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Timing of endoscopic intervention in patients with cirrhosis with acute variceal haemorrhage (TEACH trial): protocol for a randomised clinical trial (RCT)

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ABSTRACT

Introduction Acute variceal haemorrhage (AVH) in patients with cirrhosis remains a topic of great interest. Although several guidelines recommend endoscopy within 24 hours after AVH, there is no consensus on the most appropriate time to perform this intervention. The purpose of this study is to identify whether urgent endoscopy (within 6 hours after gastroenterological consultation) is superior to non-urgent endoscopy (between 6 hours and 24 hours after gastroenterological consultation) in reducing the rebleeding rate of these patients.

Methods and analysis This is a single-centred, prospective, randomised clinical trial. Between March 2021 and December 2023, an estimated 400 patients will be randomised in a 1:1 ratio to receive endoscopic intervention either within 6 hours or between 6 and 24 hours after gastroenterological consultation. Randomisation will be conducted by permuted block randomisation, with stratification by age, systolic blood pressure and pulse rate. The primary efficacy endpoint is rebleeding within 42 days after control of AVH. The secondary efficacy endpoints mainly include all-cause mortality within 42 days after randomisation, persistent bleeding, length of hospitalisation, etc.

Ethics and dissemination The study protocol was approved by the Ethical Committees of Jinling Hospital (authorised ethics no. DZQH-KYLL-21-01). This trial will provide valuable insights into the timing of endoscopic intervention for AVH in patients with cirrhosis. Furthermore, the trial results and conclusions could provide high-quality evidence to guide clinical research and treatment.

Trial registration number NCT04786743.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This prospective trial will strictly group patients following the randomisation principle of the study protocol; it will reduce the effect of confounding factors and selection bias, which means that the conclusion is authentic and believable.

⇒ Due to the high efficiency of the emergency green channel, the interval before gastroenterological consultation will be controlled within 10 min after admission to the emergency department, which could greatly increase the possibility of patient survival.

⇒ In this randomised controlled trial (RCT), we attempt to further validate the efficacy of predicting the prognosis of patients with cirrhosis with acute variceal haemorrhage by the scores mentioned in the manuscript. The results will provide an important reference for clinical treatment.

⇒ One limitation is that it will be implemented at a single centre only, so the evidence may be lower than that of a multicentre RCT.

⇒ Another limitation is that we will exclude patients with haemodynamic instability occurring before or after the initial fluid resuscitation. Therefore, the conclusion may not be generalisable for patients with the aforementioned status who undergo emergency treatment.

INTRODUCTION

In China, chronic liver disease (CLD) is a primary cause of morbidity and mortality. Its aetiologies mainly include chronic hepatitis B or C virus infection, alcoholism and autoimmune liver disease. Approximately 400 million people suffer from CLD, and 25% of them are carriers of hepatitis B surface antigen.[1 2] Cirrhosis is the end stage of CLD. Acute oesophagogastric variceal haemorrhage, also abbreviated as 'acute variceal haemorrhage' (AVH), is a primary and severe complication of cirrhosis. For patients with AVH undergoing standard therapy (band ligation, vasoactive drugs and antibiotics), mortality during AVH could be as high as 16%.[3] With the development of minimally invasive techniques, early endoscopic intervention has been increasingly considered as the first-line treatment for patients with AVH.[4 5]

Table 1 The scheme for patient enrolment, assessment and follow-up in the trial

Stage	Record							
Time	Admission	Before endoscopic intervention	Follow-up					
Consent			W1	W2	W3	W4	W5	W6
Basic medical history								
Signing ICF	☑							
Identifying inclusion and exclusion criteria	☑	☑						
Filling population information	☑							
Medical and treatment history	☑							
Physical examination	☑	☑	☑	☑	☑	☑	☑	☑
GBS, CAGIB and MELD score	☑							
Observational indices								
Blood routine	☑	☑		☑		☑		☑
CRP	☑							
Blood biochemistry (renal and liver function)	☑			☑		☑		☑
Blood electrolytes	☑			☑		☑		☑
Blood ammonia	☑			☑		☑		☑
HBV-DNA	☑							☑
HBV markers (HBsAg|HBsAb|HBeAg|HBeAb|HBcAb)	☑							
HCV, syphilis and AIDS markers (HCVAg|HCVAb|TPAb|HIVAb)	☑							
Coagulation indicators	☑			☑		☑		☑
Abdominal ultrasound or CT	☑					☑		

