Diabetes does not increase infection risk or mortality following an infection in patients with cirrhosis and ascites

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Graphical abstract

Highlights
- Cirrhosis and diabetes both increase the risk of infections.
- In patients with cirrhosis, diabetes does not increase the risk of infection.
- In patients with cirrhosis, diabetes does not increase mortality among those infected.

Lay summary
Cirrhosis and diabetes are chronic diseases that weaken the immune system and increase the risk of infections, but it is unknown whether their combined effects exceed the effect of cirrhosis alone. We showed that the risk of infections was the same in patients with cirrhosis, ascites and diabetes as in patients with cirrhosis and ascites alone. Thus, their combined effects do not exceed the effect of cirrhosis alone.

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Diabetes does not increase infection risk or mortality following an infection in patients with cirrhosis and ascites

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Background & Aims: Both cirrhosis and diabetes are established risk factors for infections. However, it remains uncertain whether diabetes adds to the risk of infections in patients with cirrhosis who are already at high risk of infections, or increases the mortality following an infection. To answer these questions, we followed a cohort of trial participants with cirrhosis and ascites for 1 year to compare the incidence of infections and post-infection mortality between those with or without diabetes.

Methods: We used Cox regression to estimate the hazard ratio (HR) of any infection, adjusting for confounding by patient age, gender, MELD score, albumin, use of proton pump inhibitors and lactulose, cirrhosis aetiology, and severity of ascites. Further, we analysed the mortality after infection.

Results: Among 1,198 patients with cirrhosis and ascites, diabetics (n = 289, 24%) were more likely than non-diabetics (n = 909, 76%) to be old and male, to have low platelets, and to use lactulose. At inclusion, similar proportions of diabetic and non-diabetic patients were taking a quinolone antibiotic (13% vs. 12%) and they had similar median MELD scores (14 vs. 15). During the follow-up, 446 patients had an infection. Diabetes did not increase the HR of infections (adjusted HR 1.08; 95% CI 0.87–1.35). Further, diabetes did not increase the mortality following an infection (adjusted HR 0.93; 95% CI 0.64–1.35).

Conclusions: In patients with cirrhosis and ascites, diabetes did not increase infection risk or mortality after infection. The immune incompetence of each disease did not appear to be additive. In clinical terms, this means that particular attention to infections is not indicated in patients with cirrhosis and diabetes.

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Introduction
Liver cirrhosis is the end stage of all chronic liver diseases, but it is also one of the most common forms of acquired immunodeficiency.1 This immunodeficiency increases the risk of infections. The incidence of infections among patients with cirrhosis is not firmly established, but infections quadruple the risk of mortality.2,3 This makes it important to identify groups of patients with cirrhosis who may be at greater risk of infections. Approximately one-quarter of patients with cirrhosis also have diabetes,4–7 and these patients could be at an increased risk of infections because diabetes itself is an immune-deficient state that markedly increases the risk of infections. In 2003, a large Canadian study of diabetes patients without cirrhosis found a risk ratio of 1.21 (99% CI 1.20–1.22) for infections compared to non-diabetic patients.8 Others have found a similar association.9,10

Multiple mechanisms may contribute towards the increased risk of infections in cirrhosis11,12: decreased opsonisation, dysfunctional phagocytic activity, and portosystemic shunting all compromise the hepatic clearing of bacteria and bacterial products, leaving the patients vulnerable to bacterial translocation.11–12 In diabetes, too, the innate immune system is altered, with complement dysfunction and impaired function of polymorphonuclear cells.13–15 Likewise, in 1985 Kelly et al. found impaired neutrophil and monocyte adherence as a common trait in 12 patients with alcoholic cirrhosis and 15 patients with diabetes.16 Thus, it seems that there could be an overlap between the mechanisms responsible for the increased risks of infection in cirrhosis and in diabetes. This raises the question of whether the infection risk is additive in patients with more than 1 risk disease, and specifically whether this is the case in patients with cirrhosis and diabetes. Only a few studies have dealt with the issue,17–21 and it remains unclear whether there is a difference in the risk of infections between patients with cirrhosis, with or without diabetes, particularly among patients with decompensated cirrhosis. It is also unclear whether diabetes affects mortality following an infection in patients with cirrhosis.

