AP&T Alimentary Pharmacology and Therapeutics

Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis

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Publication data
Submitted 20 September 2014
First decision 6 October 2014
Resubmitted 26 October 2014
Resubmitted 2 December 2014
Accepted 2 December 2014
EV Pub Online 19 December 2014

This article was accepted for publication after full peer-review.

SUMMARY

Background
Proton pump inhibitors (PPI) are widely used in patients with liver diseases. Within the last years, there have been concerns about the PPI use as they may promote infections in patients with cirrhosis.

Aim
As there are sparse data of the prognostic relevance of PPI treatment, to perform a prospective study investigating the relation of PPI treatment and overall survival (OS) in cirrhotic individuals.

Methods
Patients with cirrhosis were enrolled and followed prospectively. The primary end point was OS. PPI treatment and additional clinical and laboratory data were assessed at the day of the study inclusion. The time until the end point death was assessed and the individual risks were calculated with Cox regression analyses.

Results
A total of 272 patients were included and 213 individuals (78.3%) were on PPI treatment. In multivariate logistic regression analysis, PPI treatment was associated with higher MELD scores ($P = 0.027$) and ascites ($P = 0.039$). In a multivariate Cox regression model, PPI use was an independent predictor of mortality (hazard ratio 2.330, 95% confidence interval 1.264–4.296, $P = 0.007$) in addition to the model of end-stage liver disease (MELD) score, hepatocellular carcinoma and hepatic decompensation.

Conclusions
PPI use is an independent risk factor for mortality in patients with cirrhosis. Although a causative role for increased mortality in patients taking PPI is still missing, the prescription of PPI in cirrhotics should be considered carefully taking into account its potential adverse effects.

Aliment Pharmacol Ther 2015; **41:** 459–466

doi:10.1111/apt.13061

INTRODUCTION

Cirrhosis is the consequence of different chronic liver diseases characterised by hepatic cell death, inflammation and fibrotic conversion of the liver.[1] Compensated cirrhosis often only slightly worsens patients′ general condition. However, if decompensation of cirrhosis occurs and cirrhosis related complications are arising, morbidity and mortality are increasing rapidly.[2, 3] A common complication of cirrhosis is gastrointestinal bleeding including acute bleeding from varices or ulcers and chronic blood loss from portal hypertensive gastropathy (PGH) or gastric vascular ectasia (GAVE) syndrome. Acute bleeding from varices is managed using vasoconstrictors, antibiotics and endoscopic ligation or sclerotherapy.[4] In such patients proton pump inhibitors (PPI) reduce the risk of death irrespective of concomitant endoscopic hemostasis.[5] Patients undergoing endoscopic band ligation benefit from PPI treatment as PPI reduce the size of post-banding ulcers.[6] However, there is evidence that PPI may have adverse effects in patients with cirrhosis. PPI intake favours bacterial infections including spontaneous bacterial peritonitis (SBP),[7–10] but there are conflicting data if PPI worsen the prognosis of patients with SBP.[11, 12] Furthermore, even in noncirrhotic patients PPI usage may increase the risk of bacterial infections including pneumonia or *Clostridium difficile* colitis.[13, 14] Multi-drug resistant (MDR) bacteria are a severe and increasing healthcare challenge.[15] As PPI may facilitate bacterial colonisation of the upper gastrointestinal tract and the small bowel, cirrhotic patients receiving acid suppression therapy might also be at an increased risk of being colonised with MDR bacteria. Studies in mice have shown a higher susceptibility to colonisation with Vancomycin-resistant *Enterococcus faecium* (VRE) or resistant *Klebsiella pneumoniae* in animals receiving PPI.[16] However, there is only little data concerning a possible relation between acid suppression with PPI and colonisation with MDR bacteria in humans. In a cohort of cirrhotic patients awaiting liver transplantation VRE colonisation was associated with antibiotic treatment and PPI treatment.[17] However, beneath the indicated studies there is little data concerning the relation between PPI intake and infectious complications, colonisation with MDR bacteria and overall mortality of cirrhotic patients. Therefore, we performed a prospective mono centre study in a German university hospital investigating the relation of PPI treatment and overall mortality in cirrhotic individuals.

PATIENTS AND METHODS

Selection of patients

Patients with cirrhosis who were under medical treatment in our clinic as out- or in-patients between May 2009 and June 2011 were prospectively enrolled into the study. All patients gave their written informed consent to participate in the study. The inclusion criterion was cirrhosis confirmed by liver histopathological examination or pathognomonic results in ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria were history of cancer other than hepatocellular carcinoma (HCC) within the last 5 years, a history of solid organ transplantation and an age of below 18 years. Listing for liver transplantation was carried out if the patient was eligible for liver transplantation. Organs were allocated by Eurotransplant according to Eurotransplant and German guidelines.

