Official Title: A randomized controlled study on effects of proton pump inhibitor on gastroesophageal varices of cirrhosis

Brief Title: PPIs and Gastroesophageal Varices in Liver Cirrhosis

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Study Protocol

- **Patients' selection**

Cirrhotic patients with GEVs will be considered for enrollment in this randomized controlled study from May 2017 and June 2019. The following inclusion criteria will be applied: (1) age ≥ 18 years; (2) diagnosed cirrhosis based on clinical, laboratory, and radiological parameters and/or liver biopsy; (3) diagnosed GEVs based on endoscopy. The exclusion criteria: (1) acute gastrointestinal bleeding requiring emergency surgery; (2) acid-related disease, such as peptic ulcer disease or gastroesophageal reflux diseases; (3) hepatocellular carcinoma or other malignant tumor; (4) history of surgery of the esophagus, stomach or liver; (5) Child–Pugh grade C disease that cannot be improved to grade A or B; (6) preparing to be pregnant, pregnant, or breast feeding; (7) PPI allergies; and 8) missing informed consent.

- **Randomization and masking**

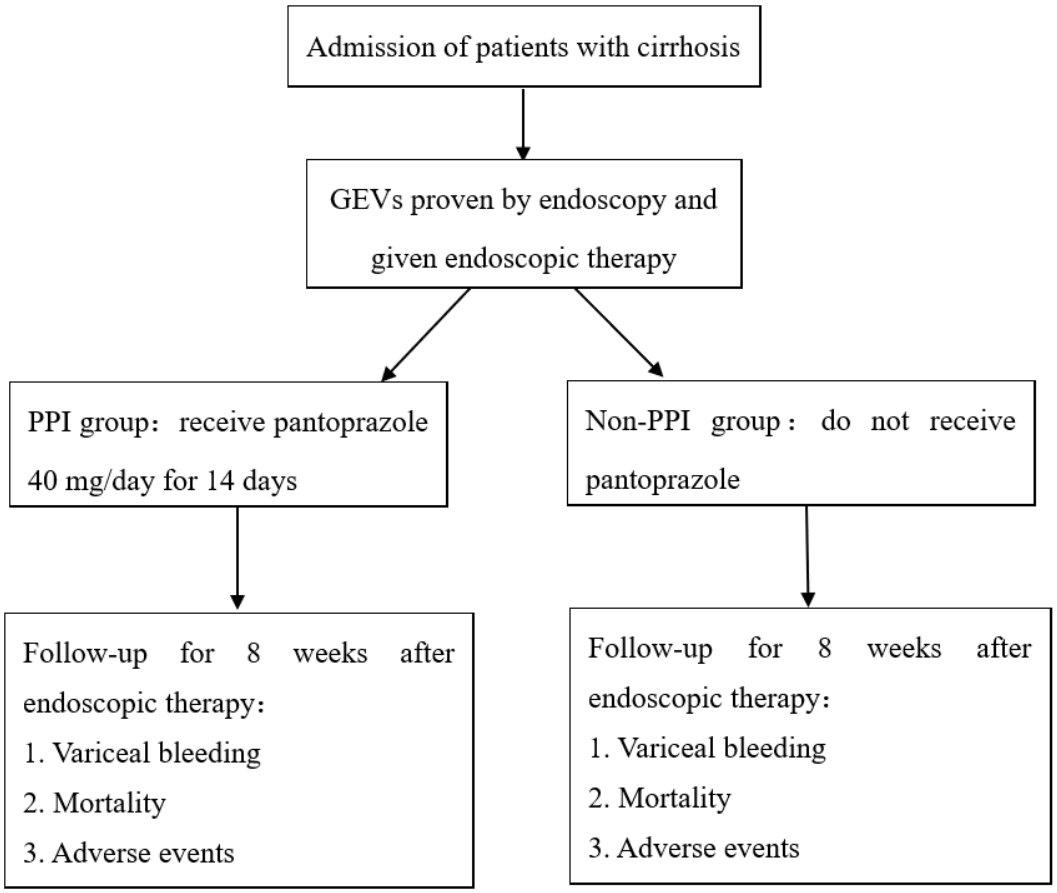
Randomization will be performed after GEVs confirmed by endoscopy. Eligible patients will be randomized into PPI and non-PPI groups in a 1:1 ratio using a computer-generated list of random numbers. The numbers will be written on papers placed in sealed and opaque envelopes by an independent research assistant. After confirmation of GEVs by endoscopy and inclusion in this study, one envelope will be opened. The expert endoscopists will be blinded to the randomization and patient's data.

- **Procedures**

An initial endoscopy will be performed with endoscopic findings classified according to the grading system outlined in the guidelines released by Chinese Medical

Association[8]. After an initial endoscopy, endoscopic therapy will be undertaken according to updated UK guidelines [6]. All participants enrolled in this study will be banded every 2 weeks; however, patients who suffered from rebleeding will receive rescue EVL/ETA as soon as possible. Endoscopic therapy will be performed by three expert endoscopists with more than 10 years of relevant experience.

After endoscopic therapy, eligible patients will be randomly assigned to the PPI group (receive pantoprazole 40 mg/day intravenously/orally for 14 days) or the non-PPI group (do not receive PPI treatment).



- **Statistical Analysis Plan**

To calculate the sample size, the overall variceal bleeding rate after endoscopic therapy will be chosen as the primary outcome. According to published data[9], and assuming a

22% difference in the rate of variceal bleeding between the non-PPI group (27%) and the PPI group (5%), at least 46 patients will be required in each group to provide 90% confidence in the results, with the upper limit of the one-sided 95% confidence interval (α=0.05, β=0.10). Moreover, assuming a flow off rate of 10%, at least 100 patients will be required in this study.

Quantitative variables will be compared using Student's *t*-test or Mann–Whitney U-test, and the χ^2 test or Fisher's exact test will be used to compare qualitative variables. The cumulative rate of bleeding will be calculated using the Kaplan–Meier method, and log-rank tests will be performed for comparison of differences. *P* values <0.05 will be considered statistically significant.