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Proton Pump Inhibitors Are Associated With Minimal and Overt Hepatic Encephalopathy and Increased Mortality in Patients With Cirrhosis

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Minimal hepatic encephalopathy (MHE) is a subclinical cognitive impairment frequently observable in patients with cirrhosis. Proton pump inhibitors (PPIs) can contribute to small-bowel bacterial overgrowth, but no study has investigated the link between PPIs and MHE. We investigated the relationship between MHE and PPI use as well as the role of PPI use in the development of overt HE and survival. Consecutive patients with cirrhosis (n = 310) were included in the study and followed up for 14.1 ± 12.3 months. At entry, MHE was diagnosed when the Psychometric Hepatic Encephalopathy Score was ≤−4. Data were analyzed by logistic regression for the factors associated with MHE and by time-related models for overt HE development and survival. At inclusion, 131 out of 310 patients with cirrhosis (42%) were affected by MHE. One hundred and twenty-five patients (40%) were using PPIs. The variables independently associated with the presence of MHE were PPI use, previous overt HE, low albumin, low sodium, and age. During follow-up, the development of overt HE was higher (64% versus 25%, $P < 0.001$) and overall survival lower (41% versus 81%, $P < 0.001$) in PPI users than in nonusers. Variables independently associated with the development of overt HE were PPIs, history of overt HE, low albumin, MHE, and age, while variables independently associated with mortality were PPIs, development of overt HE, Model for End-Stage Liver Disease score, low sodium, and age. *Conclusion:* The study identifies a potentially removable factor associated with the presence of MHE and related to the development of overt HE and survival in patients with liver cirrhosis. (Hepatology 2019;0:1-10).

Overt hepatic encephalopathy (HE) is a spectrum of neuropsychiatric alterations, ranging from mild confusion to coma, which are observable in patients with advanced cirrhosis or portosystemic shunts.[1] The pathogenesis of HE is not completely understood, but a relationship between HE and gut bacteria has been suggested for a long time.[2] In fact, gut bacteria are responsible for the formation and release of products such as ammonia and endotoxins, implicated in the pathophysiology of HE.[3] Moreover, treatments able to modify the gut flora such as antibiotics,[4-6] disaccharides,[6,7] probiotics,[7-9] and fecal transplantation[10,11] have been shown to have a beneficial effect on HE. Thus, factors able to modify the gut microbiota may affect HE. Proton pump inhibitors (PPIs) are strong gastric acid suppressants, widely prescribed, often inappropriately, in patients with chronic liver disease,[12] which cause quantitative and qualitative alterations in gut microbiota.[13-16] In fact, PPIs can directly target the proton pumps of the bacteria[17] or affect the microenvironment by changing the pH within

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; MHE, minimal HE; PHES, Psychometric Hepatic Encephalopathy Score; PPI, proton pump inhibitor.

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the alimentary tract. The elimination of the gastric acid barrier facilitates intestinal microbiota dysbiosis, causing bacterial overgrowth. Different studies have shown that PPIs, by altering the gut microbiota, may increase the occurrence of spontaneous bacterial peritonitis[18,19] and other bacterial infections in patients with cirrhosis.[20] A recent American study demonstrated that PPIs modulate readmission risk and microbiota composition in cirrhosis, which respond to withdrawal.[21] Based on the relationship between PPIs, gut microbiota, and HE, three recent studies have investigated the correlation between PPI use and the risk of overt HE in patients with cirrhosis and found a significant association.[22-24] Given their retrospective nature[22,23] or the use of a population-based registry,[24] in none of these studies was the presence of minimal HE (MHE) detected.

Actually, up to 60% of patients with cirrhosis are affected by a peculiar type of mild cognitive impairment regarding the selective attention and executive functions, visuomotor ability, psychomotor speed, response inhibition, and response selection that can be detected only by psychometry.[25,26] The term *minimal hepatic encephalopathy* is used to indicate the presence of such subclinical cognitive alterations in patients who appear absolutely normal at clinical examination. Although subclinical, MHE has been shown to have important clinical implications, being associated with the development of overt HE,[27] lower survival,[28] and lower quality of life.[29] Moreover, car accidents[30] and falls[31] are more frequent in patients with MHE. The alteration in gut microbiota may be implicated also in the occurrence of MHE. In particular, Gupta et al. demonstrated a higher prevalence of small intestine bacterial overgrowth in patients with cirrhosis and MHE.[32] Thus, PPIs being associated with small intestine bacterial overgrowth and bacterial translocation[33] may be implicated in the genesis of MHE and its consequences, but no study has investigated the link between these drugs and MHE. Moreover, the prolonged use of high-dose PPIs has been associated with increased mortality in older patients discharged from acute-care hospitals[34] as well as in a group of patients with cirrhosis.[35]