On the day of the patient′s inclusion into the study the presence of complications of cirrhosis, namely ascites, SBP, HRS, gastrointestinal bleeding including variceal bleeding and hepatic encephalopathy were determined. From the day of written informed consent patients were followed up until death, liver transplantation or last contact. Subjects who received liver transplantation were excluded from further analysis from the day of transplantation. At the day of study inclusion blood samples were taken for the assessment of clinical routine parameters.

At the day of admittance to the hospital, the patients′ medication including usage of PPI was assessed. It was examined, whether PPI treatment was given for strong indications (gastrointestinal bleeding, peptic ulcer disease, gastroesophageal reflux disease, endoscopic variceal ligation) or symptomatically for epigastric pain, nausea or vomiting. The presence of ascites was assessed by clinical examination and abdominal ultrasound examination. In patients with ascites paracentesis was performed and cultures as well as neutrophil counts from ascites were initiated. SBP diagnosis was made, if neutrophil counts were >250/mm^3 as defined by current guidelines.[2] Diagnosis of hepatorenal syndrome (HRS) was made by exclusion of other causes of elevated serum creatinine according to current guidelines.[2] Hepatic decompensation was defined as presence of ascites, SBP, gastrointestinal bleeding, HRS or hepatic encephalopathy. Diagnosis of HCC was based on histopathological examinations or distinct findings in MRI or CT imaging following the European guidelines.[18] Patients with known colonisation

with MDR bacteria were isolated. Screening for colonisation with MDR bacteria was performed according to the local infection control guidelines every time the indicated individual was admitted to in-patient treatment: A nasal swab for testing for Methicillin-resistant *Staphylococcus aureus* (MRSA) was taken in patients who were treated at least 3 days as in-patients within the last twelve months or were admitted by special-care homes. In patients who were treated on intensive care unit within the present hospital stay or in whom an invasive procedure including surgery or listing for liver transplantation was planned, additional swabs for testing for MDR gram-negative bacteria and VRE were taken including rectal smears and swabs from wounds, central venous catheters or tracheostoma if present. In patients who presented with clinical signs of infections (fever, chills, coughing or dysuria) or showed elevated CRP or leucocyte values in the blood tests, urinalysis and x-ray of the chest were performed. If urinalysis showed presence of leucocytes, urine cultures were initiated. In patients who had clinical or radiological signs of lung infections sputum cultures were done. In severely sick patients with pneumonia bronchoalveolar lavage was performed to gain material for cultures. If diarrhoea was reported, stool cultures were initiated.

The MELD and Child–Pugh scores were calculated by clinical examination, laboratory parameters and the results of abdominal ultrasound examination, CT or MRI.[19, 20] For all patients endoscopic examination of the upper gastrointestinal tract to screen for oesophageal varices was recommended.

The present study was approved by the Institutional Review Board of the Goethe University Hospital Frankfurt. The study was performed in accordance with the 1975 Declaration of Helsinki and the REMARK guidelines for prospective biomarker studies.[21]

Statistical analysis

Data analysis was performed with BiAS software for windows (version 10.03, Epsilon-Verlag, Darmstadt, Germany) and SPSS (Version 22.0; IBM, New York, USA). Differences between groups of patients were determined using the nonparametric Wilcoxon–Mann–Whitney test. For the multivariate regression analysis a backward stepwise logistic regression model was used. In the backward stepwise logistic regression model variables with P values > 0.10 were eliminated from the model. The primary end point was OS and death was considered as event. The time in the study was defined as time from inclusion into the study until death or last contact. An univariate Cox regression hazard model was used to identify predictors of survival. For the assessment of independent predictors of survival a multivariate Cox regression with forward stepwise likelihood ratio was performed. Survival curves for indicated patients groups were calculated with the Cox regression model.

