



# Laparoscopic total left-sided surgical approach versus traditional bilateral surgical approach for treating hiatal hernia: a study protocol for a randomized controlled trial

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**Background:** In China, guidelines for the treatment of hiatal hernia (HH) are lacking. Furthermore, efficacy and safety assessments of surgical approaches for HH and for the protection of the vagus nerve and organ function are needed. Therefore, the present clinical trial is being conducted to establish the normative treatment for HH.

**Methods:** The current trial is an ongoing, single-center, randomized controlled trial of patients with HH. The total sample size required for the trial (July 2020–December 2023) is approximately 114 patients. Patients will be randomly assigned to either an experimental group (total left-sided surgical approach; TLSA) or a control group (traditional bilateral surgical approach; TBSA) at a ratio of 1:1 using the block randomization method. We will use case report forms (CRFs) and electronic data capture (EDC) systems to obtain demographic information, preoperative laboratory tests, auxiliary examination results, operation information, and postoperative condition. The patients will be followed up for 3 years after surgery. The primary endpoint is the gastrointestinal quality-of-life index (GIQLI) at 1 year. The secondary endpoints include an efficacy evaluation index [consisting of the incidence of gallstones and gastric emptying disorders, gastrointestinal function recovery time, visual analog scale (VAS) scores, objective evaluation of postoperative indices, and surgical information] and a safety evaluation index (consisting of the incidence of postoperative complications, the 30-day postoperative mortality rate, and the HH recurrence rate at 1 and 3 years after surgery).

**Discussion:** TLSA can protect the normal physiological function of organs to a certain extent by protecting the vagus nerve from injury, and has satisfactory short- and long-term efficacy. There is no significant difference in the incidence of postoperative complications and surgical safety between TLSA and TBSA. Our findings will facilitate clinical decision-making for HH and improve the life quality of patients.

**Trial registration:** Chinese Clinical Trial Registry, ChiCTR2000034028 (registration date: June 21, 2020).

**Keywords:** Hiatal hernia (HH); surgical approach; efficacy; safety; randomized controlled trial

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## Introduction

Hiatal hernia (HH) is a disease caused by the temporary or permanent entry of abdominal organs or tissue into the thoracic cavity via the diaphragmatic esophageal hiatus (1). HH can contribute to gastroesophageal reflux and produce a burning sensation behind the sternum. At present, China is still lacking treatment guidelines for HH (2,3). Contrary to the therapeutic principles of malignant tumors, in cases of HH, there is no need for radical resection of organs or tissues, due to the absence of tumorigenic factors, and there is no disease recurrence. Therefore, for the treatment of benign diseases, including HH, effectively protecting organ function and the vagus nerve during treatment, reducing the occurrence of complications, and maximizing patients' quality of life (QOL) have gradually become foci of clinicians (4).

Surgeons tend to adopt minimally invasive laparoscopic techniques to treat HH. The primary treatment the traditional bilateral surgical approach (TBSA) for laparoscopic HH repair combined with fundoplication (5). The advantage of the TBSA is that it can preserve short gastric blood vessels to the greatest extent, ensure blood return from the veins around the stomach, and help to reduce the occurrence of gastrointestinal emptying disorders resulting from organ congestion. However, the disadvantage of this approach is that, although local protection of the vagus nerve can be achieved during the surgery, the integrity of the vagus nerve cannot be judged as a whole. For cases in which the nerve is injured, there is a possibility that it cannot be located, which seriously affects the patient's QOL (6).

To further improve patients' short- and long-term postoperative QOL, our center used a total left-sided surgical approach (TLSA) for laparoscopic HH repair combined with fundoplication. The advantage of the TLSA is that the lesser omentum and hepatogastric ligament are completely preserved according to the anatomical characteristics of the vagus nerve. Therefore, iatrogenic injury to the vagus nerve trunk and its hepatic branch in the lesser omentum can be avoided, meaning the vagus nerve and the function of its innervating organs can be fully protected, thus improving the patient's postoperative QOL.