Given this background, we hypothesized that the chronic use of PPIs could be associated with the presence of MHE. For this aim we analyzed our database, in which a cohort of patients with cirrhosis prospectively enrolled and followed up was administered the Psychometric Hepatic Encephalopathy Score (PHES), which is considered the gold standard for the diagnosis of MHE, at entry and followed up to establish the incidence of overt HE and patient survival. A number of multivariate analyses were performed to establish the independent role of PPIs in the occurrence of MHE as well as in the development of overt HE and survival.

Patients and Methods

From January 2014 to August 2016, all patients with cirrhosis, both inpatients and outpatients, without overt HE admitted to the Center for the Study of Portal Hypertension in Rome were prospectively enrolled and their data included into a database aimed at establishing the prevalence of MHE and its risk factors. The diagnosis of liver cirrhosis was based on clinical, biochemical, and radiological signs. Clinical and biochemical characteristics and a detailed pharmacological treatment were collected for each patient. In the present study, the database was used specifically to analyze the role of PPIs on MHE and overt HE. At entry, overt HE was excluded by using a set of standardized closed questions based on the West-Haven criteria.[36] Further exclusion criteria were alcohol/

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psychoactive drug intake (positive alcoholemia and/or benzodiazepines or opioid urine metabolites) at the moment of the psychometric evaluation, unrelated neurological disease, and lack of compliance with psychometric evaluation because of language barriers or reduced visual acuity. The presence of dementia was also excluded by using the Mini-Mental State Examination, as described.[37] Patients with advanced hepatocellular carcinoma, outside the Milan criteria, were also excluded because in these patients the prognosis is strongly influenced by neoplastic disease. Patients with transjugular intrahepatic portosystemic shunts and/or large portosystemic shunts and patients with a history of persistent or recurrent HE defined by two or more episodes within the last 6 months, even if without overt HE on first observation, were also excluded. A detailed clinical history was obtained in relation to previous complications of liver cirrhosis, particularly previous episodes of overt HE. The patients were qualified as having a positive history if a previous episode of overt HE grade II or above (according to the West Haven criteria) was documented by a previous hospitalization. All of the other parameters (Child-Pugh class and score, Model for End-Stage Liver Disease [MELD] score, serum sodium and albumin levels) were collected during the enrollment hospitalization.

Informed, written consent for the collection and evaluation of demographic and clinical data was obtained. The "Sapienza" University of Rome Ethical Committee approved the study and allowed collection of the data (Rif.1720/01.10.09).

PHARMACOLOGICAL ASSESSMENT

Therapeutic regimens at baseline were carefully noted with regard to dose and duration of therapy. Information regarding drug exposure were retrieved from physician admission notes for inpatients and from medication lists in notes for outpatients. Patients were considered "PPI users" when the treatment started at least 4 weeks prior to admission. This timing was chosen according to pharmacodynamics and in keeping with the available literature.[38] Regarding PPIs, we defined as "standard dosages" the daily administration of 20 mg of omeprazole, 30 mg of lansoprazole, and 40 mg of pantoprazole or esomeprazole.[38] We determined 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. To assess the duration of PPI therapy during follow-up, medical records were reviewed. At inclusion and during follow-up, only patients with a previous history of HE (25%) took lactulose or nonabsorbable antibiotics or both. Some patients were on diuretics (57%) or β-blockers (34%). None of the patients took H2 blockers as acid-suppressive medications.

