[2,4] | Frank Lammert[1,5] | Cristina Ripoll[2]

[1]Department of Medicine II, Saarland University Medical Center, Homburg, Germany

[2]Department of Medicine I, Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany

[3]Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany

[4]Department of Internal Medicine IV, Friedrich-Schiller-University Jena, Jena, Germany

[5]Hannover Medical School, Hannover, Germany

Correspondence
Cristina Ripoll, MD, PhD, Department of Medicine I, Martin-Luther University Halle-Wittenberg, Ernst Grube Str. 40, Halle 06120, Germany.
Email: cristina.ripoll@uk-halle.de

Funding information
The INCA trial (German Clinical Trials Register DRKS00005616) is funded by the independent clinical trials funding program of the German Federal Ministry of Education and Research (grant number 01KG1201 to FL). This study was supported by additional grants from the Federal Ministry of Education and Research of Germany (BMBF LiSyM 031L0051 to FL), a grant from the Schwiete Foundation (grant 01/2017 to CR), and a grant from the Faculty of Medicine of Saarland University (HOMFOR T201000747) to MCR.

Handling Editor: Minneke Coenraad

Abstract

Background & Aims: Bacterial infections (BI) affect the natural course of cirrhosis and were suggested to be a landmark event marking the transition to the decompensated stage. Our specific aim was to evaluate the impact of BI on the natural history of compensated cirrhosis.

Methods: We analyzed 858 patients with cirrhosis, evaluated for the INCA trial (EudraCT 2013-001626-26) in 2 academic medical centers between February 2014 and May 2019. Only patients with previously compensated disease were included. They were divided into 4 groups: compensated without BI, compensated with BI, 1st decompensation without BI, and 1st decompensation with BI.

Results: 425 patients (median 61 [53-69] years) were included in the final prospective analysis. At baseline, 257 patients were compensated (12 [4.7%] with BI), whereas 168 patients presented with their 1st decompensation (42 [25.0%] with BI). In patients who remained compensated MELD scores were similar in those with and without BI. Patients with their first decompensation and BI had higher MELD scores than those without BI. Amongst patients who remained compensated, BI had no influence on transplant-free survival, whereas patients with their 1st decompensation and concurrent BI had significantly reduced transplant-free survival as compared with those without BI. The development of BI or decompensation during follow-up had a greater impact on survival than each of these complications at baseline.

Conclusions: In compensated patients with cirrhosis, the 1st decompensation associated to BI has worse survival than decompensation without BI. By contrast, BI without decompensation does not negatively impact survival of patients with compensated cirrhosis.

KEYWORDS

bacterial infection, cirrhosis, compensated, decompensated, survival

Abbreviations: ACLF, Acute on chronic liver failure; ALAT, Alanine aminotransferase; AP, Alkaline phosphatase; ASAT, Aspartate aminotransferase; BI, Bacterial infection; BT, Bacterial translocation; CSPH, Clinically significant portal hypertension; CTP, Child-Turcotte-Pugh score; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HE, Hepatic encephalopathy; HVPG, Hepatic venous pressure gradient; INR, International normalized ratio; IQR, Interquartile range; MELD, Model for end-stage liver disease; PAMP, Pathogen-associated molecular pattern; PTT, Partial thromboplastin time; SB, Spontaneous bacteremia; SBP, Spontaneous bacterial peritonitis; SD, Standard deviation; SVR, Sustained virological response; UTI, Urinary tract infection; VB, Variceal bleeding; WBC, White blood cell; γGT, Gamma-glutamyl transpeptidase.

1 | INTRODUCTION

Patients with cirrhosis can be divided in 2 stages with different prognosis, namely compensated cirrhosis, in which the patient has neither previous history of nor actual decompensation (variceal bleeding, ascites, hepatic encephalopathy, or jaundice), and decompensated cirrhosis, denoting patients who have had or actually present with clinical signs of decompensation.[1-6] Distinction between these 2 entities is of clinical relevance, because patients in the compensated stage have a median survival time greater than a decade as long as they remain compensated, whereas those who are decompensated are at a higher risk of death.[1,3,6]

Bacterial infections (BI) play a significant role in the natural history of cirrhosis, leading to a dramatic increase in mortality.[7-9] Furthermore, bacterial translocation and bacterial products (pathogen-associated molecular patterns, PAMPs) have been reported to be a major player in the development of complications of cirrhosis.[10] This has led to the suggestion that BI define a distinct prognostic stage in patients with cirrhosis and the transition from the compensated to the decompensated state.[8,11]

Indeed, BI and decompensation are closely intertwined. BI are frequently a cause of decompensation,[8,9] whereas some decompensation events (i.e. variceal bleeding) can typically cause BI.[12,13] Therefore, it is difficult to disentangle whether BI lead to an increase in mortality in patients because the patients are decompensated, or whether BI per se increase mortality even if the patient is not decompensated. A single study has evaluated the prognostic role of BI in compensated patients.[14] This cohort study observed an increase in the risk of decompensation and death in those patients with HBV or HCV cirrhosis who developed a BI. However, specific evaluation of the impact of BI according to the presence or absence of simultaneous decompensation was not undertaken.

Therefore, the aim of our study was to evaluate the survival of patients with previously compensated cirrhosis who develop BI with or without clinical decompensation.

Lay summary

Bacterial infections (BI) affect the natural course of cirrhosis. Within a cohort of 858 patients with cirrhosis, we analyzed 425 previously compensated patients in 4 groups: compensated without BI, compensated with BI, 1st decompensation without BI, and 1st decompensation with BI. In compensated patients, the 1st decompensation associated to BI has worse survival than decompensation without BI. By contrast, BI without decompensation did not negatively impact the survival of patients with compensated cirrhosis.