Given this background, we compared the risk of infections and mortality following an infection between patients with cirrhosis, with or without diabetes. Our a priori expectation was that diabetes would increase the risk of infections, as well as mortality following an infection.

Keywords: Infection; diabetes; Liver cirrhosis; prognosis.

Patients and methods
Patients
In 2006–2008, 1,198 outpatients with cirrhosis and ascites were included in 3 multicentre randomised controlled trials conducted to examine the efficacy of satavaptan in treating ascites in...
patients with cirrhosis (www.clinicaltrials.gov registration numbers NCT00358878, NCT00359437 and NCT00366795). More than 100 hospitals in more than 20 countries included patients in this study. The responsible local and national Ethics Committees and IRBs for each participating site approved the study protocols, patient information and consent forms prior to starting the study as required by Good Clinical Practice and national laws. We refer to the approval by the Barcelona clinical research ethics committee (Barcelona Comités de Ética en Investigación Clínica de referencia, CEIC-Ref), which was used as a reference committee for other sites.

The 3 trials had slightly different target populations: Patients with diuretic-manageable ascites (n = 462), patients with ascites managed with diuretics and occasional therapeutic paracentesis (n = 496), and patients with diuretic-resistant ascites managed primarily with therapeutic paracentesis (n = 240). Otherwise, the trials were identical. Patients with spontaneous bacterial peritonitis (SBP) or variceal bleeding in the 10 days before randomisation were excluded. Other reasons for exclusion were: hepatic encephalopathy ≥ grade 2 at randomisation, a functioning transjugular intrahepatic portosystemic shunt, serum creatinine >150 μmol/L, serum potassium >5.0 mmol/L, serum sodium >143 mmol/L, serum bilirubin >150 μmol/L, international normalized ratio (INR) >3.0, platelets <30,000/mm³, neutrophils <1,000/mm³, systolic arterial pressure <80 mmHg or symptomatic orthostatic hypotension, hepatocellular carcinoma exceeding the Milan criteria, use of a potent modifier of the cytochrome P450 3A pathway, or use of drugs that increase the risk of QT interval prolongation.

Study design
Treatment duration in the trials was 1 year. In the analyses presented in this study, all patients were followed from randomisation until the first of the following events: infection, death, or the date of the final drug safety assessment.

Data collection
Baseline data were collected at inclusion. During the follow-up patients were seen every 4 weeks in their specialised hepatology departments. Blood biochemistry, urine dipstick analysis, use of medical drugs, and development of infections were recorded in detail at each of these visits and on the date of the final drug safety assessment. The protocols for the trials did not specify diagnostic criteria for infections, so all infections in our study rely on the diagnostic criteria used in the participating hepatology departments. Infections were recorded and classified according to the ICD-10 system, a standard WHO system for classifying diagnoses, and were categorised according to infection agent and site. An infection could be classified as bacterial, viral, or fungal based on clinical criteria; the trial protocols did not require confirmation by culture or other means. The results of microbiological tests were not recorded, even if they had been done. For the analysis presented here we counted all SBP episodes as bacterial infections. Sepsis was recorded as a severe adverse event in the trials, but the diagnostic criteria were not specified. Data on survival was collected at the end of the planned trial duration.