Due to the lack of relevant guidelines for the treatment

of HH in China, as well as the lack of efficacy and safety assessments of the different surgical approaches for protecting the vagus nerve and organ function (5), a clinical study to establish the normative treatment for HH is essential. Furthermore, although there have been many studies on the degree of fundoplication, discussions on different surgical approaches are still rare. Therefore, the present study aims to compare the short- and long-term efficacy and perioperative safety of TLSA and TBSA in the treatment of esophageal HH in order to maximize the protection of nerve and organ function, reduce the occurrence of complications, improve patients' QOL, and provide evidentiary support for the standardization of esophageal HH surgical treatment. We present the following article in accordance with the SPIRIT reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-8000>).

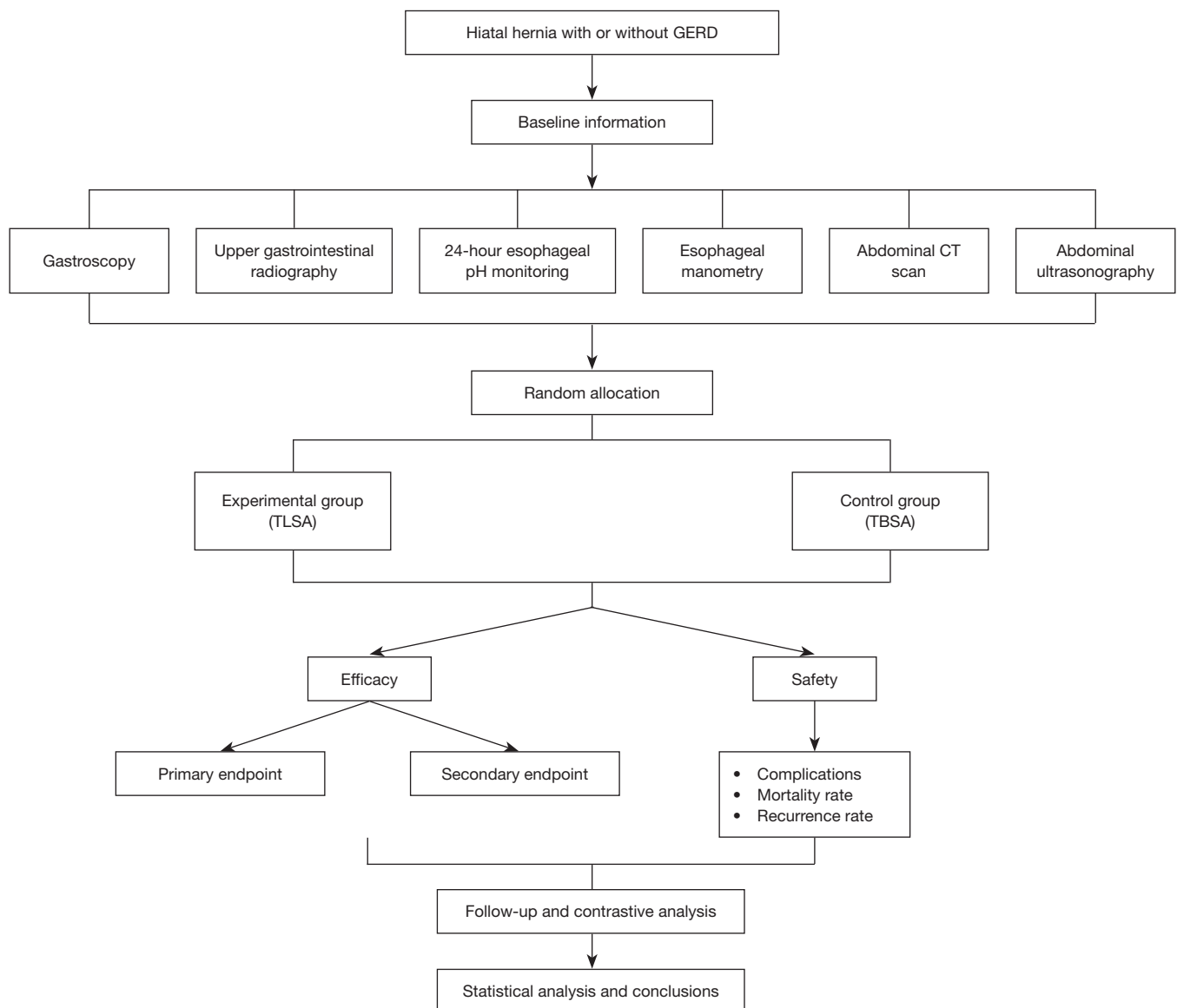
## Methods

### *Study design and setting*

The present study is a single-center, randomized controlled trial. The research was initiated on July 1, 2020 and is anticipated to end on December 31, 2023. During the research period, patients will be selected from Beijing Friendship Hospital, Capital Medical University for treatment. A total of 114 patients will be enrolled in the study. After providing informed consent, enrolled patients will be randomly assigned for surgical treatment to either the experimental group (TLSA) or the control group (TBSA) at a ratio of 1:1 using the block randomization method. Each patient will then receive a numeric randomization code. The detailed research process is described in *Figure 1*.

### *Ethics approval and informed consent*

The present study has been approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (approval No.: L-2020-019). According to the requirements of the Ethics Committee, clinical research will be conducted only after the enrolled patients have signed the informed consent forms. The design of the



**Figure 1** Research process and flow chart. GERD, gastroesophageal reflux disease; TBSA, traditional bilateral surgical approach; TLSA, total left-sided surgical approach.

present study is consistent with the principles of the Declaration of Helsinki (as revised in 2013). All data will be recorded and analyzed anonymously to protect patient privacy. The trial was registered in June 2020 (registration no.: ChiCTR2000034028) on the Chinese Clinical Trial Registry website (<http://www.chictr.org.cn/index.aspx>). Participating patients will be informed of the purpose and significance of the study, the benefits and possible risks of participation, and their anonymity in the study.

### ***Inclusion criteria***

Patients must meet the following criteria for inclusion in the study: (I) HH (type II/III/IV), with or without gastroesophageal reflux disease (GERD), as diagnosed by gastroscopy, high-resolution esophageal manometry, and 24-hour esophageal pH monitoring. Type I HH patients with typical reflux symptoms (as discussed later) will also be included. Upper gastrointestinal radiography and abdominal computed tomography (CT) must be performed with 1 or

