Adverse Effects of Long-term

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Adverse Effects of Long-term Proton Pump Inhibitors in Chronic Liver Disease Patients – A Preliminary Article Review

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Abstract

Background: Proton pump inhibitors (PPIs) are widely prescribed medications for the management of gastroesophageal reflux disease (GERD) and peptic ulcer disease. Despite their efficacy, concerns have emerged regarding their potential adverse effects, particularly in patients with chronic liver disease (CLD). CLD patients often experience gastrointestinal symptoms and may be prescribed PPIs, but the impact of PPI use on liver function and disease progression remains uncertain.

Scope: This study aims to evaluate the adverse effects of PPIs on CLD patients through a review of available literature. The scope encompasses a review of studies examining the association between PPI use and liver-related outcomes, including hepatic encephalopathy, hepatic decompensation, liver cirrhosis progression, and mortality, among CLD patients.

Method: A scoping review of relevant literature were conducted to identify studies investigating the adverse effects of PPIs in CLD patients. Databases including PubMed and Google Scholar were searched for articles published up to January, 1 2023. Eligible studies were selected based on predefined inclusion criteria.

Results: The review identified 27 studies meeting the inclusion criteria, comprising observational studies and meta-analysis. The review revealed a significant association between PPI use and adverse liver outcomes in CLD patients. Specifically, PPI use was associated with increased risk of SBP based on studies reviewed, while other complications remained inconclusive.

Conclusion: The findings suggest that PPI use may have detrimental effects on disease progression in CLD patients, Long-term use of PPIs can lead to higher risk of SBP in CLD patients. Clinicians should exercise caution when prescribing PPIs to this vulnerable population and consider alternative treatment options or minimize PPI use to mitigate potential adverse outcomes. Further research is warranted to elucidate the underlying mechanisms, confirm the effect of PPIs toward other complications of CLD and establish guidelines for PPI use in CLD patients.

KEYWORDS
proton pump inhibitors, chronic liver disease, hepatitis, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatocellular carcinoma

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1. INTRODUCTION

Chronic liver disease (CLD) is a steady decline in liver function lasting for at least six months. This constant cycle of inflammation, deterioration, and regeneration of liver parenchyma leads to fibrosis and cirrhosis. On a cellular level, fibrosis and cirrhosis are caused by the accumulation of stellate cells and fibroblasts, resulting in fibrosis, whereas parenchymal restoration is dependent on hepatic stem cells [1]. Viral hepatitis is a prevalent cause of CLD [2].

According to the third phase of the 2015 Global Health Estimates (GHE) from the World Health Organization, 48.2% of liver-related deaths in the Asia-Pacific region were attributable to cirrhosis in 2015. In 2015, 54.3% of worldwide cirrhosis-related patients died in Asia-Pacific. HBV causes nearly 70% of global cirrhosis-related deaths and nearly 70% of global cirrhosis-related deaths and roughly 40% of deaths caused by HCV occurred in this region. Liver cancer is the second most significant cause of liver-related mortality in the region, accounting for over 80% of the world's total liver cancer deaths caused by HBV. HBV and HCV substantially contribute to the prevalence of liver disease in Indonesia. According to the GHE 2015 data set, hepatitis B infection accounted for 37% of all fatalities in Indonesia caused by cirrhosis and other chronic liver diseases, whereas hepatitis C was responsible for 35.8% [3].

In 1989, proton pump inhibitors (PPIs) were established as a treatment for gastroesophageal reflux disease (GERD) by blocking H/K adenosine triphosphatase in the gastric parietal cell [4]. PPIs are one of the most commonly given drugs globally [5,6]. Recent scientific evidence indicates that PPIs are safe when appropriately used [7,8] but long-term PPI medication is related to the onset of pneumonia, spontaneous bacterial peritonitis, gastric cancer, vitamin B12 insufficiency, Clostridium difficile-associated diarrhea, myocardial infarction, hypomagnesemia, chronic kidney disease, and hip fracture [9–14].