2 | PATIENTS AND METHODS

This study is a secondary analysis of a prospectively registered cohort of 858 consecutive patients with cirrhosis from 2 German academic medical centers in Homburg and Halle. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice (European guidelines). Institutional review board approval was obtained (Approval Homburg: 271/11, Approval Halle 2017-85). All participants provided written informed consent. These patients were included in the prescreening cohort of the INCA trial (Impact of *NOD2* genotype-guided antibiotic prevention on survival in patients with liver cirrhosis and Ascites) (EudraCT 2013-001626-26).[15,16] All consecutive patients with cirrhosis, hospitalized on the wards, or attending our liver outpatient clinics were considered for inclusion. Cirrhosis was defined by (i) liver biopsy, (ii) a combination of clinical, laboratory, ultrasound, and endoscopy findings, or (iii) transient elastography ≥ 13.0 kPa; in patients with transient elastography < 19.7 kPa,[17] diagnosis of cirrhosis was additionally confirmed by (i) or (ii). Patients with severe comorbidities with life expectancy less than that of the underlying liver disease, such as end-stage heart failure, HIV infection (with AIDS), and unresectable non-liver cancer or HCC BCLC stage D, as well as previously decompensated patients were excluded (Figure 1). Patients were included between February 2014 and December 2017 and followed-up until May 2019. Events occurring during follow-up including BI and decompensation were recorded. The situation at the last follow-up was recorded (alive, dead, or liver transplantation). In the present analysis, only patients with compensated cirrhosis were included (N = 425). These patients were stratified according to the presence or absence of 1st decompensation at the time of BI. All electronic inpatient and outpatient medical records were reviewed for past and present decompensation and BI. Further information regarding laboratory parameters and medication (such as β-blockers, long-term antibiotic therapy, lactulose, and statins) at the time of inclusion were recorded. All patients were previously compensated, and most patients who were prescribed long-term antibiotics and lactulose received these medications in the context of their first decompensation. To assess the impact of portal hypertension, we created a composite variable, clinically significant portal hypertension (CSPH), which included patients with esophageal varices, patients with hepatic venous pressure gradient (HVPG) ≥ 10 mm Hg (140 patients underwent hemodynamic measurement), and patients with a LSPS over 1.72 (according to Berzigotti et al[23]).

2.1 | Bacterial infections

BI were defined according to the criteria outlined by Bajaj et al[18] This definition had been previously applied in this population.[16] Only BI that were treated with antibiotics were considered as such. BI within a maximum time frame of ± 14 days were defined as current BI at baseline. Specifically, criteria were as follows: (i) SBP: ascitic fluid with a polymorphonuclear cell count > 250/μL; (ii) pulmonary BI was defined as the presence of an infiltrate/consolidation/cavity plus at least 2 of the following criteria: fever ≥ 38°C or hypothermia < 35°C,

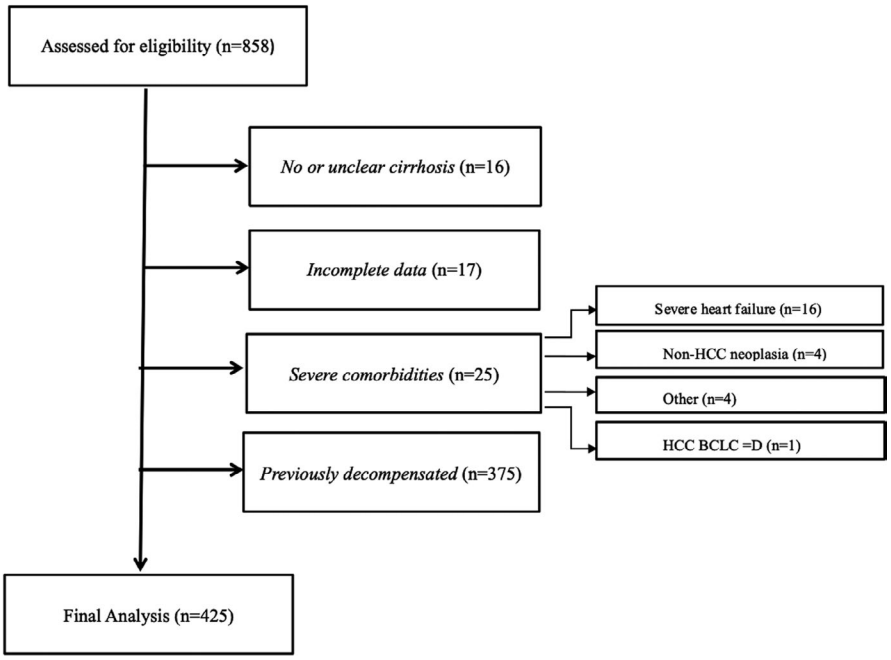


FIGURE 1 Flow chart outlining inclusion and exclusion of patients in the study

dyspnoea or clinical signs of pulmonary BI (cough and purulent sputum, pleuritic chest pain); (iii) urinary tract infection (UTI) was defined as > 10 white blood cells (WBC) per high-power field in urine microscopy and positive urine cultures, or significant WBC count in urine (> 500/μL) with typical complaints (fever/pain/dysuria/pollakisuria); and (iv) spontaneous bacteremia (SB) was defined as growth of a non-common skin contaminant in blood cultures, without evidence of infection located at another body site.[19] When bacteremia was detected in a patient with SBP, pulmonary BI, urinary tract infection, sepsis, or other BI, this was interpreted as secondary to the specific infection. Sepsis was diagnosed and evaluated separately by the combination of BI with impaired host response and organ dysfunction, as described in international consensus criteria.[20]

2.2 | Hepatic decompensation

Decompensation was defined by present or past variceal bleeding (VB), hepatic encephalopathy (HE), ascites, and/or jaundice, as recommended by the American Association for the Study of the Liver Diseases[5] and the European Association for the Study of the Liver.[6] This definition has previously been shown to be of prognostic relevance.[1,3,4] Specifically, VB was assessed according to the Baveno VI definition.[2] HE was graded following the West Haven criteria.[21] Ascites was defined by the presence of signs of ascites on physical examination and/or confirmed by abdominal ultrasound. Patients without clinical ascites who were dependent on diuretics (e.g. spironolactone) to treat ascites were considered as decompensated because of the presence of ascites. Jaundice was defined arbitrarily by a total serum bilirubin concentration ≥ 3 mg/dL. According to this definition, patients with a history of decompensation (e.g. ascites) were considered to have reached the decompensated stage of the disease even though at the time of inclusion they displayed no clinically evident decompensation and were therefore excluded from the analysis (Figure 1).