multiple auxiliary examinations to confirm the condition; (II) typical reflux symptoms, such as acid reflux, heartburn, and burning pain in the chest area, which have not responded well to regular conservative medical treatments; (III) aged 18–65 years, with no sex restrictions. Bariatric and morbidly obese patients will also be included; (IV) Eastern Cooperative Oncology Group score of  $\leq 2$  points and an American Society of Anesthesiologists score of  $\leq 2$  points, and the ability to tolerate the HH repair surgery; (V) normal organ function (such as alanine transaminase and aspartate aminotransferase levels  $\leq 2.5$  times the upper limit of normal, serum creatinine level  $< 1$  time the upper limit of normal, and platelet blood count  $\geq 75 \times 10^9/L$ ); (VI) the ability to comply with the research protocol during the study period and sign the informed consent form; (VII) willingness to undergo follow-up and to cooperate with staff for the assembly of perioperative index records.

### *Exclusion criteria*

Patients meeting any of the following criteria will be excluded from the study: (I) patients with GERD without HH; (II) patients with severe HH (types III and V) who are unable to undergo esophageal manometry and pH monitoring tests due to difficulty in placing the catheter; (III) patients who are unable to receive anesthesia or surgery due to a physical condition, or who are unwilling to undergo surgery; (IV) patients with cerebrovascular injury that occurred within the 6 months prior, unstable angina, or myocardial infarction; (V) patients with a history of uncontrolled epilepsy, central nervous system disease, or malignant tumor, or those with impaired judgment or mental illness who cannot cooperate with the research; (VI) patients with severe uncontrolled recurrent infection or other severe uncontrolled concomitant disease; (VII) patients who require immunosuppressive therapy for organ transplantation; (VIII) patients on continuous systemic steroid therapy, or those who are pregnant or lactating; (IX) patients with a past history of cholecystectomy; (X) patients with a history of digestive system tumors, or thoracic or abdominal surgery; and (XI) patients enrolled in other clinical research.

Patients will be eliminated from the study under the following conditions: (I) if the researcher decides that elimination is to the benefit of the patient; (II) if the patient violates the research protocol and receives other treatments during the research period; (III) if the patient's clinical data are incomplete and cannot be used for the statistical analysis; (IV) if the patient cannot cooperate with

randomized grouping; or (V) if the patient cannot follow the study treatment protocol.