RESULTS

A total of 272 subjects with cirrhosis were prospectively enrolled into the study. The patients′ characteristics are shown in Table 1. The predominant etiologies of cirrhosis were former alcohol abuse and chronic infections with the hepatitis C virus or the hepatitis B virus. Several patients had two or more chronic liver diseases leading to cirrhosis. 199 of the 272 patients showed hepatic decompensation, including ascites, gastrointestinal bleeding, HRS or hepatic encephalopathy at the day of inclusion into the study. 47 patients (17.3%) suffered from HCC. 213 (78.3%) of 272 patients received PPI, namely omeprazole, esomeprazole or pantoprazole in a daily dose of 20–200 mg. In 89 of 213 patients the indication for PPI use was recent gastrointestinal bleeding, recent endoscopic ligation of varices, severe reflux or peptic ulcer disease. In the remaining 124 patients PPI was prescribed symptomatically for epigastric pain or abdominal discomfort.

The median follow-up time was 266 days with a range of 1–1382 days. 38 (14.0%) patients received liver transplantation and were excluded from further analysis from the day of transplantation. 86 (31.6%) patients died within the observation time. The predominant reasons of death were liver failure, sepsis with concomitant multi organ failure and variceal bleeding.

PPI and complications of cirrhosis

Proton pump inhibitors are considered to facilitate bacterial overgrowth of the gastrointestinal tract and thereby may promote infections leading to worsening of liver function. Therefore, the relation of PPI use and specific complications of cirrhosis was assessed with univariate nonparametric tests as well as using a multivariate logistic regression model with backward elimination. Patients receiving PPI treatment had more advanced cirrhosis reflected by a significantly higher MELD score compared to individuals without PPI prescription (median MELD 16 vs. 12, $P < 0.001$) and more patients taking PPI suffered from ascites (77.0% vs. 55.9%, $P = 0.001$). However, there was no difference in PPI use in the patients according to aetiology of cirrhosis (alcoholic

Table 1 | Patients' characteristics

Parameter	All	PPI takers	Non-PPI takers
Epidemiology			
Patients, *n*	272	213	59
Gender, m/f, *n* (%)	182/90 (66.9/33.1)	141/72 (66.2/33.8)	41/18 (69.5/30.5)
Age, median, range, years	57 (25–84)	57 (27–84)	57 (25–78)
Aetiology of liver disease			
Alcohol abuse, *n* (%)	136 (50.0)	109 (51.2)	27 (45.8)
Hepatitis C, *n* (%)	74 (27.2)	59 (27.7)	15 (25.4)
Hepatitis B, *n* (%)	35 (12.9)	26 (12.2)	9 (15.3)
Non-alcoholic steatohepatitis, *n* (%)	7 (2.6)	7 (3.3)	0 (0)
Hereditary Hemochromatosis, *n* (%)	7 (2.6)	3 (1.4)	4 (6.8)
Cryptogenic, *n* (%)	24 (8.8)	20 (9.4)	4 (6.8)
Primary sclerosing cholangitis	16 (5.9)	10 (4.7)	6 (10.2)
Primary biliary cirrhosis	3 (1.1)	3 (1.4)	0 (0)
Autoimmune hepatitis	10 (3.7)	7 (3.3)	3 (5.1)
Child-Pugh stage			
A, *n* (%)	58 (21.3)	34 (16.0)	24 (40.7)
B, *n* (%)	129 (47.4)	107 (50.2)	22 (37.3)
C, *n* (%)	85 (31.3)	72 (33.8)	13 (22.0)
MELD,[1] median, range	15 (6–40)	16 (6–40)	12 (6–32)
Laboratory results			
Leucocytes, median, range/nL	5.2 (0.6–56.5)	5.3 (0.6–56.5)	4.7 (2.4–20.0)
Haemoglobin, median, range g/dL	10.5 (6.3–17.6)	10.4 (6.0–18.0)	12.7 (7.0–16.0)
Thrombocytes, median, range/nL	99 (17–1507)	98 (17–410)	98 (26–1507)
Sodium, median, range mmol/L	138 (111–150)	138 (111–150)	140 (125–147)
Creatinine, median, range mg/dL	1.00 (0.38–6.77)	1.1 (0.4–6.8)	0.9 (0.5–2.3)
Albumin, median, range mg/dL	3.2 (1.6–5.2)	3.2 (1.6–5.2)	3.3 (1.9–5.2)
INR,[2] median, range	1.4 (0.9–4.2)	1.4 (0.9–3.1)	1.3 (0.9–4.2)
Bilirubin, median, range mg/dL	2.1 (0.2–51.0)	2.1 (0.2–51.0)	1.5 (0.2–22.5)
ALT,[3] median, range U/L	32 (2–1594)	31 (2–1594)	39 (10–188)
AST,[4] median, range U/L	53 (15–2823)	53 (15–2823)	53 (24–377)
GGT,[5] median, range U/L	104 (14–1178)	101 (15–1178)	110 (14–839)
ALP,[6] median, range U/L	118 (31–688)	116 (31–688)	129 (58–374)

[1]MELD, model of end stage liver disease.