2.3 | Statistical analysis

All variables are described as proportions, means with standard deviation (SD), or medians with interquartile range (IQR). Univariate analysis was performed with χ^2 tests, *t* tests, or Mann-Whitney U tests, according to the distribution of the test variables. All previously compensated patients were divided into 4 groups according to their status at inclusion in the cohort (baseline): compensated without current BI, compensated with current BI, 1st decompensation without current BI, and 1st decompensation with current BI. Kaplan–Meier curves were calculated and compared with log rank tests. Bivariable backward stepwise Cox-regression survival analyses in each strata were planned to evaluate the effect of BI on survival, adjusted by MELD score. Backward stepwise multivariable Cox regression competing risk analysis[22] was performed to evaluate the effect of BI and decompensation on death during follow-up, with liver transplantation as a competing risk. Time-dependent Cox regression analysis including BI and decompensation at baseline and the development of BI and decompensation during follow-up (time-dependent variables) was performed. The impact of the development of BI or decompensation during follow-up was only considered for those patients who were not infected or who were compensated at baseline respectively. BI and/or decompensation during follow-up among patients who already had these complications were not considered in this analysis, as these patients had already attained the decompensated or infected status at baseline. Statistical analyses were performed with SPSS 22.0 (SPSS, Munich, Germany) and SAS version 9.4. Two-sided *P* values ≤ .05 were regarded as significant.

3 | RESULTS

3.1 | Patients characteristics

Among the 425 previously compensated patients with cirrhosis, 168 (39.5%) were included in the study at the time of their 1st decompensation and 257 (60.5%) were compensated at inclusion. Table 1 summarizes the baseline characteristics of all the patients, whereas Tables 2 and 3 summarize the baseline characteristics of compensated and decompensated patients respectively. Overall, patients were mainly men (n = 272, 64.0%) with a median age of 61 (IQR 53-69) years. The predominant etiology was alcoholic cirrhosis (183 patients, 43.1%).

3.2 | Bacterial infections

Among the patients who remained compensated, 12 patients (4.7%) had a simultaneous BI. The proportion of simultaneous BI among the decompensated patients was markedly higher (N = 42, 25.0%), which underlines the association between BI and decompensation ($P < .001$). Table S1 summarizes the sites of BI. Urinary tract BI were the most common BI in both groups, followed by SBP (per definition only possible in decompensated patients), and pulmonary BI.

3.3 | BI in patients remaining compensated/developing a 1st decompensation

MELD and Child-Turcotte-Pugh scores (CTP) did not differ between patients without and with BI who remained compensated (no BI MELD 8 [IQR 7-10] and CTP 5 [IQR 5-6]; with BI MELD 8.6 [IQR 7-11] and CTP 5 [IQR 5-7]; $P = .72$ for MELD and $P = .37$ for CTP). Whereas amongst patients presenting with 1st decompensation, a higher MELD and worse CTP was observed in those patients who presented with BI (no BI MELD 13 [IQR 10-16] and CTP 9 [IQR 8-10], with BI MELD 14 [IQR 11-21] and CTP 9 [IQR 8-11]; $P = .02$ for MELD and .007 for CTP). Patients with BI in the compensated stage had lower serum albumin concentrations and hemoglobin levels and higher CRP than those without BI (Table 2). In the patients presenting with 1st decompensation, those with simultaneous BI presented more frequently with jaundice (as reflected by higher total bilirubin concentrations) and increased inflammation markers (CRP, WBC, ASAT); INR and PTT were also slightly increased in patients presenting with BI (Table 3).

3.4 | Portal hypertension

Among the patients who remained compensated, an evaluation of portal hypertension was available in 205 patients, of which 137 had CSPH (5 with BI), and 68 had no CSPH (of which 2 had a BI). Unfortunately, this sample size precluded further analysis.

TABLE 1 Baseline characteristics of all included patients

Parameter	No BI (N = 371)	BI (N = 54)	*P*-value
Age (y)	61 (53.0-70.0)	61 (52.5-69.0)	.95
Gender (male)	233 (62.6)	39 (73.6)	.23
Diabetes mellitus (yes)	119 (32.1)	20 (37.0)	.44
MELD (points)	9.0 (7.5-12.7)	13.4 (9.5-20.3)	**<.001**
CPS (points)	5 (5.0-6.0)	7.0 (6.0-8.0)	**<.001**
HCC (yes)	104 (28.0)	22 (40.7)	.13
Varices (yes)	130 (35.3)	26 (49.1)	.05
Aetiology of cirrhosis			.26
Alcoholic	150 (40.4)	33 (61.1)	
NASH	41 (11.1)	3 (5.6)	
Hepatitis C	68 (18.3)	7 (13.0)	
Hepatitis B	15 (4.0)	1 (1.9)	
Others	41 (11.1)	5 (9.3)	
Cryptogenic	56 (15.1)	5 (9.3)	
Medication			
Beta-blocker (yes)	163 (44.4)	24 (46.2)	.88
Antibiotic long-term therapy (yes)	35 (9.5)	16 (31.4)	**<.001**
Lactulose (yes)	67 (18.5)	26 (49)	**<.001**
Statin (yes)	73 (19.9)	12 (22.6)	.58
PPI (yes)	218 (59.2)	35 (68.6)	.22
Laboratory values			
Serum sodium (mmol/L)	139 (137-141)	137 (134-140)	**.001**
Creatinine (mg/dL)	0.88 (0.72-1.06)	0.96 (0.73-1.46)	.11
Total bilirubin (mg/dL)	0.9 (0.53-1.6)	1.92 (0.93-4.55)	**<.001**
ASAT (U/L)	45 (32.0-75.0)	66.5 (45-100.2)	**.003**
ALAT (U/L)	36 (23.7-65.0)	31.8 (20.0-52.4)	.14
γGT (U/L)	140 (62.9-318)	184 (68.6-519.5)	.19
AP (U/L)	105 (78-157)	142.6 (97-274.4)	**<.001**
CRP (mg/dL)	4.1 (1.5-14.5)	24.1 (6.8-57.4)	**<.001**
Albumin (g/dL)	39 (33.0-43.0)	32.0 (28.0-36.3)	**<.001**
Haemoglobin (g/dL)	13.0 (10.9-14.6)	11.3 (9.0-13.3)	**<.001**
WBC ($\times 10^9$)	6.4 (4.8-8.1)	8.2 (5.5-10.5)	**.002**
Platelets ($\times 10^9$)	153 (99-210)	158 (112.5-222.5)	.28
INR	1.13 (1.05-1.26)	1.29 (1.10-1.42)	**<.001**
PTT (s)	29 (26-32.8)	32.9 (27.7-38.8)	**.001**