### *Participating surgeons*

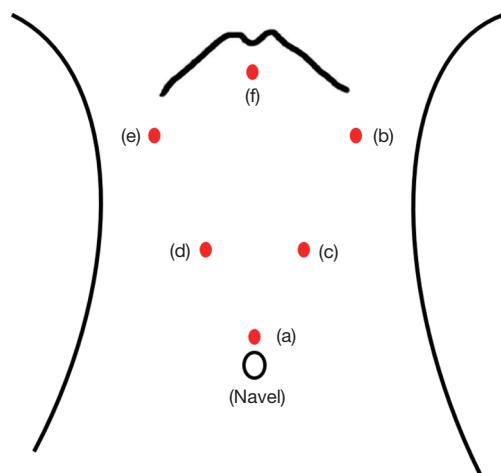
Surgical proficiency and experience have been found to be associated with postoperative complication and HH recurrence rates (7). One study showed that if a surgeon can complete 20 operations alone, they will have crossed the surgical learning curve and be able to handle emergencies independently during the operation (8). The incidences of intraoperative and postoperative complications, the hernia recurrence rate, operation time, the laparoscopic conversion rate, and hospital stay have also been found to be reduced for surgeons who have completed 20 operations alone (7,8). We have selected 3 experienced gastrointestinal surgeons and several nurses for our medical and research team, which will perform surgeries and postoperative care for the enrolled patients. To ensure the treatment quality for the enrolled patients, the surgeons selected for the present clinical study have each completed at least 30 laparoscopic or open HH repair surgeries. In addition, they all have associate senior or senior titles.

### *Primary endpoint*

The primary outcome of the study is the postoperative 1-year gastrointestinal quality-of-life index (GIQLI), which is related to the QOL for gastrointestinal disorders (9). It contains 5 subscales, with a total score of 144 points. The higher the score, the better the patient's QOL and the better the surgical effect (10).

### *Secondary endpoints*

The secondary endpoint mainly includes 2 parts; the efficacy evaluation index and the safety evaluation index. The efficacy evaluation index comprises: the postoperative 3-year incidence of gallstones; the incidence of gastric emptying disorders within 1 year after surgery; the gastrointestinal function recovery time; blood glucose and serum lipid levels within 3 years after surgery; the operation time, blood loss, abdominal drainage fluid volume, total duration of hospitalization, and total cost of hospitalization; the visual analog scale (VAS) score, which will be used to evaluate preoperative and postoperative subjective symptoms, including heartburn, regurgitation, belching, chest pain, fullness, and dysphagia (VAS scale is 0–10 points,



**Figure 2** Puncture port placement. (a) A 12-mm trocar will be inserted through a transverse incision 1 cm above the navel to establish the pneumoperitoneum and insert the laparoscopic lens. (b) A left anterior axillary subcostal incision will be made to permit the insertion of a 12-mm trocar, which will serve as the surgeon's primary operating port. (c) A left central clavicle incision will be made 2 cm above the navel to permit the insertion of a 5-mm trocar, which will serve as the auxiliary operating port. (d) A right central clavicle incision will be made 2 cm above the navel to permit the insertion of a 12-mm trocar, which will serve as a port for assistant instruments. (e) The right anterior axillary subcostal incision with the 5-mm trocar. (f) An incision will be made 2 cm below the xiphoid process, allowing the 5-mm trocar to expose the left lobe of the liver.

with 0 representing asymptomatic and 10 representing very severe) (11); the results of objective evaluations within 3 years, including upper gastrointestinal radiography, gastroscopy, high-resolution esophageal manometry, and 24-hour esophageal pH monitoring; and the DeMeester score and the rate of postoperative acid suppressant use.

The safety evaluation index comprises: the 30-day incidence of postoperative complications, including delayed bleeding, dysphagia, patch rejection reaction, and incision-related complications (postoperative complications classified as higher than grade II according to the Clavien-Dindo classification will be considered clinically significant) (11); the 30-day mortality rate after surgery; and the recurrence rate of HH at 1 year and 3 years after surgery.