CAGIB, cirrhosis acute gastrointestinal bleeding; CRP, C reactive protein; GBS, Glasgow-Blatchford score; HBcAb, hepatitis B core antibody; HBeAb, hepatitis Be antibody; HBeAg, hepatitis Be antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HCVAb, hepatitis C virus antibody; HCVAg, hepatitis C virus antigen; HIVAb, HIV antibody; ICF, informed consent form; MELD, model for end-stage liver disease; TPAb, *Treponema pallidum*-specific antibody; W1, week 1; W2, week 2; W3, week 3; W4, week 4; W5, week 5; W6, week 6.

Several guidelines recommend endoscopy within 24 hours after AVH,[6–8] but there is no consensus on the most appropriate time to perform endoscopic intervention during this period. Two observational studies[9 10] and one systematic review[11] reported no difference in mortality between patients subjected to endoscopy within 12 hours and after 12 hours. Nevertheless, one study showed that performing endoscopy more than 12 hours after admission could significantly decrease mortality and rebleeding.[12] Furthermore, some reliable studies demonstrated that performing endoscopy more than 12 hours after admission could significantly increase rebleeding and mortality rates in patients with AVH[13–15]; one recent meta-analysis also concluded that endoscopy within 12 hours might improve the survival of patients with AVH, but it seemed to have no obvious efficacy on rebleeding.[16] However, few relevant studies have explored the differences in efficacy between urgent endoscopy (<6 hours after gastroenterological consultation) and non-urgent endoscopy (6–24 hours after gastroenterological consultation) for patients with cirrhosis with AVH.

Recently, a prospective randomised controlled trial (RCT) conducted by a team from the Chinese University of Hong Kong showed that for patients with acute upper gastrointestinal haemorrhage (AUGIH) and a Glasgow-Blatchford score (GBS) of 12 or higher, there was no significant difference in mortality or further bleeding between the groups on <6-hour urgent endoscopy and non-urgent endoscopy 6–24 hours after gastroenterological consultation.[17] For patients with AUGIH, a GBS of 12 or higher is indicative of a higher risk of further bleeding or mortality.[17] Although this study included a range of aetiologies, including peptic ulcers, gastro-oesophageal varicosity, malignant upper gastrointestinal tumours and other diseases that could cause AUGIH, only 9.7% (25 cases) and 7.4% (19 cases) of patients included in the group <6 hours and the group 6–24 hours, respectively, were patients with cirrhosis with AVH. Therefore, the results are not generalisable enough to describe the effectiveness of endoscopy within 24 hours for these patients after gastroenterological consultation.

Based on the studies mentioned above, we made the bold assumption that patients with cirrhosis with AVH undergoing non-urgent endoscopy (6–24 hours) would have higher rebleeding rates than those undergoing urgent endoscopy (<6 hours) after gastroenterological consultation. The purpose of this study was to conduct an RCT to further define the role of urgent endoscopy

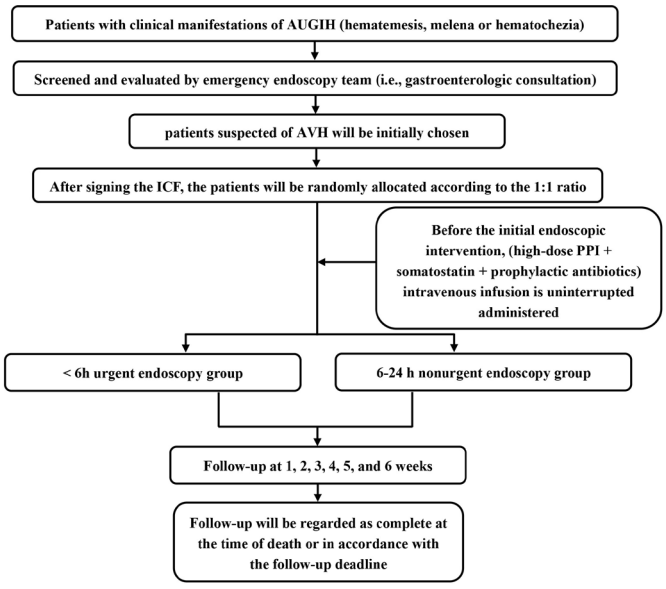

Figure 1 Flow chart of the trial protocol. AUGIH, acute upper gastrointestinal haemorrhage; AVH, acute variceal haemorrhage; ICF, informed consent form; PPI, proton pump inhibitor.

and non-urgent endoscopy in patients with cirrhosis with AVH.