Note: Values are given as median and interquartile range (IQR), or frequencies and percentages. Significant *p* values ($p < 0.05$) are marked in bold.

Abbreviations: ALAT, Alanine aminotransferase; AP, alkaline phosphatase; ASAT, Aspartate aminotransferase; Ascites, patients treated with diuretics and refractory ascites vs no ascites; BI, bacterial infection; CPS, Child-Pugh-Score; CRP, C-reactive protein; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; MELD-Score, Model of end stage liver disease; NASH, non-alcoholic steatohepatitis; PPI, proton pump inhibitor, PTT, partial thromboplastin time; VB, variceal bleeding; WBC, white blood cells; γGT, Gamma-glutamyl transpeptidase.

TABLE 2 Baseline characteristics of patients who remain compensated

Parameter	No BI (N = 245)	BI (N = 12)	*P*-value
Age (y)	61 (53-69)	61 (47.3-65.5)	.57
Gender (male)	157 (64.1)	9 (75)	.55
Diabetes mellitus (yes)	85 (35.1)	5 (41.7)	.76
MELD (points)	8 (7-10)	8.6 (6.8-10.5)	.72
CPS (points)	5 (5-6)	5 (5-7)	.37
HCC (yes)	63 (25.7)	4 (33.3)	.21
Varices (yes)	62 (25.5)	1 (8.3)	.30
Aetiology of cirrhosis			.28
Alcoholic	79 (32.2)	5 (41.7)	
NASH	34 (13.9)	1 (8.3)	
Hepatitis C	56 (22.9)	1 (8.3)	
Hepatitis B	13 (5.3)	1 (8.3)	
Others	30 (12.2)	2 (16.7)	
Cryptogenic	33 (13.5)	2 (16.7)	
Medication			
Beta-blocker (yes)	96 (40.0)	4 (33.3)	.77
Antibiotic long-term therapy (yes)*	7 (2.9)	0 (0)	1.0
Lactulose (yes)**	11 (4.5)	0 (0)	1.0
Statin (yes)	55 (22.7)	5 (41.2)	.16
PPI (yes)	129 (53.3)	9 (75.0)	.23
Laboratory values			
Serum sodium (mmol/L)	140 (138-142)	139 (136.8-140.8)	.52
Creatinine (mg/dL)	0.85 (0.72-0.98)	0.85 (0.74-1.2)	.61
Total bilirubin (mg/dL)	0.7 (0.5-1.2)	0.8 (0.43-0.99)	.87
ASAT (U/L)	44 (29.75-73.3)	49.5 (40.4-55.5)	.78
ALAT (U/L)	38.5 (26.0-69.8)	36.9 (21.75-43.7)	.16
γGT (U/L)	132 (55-282)	171 (50-646)	.41
AP (U/L)	92 (72-125)	141 (81-359)	.06
CRP (mg/dL)	2.4 (1.0-6.2)	5.0 (2.38-14.0)	**.05**
Albumin (g/dL)	42 (38-44)	36 (29.4-38.0)	**<.001**
Haemoglobin (g/dL)	13.9 (12.9-15.1)	12.85 (0.94-13.79)	**.03**
WBC ($\times 10^9$)	6.5 (4.81-7.9)	6.5 (4.73-9.62)	.80
Platelets ($\times 10^9$)	156 (104-209)	172 (127-309)	.14
INR	1.10 (1.04-1.2)	1.08 (1.01-1.19)	.53
PTT (s)	28 (26-31)	29.1 (25.3-34.3)	.51

Note: Values are given as median and interquartile range (IQR), or frequencies and percentages.

Abbreviations: ALAT, Alanine aminotransferase; AP, alkaline phosphatase; ASAT, Aspartate aminotransferase; Ascites, patients treated with diuretics and refractory ascites vs no ascites; BI, bacterial infection; CPS, Child-Pugh-Score; CRP, C-reactive protein; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; MELD-Score, Model of end stage liver disease; NASH, nonalcoholic steatohepatitis; PPI, proton pump inhibitor, PTT, partial thromboplastin time; VB, variceal bleeding; WBC, white blood cells; γGT, Gamma-glutamyl transpeptidase.

*Among these 7 patients (2.9% of the compensated cohort) with long-term antibiotic therapy, 1 patient received ciprofloxacin for recurrent urinary tract infections, 3 patients received rifaximin, and 3 patients received norfloxacin.

**Among these 11 patients (4.5% of the compensated cohort), no clear reason for lactulose treatment could be identified in 8 patients, and in 3 patients lactulose was prescribed due to constipation.