### **Interventions**

All enrolled patients will undergo laparoscopic surgery.

Before surgery, patients will be required to undergo gastroscopy, high-resolution esophageal manometry, and 24-hour esophageal pH monitoring. For the assessment of disease status and surgical risk, the enrolled patients will also be required to undergo laboratory examinations (including routine blood test, blood biochemical test, salivary pepsin and serum pepsinogen test, and coagulation function test), upper gastrointestinal radiography, and chest and abdominal CT. Patients with HH (type II/III/IV) with or without GERD and patients with type I HH with GERD will undergo laparoscopic surgery.

In all patients, surgery will be performed in the supine position after successful anesthesia and tracheal intubation. A 12-mm trocar will be inserted through a transverse incision 1 cm above the navel to establish the pneumoperitoneum and maintain pressure at 12–15 mmHg. The puncture port placement is detailed in *Figure 2*.

### ***Esophageal HH repair and fundoplication with TLSA (experimental group)***

The TSLA is described in *Figure 3*.

### ***Esophageal HH repair and fundoplication TBSA (control group)***

The TBSA is described in *Figure 4*.

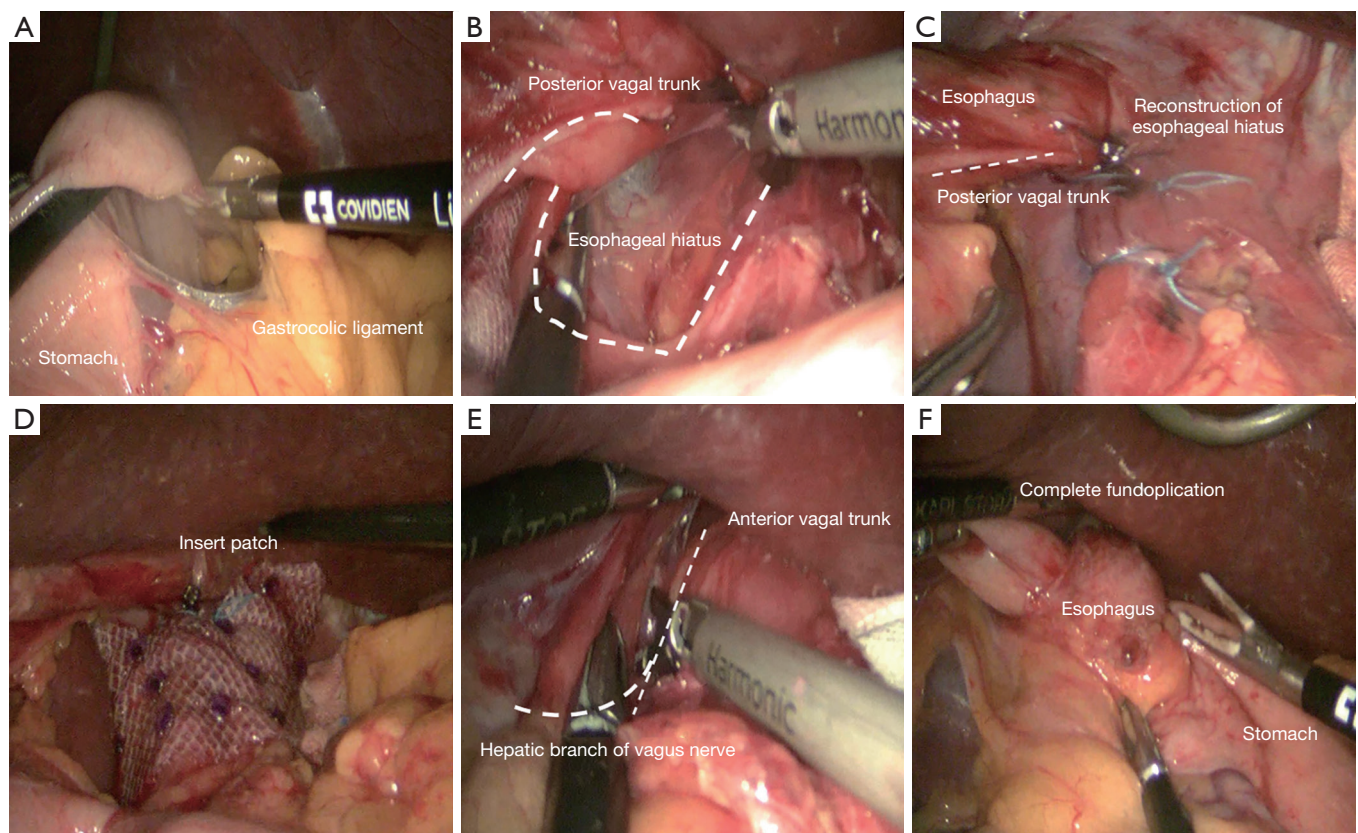
### ***Perioperative treatment for enrolled patients***