EVALUATION OF MHE

The psychometric evaluation was performed in a quiet room, with no distracting noises. All patients (n = 310) underwent the PHES battery, including the digit-symbol test, the trail-making tests A and B, the serial-dotting test, and the line-tracing test.[39] Each test was scored against age-adjusted and education-adjusted norms for the Italian population. The PHES is the sum of integer scores of each test computed from the adjusted Z values, as follows: score = −3 for $Z \leq -3$, score −2 for $-3 < Z \leq -2$, score −1 for $-2 < Z \leq -1$, score 0 for $-1 < Z < 1$, score 1 for $Z \geq 1$. The PHES ≤−4 was considered abnormal.[40] Moreover, to support the diagnosis of MHE, all patients underwent the animal naming test, which assesses the maximum number of animals listed in 1 minute, as described.[41] The assessors of MHE were blinded to patients' pharmacological therapy.

FOLLOW-UP

All patients were offered follow-up in the outpatient department with repeated ultrasound and laboratory investigations every 6 months and endoscopic evaluation every 1 or 2 years. The patients and their families were instructed on the importance of adhering to the scheduled visits and to contact the medical staff immediately should any alteration in the mental status or neuromuscular function (especially asterixis and flapping tremor) occur between scheduled reviews. In particular, the family was instructed to report the occurrence of lethargy, apathy, obvious personality change, inappropriate behavior, or disorientation in time and place, which correspond to the occurrence of a grade II alteration in mental status. In this case, HE evaluation including the psychometric

performance was repeated to confirm and stage the degree of HE. Patients with an overt episode of HE reached the main endpoint of the study. Patients were contacted by phone every 3 months to check on their adherence to the scheduled follow-up.

The patients were followed up until death, liver transplantation, or the last available outpatient review. During the whole follow-up none of the patients stopped PPI consumption.

STATISTICAL ANALYSIS

The data are reported as mean ± SD. Comparisons between groups were performed by an unpaired Student *t* test or chi-squared test. Logistic regression analysis was used to identify clinical and biochemical variables independently and significantly associated with MHE. We estimated the cumulative incidence of the first episode of HE during the follow-up, taking into account the nature of the competing risks in the data (HE before liver transplantation, death, or liver transplantation are competing events) with the subdistribution model of Fine and Gray. The conditional subdistribution hazard at multivariate analysis was evaluated using the model of Fine and Gray.[42] We therefore report on the subdistribution hazard ratios (HRs) rather than the usual HR, but the former have similar interpretations to the latter. The factors associated with the development of HE were initially evaluated by univariate models (using univariate Fine and Gray models) and then included in a multivariate analysis (according to multivariate Fine and Gray models). The Cox regression model was used to identify clinical and biochemical variables independently and significantly associated with mortality. The final multivariate models were chosen in a forward fashion by minimizing the Bayesian information criterion. Software R, version 3.4.2, was used for all computations. The analyses described above were repeated by excluding patients with previous episodes of overt HE in order to show the association between the analyzed variable in the subgroup of patients without previous HE.

Regarding the sample size calculation, assuming an overall risk of MHE of 50% and a relative risk of 1.5 for PPI users, a sample size of at least 263 patients guarantees a power of 90% to a chi-squared test at the 5% level for detecting an association between PPI and MHE.

Results

Of the 355 patients admitted to our department, some were excluded: 17 for the presence of overt HE (grade II or more), 4 for positive alcoholemia, 6 for psychoactive drug intake, 10 for altered Mini-Mental State Examination or neurological diseases, and 8 for lack of compliance with psychometric tests. Of the 310 patients enrolled, only 38 were inpatients, without signs of infections or acute decompensation of cirrhosis, admitted for elective procedures (prophylactic variceal band ligation, liver biopsy, locoregional treatments of early hepatocellular carcinoma). There were 207 patients considered affected by a decompensated disease (for the previous history of variceal bleeding or hepatic encephalopathy or the presence of ascites). The demographic, clinical, and biochemical characteristics of all patients enrolled in the study are reported in Table 1.