In addition, PPIs are one of the most frequently prescribed pharmacological types for cirrhosis [15]. Patients suffering from chronic liver disease may be prescribed long-term PPIs with the purpose of preventing bleeding caused by portal hypertensive gastropathy. Studies have demonstrated that this treatment approach is futile [16] or due to the unintentional continuation of PPIs following an episode of upper gastrointestinal bleeding or variceal banding [17]. Unfortunately, PPIs are only indicated to be taken under a restricted number of circumstances and for a brief time [18] Patients with significant oesophageal varices are typically not prescribed PPIs for primary or secondary prevention of gastrointestinal haemorrhage [19].

According to recent studies, approximately 60% of PPIs are prescribed improperly [20,21]. The long-term therapy of PPIs lacks precise definitions. Nevertheless, the extended utilisation (beyond 4-8 weeks) may be regarded as prolonged use of PPIs [22]. The use of PPIs may be linked to adverse outcomes in cirrhotic patients, including spontaneous bacterial peritonitis [23–31], hepatic encephalopathy [29,32–35], hepatocellular carcinoma [4,36], and a higher risk of mortality [4,37]. The summary of the potential mechanisms underlying these complications are illustrated in Figure 1. Nevertheless, previous studies yield incongruous findings. This review seeks to elucidate the potential complications that may arise in patients with chronic liver disease who engage in prolonged consumption of PPIs. It also highlights the latest relevant studies and emphasises the significance of further research in order to safeguard a high quality of life for individuals with chronic liver disease.

2. METHODS

This review utilized information from PubMed and Google Scholar databases up to January 1, 2023, using key terms including but were not limited to “proton pump inhibitors”, “long-term effects”, “spontaneous bacterial peritonitis”, “hepatic encephalopathy”, “hepatocellular carcinoma”, “mortality risk”, and “chronic liver disease”. Additional hand search was performed and in-text references of evaluated articles were also reviewed. The review aims to discuss the adverse consequences of prolonged use of PPIs in individuals with CLD. This study aims to offer clinicians treating patients with CLD a fresh viewpoint on the potential implications of administering PPIs to this specific patient population. From 247 studies obtained, we included 27 studies to be reviewed after matching the inclusion criteria: English language article, study design (meta-analysis and observational study), the ability to access the full-text manuscript, and the transparency of study reporting.

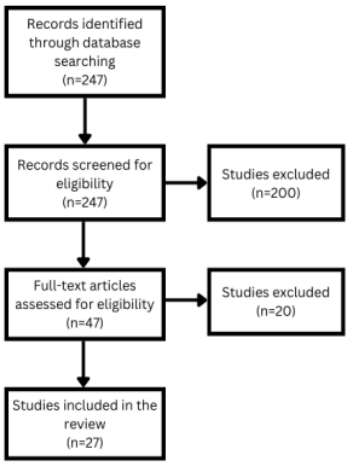

Figure 1. The flowchart of studies included.

3. RESULTS

3.1. Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is an infection of ascitic fluid without an identifiable intra-abdominal cause. The incidence ranges from 7 to 30% in ascitic patients [38]. SBP is one of the most important clinical issues in individuals with cirrhosis and a common cause of death [39]. SBP must be presumed when a patient with ascites exhibits one or more of the following: a temperature above 37.8°C (100 °F), abdominal discomfort and/or tenderness, an alteration in mental status, or an ascitic fluid polymorphonuclear leukocyte (PMN) count exceeds 250 cells/mm^3 based on fluid analysis [40]. There are several proposed mechanisms of PPIs causing SBP in CLD patients. An in vitro study has shown that omeprazole could affect the function of neutrophil by inhibit its phagocytosis and acidification of phagolysosomes [41].