We present the following article in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting checklist (online supplemental material 1).

METHODS AND ANALYSIS

Study design

This investigator-initiated study is designed as a single-centred, randomised clinical superiority trial with two parallel groups and a primary efficacy endpoint of rebleeding within 42 days after control of AVH. The study protocol will strictly adhere to the 2013 SPIRIT guidelines.[18 19] We intend to compare the effectiveness of improving the rebleeding rates of patients with cirrhosis with AVH between the urgent endoscopy and non-urgent endoscopy groups. The Department of Gastroenterology and Hepatology, Affiliated Jinling Hospital, Medical School of Nanjing University will take full responsibility for this trial, including recruitment of patients, endoscopic intervention, admission education, in-hospital nursing and subsequent follow-up work. This trial has been registered at ClinicalTrials.gov (ID: NCT04786743).

Data processing

Two investigators in our department are responsible for the data collection and storage. One investigator will inspect the data collected by the other investigator. After completing the inspection, the data, which are open to the analysts, will be kept in secret and input into the offline database constructed by the investigators. As soon as they complete all the data storage, the two investigators will conduct a double inspection. The collected data will be used for data analysis. The investigators will strictly follow the study protocol to inspect, collect, record and preserve the data in a timely manner to minimise the occurrence of missing data. If missing data occur in a small percentage of patients, we will handle it with multiple imputation. We will perform source data verification by comparing them with authentic medical records to assess the accuracy, completeness and representativeness of registry data.

Patient enrolment

An estimated 400 patients will be consecutively included in the study between March 2021 and December 2023. Patients or their statutory agents must provide written informed consent before participating in any of the study procedures. The model for end-stage liver disease (MELD) score,[20] Child-Pugh score, cirrhosis acute gastrointestinal bleeding (CAGIB) score[21] and original GBS, instead of the modified version,[22] will be used to evaluate the condition of each patient. The flow chart and the experimental record of this trial are shown in table 1 and figure 1, respectively. Although the informed consent form and case report form in this article are provided in English, they will be provided to the patients in Chinese during the trial.

Inclusion criteria

Patients eligible for the trial must comply with all the following criteria at randomisation: (1) patients who have pathological or clinical and imaging evidence indicating a diagnosis of cirrhosis; (2) patients with clinical symptoms associated with AVH (haematemesis, melaena or haematochezia) before admission or during hospitalisation; and (3) patients who are haemodynamically stable before or after initial fluid resuscitation.

Exclusion criteria

The exclusion criteria are as follows: (1) pregnancy; (2) lactation; (3) age under 18 years; and (4) patients with a history of taking anticoagulant or antiplatelet drugs within 2 weeks.

Sample size

According to a study by Ardevol *et al*,[23] among 646 patients with cirrhosis with AVH who underwent endoscopy within 6 hours after admission, the 45-day rebleeding rate was 26%, which was similar to that in another study by Chen *et al*,[14] who reported that the overall 6-week rebleeding rate was 25.7%. Regarding the experience at our centre, it is difficult for emergency endoscopy team members to identify the bleeding site of the AVH by endoscopy for some patients who are assigned to the group 6–24 hours; we attribute this to the efficacy of the combination of proton pump inhibitors (PPIs) and somatostatin. If the bleeding site is undetectable, the endoscopic haemostatic procedure cannot be completed. Although conservative treatment could contribute to temporary control of AVH, the risk of rebleeding could greatly increase over the following days; additionally, patients assigned to the group 6–24 hours would have a higher volume of fluid infused,

which could contribute to the rebleeding and restoration of portal venous pressure. Thus, we speculated that the rebleeding rate of the group 6–24 hours might be statistically significantly higher than that of the group 6 hours. To the best of our knowledge, there are no high-quality, large-sample RCT data on endoscopic treatment for AVH within 6–24 hours and within 6 hours after gastroenterological consultation. Considering the resource limitations of a single centre, we assumed a clinically significant difference of 14% to implement this exploratory trial and provide support for further confirmatory trials. Next, we calculated that having at least 189 patients in each group would reveal differences (26% vs 40%), with a statistical power of 80% and a two-sided α level of 5%. Considering withdrawal and loss to follow-up, the sample size was increased to 200 patients per group.