Of the 310 patients enrolled, 125 (40%) were considered PPI users, as described. Within this class, the majority of the patients (80%) were taking medications at a "standard dosage" for more than 12 months, and the remaining 25 patients (20%) took PPIs for 3-12 months; none of the patients took PPIs for less than 3 months. The mean length of PPI use at baseline was 14.5 ± 12.6 months. In 52 of 125 patients the indications for PPI use were recent gastrointestinal

TABLE 1. Demographic and Clinical Characteristics of the Patients Enrolled in the Study*

	Patients (n = 310)
Sex (M/F)	221/89
Age (years)	62.2 ± 11.8
Etiology (virus/alcohol/other)	189/84/37
MELD	12.7 ± 4.9
Child-Pugh class (A/B/C)	142/133/35
Child-Pugh score	7 ± 1.7
Previous HE (no/yes)	233/77
Ascites (no/yes)	150/160
Gastrointestinal bleeding (no/yes)	225/85
Decompensated cirrhosis (no/yes)	103/207
Hemoglobin (g/dL)	11.2 ± 2.3
Bilirubin (mg/dL)	2.7 ± 4.8
Albumin (g/dL)	3.4 ± 0.6
International normalized ratio	1.4 ± 0.3
Sodium (mEq/L)	137 ± 4.4

*Values are mean ± SD.

bleeding, recent endoscopic ligation of varices, severe reflux, or peptic ulcer disease. In the remaining 73 patients PPIs were prescribed symptomatically for epigastric pain or abdominal discomfort, so an appropriate indication was lacking in a considerable number (58%) of patients taking PPI therapy.

At the time of inclusion, PPI users and nonusers were similar in gender, age, severity of liver disease (expressed with MELD and Child-Pugh score), previous history of HE, and presence of ascites. In PPI users serum sodium and albumin levels were significantly lower than those in nonusers. Moreover, the prevalence of MHE, diagnosed with PHES ≤–4, was significantly higher in PPI users than in nonusers (62% versus 29%; $P < 0.001$) (Table 2). The prevalence of MHE in PPI users was higher than that in nonusers even when the 77 patients with previous overt HE were excluded from the analysis (PPI users, n = 89, MHE = 57%, versus PPI nonusers, n = 144, MHE 20%; $P < 0.001$).

The comparison between patients with and without MHE is reported in Table 3. Patients with MHE, compared to those without, had a more severe stage of liver disease and a higher prevalence of overt HE in the past. Notably, in patients with MHE, more patients were taking PPI than in the group without MHE. The difference was maintained even when the 77 patients with previous overt HE were excluded from the analysis (MHE^+, n = 80, PPI users = 64%, versus MHE^-, n = 153, PPI users 25%; $P < 0.001$).

On multivariate analysis, including MELD scores, previous overt HE, PPIs, age, albumin, and sodium levels, the variables independently associated with the presence of MHE were PPIs, history of previous overt HE, albumin and sodium levels, and age (Table 4). The area under the receiver operating characteristic curve (AUROC) was 0.83. The significant relationship between PPI use and MHE was maintained when the multivariate analysis was repeated after exclusion of the 77 patients with overt HE in the past (PPI, odds ratio, 5.04; confidence interval [CI], 2.64-9.63; $P < 0.001$).

During a mean follow-up of 14.1 ± 12.3 months, 127 patients experienced grade II or higher HE. A precipitating factor was identified in 98 patients (77%): 31 episodes (32%) were caused by infections, 21 (21.5%) by diuretic overdose and electrolyte disorders, 21 (21.5%) by dehydration induced by vomiting and diarrhea, 13 (13%) by gastrointestinal bleeding, 9 (9%) by constipation, and 3 (3%) by benzodiazepines. The incidence of HE, taking into account as a competitive risk death or liver transplantation, was significantly higher in PPI users than in nonusers (64% versus 25%, $P < 0.001$) (Fig. 1).

TABLE 2. Comparison of Demographic and Clinical Characteristics Between PPI Users and Nonusers

	PPI^- (n = 185)	PPI^+ (n = 125)	*P*
Sex (M/F)	137/48	84/41	NS
Age (years)	61.5 ± 11.9	63.3 ± 11.6	NS
Etiology (virus/alcohol/other)	105/54/26	84/30/11	NS
MELD	12.3 ± 4.5	13.3 ± 5.5	NS
Child-Pugh class (A/B/C)	87/82/16	55/51/19	NS
Child-Pugh score	6.9 ± 1.7	7.2 ± 1.8	NS
Previous HE (no/yes)	144/41	89/36	NS
Ascites (no/yes)	92/93	57/68	NS
Gastrointestinal bleeding (no/yes)	138/47	87/38	NS
Decompensated cirrhosis (no/yes)	68/117	35/90	NS
MHE (no/yes)	131/54	48/77	<0.001
Hemoglobin (g/dL)	11.1 ± 2.3	11.5 ± 2.1	NS
Bilirubin (mg/dL)	2.2 ± 3.2	3.3 ± 6.4	0.04
Albumin (g/dL)	3.4 ± 0.6	3.3 ± 0.6	0.21
International normalized ratio	1.3 ± 0.3	1.4 ± 0.3	NS
Sodium (mEq/L)	137.6 ± 3.8	136.1 ± 5.1	0.005

*Values are mean ± SD.
Abbreviation: NS, not significant.