[2]INR, internationalized ratio.

[3]ALT, alanine aminotransferase.

[4]AST, aspartate aminotransferase.

[5]GGT, gamma-glutamyl-transferase.

[6]ALP, alkaline phosphatase.

liver disease vs. non-alcoholic; $P = 0.463$ as well as viral hepatitis vs. nonviral hepatitis; $P = 0.553$). Regarding gender and age no significant differences between the two groups were observed ($P = 0.635$ and 0.187, respectively). A statistical trend for a higher number of infectious complications at the day of study inclusion in patients taking PPI was observed (35.2% vs. 22.0%, $P = 0.056$). The number of patients with HRS did not differ between the groups ($P = 0.115$). PPI-treated patients were colonised more frequently with MDR bacteria than patients without PPI treatment (12.7% vs. 1.7%, $P = 0.014$): 28 of the 272 patients were colonised with MDR bacteria of whose 27 patients took PPI. In 13 individuals Extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL) were identified from rectal swaps. In eight patients MRSA was found, and VRE was detected in six patients. One patient showed colonisation with ESBL and VRE. As PPI use was associated with the severity of liver disease (higher MELD score, ascites) and infectious complications (clinical apparent infections), an age and gender corrected multivariate logistic regression model was used to identify independent parameters associated with PPI treatment. As shown in Table 2 the MELD score and ascites were independently associated

Table 2 | Association of PPI treatment with patients' characteristics and complications of cirrhosis

Parameter	PPI-therapy		Univariate	Multivariate
	Yes	No	*P*-value	*P*-value
Ascites	164 (77.0)	33 (55.9)	0.001	0.039
Colonisation with MDR bacteria	27 (12.7)	1 (1.7)	0.014	0.091
Infectious complications	75 (35.2)	13 (22.0)	0.056	–
HRS	31 (14.6)	4 (6.8)	0.115	–
Male sex	142 (66.2)	41 (69.5)	0.635	–
MELD	16 (6–40)	12 (6–32)	<0.001	0.027
Age	57 (27–84)	57 (25–78)	0.187	–
Alcoholic cirrhosis	109 (51.2)	27 (45.8)	0.463	–
HBV/HCV cirrhosis	55 (25.8)	13 (22.0)	0.553	–

PPI, proton pump inhibitor; MDR, multiple drug resistance; HRS, hepatorenal syndrome; MELD, model of end-stage liver disease.

Continuous parameters are expressed as medians with range, nominal parameters as number of patients with percentage of occurrence in the group with or without PPI-therapy, respectively.

with PPI treatment. There was a trend for a relation of PPI treatment and colonisation with MDR bacteria. As the indication for PPI treatment was symptomatic therapy of abdominal complaints in more than 50% of the patients who used PPI the association of the clinical indication for treatment (specific vs. symptomatic) with patient parameters and specific complications of cirrhosis was assessed. The indication for PPI (specific vs. symptomatic) was not associated with the severity of disease or other factors at the day of study inclusion: ascites ($P = 0.534$), colonisation with MDR bacteria ($P = 0.868$), infectious complications ($P = 0.740$), HRS ($P = 0.117$), gender ($P = 0.831$), MELD ($P = 0.081$) or age ($P = 0.513$).

PPI use is independently associated with mortality in cirrhotic patients. Given the association of PPI treatment with negative prognostic indicators such as complications of cirrhosis and higher MELD scores, we hypothesised that PPI treatment itself might be an adverse prognostic factor. Therefore, the relation of PPI use and OS was assessed. PPI treatment was associated with higher mortality in the univariate Cox regression model (hazard ratio (HR) 2.330, 95% confidence interval (CI) 1.264–4.296, $P = 0.007$). The survival curve is shown in Figure 1. Further predictors of mortality were infectious complications (HR 2.704, 95% CI 1.759–4.158, $P < 0.001$), hepatic decompensation (HR 2.700, 95% CI 1.542–4.730, $P = 0.01$), HCC (HR 2.542, 95% CI 1.557–