Randomisation and time set

Eligible patients will be randomly assigned in a 1:1 ratio to receive endoscopic intervention either within 6 hours or between 6 and 24 hours after gastroenterological consultation. Randomisation will be conducted by permuted block randomisation stratified by age (≥60 years or <60 years), systolic blood pressure (SBP) (≥90 mm Hg or <90 mm Hg) and pulse rate (≥100 beats/min or <100 beats/min). The purpose of using stratified randomisation is to reduce the imbalance of covariates because they are strongly correlated with the outcome indicators between groups, and to further control bias. The block size is prespecified, but physicians and investigators will not be notified of this fact during the study. The randomisation sequence generation and allocation concealment will be implemented by the mobile client randomisation tool 'Randomization Allocation Tool'. There are two primary sources of patients. Most of these patients are from the emergency department, and the others are patients with cirrhosis who developed AVH during hospitalisation. For patients from the emergency department, the interval between admission and receiving gastroenterological consultation will be controlled within 10 min by applying the emergency green channel in our centre. However, for patients who develop AVH during hospitalisation, the time will be recorded according to when they are evaluated by the emergency endoscopy team (ie, gastroenterological consultation). To facilitate data recording, the time will be uniformly calculated for all patients according to when the gastroenterological consultation is received. The patients will be randomly allocated to undergo urgent endoscopy within 6 hours or non-urgent endoscopy between 6 hours and 24 hours after gastroenterological consultation. The following time data will be recorded: (1) time from presenting with symptoms of AVH to admission (patients from the emergency department); (2) time from admission to gastroenterological consultation (patients from the emergency department); (3) time from presentation to gastroenterological consultation (patients who develop AVH during hospitalisation) and (4) time from gastroenterological consultation to endoscopic intervention (all of the patients).

Blinding

The outcome assessors will be blinded to the randomisation allocation and will not participate in the practical treatment and intervention; in particular, two scientific researchers specialising in gastroenterology with more than 3 years of clinical rotation experience will serve as the outcome assessors. Professional academic statisticians blinded to the group allocation will conduct all the analyses. However, the endoscopists will not participate in the outcome assessment. Furthermore, they will not need to disclose details of their interventional procedures to the outcome assessors.

Control of AVH, persistent bleeding and rebleeding

AVH under endoscopy mainly refers to blood gushing or seeping from oesophageal or gastric varices; however, if there is no blood gush or seepage detected, thrombus stigmata attached to varices together with massive haematocele of the stomach will also be regarded as one kind of AVH under endoscopy. Control of AVH refers to a lack of persistent bleeding signs within 24 hours after the initial endoscopic intervention; otherwise, the patients will be regarded as having persistent bleeding, which is defined as the occurrence of at least one of the following items: (1) vomiting of fresh blood or suction of more than 100 mL of fresh blood from the nasogastric tube; (2) occurrence of haemorrhagic shock and (3) decrease in haemoglobin level of 30 g/L in the absence of a blood transfusion. Rebleeding refers to recurrent bleeding after the control of AVH, which is defined as the occurrence of at least one of the following items: (1) haematemesis, melaena or haematochezia; (2) decrease in SBP of more than 20 mm Hg from the original level or an increase in heart rate of 20 beats/min; and (3) decrease in haemoglobin level of 30 g/L in the absence of a blood transfusion. Patients with persistent bleeding or rebleeding will immediately undergo a secondary endoscopic intervention or be transferred for other salvage treatment (surgery, percutaneous transhepatic variceal embolisation or transjugular intrahepatic portosystemic stent shunt (TIPSS)) according to their condition and wishes. Although the vast majority of acute haemorrhage and rebleeding is caused by oesophagogastric varices in this trial, acute haemorrhage and rebleeding caused by non-variceal factors will also be recorded and included in the statistical analysis.