TABLE 3. Comparison of Demographic and Clinical Characteristics Between Patients With and Without MHE

	MHE^- (n = 179)	MHE^+ (n = 131)	*P*
Sex (M/F)	130/49	91/40	NS
Age (years)	62.2 ± 11.6	62.3 ± 12.2	NS
Etiology (virus/alcohol/other)	108/45/26	81/39/11	NS
MELD	12.1 ± 4.7	13.7 ± 5.2	0.005
Child-Pugh class (A/B/C)	99/68/12	43/65/23	<0.001
Child-Pugh score	6.6 ± 1.6	7.6 ± 1.8	<0.001
Previous HE (no/yes)	153/26	80/51	<0.001
Ascites (no/yes)	106/73	43/88	<0.001
Decompensated cirrhosis (no/yes)	74/105	29/102	<0.001
PPIs (no/yes)	131/48	54/77	<0.001
Bilirubin (mg/dL)	2.2 ± 3.7	3.2 ± 5.9	NS
Albumin (g/dL)	3.5 ± 0.6	3.2 ± 0.6	<0.001
International normalized ratio	1.3 ± 0.3	1.4 ± 0.3	NS
Sodium (mEq/L)	138.1 ± 3.6	135.7 ± 5.1	<0.001
Animal naming test (no. of animals)	16.4 ± 5.4	12.9 ± 4.7	<0.001

*Values are mean ± SD.
Abbreviation: NS, not significant.

TABLE 4. Results of Multivariate Analyses

A. Results of the Logistic Regression Analysis Predicting the Presence of MHE

Patients (n = 310)	OR	CI	*P*
PPI	3.96	2.27-6.92	<0.001
Previous overt HE	3.38	1.74-6.57	<0.001
Sodium	0.90	0.84-0.97	0.006
Albumin	0.37	0.22-0.62	<0.001
Age	1.03	0.99-1.05	0.055
MELD score	0.97	0.91-1.03	0.44

B. Results of the Competitive Risk Analysis (Fine and Gray Model) Predicting the Occurrence of Overt HE

	Subdistribution HR	CI	*P*
PPI	1.83	1.22-2.74	0.003
Previous overt HE	2.45	1.66-3.58	<0.001
Albumin	0.47	0.33-0.69	<0.001
MHE	1.79	1.21-2.65	0.003
Age	1.01	0.99-1.02	0.21
MELD score	1.01	0.96-1.06	0.63
Sodium	0.98	0.95-1.02	0.55

C. Results of the Cox Regression Analysis Predicting the Mortality

	HR	CI	*P*
PPI	2.37	1.45-3.87	<0.001
Age	1.03	1.02-1.06	<0.001
Sodium	0.93	0.89-0.97	<0.001
MELD score	1.10	1.06-1.15	<0.001
Albumin	0.64	0.43-0.95	0.03
MHE	1.53	0.97-2.42	0.03
Development of overt HE	1.82	1.09-3.01	0.01
Previous HE	1.02	0.98-1.04	0.21

On multivariate analysis, including MELD score, previous overt HE, MHE (diagnosed with PHES ≤–4), PPIs, age, albumin and sodium levels; the variables independently associated with the development of overt HE were PPIs, history of overt HE, albumin levels, and MHE (Table 4). The AUROC was 0.78. The significant relationship between PPI use and the development of overt HE during the follow-up was maintained when the multivariate analysis was repeated after exclusion of the 77 patients with overt HE in the past (PPI, subdistribution HR = 2.44; CI 1.35-4,39; $P = 0.003$).

During the same follow-up, 7 patients (2%) were lost to follow-up, 16 (5%) underwent liver transplantation, and 108 (35%) died. The main causes of death were infections and sepsis (36%), liver failure (33%), variceal bleeding (12%), and other causes not related to liver disease (19%).