TABLE 3 Baseline characteristics of decompensated patients

Parameter	No BI (N = 126)	BI (N = 42)
Age (y)	60 (54-70)	61 (53-70)
Gender (male)	77 (61)	29 (71)
Diabetes mellitus (yes)	34 (26.8)	15 (36.6)
MELD (points)	13 (10.0-16.0)	14 (11-21.0)
CPS (points)	9 (7.5-10.0)	9 (8.0-11.0)
HCC (yes)	41 (32.2)	18 (43.9)
Varices (yes)	68 (54.4)	25(61)
Aetiology of cirrhosis		
Alcoholic	71 (56.3)	28 (66.7)
NASH	7 (5.6)	2 (4.8)
Hepatitis C	12 (9.5)	6 (14.3)
Hepatitis B	2 (1.6)	0 (0)
Others	11 (8.7)	3 (7.1)
Cryptogenic	23 (18.3)	3 (7.1)
Decompensation		
Ascites (yes)	93 (73.2)	37 (90)
HE (yes)	31 (24.4)	14 (34.4)
VB (yes)	19 (14.9)	3 (7.3)
Jaundice (yes)	44 (34.6)	23 (56.0)
Medication		
Beta-blocker (yes)	67 (53.2)	20 (51.3)
Antibiotic-long-term therapy (yes)	28 (22.2)	16 (40)
Lactulose (yes)	56 (45.2)	26 (64)
Statin (yes)	18 (14.2)	7 (17.5)
PPI (yes)	89 (70.4)	26 (66.6)
Laboratory values		
Serum sodium (mmol/L)	137 (134-140)	136 (133-139.5)
Creatinine (mg/dL)	0.95 (0.75-1.23)	0.97 (0.73-1.70)
Total bilirubin (mg/dL)	1.69 (0.88-4.0)	2.70 (1.39-6.20)
ASAT (U/L)	57.6 (40.1-81.9)	84.6 (57.25-136.4)
ALAT (U/L)	32.0 (21.0-57.6)	31 (20.0-56.3)
γGT (U/L)	161 (81-377)	184 (79-396)
AP (U/L)	142 (103-193)	143 (106-199)
CRP (mg/dL)	14.3 (5.7-26.1)	39.6 (11.41-69.3)
Albumin (g/dL)	32 (28.0-36.8)	31.8 (27.0-35.0)
Haemoglobin (g/dL)	11.2 (9.50-12.9)	10.80(8.8-12.5)
WBC ($\times 10^9$)	6.4 (4.50-8.545)	8.4 (5.7-11.11)
Platelets ($\times 0^9$)	144 (94-229)	147 (96-223)
INR	1.22 (1.11-1.39)	1.34 (1.23-1.51)
PTT (s)	31.0 (27.3-35.2)	33.0 (29.5-39.2)

Note: Values are given as median and interquartile range (IQR), or frequencies and percentages.

Abbreviations: ALAT, Alanine aminotransferase; AP, alkaline phosphatase; ASAT, Aspartate aminotransferase; Ascites, patients treated with diuretics and refractory ascites vs no ascites; BI, bacterial infection; CPS, Child-Pugh-Score; CRP, C-reactive protein; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; MELD-Score, Model of end stage liver disease; NASH, nonalcoholic steatohepatitis; PPI, proton pump inhibitor, PTT, partial thromboplastin time; VB, variceal bleeding; WBC, white blood cells; γGT, Gamma-glutamyl transpeptidase.

3.5 | Follow-up

Median follow-up was 617 (IQR 140-1000) days. During follow-up, a total of 58 patients died (N = 49, 11.5%) or were transplanted (N = 9, 2.1%). Among those who presented with their 1st decompensation, 30 patients (17.9%) died, whereas among the patients in the compensated stage, 19 patients (7.4%) died during follow-up. The most common reasons for death were liver failure or BI in both groups (Table S2). During follow-up, 86 (23.4%) patients developed BI (Figure 2), 17 (31.5%) among patients who had previously presented with BI and 69 (18.6%) among patients who had no previous BI. Among the compensated patients, 43 (16.7%) had a BI (31 [12.7%] without previous BI and all 12 with previous BI). In the decompensated patients, 43 (26.0%) had a BI (12 in patients with previous BI [28.6%], 31 in patients without previous BI [24.6%]). Table S3 summarizes the different BI that developed during follow-up. Furthermore, among the compensated patients, 32 patients (14.3%) developed their first decompensation during follow-up. Clinical decompensation during follow-up occurred only in all 32 patients who did not have BI at baseline. In 12 patients (37.5%), clinical decompensation in the follow-up was associated with simultaneous BI (Table S4). Table S5 summarizes the information on the first decompensation episodes.

Not unexpectedly, when all patients (those who remain compensated and those with 1st decompensation) were considered, patients with BI at baseline showed worse survival than those without (Figure 3).

When analyzing only patients remaining in the compensated stage at baseline, survival in patients with and without BI was similar (Figure 4A). Survival in patients who developed their 1st decompensation accompanying the BI was reduced (Figure 4B).

Bivariable Cox-regression survival analysis including the presence of BI and MELD Score was planned in each group. Given the lack of events in the compensated patients with BI at baseline (Figure 4A), the planned bivariable Cox-regression analysis could not be performed, because the results might lead to an instable model. In patients who presented with their first decompensation both MELD score [HR 1.16 95% CI (1.08-1.23)] and BI [HR 2.64 (1.04-6.70)] were independent predictors of survival. Competing risks analysis could only be performed in the patients who presented with their first decompensation, with liver transplantation as competing risk. The magnitude of the effect of each of the variables MELD score and BI was similar to the previous multivariable analysis (MELD HR 1.13 95% CI 1.04-1.22; BI HR 1.91 95% CI 0.59-6.21).

On time-dependent Cox regression analysis of the whole group, the development of BI and decompensation during follow-up were independent predictors of survival in addition to these events at baseline (Table 4). Interestingly, the impact of the effect of the development of these complications during follow-up was markedly greater than their impact at baseline.