Statistical analysis
The 1-year cumulative risk of infection was calculated using the cumulative incidence function with death as a competing risk. We used Cox proportional hazards regression to estimate the effect of diabetes on the hazard ratio (HR) of infection of any kind, meaning any site and any infectious agent. We adjusted for confounding by patient age; gender; cirrhosis aetiology (alcoholic or other) and severity as indicated by severity of ascites (refractory or diuretic-responsive), model for end-stage liver disease (MELD) score, serum albumin, use of lactulose (yes or no), and use of proton pump inhibitors (PPI) (yes or no). We computed the MELD score using serum bilirubin, creatinine, INR, and sodium, computed according to current guidelines from the United Network of Organ Sharing [https://optn.transplant.hrsa.gov/media/1575/policynotice_20151101.pdf]. The measures of cirrhosis severity were included as time-dependent variables, updated whenever they were measured.

We conducted additional analyses: first, we examined the effect of diabetes on the HR of sepsis, because sepsis is a specific and clinically well-defined marker of dangerous infection. We adjusted for the same confounders as in the primary analysis. Second, we conducted analyses excluding (a) patients with a history of SBP, and (b) patients with a history of SBP and patients taking quinolone antibiotics. In both cases, we investigated the risk of any infection and the risk of SBP in patients with and without diabetes while controlling for the same confounders as in the primary analysis. Third, we stratified the patients into 3 equal-sized groups by their MELD score at inclusion and repeated the primary analysis within each group to clarify whether the effect of diabetes depends on cirrhosis severity. Fourth, we investigated the effect of diabetes treatment on the HR of infection. Thus, patients with diabetes were categorised according to current treatment: 1) diet/no treatment, 2) metformin-treated, 3) insulin-treated, and 4) other antidiabetic treatments. The treatments were included as a categorical variable in a Cox regression with patients without diabetes being the reference category. We included the same confounding variables as in the primary analysis. Fifth, we investigated the effect of diabetes control on the HR of infection by categorising patients with diabetes according to positive or negative dipstick analysis for glycosuria. Again, non-diabetic patients were the reference category, and we included the same confounding variables.

Table 1. Baseline characteristics in patients with cirrhosis and ascites, with and without diabetes.

|                        | Diabetes | No diabetes |
|------------------------|----------|-------------|
| Number of patients     | 289      | 909         |
| Age (median, IQR)      | 60 (55–67) | 56 (49–63) |
| Men (%)                | 210 (73)  | 624 (69)    |
| Cirrhosis aetiology (%)|          |             |
| Alcohol alone          | 153 (53)  | 540 (59)    |
| Other                  | 136 (47)  | 369 (41)    |
| Child-Pugh score (median, IQR) | 8 (7–9) | 8 (7–10) |
| MELD score (median, IQR) | 14 (11–18) | 15 (11–18) |
| Serum sodium, mmol/L (median, IQR) | 137 (134–139) | 136 (133–139) |
| Albumin, g/L (median, IQR) | 34 (30–38) | 33 (29–37) |
| Platelet count, *1.000*μL (median, IQR) | 113 (82–160) | 134 (92–195) |
| Previous spontaneous bacterial peritonitis (%) | 51 (18) | 126 (14) |
| Lactulose, any dose (%) | 102 (35) | 272 (30) |
| Quinolone, any dose (%) | 39 (13) | 111 (12) |
| Non-selective β-blockers, any dose (%) | 145 (50) | 417 (46) |
| Proton pump inhibitors, any dose (%) | 150 (52) | 374 (41) |
end of the planned trial duration.

were censored alive on the date of survival assessment at the lowed from the day of their first infection to death, or they had an infection during the follow-up, and patients were fol-

primary analysis. This analysis included only those patients who were followed for 569 person-years in total. During the follow-up, A total of 1,198 patients, of whom 289 (24%) had diabetes, were followed from the day of their first infection to death, or they were censored alive on the date of survival assessment at the end of the planned trial duration.

Results
A total of 1,198 patients, of whom 289 (24%) had diabetes, were followed for 569 person-years in total. During the follow-up, 446 patients had an infection (Fig. 51), the 1-year cumulative risk of infection being 44.5% (95% CI 41.2%–47.8%). At inclusion, the patients with diabetes were older, more often men, had lower platelets, and were more likely to use lactulose than those without diabetes (Table 1). Satavaptan use did not influence the rate of infections (adjusted HR 0.98; 95% CI 0.81–1.19).