Preclinical evidence indicates that PPIs may potentially cause immunosuppression by impeding neutrophil function, natural killer cell activity, and reducing cellular oxidative burst [42,43]. PPIs may promote the growth of gut bacteria by inhibiting the production of gastric acid and gastrointestinal motility [44,45]. SBP is aggravated by the persistent use of PPIs in cirrhotic patients with ascites, which results in an expansion of intestinal permeability, which promotes bacterial migration and colonization of mesenteric lymph nodes [44,46,47]. Patients with liver cirrhosis tend to suffer from immune system impairment through decrease of T-helper level and the ability of monocyte and neutrophil's phagocytosis [48], increase of cyclooxygenase-derived eicosanoid prostaglandin E2 [49], and decrease of HLA-DR expression on monocytic cells defined as immune paralysis [50]. PPIs could also decrease granulocyte and monocyte cellular oxidative burst in cirrhotic patients [51].

A meta-analysis conducted by Deshpande et al. examined 8 studies comprising 3815 patients with cirrhosis and they revealed that cirrhotic patients who use PPIs have a threefold higher risk of developing SBP and the utilisation of PPIs would lead to a Number Needed to Harm (NNH) of nine for a single occurrence of SBP. Due to the limited number of studies (less than 10) included in the meta-analysis, it is advisable to exercise caution when interpreting the results of the tests for publication bias [25]. In their meta-analysis involving 7822 patients from 14 observational studies, Khan et al. identified minor but statistically significant relationships between SBP and the use of PPIs or H2RAs. Nevertheless, accounting for publication bias and acknowledging the moderate heterogeneity among various study types, the evidence supporting this connection is of extremely low quality [26]. According to a study by Xu et al., cirrhotic individuals who take PPIs had a twofold significant risk of suffering from SBP. The meta-analysis they conducted utilised 17 observational studies, encompassing a total of more than 8000 people diagnosed with cirrhosis [27].

Wang et al. in their analysis of 25 studies found that PPIs users were at risk of suffering from SBP compared with non-PPIs users. Their meta-analysis revealed that, even after accounting for the level of liver dysfunction, PPIs were identified as a separate risk factor for the occurrence of SBP in patients with CLD. Nevertheless, the presence of residual confusion could not be ruled out [31]. The most recent study by Hwang et al. demonstrated that PPIs are related to an increased incidence of SBP in individuals with cirrhosis. The cohort studies yielded non-significant findings, indicating a tendency, while the case-control studies demonstrated statistical significance, thereby corroborating the tendencies observed in the cohort studies [29].

A study by Yu et al. reported that PPIs use was associated with the risk of SBP. However, this detrimental correlation was confined to the case-control investigations. The results from cohort studies did not establish any causal links between the usage of PPIs and SBP. The connection did not show statistical significance in the

subgroups of the prospective design and multicenter design [28]. Meanwhile, Alhumaid et al. observed in a meta-analysis from 23 observational studies that cirrhotic patients on PPIs had a 1.8-fold higher chance of acquiring SBP, although the strength of the association was weak. This detrimental correlation was restricted to cohort studies while no causal correlations were found in the data from case-control studies. The harmful impacts of PPIs may be limited to some subcategories, such as individuals with decompensated cirrhosis, particularly when ascites is present [30].

3.2. Hepatic Encephalopathy

Hepatic encephalopathy (HE) represents a spectrum of neuropsychiatric symptoms linked with acute and chronic liver impairment [52,53]. In cirrhosis, the correlation between PPIs and HE is still unclear. Several proposed mechanism include gut dysbiosis in cirrhotic patients after long-term consumption of PPIs, while modified gut microbiota can precede or aggravate HE [54,55]. Intestinal bacteria in the colon release ammonia and small intestine bacterial overgrowth (SIBO) following the long-term use of PPIs lead to the elevated ammonia concentration in the brain causes HE by affecting the brain's metabolism and central nervous system [56,57]. PPIs could affect gastrointestinal motility and damage the mucosal barrier, leading to the increase of nitrogenous substances absorption [57,58]. Moreover, using PPIs suppresses neutrophil-endothelial cell interactions and lowers natural killer cell function and neutrophils [59], hence likely encouraging HE owing to the inability of immunological response [60].