Treatment

1. Before endoscopic intervention: all patients will receive uninterrupted intravenous administration of high-dose PPIs (8 mg/hour) and somatostatin (250 μg/hour) and antibiotic prophylaxis.
2. Initial endoscopic intervention: patients who have non-variceal bleeding under endoscopy will not be excluded from this trial; as patients are screened strictly according to the inclusion and exclusion criteria, there

will theoretically not be many of these patients. Moreover, professional academic statisticians will conduct intent-to-treat analysis and per-protocol analysis, which are described in detail in the following statistical analysis. For patients meeting the criteria for AVH, numerous methods could be applied, including histoacryl injection, sclerotherapy, variceal ligation, a covered stent or combinations of these. The patient's position will be chosen to expose the best field of view under endoscopy, and an external cannula for endoscopy could be used to prevent asphyxiation. Furthermore, initial endoscopic intervention will be aimed solely at the bleeding site. After endoscopic intervention, we will transfer the patient to the general ward or intensive care unit (ICU) according to the patient's condition.

3. After the initial endoscopic intervention, all the patients will be treated with continuous high-dose PPIs (8 mg/hour) and intravenous infusion of somatostatin (250 µg/hour) for 72 hours, together with the preventive administration of antibiotics for no more than 120 hours; during the follow-up, oral propranolol and ultrasound-guided histoacryl injection could be used as secondary preventive measures according to the patient's condition.
4. The emergency endoscopy team consists of three experienced endoscopists, each with more than 10 years of experience in endoscopy and over 500 cases of variceal haemostasis experience under endoscopy. Furthermore, several seasoned endoscopic nurses who are proficient in applying endoscopic treatment instruments and cooperating with endoscopists will also be included.

Endpoint setting

The primary efficacy endpoint refers to rebleeding within 42 days after the control of AVH. The secondary efficacy endpoints mainly include: (1) all-cause mortality within 42 days after randomisation; (2) persistent bleeding; (3) length of hospitalisation; (4) transfer to the ICU; (5) secondary endoscopic intervention because of rebleeding or persistent bleeding; (6) blood transfusion therapy; (7) in-hospital costs during the first admission; (8) any adverse events that occur between randomisation and the end of follow-up; (9) transfer to undergo TIPSS; (10) transfer to undergo surgery; (11) concurrent infection; (12) the patient's position during endoscopy; (13) application of an external cannula for endoscopy; and (14) secondary prophylaxis such as endoscopic intervention, TIPSS and surgery.

Follow-up time

After randomisation, follow-up work will begin. All the patients included will be followed up for no less than 42 days after controlling for AVH. When the patients' conditions are stable, further treatment of varices will be determined according to their wishes and statutory agents. Patients with good compliance will be administered standard endoscopic secondary prophylaxis after 5 days of AVH control, and the follow-up time should be once a week. Patients who decline to accept further endoscopic intervention will undergo only weekly follow-up. Follow-up could be in the form of a telephone or outpatient review. Follow-up will be regarded as complete at the time of death or in accordance with the follow-up deadline.

Adverse events

Any adverse events, defined as any functional or organic lesion caused by the trial, fever, chest pain, dysphagia, perforation of the oesophagus or pulmonary embolism, will be documented. If any adverse event occurs, the physicians will treat the patients immediately, and the study protocol will be changed or terminated according to their wishes. The emergency endoscopy team member on duty will instantly inform the primary investigator and ethics committee of the severe adverse events to decide whether the patient should be withdrawn from the trial and unblinded.

Statistical analysis

Primary analyses for the primary efficacy endpoint between the urgent endoscopy and non-urgent endoscopy groups will be performed in the intention-to-treat population, which will include all patients who are randomised to a study therapy group, regardless of whether they receive the endoscopic intervention. Multiple imputations with the Markov chain Monte Carlo method will be applied to impute the missing endpoints. Secondary analyses will be based on the per-protocol population, which will include all patients who receive the intended endoscopic intervention without a major protocol violation or loss to follow-up.

Descriptive statistics will be used to compare patients randomised to the urgent endoscopy and non-urgent endoscopy groups with respect to baseline variables. Continuous variables will be expressed as the means and SDs (normally distributed) or medians and IQRs (non-normally distributed). Assessments of normality for continuous variables will be performed using the Shapiro-Wilk test. Categorical variables will be calculated as frequencies and percentages.

