Association between proton pump inhibitors and hepatic encephalopathy
A meta-analysis

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Abstract
Background & aims: Several studies have shown that proton pump inhibitors (PPIs) use can increase the risk of developing hepatic encephalopathy (HE) in patients with liver dysfunction. However, no definite conclusion is drawn because of study design limitations. Therefore, we conducted a meta-analysis to explore the association between PPIs and HE.

Methods: We searched PubMed, EMBASE, and the Cochrane Library from inception until November 2016. Data from the identified studies were combined using a random effects model, and odds ratios (ORs) were calculated.

Results: Three case-control studies were included. Compared with nonusers, hepatic insufficiency patients receiving PPIs therapy had a significantly increased risk of developing HE (OR = 1.76, 95% CI: 1.15–2.69), with notable heterogeneity (I² = 61.4%, P = .075) and publication bias. No relevance was found between PPIs and HE after using the trim and fill method (OR = 1.360, 95% CI: 0.909–2.035, P = .135).

Conclusions: PPIs are associated with a higher risk of HE among patients with chronic and acute liver dysfunction. A final conclusion cannot be drawn because of the limited number of studies and a lack of prospective studies.

Abbreviations: HE = hepatic encephalopathy, PPIs = proton pump inhibitors, SBP = spontaneous bacterial peritonitis, SIBO = small intestinal bacterial overgrowth.

Keywords: hepatic encephalopathy, meta-analysis, microbiota, proton pump inhibitors

1. Introduction
Hepatic encephalopathy (HE) constitutes a spectrum of neuropsychiatric manifestations associated with both acute and chronic liver dysfunction.[1,2] Previous studies have suggested that an altered gut microbiome may play an essential role in the pathology of HE, possibly by increasing ammonia levels, and interacting with the inflammation and oxidative stress pathways.[3,4] Thus, therapy targeting the regulation of microbiota imbalance may have important implications for management of HE. The quality of life and long-term prognosis for patients who develop HE is discouraging, and a cohort study conducted in a cirrhotic patient population showed a 1-year survival rate of 36% after the onset of HE.[5] Therefore, proper management is needed to lower the incidence of HE, including avoiding abusive use of certain medications that may contribute to HE onset.

Proton pump inhibitors (PPIs) are effective gastric acid suppressants that have been widely prescribed in patients with acute and chronic liver disease, mainly for the prophylaxis and treatment of upper gastrointestinal hemorrhage. Overuse of PPIs is common among cirrhotic patients.[6,7] However, inappropriate use of PPIs can also lead to rare but serious adverse effects including bone fracture, community-acquired pneumonia, Clostridium difficile infection, and acute kidney injury (AKI) or chronic kidney disease (CKD).[8–11] Previous studies have reported some adverse effects of PPIs in patients with acute liver failure and chronic hepatitis or cirrhosis. These studies mainly focused on the relatively high prevalence of spontaneous bacterial peritonitis (SBP) in cirrhotic patients who are prescribed PPIs.[12–15] Recent research from 3 individual centers raised concerns that PPIs may affect the risk of HE in patients with liver dysfunction.
dysfunction.\cite{16-18} Therefore, we conducted a meta-analysis to explore the association between PPIs and HE.

2. Methods

2.1. Search strategy
We performed a computerized literature search of 3 electronic databases including PubMed, EMBASE, and The Cochrane Library from inception until November 2016. The search items were (proton pump inhibitors OR rabeprazole OR esomeprazole OR lansoprazole OR omeprazole OR pantoprazole) AND (hepatic encephalopathy). Ethical approval was not necessary because our article is a review.

2.2. Study selection
Two independent reviewers read the abstracts or full-text articles to assess the eligibility of studies in a standardized manner. We also reviewed all references from the included articles and further selected eligible studies. The following criteria were used to select the articles: (i) randomized controlled trial, case-control or cohort studies; (ii) studies conducted in humans; and (iii) the value of the relative risk (RR), hazard ratio (HR), or odds ratio (OR) with corresponding 95% confidence intervals (CIs), or the original data to calculate them were reported. Exclusion criteria were as follows: (i) no control group of patients; (ii) patients with previous brain function impairment were included in the study; and (iii) papers were letters, commentaries, or reviews. Disagreements were resolved by consensus.

2.3. Data extraction
Two investigators independently extracted data from the full text of the included studies. Data collected included study design, study population, years of publication, type of acid-suppressive therapy, comparison of exposure level, dose, and duration of acid-suppressive therapy, and adjusted confounding variables. The estimates of OR/HR, their associated 95% CIs, and the P value were also extracted. We assumed that there was similarity between the OR and HR because hepatic encephalopathy events were relatively rare.\cite{19} Any disagreements or discrepancies were resolved in consensus.

2.4. Statistical analyses
We extracted the OR/HR and 95% CIs from each of the 3 studies. We then calculated the standard error (SE) of the logOR/HR using the following equation: SE = ln(OR/HR_upper – ln OR/HR_lower)/3.92. We used I^2 to evaluate the heterogeneity, and an I^2 of 30%–60% was considered to represent moderate heterogeneity.\cite{20} We performed a meta-analysis using a random effect model in a conservative manner.