4 | DISCUSSION

Distinguishing between compensated and decompensated cirrhosis has prognostic relevance, which is clinically significant for

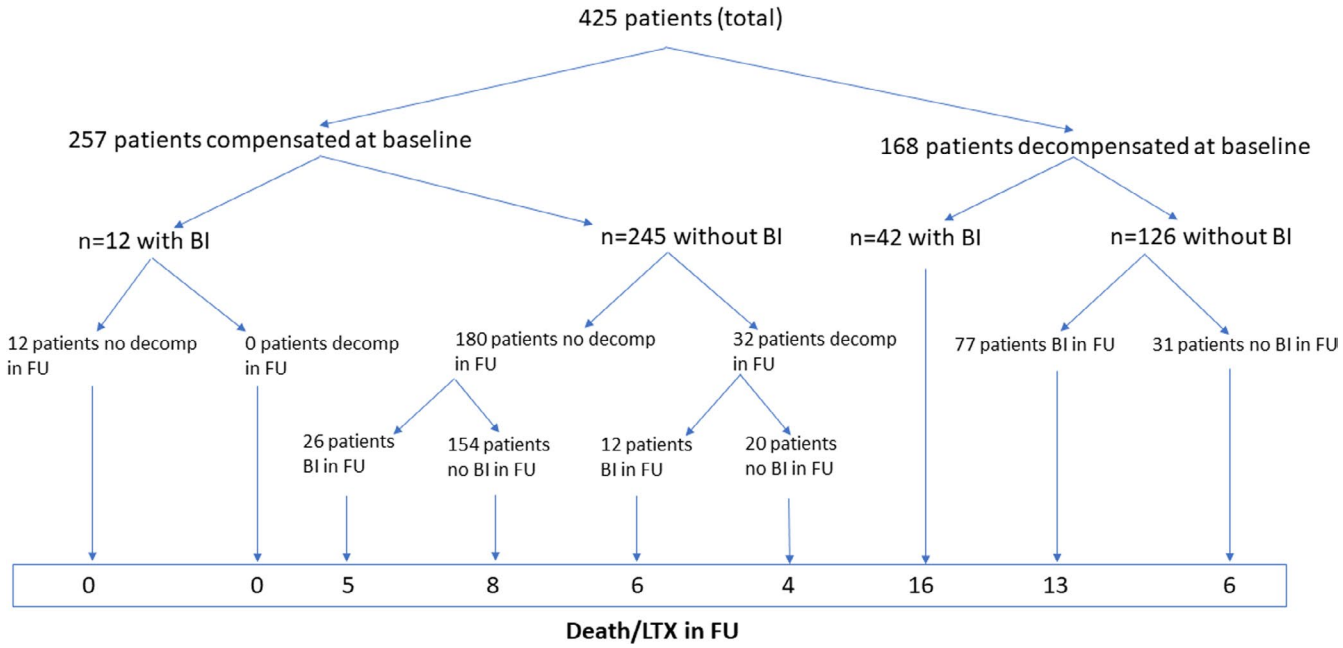
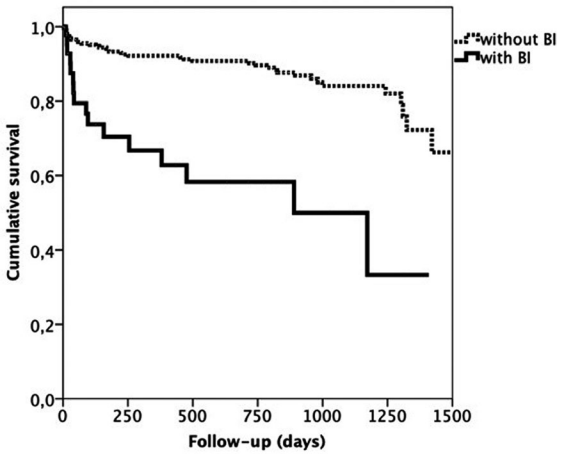
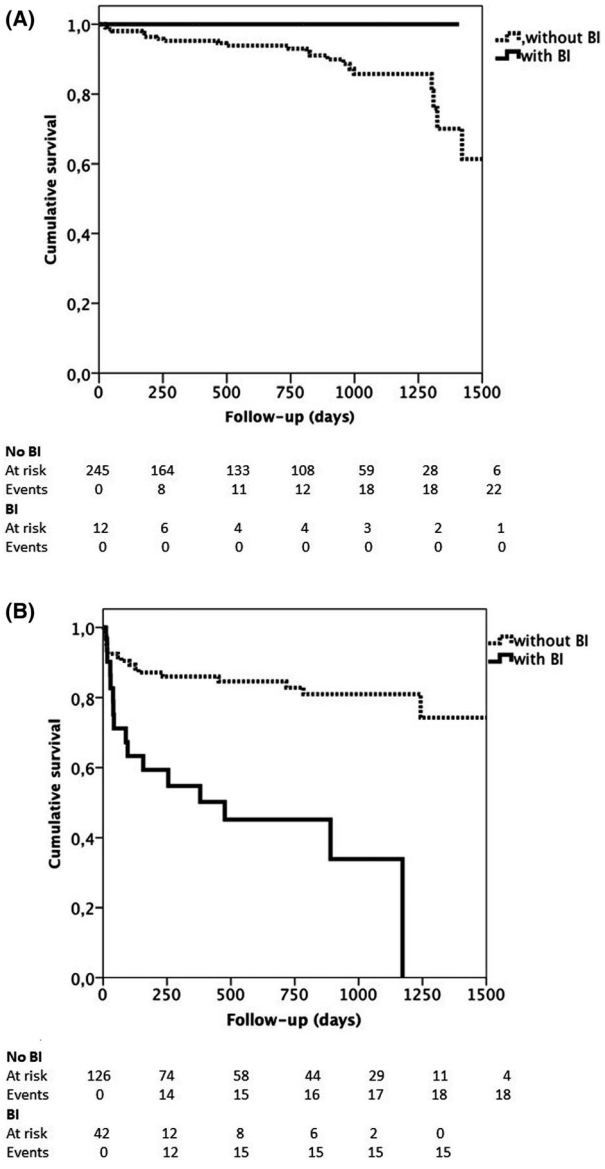