Patients with diabetes did not increase the rate of infection compared to those without diabetes (adjusted HR 1.08; 95% CI 0.87–1.35, Table 2), nor did they have an increased rate of sepsis (57 episodes in total, 12 of them in diabetics; adjusted HR 0.88; 95% CI 0.45–1.69), of bacterial infections (adjusted HR 1.33; 95% CI 0.90–1.95), or of any other infection (Fig. 1). We found no association between diabetes and risk of any infection (adjusted HR 0.99; 95% CI 0.77–1.27) or of SBP (adjusted HR 1.05; 95% CI 0.59–1.84) among the 1,021 patients without a history of SBP. Likewise, we found no association between diabetes and risk of any infection (adjusted HR 1.03; 95% CI 0.78–1.34) or of SBP (adjusted HR 1.28; 95% CI 0.79–2.05) among the 987 who had no history of SBP and were not taking quinolone antibiotics.

Moreover, diabetes was not associated with an increased risk of infections in any of the groups defined by MELD score, i.e. adjusted HR among patients with an MELD score of 6 to 11: 0.97 (95% CI 0.64–1.47); MELD 12 to 16: 1.26 (95% CI 0.84–1.89); MELD 17 to 36: 1.02 (95% CI 0.71–1.45). Finally, diabetes was not a risk factor for infections in any of the diabetes categories defined by antidiabetic treatment or by glycosuria (Table 3).

We used Cox regression to examine whether patients with cirrhosis and diabetes had a higher HR of death after they developed a) any infection or b) sepsis, compared to patients with cirrhosis without diabetes, adjusting for the same confounders as in the primary analysis. This analysis included only those patients who had an infection during the follow-up, and patients were followed from the day of their first infection to death, or they were censored alive on the date of survival assessment at the end of the planned trial duration.

Table 2. Adjusted hazard ratios of infection.

|                     | Adjusted hazard ratio (95% CI) |
|---------------------|--------------------------------|
| Diabetes, yes vs. no | 1.08 (0.87–1.35)               |
| Age, per 10 years   | 0.90 (0.82–0.99)               |
| Male vs. female     | 0.82 (0.67–1.01)               |
| MELD score, per point increase | 1.03 (1.01–1.05) |
| Albumin, per 5 g/L increase | 0.79 (0.72–0.86) |
| Lactulose use, yes vs. no | 1.34 (1.09–1.64) |
| Refractory ascites, yes vs. no | 1.10 (0.91–1.33) |
| Cirrhosis aetiology, alcohol vs. other | 0.81 (0.66–0.99) |
| Proton pump inhibitor use, yes vs. no | 1.45 (1.19–1.76) |

Statistically significant results are highlighted with bold font.

Table 3. Adjusted hazard ratios of infection within categories of diabetes patients.

|                     | Adjusted hazard ratio (95% CI) |
|---------------------|--------------------------------|
| By antidiabetic treatment (N at the beginning of follow-up) |                                |
| Diet (n = 84)       | 0.88 (0.58–1.32)               |
| Metformin-treated (n = 29) | 1.53 (0.89–2.63)               |
| Insulin-treated (n = 134) | 1.15 (0.86–1.52)               |
| Other oral antidiabetic (n = 42) | 0.96 (0.54–1.72)               |
| Patients without diabetes (n = 909) | Reference              |
| By urinary glucose  |                                |
| Diabetes and positive dipstick for glycosuria (n = 44) | 0.87 (0.50–1.53)               |
| Diabetes and negative dipstick for glycosuria (n = 245) | 1.12 (0.89–1.41)               |
| Patients without diabetes (n = 909) | Reference              |

MELD, model for end-stage liver disease; PPI, proton pump inhibitor. Hazard ratios are adjusted for confounding by patient age, gender, cirrhosis aetiology, severity of ascites, MELD score, serum albumin, use of lactulose, and use of PPI.