To evaluate publication bias, we generated a funnel plot and visually examined it for asymmetry. The trim and fill method was used to recalculate the effect if an obvious publication bias was observed. STATA (Version 12.0, StataCorp, College Station, TX) was used to perform all data analysis.

3. Results

3.1. Search results
The computerized search yielded 22 references; no relevant articles were identified from the references. We excluded 19 articles according to our inclusion and exclusion criteria. A total of 3 articles were eventually included, all of which were retrospective studies (Fig. 1).

3.2. Study characteristics
The main study characteristics are listed in Table 1. All 3 studies investigated the association between PPI use and HE, and age and sex were adjusted-for in all these studies. Tsai et al’s study included 1166 patients with HE; Dam et al’s study included 340 PPI users, of whom 88 subsequently developed HE; and Lin’s research comprised a smaller population of 55 HE patients.\cite{16-18} The adjusted ORs of the 3 studies were 1.738, 1.36, and 4.392, respectively.

3.3. Pooled results and heterogeneity
The overall OR derived from using a random effects model was 1.76 (95% CI = 1.15, 2.69), indicating a rising risk of onset of HE in PPI users compared to nonusers (Fig. 2). Heterogeneity was significant among the pooled results (I^2 = 61.4%, P = .075), when an I^2 of 30% to 60% is considered to be a moderate heterogeneity level.\cite{20}

3.4. Publication bias
A funnel plot was generated from the 3 studies, and it showed visual asymmetry that was mainly caused by the study of Lin et al\cite{17} (Fig. 3). Since the trim and fill method is a well-established method to estimate the number of missing studies and reduce the publication bias,\cite{21} we also performed the trim and fill analysis. Because significant heterogeneity was observed using the fixed effects model (Q = 13.881, P = .008), we used a random effects model. In contrast to previous results, the adjustment for publication bias using the trim and fill procedure resulted in an OR of 1.36 (95% CI: 0.909 to 2.035, P = .131), indicating that there was no relevance between PPIs and HE.

4. Discussion
To our knowledge, this is the first meta-analysis on the relationship between PPIs and HE. The results from our analysis revealed the association between PPIs and HE, with an average
OR of 1.76 (95% CI 1.15, 2.69), which indicates that there is a higher risk of developing HE in PPI users with liver dysfunction. However, when publication bias was taken into consideration, no significant relationship was observed after using the trim and fill procedure, and this needs further investigation. While existing studies based on the hepatic insufficiency population suggest that PPIs may harm brain function, these results should be interpreted with caution because of limited research.

Our study has some limitations. Because there are only 3 articles on association of PPIs and HE, the outcomes of analysis based on this small number of studies can be controversial. Except for Tsai’s study, variables such as type, dose, and duration of PPIs, patients’ baseline conditions, and other therapeutic interventions were not well adjusted. In Tsai et al’s study, the drug dosage and supply days were extracted, and cumulative defined daily dose (cDDD) was used. They found a dose-dependent risk of HE among PPIs users in cirrhotic patients. However, in the other 2 studies, the dose and duration of PPIs were not mentioned or difficult to obtain due to lack of data.

Additionally, all the studies were retrospective and recall bias may be difficult to ignore. Thus, residual confounding factors may influence the results. As described in their methods, hepatic encephalopathy was assessed differently in all the included studies. Clinical features of HE can be confusing, and it is especially difficult to diagnose minimal and Grade 1 HE. Thus, HE morbidity may be underestimated.

Our analysis showed obvious heterogeneity among the 3 included studies, with $I^2 = 61.4\%$. There was a high degree of variability in study populations, recruitment, and assessment, as well as differences in the way data was recorded and handled in these retrospective studies. Thus, the included studies showed a high degree of heterogeneity. We assumed that different study populations impacted the heterogeneity; Dam et al. and Tsai et al conducted their studies in cirrhotic patients, whereas Lin et al’s study comprised a relatively small population who had acute liver failure. The OR in the study by Lin et al was larger, whereas Tsai et al and Dam et al had reported similar ORs. It can be speculated that acute liver failure was more complicated and
other studies found no such significant association. However, other studies found no such significant association. Accumulating evidence suggests that there is a relationship between PPIs and the microbiota. PPIs are powerful gastric acid-suppressing drugs, and they can directly target the proton pumps of the bacteria, or affect the microenvironment of the flora by changing the pH within the alimentary tract; both of these can result in gastrointestinal microbiota dysbiosis. Some studies have shown negative results, but convincing evidence shows that PPIs alter the gut microbiota and possibly increase the occurrence of SBP. Recent retrospective studies also showed that PPIs are implicated during the onset of HE both in acute and chronic liver dysfunction, and Dam et al. found that PPIs were an independent risk factor for SBP, which could be an infection that is caused by PPIs. Thus, we postulate that PPIs act as a risk factor for HE by promoting gut microbiota translocation and subsequent bacterial infection. Oxidative stress and systemic inflammation implicated with dysbia may partially account for HE pathophysiology.

Our results may be restricted because of the study design and the inclusion of a relatively small number of studies. However, considering the wide use of PPIs in hospitalized patients and their potential risk for developing of HE, it is important to evaluate the positives and negatives of PPI administration, to provide guidance for healthcare practitioners. We found that PPIs did not increase the risk of HE after trim and fill analysis, which is in contrast to the conclusions drawn by the included studies. Therefore, additional prospective studies are needed to address these controversies.

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