FIGURE 2 Flow chart showing the development of bacterial infections (BI) and decompensation (decomp) during follow-up (FU). The patients are divided depending on the status at baseline (compensated/decompensated ± concomitant BI) and the development of decompensation ± BI in FU. Among the 180 compensated patients who remained compensated during FU, 4 died of sepsis because of BI, 4 died of non-hepatic causes (one with BI, 3 without BI), and 4 underwent liver transplantation (LTX; all without BI). Multiple BI in 1 patient were not included in the flow chart



No BI							
At risk	371	238	191	152	88	39	10
Events	0	22	26	28	35	36	40
BI							
At risk	54	19	13	11	5	2	0
Events	0	11	14	14	15	16	16

FIGURE 3 Kaplan–Meier survival plots. BI, bacterial infection. Patients transplant-free survival with- and without BI and in all patients. Survival in patients with BI is significantly reduced (log-rank *P*-value < .001)



No BI							
At risk	245	164	133	108	59	28	6
Events	0	8	11	12	18	18	22
BI							
At risk	12	6	4	4	3	2	1
Events	0	0	0	0	0	0	0

No BI							
At risk	126	74	58	44	29	11	4
Events	0	14	15	16	17	18	18
BI							
At risk	42	12	8	6	2	0	
Events	0	12	15	15	15	15	

FIGURE 4 (A) Kaplan–Meier survival plots. BI, bacterial infection. Patients transplant-free survival in compensated stage of cirrhosis in patients with BI is not reduced as compared with patients without BI (log-rank *P*-value = .31). (B) Kaplan–Meier survival plots. BI, bacterial infection. Patients transplant-free survival with BI and concurrent 1st decompensation is significantly reduced compared with patients with 1st decompensation but no BI (log-rank *P*-value < .001)

the care of patients with end-stage liver disease. Transition to the decompensated stage is defined by the development of ascites, variceal bleeding, hepatic encephalopathy, or jaundice. Previous studies have underlined the prognostic impact of BI in cirrhosis,[1,3] and BI has been proposed to be one of the landmark events that defines the transition to the decompensated stage.[11] However, our results show that isolated BI have no impact on survival in patients who remain compensated. By contrast, among the patients who present with their first decompensation, patients with BI have worse survival than those without simultaneous BI. Therefore, our results suggest that BI should not be considered a "decompensating" event per se.

Although the study by Dionigi et al[11] was not designed to clarify the impact of BI on survival according to the compensated or decompensated stage, a subgroup analysis suggested similar results in patients with predominantly alcoholic cirrhosis. Indeed, no significant differences were observed among patients with CTP A, as compared to CTP B and C, although the lack of differences may be because of low statistical power. Nevertheless, there are differences between this previous and our study. Most importantly, the definitions of CTP A and compensated patients do not match completely and therefore are not fully interchangeable. Indeed, CTP is calculated at a specific point in time and does not consider previous decompensation, and secondly from a mathematical point of view, patients with diuretic-sensitive ascites are often categorized as CTP A. Therefore, it is likely that previously decompensated patients were included in this group in the study by Dionigi et al.[11]

Another study has evaluated the impact of BI in patients with compensated disease because of viral cirrhosis.[14] This study concluded that BI in compensated cirrhosis impacts survival. However, this study did not distinguish between patients who decompensated and those who did not decompensate at the time of the BI. Indeed, we also report that BI have an impact on survival in compensated patients, but it becomes apparent that this effect on survival occurs in those patients who have simultaneous first decompensation at the time of BI.

BI are frequent in cirrhosis.[24] Indeed, the increased risk for BI in cirrhosis is mediated by multiple factors, most of which are associated directly or indirectly to the severity of liver disease. These

TABLE 4 Time-dependent Cox regression analysis

Parameter	OR	95% CI
BI at baseline	5.87	2.95-11.69
Decompensation at baseline	3.34	1.74-6.78
BI during follow-up	8.06	4.02-16.14
Decompensation during follow-up	22.73	9.23-55.97

Note: Development of decompensation and BI during follow-up was only considered among those who did not have these complications at baseline respectively.

Abbreviations: BI, bacterial infection; CI, confidence interval; OR, odds ratio.

factors include portal hypertension, altered intestinal microbiome, increased bacterial translocation, and cirrhosis-associated immune dysfunction.[6,25-27] On the other hand, according to the recently proposed systemic inflammation hypothesis, bacterial products (PAMPs) play a major role in the development and perpetuation of complications of end-stage liver disease. The present study and previous reports have demonstrated that the increase in mortality after BI stretches beyond the BI episode per se.[11] Indeed, BI are associated with an increase in the amount of bacterial products and systemic inflammation, which modifies the course of the liver disease.[10,28,29]

Different BIs have different pathophysiological mechanisms. One could then hypothesize that the amount of PAMPs that reach the systemic circulation could differ according to the site and severity of BI. Although our study was not designed for this purpose, patients who remained compensated had mainly urinary tract infections, whereas patients who decompensated presented with BI at other sites. Whether the infection site contributes to decompensation or not cannot be withdrawn from our data.

Patients who decompensated simultaneously to the BI had higher bilirubin levels and inflammation markers and higher CTP and MELD scores than patients without BI. This could suggest that these patients had ACLF, because BI are a frequent cause of ACLF.[9] Patients with ACLF have a worse prognosis than patients with acute decompensation. Unfortunately, the presence or absence of ACLF in the decompensated patients could not be evaluated systematically in this study.

Notably, in our patients who were in the compensated stage at inclusion, those with BI displayed lower serum albumin concentrations. Previous data indicated that the albumin level has a significant prognostic role in compensated patients, being one of the first routine laboratory markers of liver.[30,31] It might be speculated that the lower albumin levels reflect a more advanced situation within the compensated stage, nevertheless the similar mortality among those with and without BI in this subgroup as well as the lack of decompensation during follow-up among those with BI at baseline argues against this presumption.

The development of BI or decompensation during follow-up had a greater impact on survival than each of these complications at baseline. This underlines the importance of observing the dynamic course of the disease. Hence, we hypothesize that the development of these complications during follow-up, despite appropriate treatment of liver disease that was present at baseline, reflects a more aggressive course of the disease.