Overall survival was significantly lower in PPI users than in nonusers (41% versus 81%, $P < 0.001$) (Fig. 2). On multivariate analysis, including MELD score, PPI use, previous history of HE, development of overt HE, MHE, age, and albumin and sodium levels, the variables independently associated with mortality were PPIs, age, sodium and albumin levels, MELD score, presence of MHE, and development of overt HE (Table 4). The AUROC was 0.82. The significant relationship between PPI use and mortality was maintained when the multivariate analysis was repeated after exclusion of the 77 patients with overt HE in the past (PPI, HR, 2.08; CI 1.22-4.11; $P = 0.0003$).

The same results were obtained including Child-Pugh score instead of MELD score in each multivariate analysis (data not shown).

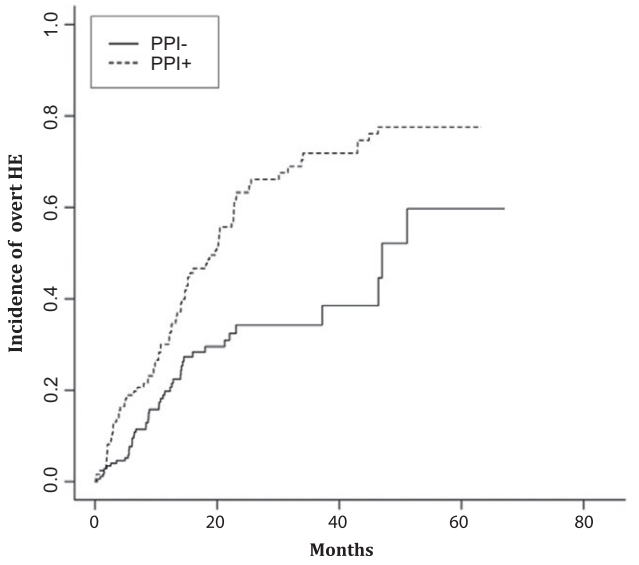

FIG. 1. Cumulative incidence of overt HE among PPI users and nonusers.

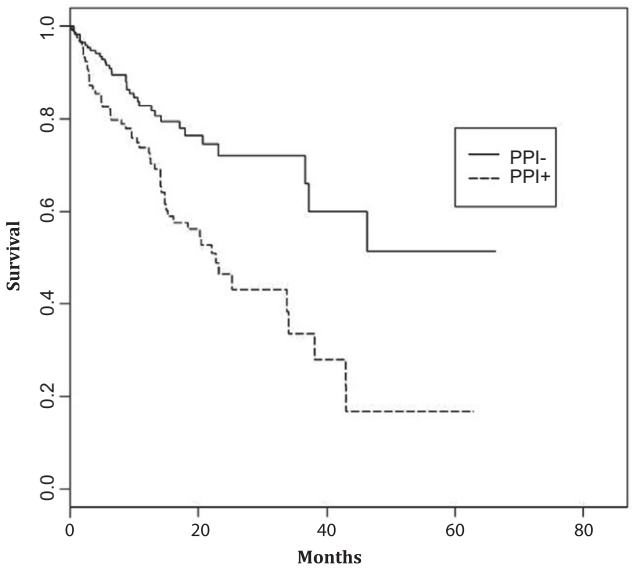

FIG. 2. Overall survival among PPI users and nonusers.

Discussion

The study showed that in patients with cirrhosis the use of PPIs is associated with the presence of MHE. The study also confirmed that PPI use is associated with an increased risk of overt HE[22-24] and that both PPI use and the development of overt HE during follow-up increase mortality independently on very important prognostic factors such as age and MELD.

In our study, MHE, detected by the animal naming test and PHES, which is considered the gold standard for the diagnosis of this complication, was much more prevalent in PPI users than in nonusers (62% versus 29%); and on multivariate logistic analysis, PPI use was associated with the presence of MHE independently of the degree of liver failure and history of overt HE. It has been shown that a cognitive impairment may persist even after a single episode of overt HE[43,44]; thus, the association between PPI use and MHE, independently on a strong risk factor such as the history of overt HE, strengthens the importance of PPI use as a risk factor for the presence of cognitive impairment in patients with cirrhosis.