Currently, there is a limited body of research that examines the specific dosages of PPIs that may lead to issues associated with hepatic encephalopathy. Tsai et al. conducted a case-control study which shown a higher prevalence of long-term usage of PPIs in the case group. The group exhibiting the largest cumulative defined daily dose (cDDD) above 365 has the utmost susceptibility to encountering hepatic encephalopathy (HE). Nevertheless, this study is subject to other limitations, such as the inability to control for all potential confounding variables and the reliance on drug dosage data derived from medical records rather than direct observation [61].

A systematic review and meta-analysis by Ma et al. revealed that PPIs use contributes to an increase of 50% risk of HE among cirrhotic patients [32]. Tantai et al. found that PPIs consumers had a 2,08-fold increased chance of having HE in a separate study. They discovered that the heightened susceptibility of those using PPIs to HE remained constant across several factors, including study design, definition of PPIs usage, study location, type of advanced liver disease, and analysed outcomes [33]. Shi et al. in their study found PPIs therapy is associated with a 1.81-fold increased risk of HE. They specified that there is a higher probability of developing HE with prolonged usage of pantoprazole in comparison to other PPIs, while the exact mechanism is still unknown. However, when accounting for publication bias, no statistically significant difference was seen [34].

According to a prior study by Hwang et al., PPIs were not substantially related to the risk of HE. Cohort studies did not identify a significant association with the detrimental effect, which was observed in only two case–control studies after subgroup analysis, indicating the presence of dispute in the findings of their study. Due to the limited number of studies included and the inability to account for factors such as gastrointestinal bleeding, infection, and medication, it is advised to approach the result with caution [29]. In accordance with a meta-analysis conducted by Bian et al., PPIs do not contribute to the risk of HE. Their analysis indicates that those with liver impairment who use PPIs have an elevated chance of acquiring HE, but after accounting for publication bias, no significant correlation was found. However, they mentioned that their study methodology and the inclusion of a relatively small number of studies may affect the generality of the results [35].

3.3. Hepatocellular Carcinoma

PPIs are regarded as possible carcinogens, but its correlation with the incidence of cancer has been debatable for years [62]. Long-term use of PPIs is suspected of raising the incidence of oesophageal, gastric, and pancreatic cancer [63-65]. Prolonged use of PPIs might result in dysbiosis of the gut microbiome and hypergastrinemia. Hypergastrinemia may cause carcinogenic effect [66,67], especially on liver cells [68]. The increase of bacteria caused by the decrease of gastric acid after long-term use of PPIs could result in toxicity, inflammation, and DNA damage on biliary tract and liver cells that lead to Hepatocellular carcinoma (HCC) [69]. The utilisation of PPIs has been discovered to result in the multiplication of cells carrying lethal genetic alterations by triggering oxidative stress and generating reactive oxygen species that cause more harm to DNA, so elevating the mutation rate. This process also leads to the augmentation of tumour suppressor genes and oncogenes, thereby heightening the susceptibility to cancer [70-73].