For the primary analyses, the rebleeding rates within 42 days will be compared between the two groups using the X^2 tests and the Cochran-Mantel-Haenszel tests, and their differences and corresponding 95% CIs will be calculated. Additionally, the rebleeding rates will be estimated using the Kaplan-Meier method. The log-rank test will be used to compare the difference in rebleeding rates between the two groups. A Cox proportional hazards regression model will be used to estimate the HR and its 95% CI. The proportional hazards assumption will be assessed using the Schoenfeld residual test. Furthermore, the Cox regression model will be performed to assess the consistency of the endoscopy regarding the primary efficacy endpoint, taking the randomisation stratification factor into consideration. Except for age, SBP and pulse rate,

the subgroup analysis also included sex, CAGIB score, the severity of liver disease, etc. For these subgroup analyses, HRs and 95% CIs for the primary efficacy endpoint will be calculated for each subgroup, and subgroup differences will be assessed based on the test for the interaction of the treatment group by subgroup in the model. Additionally, the Cox regression model will also be performed as a sensitivity analysis to assess the effect of endoscopy on the primary efficacy endpoint while accounting for a priori clinically important baseline characteristics (eg, age, sex, CAGIB score, Child-Pugh score, MELD score, etc). Two-tailed p values will be used, and a p value of <0.05 will be indicative of statistical significance.

The secondary efficacy endpoints will be assessed in the per-protocol population and compared between the two groups with X^2 test for differences in proportions and with Student's t-test and Wilcoxon's rank-sum test for normally distributed and non-normally distributed data, respectively. The results for secondary efficacy endpoints will also be presented with 95% CIs. As they will not be adjusted for multiplicity, findings for the analysis of secondary efficacy endpoints should be interpreted as exploratory. All analyses will be performed using SAS software (V.9.4; SAS Institute).

Interim analysis and monitoring

No interim analysis is planned.

Patient and public involvement

Patients or the public will not be involved in the design, conduct, reporting or dissemination plans of our research.

ETHICS AND DISSEMINATION

We intend to publish the results of the TEACH trial in a major journal.

DISCUSSION

This trial will proceed strictly based on the Consolidated Standards of Reporting Trials.[24]

Although the performance of endoscopic intervention for patients with cirrhosis within 24 hours after AVH has achieved international recognition and research on the timing of endoscopic intervention for AVH has progressed, there is still much controversy regarding the efficacy of earlier endoscopic intervention (<6 hours or 12 hours after gastroenterological consultation). Several studies have reported the 6-week rebleeding and mortality rates for patients with cirrhosis with AVH after endoscopy within 12 hours after admission. For instance, Huh *et al*[12] reported a 34.4% rate of 6-week composite endpoints (a combination of mortality and rebleeding rates) for patients with cirrhosis with AVH who underwent endoscopic intervention within 12 hours after admission, and Chen *et al*[14] and Yoo *et al*[9] reported high 6-week rebleeding rates (18.9%) and mortality rates (ranging from 22.5% to 27%), respectively. In a more recent systematic review with meta-analysis, Bai *et al* reported that performing endoscopy within 12 hours might have no obvious efficacy on the prevention of rebleeding.[16] After performing endoscopy within 6 hours after admission, Ardevol *et al*[23] found that the 6-week rebleeding rate was 26%. Furthermore, there have been no definitive prospective data on the impact of non-urgent endoscopy (between 6 and 24 hours after admission or gastroenterological consultation) on mortality and rebleeding rates of these patients. The efficacy of non-urgent endoscopy has long been controversial. To our knowledge, there are no high-quality, large-sample prospective studies that provide authentic data to verify whether endoscopic intervention is better as early as possible, or whether urgent endoscopy is truly beneficial to patients with cirrhosis with AVH (eg, reducing the rebleeding and mortality rates, reducing the length and cost of hospitalisation, etc), so we designed this RCT after carefully assessing the advantages and disadvantages of previous related studies. By strictly implementing our randomisation scheme, the patients can be evenly assigned to the two groups, which makes it possible to draw accurate, credible results and conclusions. The strict randomisation principle, which was not enforced in previous retrospective studies, can greatly improve the reliability of the article conclusions.

In China, many patients with cirrhosis present with AVH every year. Therefore, it is necessary to investigate the efficacy of urgent endoscopy (<6 hours after gastroenterological consultation) and non-urgent endoscopy (between 6 and 24 hours after gastroenterological consultation) with prospective, large-sample data. This trial is intended to provide a relatively idealised random environment that could assist us in observing differences in the efficacy between urgent endoscopy and non-urgent endoscopy in patients with cirrhosis with AVH.