The study has limitations that have to be acknowledged. Patients with compensated cirrhosis who remain compensated have a long median survival. Therefore, and despite the relatively large sample size and long follow-up, this study may have been too short to detect differences between those who had and those who did not develop BI. Furthermore, patients with compensated cirrhosis can be further subdivided according to the presence or absence of clinically significant portal hypertension. One could speculate that the effect of a BI on survival could be different according to this aspect; however, this issue could not be approached in this study because of the sample size. Another limitation is the lack of data regarding the presence or absence of ACLF at the time of decompensation. Lastly, the limited number of patients with BI does not allow evaluation of the impact of different BI on specific outcomes. In particular, in patients in the compensated stage of the disease the sample size of individuals with BI was small. However, we speculate that this observation reflects that BI is mainly associated to decompensation and that BI without decompensation is rare.

In conclusion, although BI have a negative impact on survival in previously compensated patients, this effect is associated with the development of the first decompensation. Patients with cirrhosis who develop BI but remain compensated do not have an increase in mortality. Therefore, BI should not be used to define the transition from compensated to decompensated cirrhosis.

ACKNOWLEDGEMENTS

We thank all patients who participated in the study.

CONFLICTS OF INTEREST

The authors who have taken part in this study declared that they do not have anything to disclose regarding conflicts of interest.

AUTHOR CONTRIBUTIONS

MCR, CR, and FL designed the study. MCR, RG, CS, MC, and FG participated in the acquisition of clinical data, drafted the manuscript, and together with MCR, CR, AZ and FL analyzed the data and finalized the manuscript, which was then revised by all authors. The final draft of the manuscript has been approved by all authors. The contents of this manuscript are our original work and have not been published, in whole or in part, prior to or simultaneous with our submission of the manuscript.

ETHICAL APPROVAL

Institutional review board approval was obtained (approval Homburg: 271/11, approval Halle: 2017-85).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request as permitted by data protection laws.

ORCID

Matthias C. Reichert https://orcid.org/0000-0002-8192-0575
Andreas Wienke https://orcid.org/0000-0001-5871-2586
Alexander Zipprich https://orcid.org/0000-0001-8403-7983
Frank Lammert https://orcid.org/0000-0003-4450-7201
Cristina Ripoll https://orcid.org/0000-0002-9704-4741

REFERENCES

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44:217-231.
2. De Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015;63:743-752.
3. D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. *Aliment Pharmacol Ther*. 2014;39:1180-1193.
4. Zipprich A, Garcia-Tsao G, Rogowski S, et al. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. *Liver Int*. 2012;32:1407-1414.
5. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology*. 2017;65:310-335.
6. Angeli P, Bernardi M, Villanueva C, et al. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69:406-460.
7. Fernandez J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol*. 2012;56(Suppl 1):S1-S12.
8. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology*. 2010;139:1246-1256.
9. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144:1426-1437.
10. Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. *J. Hepatol*. 2015;63:1272-1284.
11. Dionigi E, Garcovich M, Borzio M, et al. Bacterial infections change natural history of cirrhosis irrespective of liver disease severity. *Am J Gastroenterol*. 2017;112:588-596.
12. Bernard B, Grangé J-D, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology*. 1999;29:1655-1661.
13. Fernández J, del Arbol LR, Gómez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology*. 2006;131(4):1049-1056
14. Nahon P, Lescat M, Layese R, et al. Bacterial infection in compensated viral cirrhosis impairs 5-year survival (ANRS CO12 CirVir prospective cohort). *Gut*. 2017;66:330-341.
15. Casper M, Mengel M, Fuhrmann C, et al. The INCA trial (Impact of NOD2 genotype-guided antibiotic prevention on survival in patients with liver Cirrhosis and Ascites): study protocol for a randomized controlled trial. *Trials*. 2015;6:83.
16. Reichert MC, Ripoll C, Casper M, et al. Common NOD2 risk variants as major susceptibility factors for bacterial infections in compensated cirrhosis. *Clin Transl Gastroenterol*. 2019;10(1):e00002.
17. Thiele M, Detlefsen S, Sevelsted Møller L, et al. Transient and 2-dimensional shear-wave elastography provide comparable assessment of alcoholic liver fibrosis and cirrhosis. *Gastroenterology*. 2016;150:123-133.
18. Bajaj JS, O'Leary JG, Reddy KR, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. *Hepatology*. 2012;56:2328-2335.
19. Bartoletti M, Giannella M, Caraceni P, et al. Epidemiology and outcomes of bloodstream infection in patients with cirrhosis. *J Hepatol*. 2014;61:51-58.
20. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801-810.
21. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the study of liver diseases and the European Association for the study of the liver. *Hepatology*. 2014;60:715-735.
22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
23. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology*. 2013;144(1):102-111.
24. Piano S, Singh V, Caraceni P, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. *Gastroenterology*. 2019;156:1368-1380.
25. Piano S, Brocca A, Mareso S, et al. Infections complicating cirrhosis. *Liver Int*. 2018;38(Suppl 1):126-133.
26. Wasmuth HE, Kunz D, Yagmur E, et al. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. *J Hepatol*. 2005;42:195-201.
27. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL special conference 2013. *J Hepatol*. 2014;60:1310-1324.
28. Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. *Hepatology*. 2016;64:1249-1264.
29. Bruns T, Reuken PA, Stengel S, et al. The prognostic significance of bacterial DNA in patients with decompensated cirrhosis and suspected infection. *Liver Int*. 2016;36:1133-1142.
30. Ripoll C, Groszmann R, Garcia–Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology*. 2007;133:481-488.
31. Ripoll C, Bari K, Garcia-Tsao G. Serum albumin can identify patients with compensated cirrhosis with a good prognosis. *J Clin Gastroenterol*. 2015;49:613-619.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Reichert MC, Schneider C, Greinert R, et al. Isolated bacterial infection without decompensation has no impact on survival of compensated patients with cirrhosis. *Liver Int*. 2021;41:1370–1378. https://doi.org/10.1111/liv.14842