As far as the relationship between PPIs and overt HE, three studies have shown such a statistical association,[22-24] which was confirmed also in our series. In fact, during follow-up, the cumulative incidence of overt HE, taking into consideration orthotopic liver transplantation and death as possible competing risks, was significantly higher in PPI users than in nonusers and was independent of well-known risk factors such as previous overt HE. Because HE is a recurrent complication of liver cirrhosis, patients with previous episodes of overt HE are particularly at risk of having further episodes during follow-up. However, the association between PPI use and development of overt HE during follow-up was maintained even when the patients with previous overt HE were excluded.

A limitation recognized in the previous studies showing a relationship between PPIs and overt HE is represented by the fact that the patients were not tested for the presence of MHE. MHE is a well-known risk factor[27] for the development of overt HE; thus, a relationship between PPIs and HE should be tested taking into consideration the confounding role of MHE. In our study PPI use was significantly associated with overt HE independently of the presence of MHE and of previous episodes of overt HE, which is another important risk factor for the development of overt HE.

Finally, PPI use was associated with mortality independently of overt HE, age, and MELD score. The data relating PPI use and mortality in patients with cirrhosis are limited and controversial,[35,45,46] being associated with increased mortality only in two studies out of three.

In our series, 40% of patients with cirrhosis were using PPIs, and this treatment was prolonged for several months in the totality of the patients. These results are in line with previous reports on the very common use of PPIs, often inappropriately, in patients with cirrhosis.[47,48]

All of these observations strongly suggest great caution in using PPIs in patients with cirrhosis and support greater attention in limiting the use of PPIs to their strict indication and for a limited time. Actually, PPIs are often overused in patients with cirrhosis.[47] In fact, they are often prolonged after an episode of variceal bleeding or band ligation, when their use is appropriate only for less than 2 months.[48] Moreover, PPIs are frequently prescribed for a generic gastroprotection or because of dyspeptic symptoms. In our series only 42% of patients received PPI with an acid-related indication such as ulcer, reflux disease, or esophagitis.

Gastric acid is a defense mechanism against ingested microorganisms; thus, the reduction of gastric acidity by PPIs, by increasing the bacterial proliferation in the stomach and small intestine, may predispose to bacterial infections.[19,20,38] Patients with cirrhosis receiving acid-suppression therapy are also at increased risk of being colonized by multidrug resistance bacteria.[35] Finally, in advanced cirrhosis PPI metabolism may be impaired, and this can result in a higher exposure.[47] All of these mechanism may induce bacterial overgrowth and translocation, thus exposing the patients to a low-grade inflammation,[32] which has been related to HE as well as to the occurrence of infections.[38]

The main point of interest of the present study is the identification of a factor associated with MHE. MHE is an important complication of liver cirrhosis, being associated not only with the development of overt HE[27] but also with the possible occurrence of car accidents,[30] falls,[31] low quality of life,[29] and even low economic income.[49] Despite its clinical relevance, the characteristics of patients with cirrhosis affected by this complication are still poorly known. We have previously described that MHE is more frequent in patients with cirrhosis and bacterial infections and that the cognitive impairment may be reversible after resolution of the infections.[50] Herein we describe another potentially avoidable or suspendible factor associated with MHE, although the demonstration of the amelioration of MHE after the interruption of PPI use is lacking and not derivable by the present analysis.

The main limitation of the present study is inherent to the nature of our analysis. In fact, our results are based on statistical associations and not on pathophysiological data. Although PPI use maintained its independent role when submitted to complex statistical analysis which took into consideration the main identified factors associated with both the development of HE and mortality, we cannot exclude that other factors not considered or not identified may play the role attributed to PPI use, although a number of hypotheses may relate PPI use to the outcomes described herein. The amelioration of the cognitive impairment after PPI withdrawal may add further information, which is unfortunately lacking in the present study. Another limitation of the study is that the exposure of interest (PPI) was measured at the same time as the outcome (MHE); thus, at least for MHE, this can be considered a cross-sectional study.

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

Moreover, we have shown that prolonged use of PPIs is associated with the presence of MHE and with an increased risk for overt HE and mortality in a large cohort of patients with cirrhosis. Although a causative role for PPIs in the increased mortality cannot be deduced from our observations, we recommend careful prescription of PPIs in patients with cirrhosis, especially when they are used without specific indications.

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