After patients undergo surgery, the clinician will administer symptom-based treatment, including electrocardiograph monitoring for 24 hours, analgesics, and fluid replacement therapy. Routine blood tests and biochemistry tests will be used to monitor delayed bleeding, incision and/or abdominal infection, and patch rejection reaction after the operation. After the recovery of gastrointestinal function and the gradual recovery of a semi-liquid diet (with no obvious choking sensation when eating), the abdominal drainage tubes will be removed and the patient will be discharged from hospital.

### ***Assignment of interventions for allocation***

#### **Sequence generation**

To ensure the matching of clinical data between the experimental (TLSA) and control (TBSA) groups, each patient will be randomly assigned to 1 of the 2 groups by



**Figure 3** TLSA surgery procedure. (A) On the greater curvature of the stomach, the gastrocolic ligament is incised along the avascular area between the left and right gastric omentum vessels, and the gastric fundus is separated upward to the cardia to protect the vagus nerve. (B) The cardia, lower esophagus, and diaphragm is exposed, and the confluence of the left and right crus of the diaphragm is revealed. The retroperitoneum at the left and right crus of the diaphragm is incised, and the lower esophagus is dissociated for about 3–5 cm. The gastric fundus and the posterior wall of the esophagus are fully dissociated from the upper spleen. (C) Non-absorbable thread is used to intermittently suture the left and right crus of diaphragm in order to reconstruct the esophagus hiatus with a diameter of about 1.5 cm. (D) Then, the surgeon inserts the patch and fixes it on the crus of diaphragm if the hiatal hernia is larger than 5 cm or the diaphragm on both sides is weak. (E) A small incision about 2–3 cm in diameter is made above the bifurcation between the anterior vagal trunk and the hepatic branch of the vagus nerve. (F) The fundus of the stomach is rotated through the posterior of the abdominal part of the esophagus to the right front of the esophagus, intermittently sutured with non-absorbable thread, and fixed with the right crus of the diaphragm and the right side of the esophagus. The left side of the gastric fundus is also sutured to the anterior esophagus and the left crus of the diaphragm; this avoids vagus nerve injury. Finally, the surgeon completes the fundoplication and inserts abdominal drainage tubes. However, the degree of fundoplication should be based on the results of esophageal manometry and pH monitoring tests.

block randomization. The randomization sequence will be generated with SAS 9.2 software (SAS Institute, Raleigh, NCSU, USA). Each patient will then receive a numeric randomization code.