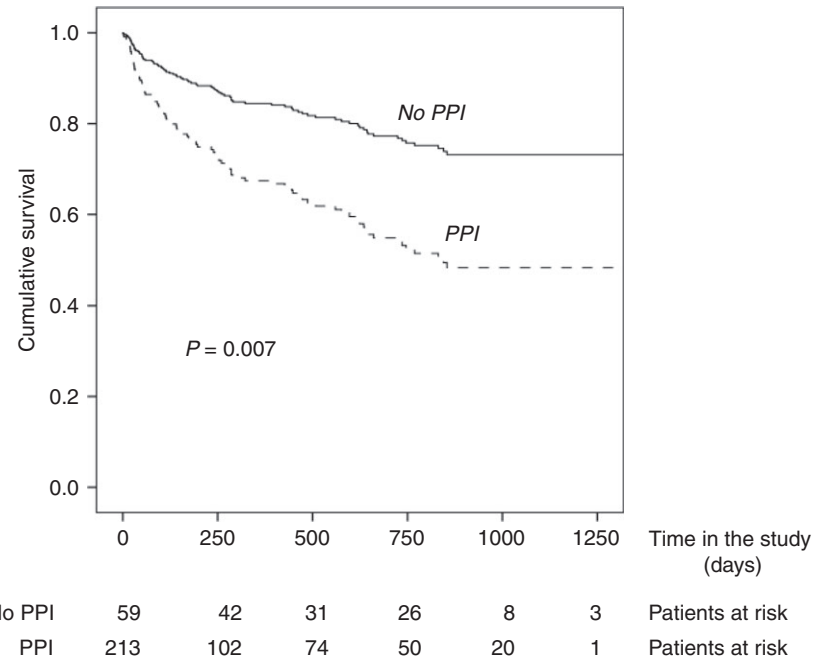

Figure 1 | PPI treatment is associated with increased mortality. Survival plots show the cumulative survival in patients with or without PPI treatment. The cumulative survival was calculated with the univariate cox regression model.

Table 3 | Factors associated with overall survival in univariate and multivariate analyses

	Univariate analysis			Multivariate analysis		
Parameter	HR	95% CI	*P* value	HR	95% CI	*P* value
PPI treatment	2.330	1.264–4.296	0.007	2.363	1.260–4.430	0.007
Male gender	0.763	0.492–1.184	0.228			N.S.
Infection	2.704	1.759–4.158	<0.001			N.S.
Decompensation	2.700	1.542–4,730	0.01	2.211	1.208–4.045	0.010
HCC	2.542	1.557–4.149	<0.001	4.971	2.909–8.497	<0.001
MELD	1.102	1.067–1.138	<0.001	1.097	1.059–1.137	<0.001
Age ≤57	0.713	0.466–1.091	0.119			N.S.
Alcoholic cirrhosis	1.378	0.900–2.111	0.140			N.S.
Viral (HBV/HCV) cirrhosis	0.782	0.470–1.303	0.345			N.S.

HR, hazard ratio; CI, confidence interval; PPI, proton pump inhibitor; n.s., not significant; HCC, hepatocellular carcinoma; MELD, model of end-stage liver disease.

4.149, $P < 0.001$) and the MELD score (HR 1.102, 95% CI 1.067–1.138, $P < 0.001$). In the present cohort age, gender and aetiology of cirrhosis were not significantly associated with survival (Table 3). Furthermore, the mortality did not differ among patients who took PPI for specific or symptomatic indication (HR 1.497, 95% CI 0.946–2.370, $P = 0.085$). As PPI use was associated with mortality in the univariate Cox regression analysis, PPI treatment was tested as independent prognostic factor for survival in a multivariate Cox regression model. As shown in Table 3 PPI treatment was an independent negative prognostic factor in addition to hepatic decompensation, HCC and the MELD score in the multivariate analysis.

DISCUSSION

Proton pump inhibitors are extensively used in individuals with cirrhosis in consequence of frequent acute and chronic gastrointestinal bleeding complications. PPI have been proven to be beneficial after variceal bleeding and endoscopic band ligation in cirrhotic patients.[6, 22] Furthermore, a substantial number of cirrhotic patients receive PPI treatment for symptomatic therapy of epigastric discomfort. The practice of broad prescription of PPI came into focus after recent studies reported an alarming association between PPI treatment and an increased risk for the development of SBP.[7, 8, 10, 23] Data on the influence of PPI on survival of patients with SBP are controversial,[11, 12] and up to now the impact of PPI treatment on OS in cirrhotic patients remains unknown. Our study prospectively analysed the prevalence of PPI intake and its relation to complications of cirrhosis and its impact on survival.