Fig. 1. The effect of diabetes on the hazard ratio of any infection, specific infectious agents, and specific sites of infection.
Patients with diabetes did not have increased mortality after an infection (adjusted HR 0.93; 95% CI 0.64–1.35) (Fig. 2), or after sepsis (adjusted HR 1.06; 95% CI 0.48–2.37).

Discussion
This analysis of data from nearly 1,200 trial participants with cirrhosis and ascites showed that concomitant diabetes did not increase their risk of infections or post-infection mortality. This result refutes our a priori expectation of an additive effect on the risk of infections.

The results and conclusions presented here are based on systematically collected data from 3 multicentre trials. Out of 5 studies previously published within this area, 4 reported a relative risk of infections of >2.5 in patients with cirrhosis and diabetes compared to those with cirrhosis without diabetes.17–21 (Table S1). One possible way to explain the discrepancy with our findings is that cirrhosis – in its most severe, decompensated state – confers such an overwhelming risk of infections that any additional risk by diabetes becomes difficult to detect. Most of those previous studies did not describe the severity of cirrhosis,17–20 but one of them was limited to patients with compensated cirrhosis21 (Table S1). It found an HR for infections of 4.08 (95% CI 1.43–11.66) among patients with cirrhosis due to hepatitis B infection, but did not attempt to control for confounding. Instead, the study identified predictors of infection risk, and diabetes was not included among the statistically significant predictors on multivariable analysis.

The infection risk in both type 1 and type 2 diabetes tends to increase with poor control of glycaemia,24,25 but we could not confirm this pattern. However, it was a limitation of our study that we did not have data on HbA1c, which would have given us a more clinically relevant measure of glycaemic control. The available data suggest that our patients’ diabetes was generally well controlled: only 44 (15%) of 289 diabetic patients had glycosuria at inclusion, and the prognosis following infection was the same for patients with or without infection. Thus, in our interpretation, diabetes did not affect the risk of infections or the mortality following an infection because our patients had ‘poorly controlled’ cirrhosis and well controlled diabetes. We cannot exclude the possibility that some cirrhotic patients with diabetes have an increased risk of infections or a worse prognosis following infection.

Reducing the incidence of complications, particularly of infections, in patients with cirrhosis is an important clinical objective. Prophylactic antibiotic therapy is tempting, but needs to be targeted to the patients with documented benefit to avoid selection of multidrug resistant bacteria,26 adverse effects, and expenses. According to the 2018 EASL Clinical Practice Guidelines, patients with cirrhosis and acute gastrointestinal haemorrhage, with a low protein content in the ascitic fluid, or with a previous history of SBP, are known to be at greater risk of SBP and should be considered for prophylactic antibiotic treatment.27 Risk factors for non-SBP bacterial infections in patients with cirrhosis include PPI use,23 ascites, advanced disease stage (Child-Pugh or MELD score), and a previous episode of bacterial infection.28,29 We found a 1.08-fold increased rate of infections in patients with diabetes within our cohort of cirrhotic patients, not much lower than the 1.1- to 1.2-fold increased rate of infections in patients with diabetes within a cohort from the general population.3 The upper confidence limit around our 1.08 estimate is 1.35, a value suggesting that prophylactic antibiotics could be considered. However, the lower confidence limit (0.87) is just as compatible with our data as the upper confidence limit, and the 1.08 point estimate gives the most solid guidance from our data for decisions about prophylactic antibiotics.30

In conclusion, we have shown that patients with cirrhosis, ascites and concomitant diabetes do not have an increased risk of infection compared to those without diabetes, nor do they have an increased mortality following an infection. These findings indicate that the immune deficiencies resulting from cirrhosis and diabetes are not additive.