As described above, randomisation will be conducted by permuted block randomisation stratified by age, SBP and pulse rate. The three indices used to stratify are also easier to obtain and grouping is less time-consuming. Moreover, we regard the randomisation only as a preliminary grouping basis. If the patient is assigned to the group on non-urgent endoscopy 6–24 hours by randomisation and has severe liver disease, persistent haematemesis, melaena or haematochezia and a deteriorated condition, then we will immediately perform endoscopic intervention regardless of the randomisation. As we are including only haemodynamically stable patients, only a very small number of them are expected to experience sudden deterioration of their condition. Some patients and their statutory agents will be confused about the grouping when the RCT is implemented. Hence, it is very important to have effective communication and establish trust between the doctors and patients, Patients will never be forced to comply with the procedures, and everything is based on their wishes and that of their statutory agents.

Theoretically, the best option is to perform emergency endoscopy first; then, after the patient is diagnosed with AVH under endoscopy, the patient will be randomly

assigned, which could prevent the interference of other AUGIH-related diseases, such as peptic ulcers and gastrointestinal carcinoma. However, it is clearly unethical to do so in practical clinical work. As the assignment of patients will be randomised, the probability of error is equal in the two groups; accordingly, assigning patients before endoscopy according to our protocol could also avert confounding by other AUGIH-related diseases.

The Baveno VI Consensus Workshop recommended that 6-week mortality should be the primary efficacy endpoint for AVH studies.[25] However, according to data from our centre, very few patients died within 6 weeks after controlling for AVH; in some cases, a proportion of patients are readmitted for rebleeding, and rebleeding is indeed an important indicator of prognosis in patients with cirrhosis with AVH. Therefore, after considering the actual situation at our centre, we chose rebleeding within 42 days after achieving AVH control as the primary efficacy endpoint for this RCT. Nevertheless, we will continue to focus on mortality and regard it as one of the secondary efficacy endpoints.

While endoscopic intervention is central to the research in this trial, some other interventions we attempt to perform during this trial may affect the outcome. First, it has been proven that timely application of antibiotics for gram-negative bacteria could positively improve overall survival, prevent early rebleeding and reduce the risk of bacterial infection, so short-term antibiotic application is recommended for all patients with cirrhosis with AVH, regardless of the presence of confirmed infection.[8 26] Therefore, we chose to use prophylactic antibiotics for all the included patients in our trial. Second, it was reported that in a review of 15 studies, salvage TIPSS could achieve control of AVH in 90%–100% of patients and result in rebleeding in 6%–16%.[8 27] In this trial, patients with persistent bleeding or rebleeding that could not be controlled by endoscopic intervention could be transferred to undergo salvage TIPSS. Clearly, salvage TIPSS could greatly benefit these patients. We will follow up with these patients carefully, evaluate the efficacy of TIPSS in our centre and provide a better treatment choice for them. Third, there is substantial evidence showing that the application of non-selective beta-blockers (NSBBs) increases the mortality rate of Child-Pugh grade C patients.[28] In our trial, we did not exclude patients with Child-Pugh grade C. Consequently, considering clinical safety, we did not plan to use NSBBs as the essential treatment for patients with Child-Pugh grade C included in this trial. Furthermore, NSBBs have been reported to increase the risk of portal vein thrombosis in patients with cirrhosis with esophagogastric varices[29–31]; at the same time, out-of-hospital application of NSBBs poses a great risk for patients with poor compliance; thus, we do not choose to routinely apply NSBBs. However, if the patients need a combination of NSBBs for secondary prophylaxis, we will administer NSBBs to them.

Overall, it is certain that the results of this trial could provide reliable evidence for the management of patients with cirrhosis with AVH; moreover, through subgroup analysis, more meaningful conclusions will be drawn to guide future treatment and improve the quality of life and prognosis of the patients. At present, COVID-19 is rampant worldwide, and urgent endoscopy in our centre has also been greatly affected by the virus. Nevertheless, we will try our best to do epidemic prevention and continue our RCT to advance the treatment of patients with cirrhosis with AVH.

Trial status

- Protocol trial version: 1.2; date: 4 May 2022.
- Recruitment start date: April 2021.
- Recruitment estimated end date: February 2024.
- Recruiting.