With 78.3% of patients receiving PPI treatment our data confirms that PPI are widely used in cirrhotic individuals. Remarkably, more than 50% of patients on PPI treatment obtained acid suppression for symptomatic treatment of abdominal complaints without acute episodes of bleeding. These results are in line with previous reports on common use of PPI in cirrhotic patients.[23, 24] Beside the common prescription of PPI for epigastric discomfort, the frequent use in cirrhotic patients is probably aggravated by a general fear of peptic ulcer disease in such patients and a lack of guidelines addressing the duration of PPI treatment after variceal bleeding and endoscopic band ligation.[5] Therefore, prospective trials investigating the duration of PPI treatment in cirrhotic patients with portal hypertension are warranted.

Patients with more advanced liver disease were more likely to be on PPI treatment reflected by a significant association with high MELD score and ascites. In patients with higher MELD score the indication for acid suppression was more frequently symptomatic therapy which has been reported previously.[24] Suppression of gastric acid production promotes bacterial overgrowth of the small intestine and impairs gastrointestinal motility.[25, 26] Additionally, PPI are known to impair neutrophil function.[27, 28] PPIs are not only associated with an increased risk for SBP but they are also associated with an increased frequency of *Clostridium difficile* colitis as reported recently.[29] In our present cohort of cirrhotic individuals PPI treatment tended to be associated with presence of bacterial infections in univariate analysis, but in multivariate analysis PPI use was not associated with infections. Remarkably, medical acid suppression therapy was also correlated with colonisation with MDR bacteria in univariate analysis and showed a trend in multivariate analysis.

The only data about mortality and PPI in cirrhotic patients is limited to a subgroup of patients with SBP and the results of the two existing studies[11, 12] are inconsistent. Only the larger study showed a higher mortality for patients with SBP under PPI treatment.[11] A relation between PPI usage and mortality was evident in our cohort of cirrhotics. Thus, the need for PPI treatment seems to indicate a poor prognosis in patients with liver disease, as medical acid suppression was associated with mortality independently from the MELD score, HCC and decompensated cirrhosis. Interestingly, PPI use was a stronger predictor of mortality in multivariate Cox regression analysis than the presence of infections. Possibly, patients with need to take PPI have more severe liver disease leading to more abdominal discomfort. Therefore, PPI should be used with caution in patients with advanced liver disease. PPIs are metabolised in the liver by cytochrome CYP450 and secreted by the kidneys. Whereas renal insufficiency has almost no effect on PPI clearance, the risk for accumulation in liver impairment is increased by a prolongation of drug half-life and an increased Area under the Curve (AUC).[30] Additionally, interactions with other drugs metabolised by the cytochrome CYP450 system need attention. As still no clear recommendations for dose adjustments in cirrhotic patients exist, it is possible that PPI are overdosed in a substantial proportion of patients.

Our study has some limitations that need to be discussed. Although, a rather large cohort of cirrhotic patients was investigated, it was a monocentric study. Furthermore, PPI takers had slightly more advanced liver disease reflected by higher MELD and Child-Pugh scores indicating a higher risk of death in patients with PPI compared to the patients without PPI intake. However, multivariate cox regression analyses were performed to adjust for severity of cirrhosis and PPI use was found as an independent adverse factor.

In summary, we have shown here for the first time that PPI use was associated with an increased risk for mortality in a large cohort of cirrhotic individuals. It was an additional risk factor together with the stage of cirrhosis, hepatic decompensation, HCC and infectious complications. Although a causative role for PPI in the increased mortality cannot and should not be deduced from our observations, we advise a careful use of PPI in cirrhotics given by the potential adverse effects of PPI especially when they are used apart from hard indications for symptomatic treatment of abdominal symptoms.

AUTHORSHIP

Guarantor of the article: OW.

Author contributions: GD: statistical analysis, analysis and interpretation of data, drafting of the manuscript. AP: interpretation of data, critical revision of the manuscript. SZ: critical revision of the manuscript, funding. BK: interpretation of data, critical revision of the manuscript. OW: study concept and design, supervision, drafting of the manuscript. All authors approved the final version of the manuscript.

ACKNOWLEDGMENTS

We thank Esther Imelmann and Yolanda Martinez for excellent technical assistance.

Declaration of personal interests: Nothing to declare.

Declaration of funding interests: This work was supported in parts by the Nachwuchsforscherprogramm 2010 of the Medical Faculty, Goethe Universität and in parts by the Deutsche Forschungsgemeinschaft DFG WA 2924/2-1 to Oliver Waidmann and the Scolari foundation to Bernd Kronenberger.

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