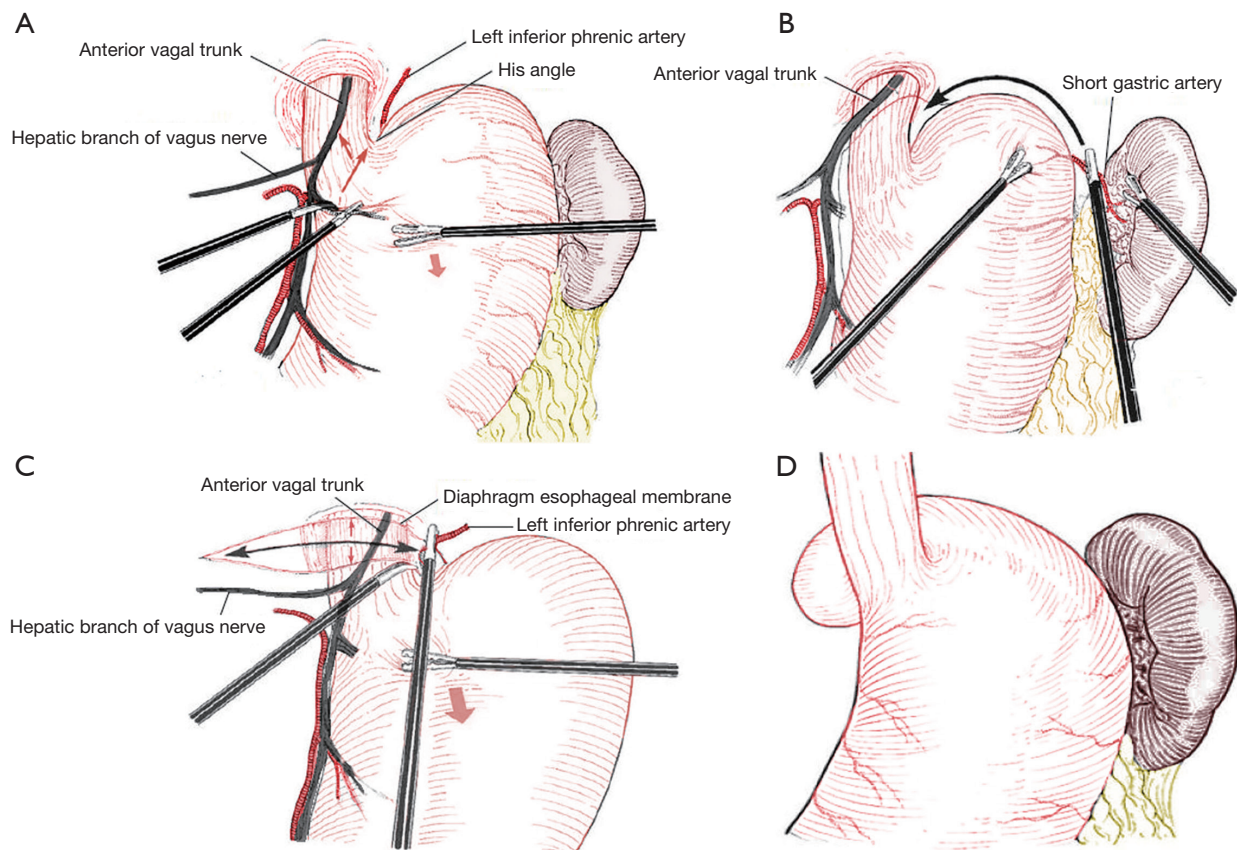
#### *Allocation concealment mechanism*

Patients will be randomly assigned to the experimental

group and the control group at a ratio of 1:1 using the block randomization method.

#### *Implementation*

The Contract Research Organization in the Beijing Friendship Hospital will generate the allocation sequence, enroll participants, and assign participants to interventions.



**Figure 4** Traditional bilateral surgical approach (TBSA) surgery procedure. (A) Separation is initiated from the avascular area of the lesser omentum, and the hepatic branch of vagus nerve is preserved as far as possible. Careful separation is performed upward to expose the right crus of diaphragm. (B) At the greater curvature of the stomach, two to three short gastric vessels are cut off to expose the left crus of diaphragm, and the space between the anterior and posterior of esophagus is dissociated. (C) The diaphragmatic esophageal membrane is incised and the lower part of the esophagus is dissociated about 4–5 cm, then the gastroesophageal valve flap is reformed and the His angle is restored. During the operation, it mainly protects the anterior and posterior trunk of the vagus nerve. The anterior and posterior trunk of the vagus nerve are mainly protected during the operation. (D) Both sides of the crus of the diaphragm are intermittently sutured with non-absorbable thread to reconstruct the esophageal hiatus with a diameter of about 1.5 cm. Then, the surgeon inserts the patch if the hiatal hernia is larger than 5 cm or the diaphragm on both sides is weak, and fixes it on the crus of the diaphragm. Finally, the fundus of the stomach is rotated through the posterior of the abdominal part of the esophagus to the right front of the esophagus, and it is intermittently sutured and fixed with the right crus of the diaphragm and the esophagus. The left side of the gastric fundus is also sutured to the anterior esophagus and the left crus of the diaphragm. Thus, the fundoplication is completed and the abdominal drainage tubes are inserted. However, the degree of fundoplication should be based on the results of esophageal manometry and pH monitoring tests.