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Conflicts of interest
Hugh Watson was formerly an employee of Sanofi. Lars Bossen, Hendrik Vilstrup, Gitte Aarøe Dam and Peter Jepsen have no conflicts of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

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Supplementary data
Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhepr.2019.07.008.

References
[1] Brann OS. Infectious complications of cirrhosis. Curr Gastroenterol Rep 2001;3:285–292.
[2] Bajaj JS, O’Leary JG, Wong F, Reddy KR, Kamath PS. Bacterial infections in end-stage liver disease: Current challenges and future directions. Gut 2012;61:1219–1225.
[3] Arvaniti V, D’Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality fourfold and should be used in determining prognosis. Gastroenterology 2010;139:1246–1256.
Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. Hepatology 2014;60:823–831.

Muller LM, Gorter KJ, Hak E, Goudswaard WL, Hoepelman AI, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2005;41:281–288.

Christou L, Pappas G, Falagas ME. Bacterial infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol 2007;102:1510–1517.

Bruns T, Zimmermann HW, Stallmach A. Risk factors and outcome of bacterial infections in cirrhosis. World J Gastroenterol 2014;20:2542–2554.

Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab 2012;16:S27–S37.

Geelings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (dm). FEMS Immunol Med Microbiol 1999;26:259–265.

Peleg AY, Weeraratna T, McCarthy JS, Davis TM. Common infections in diabetes: Pathogenesis, management and relationship to glycemic control. Diabetes Metab Res Rev 2007;23:3–13.

Kelly MK, Brown JM, Thong YH. Neutrophil and monocyte adherence in diabetes mellitus, alcoholic cirrhosis, ischaemia and elderly patients. Int Arch Allergy Appl Immunol 1985;78:132–138.

Diaz J, Monge E, Roman R, Uliba V. Diabetes as a risk factor for infections in cirrhosis. Am J Gastroenterol 2008;103:248.

Amato A, Precone DF, Caramante N, Brancaccio G, Stornaiuolo G, Galante D, et al. Prevalence and risk factors for bacteriuria in patients with cirrhosis. Infez Med 2005;13:103–108.

Wlazlo N, van Greevenbroek MM, Curvers J, Schoon EJ, Friederich P, Twisk JW, et al. Diabetes mellitus at the time of diagnosis of cirrhosis is associated with higher incidence of spontaneous bacterial peritonitis, but not with increased mortality. Clin Sci (Lond) 2013;125:341–348.

Ramachandran TM, Rajneesh AHR, Zacharias GA, Adarsh RP. Cirrhosis of liver and diabetes mellitus: The diabolic duo? J Clin Diagn Res 2017;11:OC01–OC05.

Shah BR, Lescat M, Layese R, Bourcier V, Talmat N, Allam S, et al. Bacterial infection in compensated viral cirrhosis impairs 5-year survival (ans co12 cirvir prospective cohort). Gut 2017;66:330–341.

Wong F, Watson H, Gerbes A, Vilstrup H, Badalamenti S, Bernardi M, et al. Satavapant for the management of ascites in cirrhosis: Efficacy and safety across the spectrum of ascites severity. Gut 2012;61:108–116.

Damm G, Vilstrup H, Andersen PK, Bossen L, Watson H, Jepsen P. Effect of proton pump inhibitors on the risk and prognosis of infections in patients with cirrhosis and ascites. Liver Int 2019;39:514–521.

Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sorensen HT, Thomsen RW. Impact of glycemic control on risk of infections in patients with type 2 diabetes: A population-based cohort study. Am J Epidemiol 2017;186:227–236.

Crichtley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. Diabetes Care 2018;41:2127–2135.

Fernandez J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: A prospective study. Hepatology 2012;55:1515–1516.

Moreau R, Elkrief L, Bureau C, Perarnau JM, Thevenot T, Saliba F, et al. Effect of long-term norfloxacin therapy in patients with advanced cirrhosis. Gastroenterology 2018;155:1816–1827 e1819.

Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature 2019;567:305–307.