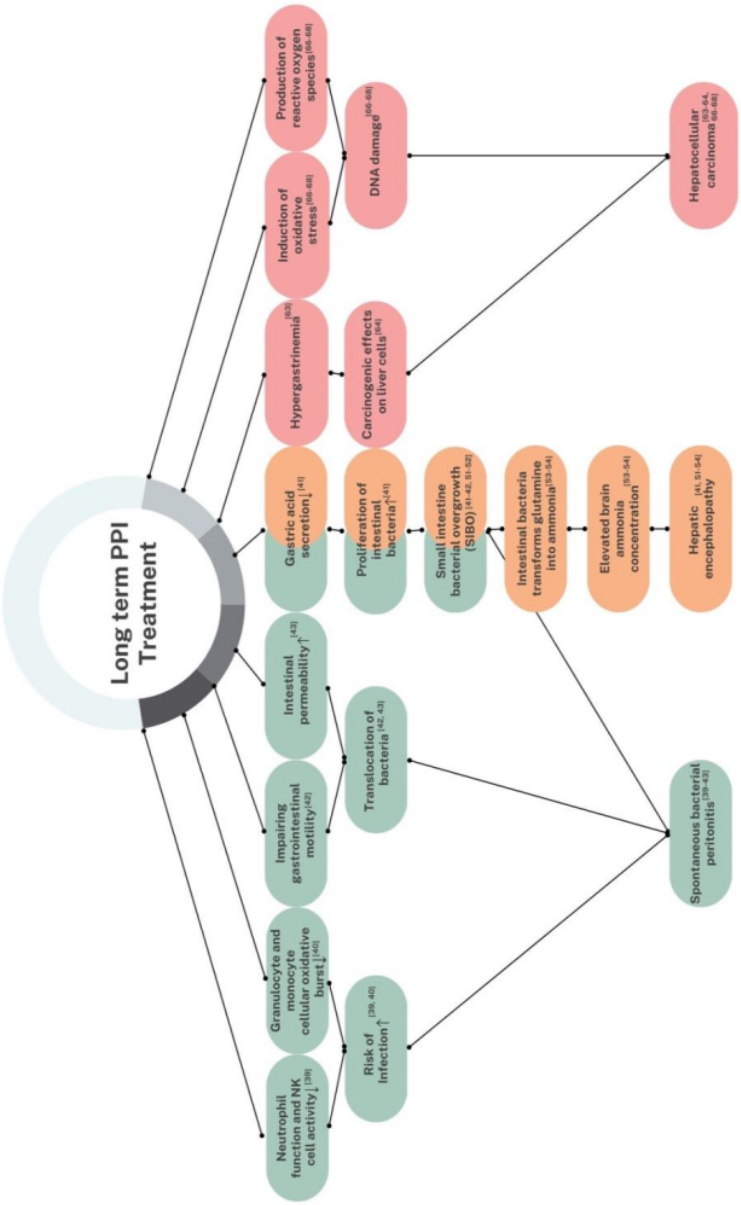

Figure 2. The proposed mechanism of the long-term effects of proton pump inhibitors on chronic liver disease.

Chang et al. concluded in their meta-analysis that there was no significant relationship between PPI use and a heightened incidence of HCC after adjusting the confounding factors. However, limited studies included in the analysis have indicated that there may be a dose-response correlation between PPIs and HCC [36]. According to a study by Song et al, patients with CLD who used PPIs had a 67% increased chance of developing HCC. During a median follow-up period of one to eight years, their analysis reported that there were 11.1% incidence of incident hepatocellular carcinoma (HCC) among users of PPIs compared to 8.3% cases among non-PPIs users. Furthermore, individuals who were on PPIs for more than one year and had a follow-up period of more than one year had a twofold higher likelihood of developing HCC compared to those who were on PPIs for one year or less. The Asia study did not find a statistically significant relationship between the usage of PPIs and an increased risk of HCC [4].

3.4. Mortality Risk

Mortality is significant among CLD patients, especially when portal hypertension-related complications or HCC occur [74]. In the other side, PPIs was found to inhibit the production of monocytes' proinflammatory cytokines and prevent lipopolysaccharide-induced mortality in a murine model [75]. Few studies examined the connection between PPIs use and the risk of death in CLD patients. A meta-analysis by Hwang et al. demonstrated no causative link between the usage of PPIs and an increase in the mortality rate of cirrhotic patients [28,29].

The usage of PPIs was substantially related to a moderate mortality rate in cirrhotic patients, according to a meta-analysis by Wu et al. The correlation between the use of PPIs and mortality in individuals with cirrhosis appeared to be unaffected by demographic variables and indicators of disease severity. The retrospective investigations found a substantial link between the use of PPIs and the risk of mortality, however the prospective studies did not find such an association [37]. Prolonged exposure to PPIs with cDDD more than 90 in patients with decompensated liver cirrhosis is associated with an elevated risk of mortality [74]. Song et al. reported that the usage of PPIs was linked with an increased likelihood of death in CLD patients. Pooled estimates from the eight studies showed that individuals who used PPIs had a 57% higher risk of mortality compared to those who did not use PPIs. The correlation remained statistically significant for patients diagnosed with cirrhosis and those who were followed up for more than one year [4].