Registry

The project is registered at the ClinicalTrials.gov database (https://clinicaltrials.gov/ct2/show/record/NCT04786743).

Dissemination policy

All the authors are committed and agree to publish the full results of the research regardless of the final results.

Data monitoring committee

The data monitoring committee comprises three clinical doctors, who are not involved in our study. The committee will meet at least once a year, monitor data and provide appropriate documentation.

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Contributors ZY contributed to the design, draft and revision of the manuscript. JX, FY, YQ, MY, HX, MJ, SS, ML, HS, KJ and HT contributed to the design of the manuscript. YL and FW contributed greatly to the design and revision of the manuscript. ZY, JX, and FY contributed equally to this work. All authors read and approved the final protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on Page Number/Line Number	Reported on Section/Paragraph
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page1/Line3-5	Title page/Paragraph1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page3/Line8	Abstract/Paragraph4
	2b	All items from the World Health Organization Trial Registration Data Set	Page3/Line8	Abstract/Paragraph4
Protocol version	3	Date and version identifier	Page23/Line14	Trial status/Paragraph1
Funding	4	Sources and types of financial, material, and other support	Page24/Line10-13	Funding/Paragraph1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page1/Line7-22;	Title page/Paragraph2-3
	5b	Name and contact information for the trial sponsor	Page2/Line4-5	Title page/Paragraph5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page24/Line7-9	Author contributions/Paragraph1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page24/Line3-5	Data monitoring committee/Paragraph1
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention		
	6b	Explanation for choice of comparators	Page4/Line21-22; Page5/Line1-22;	Introduction/Paragraph2-3
Objectives	7	Specific objectives or hypotheses	Page5/Line7-9	Introduction/Paragraph2
			Page6/Line1-5	Introduction/Paragraph4

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page6/Line12-14	Methods and analysis/Paragraph1
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page6/Line17-20	Methods and analysis/Paragraph1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page8/Line3-14	Methods and analysis/Paragraph4-5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page14/Line1-20	Methods and analysis/Paragraph10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page16/Line9-13	Methods and analysis/Paragraph 16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page15/Line18-22; Page16/Line1-4	Methods and analysis/Paragraph15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page13/Line13-17;	Methods and
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page15/Line6-15	Methods and analysis/Paragraph14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table1	Table1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page8/Line17-22;	Methods and
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page9/Line1-16	analysis/Paragraph6
Methods: Assignment of interventions (for controlled trials)			Page6/Line17-20;	Methods and
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page11/Line8-10	Methods and analysis/Paragraph7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page11/Line12-16	Methods and analysis/Paragraph7

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page11/Line14-16	Methods and analysis/Paragraph7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page12/Line13-14; Line16-17	Methods and analysis/Paragraph8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page16/Line9-13	Methods and analysis/Paragraph16
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page7/Line2-3	Methods and analysis/Paragraph2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page15/Line18-22; Page16/Line1-3;Table1	Methods and analysis/Paragraph15;
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page7/Line2-6	Methods and analysis/Paragraph2
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page17/Line8-17; Page18/Line6-10	Methods and analysis/Paragraph19-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)		
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page17/Line17-22 Page16/Line16-20	Methods and Methods and analysis/Paragraph17
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page24/Line3-5	Data monitoring committee/Paragraph1
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial		
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page18/Line16	Methods and analysis/Paragraph21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page16/Line7-13	Methods and analysis/Paragraph16
			Page24/Line3-5	Data monitoring committee/Paragraph1

Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page3/Line3-4 Page24/Line20-21	Abstract/Paragraph3 Ethics approval/Paragraph1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Supplementary material	Supplementary material
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A	N/A
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page7/Line3-5	Methods and analysis/Paragraph2
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page24/Line14	Competing interests/Paragraph1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page7/Line3-5	Methods and analysis/Paragraph2
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page14/Line16-20; Page16/Line9-13;	Methods and analysis/Paragraph12 and
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page17/Line18	Ethics and dissemination/Paragraph1
	31b	Authorship eligibility guidelines and any intended use of professional writers		
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page24/Line7-9	Author
Appendices			Page24/Line21-22	Ethics
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates		
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary material 3/Informed consent form N/A	Supplementary material 3/Informed consent form N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.