4. DISCUSSION

Numerous studies are investigating whether PPIs can bring CLD patients into harmful events. The incidence of CLD complications such as SBP, HE, and HCC is linked to the long-term administration of PPIs. Not only is the occurrence of complications, but it is also linked to the mortality rate. However, some studies confirmed the absence of this association, and other studies revealed an association but not statistically significant. Finding solutions regarding these controversial results is essential to determine the best practice for CLD patients by performing a clinical trial study.

Overall studies reviewed claimed that PPIs use is associated with increased SBP risk among CLD patients. These results seem to confirm the theory that exists regarding the relationship. However, some meta-analyses stated that this finding is found in case-control studies, and cohort studies that mainly included showed no significant association. As a result, the causality relationship cannot be determined.

Studies discussing the relationship between PPIs and HE showed contradictory results. Of the six studies we reviewed, half suggested affirmative statements regarding the association of PPIs use and HE in CLD patients. The publications we reviewed on the correlation between PPIs and HE only examined a limited number of observational studies. The quality of each study analysed in each article was deemed to be high. The majority of studies investigating the correlation between PPIs and HE are case-control studies, which introduces the possibility of recall bias. Multiple meta-analyses on this issue have indicated a lack of comprehensive data regarding the specific types of PPIs, their dosage and frequency, and the status of H pylori infection. The study conducted by Shi et al identified variations in the assessment of HE among the examined literature. In addition, the study results in each publication exhibit varying impacts, with some presenting odds ratios (OR), hazard ratios (HR), and relative risks (RR) [34].

The relationship between PPIs and HCC also revealed conflicting results although the number of the study was relatively small. The two articles we examined made reference to a limited subset of the articles they analysed. According to a meta-analysis conducted by Chang et al, they noted the possibility of an overlapping between the occurrence of hepatitis virus infection, a known risk factor for hepatocellular carcinoma (HCC), and the use of proton pump inhibitors (PPIs) in patients

with chronic liver disease (CLD). Additional limitations identified included the heterogeneous population samples, inadequate data on liver function and antiviral medication status, and predominance of case-control study designs in the majority of the studies [34]. The research undertaken by Song et al. revealed a notable correlation between the utilisation of PPIs and the occurrence of HCC was not found to be significant in studies conducted specifically in Asia. The analysed studies suggested that individuals with more severe illnesses, who were at risk of experiencing gastrointestinal bleeding, and were using PPIs, had the potential to be a confounding factor. The analysed studies also lacked comprehensive data on the length of the patients' illness [4].

The number of studies discussing the relationship between PPIs and mortality in CLD patients is also minimal. The limited study causes conclusions regarding the relationship between PPI and these impacts cannot be established. Furthermore, the majority of studies fail to include information regarding the length of time individuals were exposed to PPIs. Research on the correlation between the utilisation of PPIs and the mortality rate in individuals with chronic liver disease (CLD) yields inconsistent findings. The study conducted by Hwang et al, which examined the correlation between the utilisation of PPIs and mortality rates in patients with chronic liver disease (CLD), only analysed two cohort articles. Two more meta-analyses, yielding divergent outcomes, examined a far larger number of publications. However, the research examined by both individuals did not explicitly indicate the specific cause of death in patients with chronic liver disease who utilised proton pump inhibitors (PPIs). Moreover, they examined a reduced number of observational studies, hence precluding the establishment of a causal association [29]. Similar to earlier meta-analysis research, Wu et al. acknowledged the presence of insufficient information pertaining to the dosage, duration, and type of PPIs obtained from the analysed papers [37].

5. CONCLUSION

There are contradictory results on the relationship between PPIs use and risk in CLD patients. It is questionable whether the use of PPIs causes patient mortality related to comorbidities that increase the risk of patient mortality. The ongoing trial that strives to confirm the projected advantage of quitting long-term PPIs therapy will provide greater insight into the future management of cirrhosis patients. This study's outcome is anticipated to impact the pharmacological management recommendations for CLD patients. Further studies are required to determine the potential correlation between prolonged use of PPIs and the development of problems associated with chronic liver disease.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

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