### *Assignment of interventions for blinding*

The present study is a single-blind trial; therefore, the patients will not know their grouping. The surgeon will carry out the corresponding surgical treatments according to the patients' grouping. After patients are discharged from the hospital, the surgical methods will be sent to them in the form of medical records.

### *Data collection*

A case report form (CRF) and an electronic data capture (EDC) system have been established to collect clinical data. The clinical research coordinator will log data into the EDC system in a timely manner. Clinical research associates will then monitor the electronic database to evaluate the data quality.

Patient data will be collected through the CRF as follows: (I) demographic information, including sex, age, length of hospital stay, body mass index, concomitant disease, and medication use; (II) perioperative laboratory tests, including the results of routine blood, biochemical, salivary pepsin, serum pepsinogen, and coagulation function tests; and (III) auxiliary examination. All enrolled patients will undergo gastroscopy, thoracic and abdominal CT scan or ultrasound evaluation, high-resolution esophageal manometry, 24-hour esophageal pH monitoring, upper gastrointestinal radiography, and their GIQLI and VAS scores will be analyzed; (IV) surgical information, including date, time, blood loss, surgical approach, HH size, extent of preservation or resection of the hepatic branch of the vagus nerve, type of patch application, placement and number of abdominal drainage tubes, and intraoperative complications; and (V) postoperative recovery outcomes, including length of hospital stay, hospitalization cost, time to remove the abdominal drainage tube, intestinal function recovery time, postoperative complications, and death (*Table 1*).

The name and sex of the enrollees will be replaced with statistical codes or numbers to ensure patient anonymity. To protect the patients' privacy, all clinical data will be analyzed anonymously through the EDC system. Data will be transferred from CRFs to the EDC system (<https://edc-cloud.medsci.cn/#/login>). Detailed data will be shared with the public at the end of the study upon request.

### ***Follow-up***

The postoperative follow-up of the enrolled patients will be the responsibility of a dedicated nurse. Follow-up will begin after the operation, and each patient will be followed up after discharge by inpatient or outpatient review. The time points selected for follow-up are 3, 6, 12, 18, 24, and 36 months. During follow-up, patients will undergo physical examinations, laboratory tests, and thoracic and abdominal CT scan or ultrasound evaluation, gastroscopy, high-resolution esophageal manometry, 24-hour esophageal pH monitoring, and upper gastrointestinal radiography. The patients' GIQLI and VAS scores will also be assessed so that the efficacy and safety of the TLSA approach can be analyzed. Laboratory tests will include routine blood tests, blood biochemistry tests, salivary pepsin, and serum pepsinogen. If HH recurs, further evaluation of the disease may be required to determine whether surgery is feasible. The detailed follow-up schedule is shown in *Table 1*.

### ***Adverse events***

All serious adverse events (SAEs) occurring between the signing of the informed consent form and the trial's completion will be recorded and reported in detail within 24 hours. The researchers will then report the SAE to the ethics committee of the unit. SAEs are defined as any adverse medical event associated with or not associated with the surgery. During the study, a data monitoring committee will supervise the safety data in an unblinded manner, in accordance with the Standard Operation Procedures for Clinical Trials. Enrolled patients will receive the best treatment for any complications.

If the incidence of treatment-related death or the proportion of grade IV postoperative complications determined to be causally related to the operation exceeds 5% of the total number of patients enrolled, the enrollment of patients will be suspended immediately. Continuation of the study will then be subject to review by the Efficacy and Safety Evaluation Committee of the research group.

### ***Monitoring and quality assurance***

The study has a Data and Safety Monitoring Committee (DSMC), and the committee members have clear roles and cooperate with each other. The supervision committee comprises a senior professor in the field of gastrointestinal surgery, data managers, data inspectors, medical ethics experts, and methodological teams. The DSMC will have unrestricted access to all research data, monitors, auditors' reports, and all other records related to quality assurance activities. The DSMC will periodically review the clinical efficacy and safety data collected in the study, and will evaluate the accumulated reports of SAE. Concurrently, it can also implement emergency reviews and evaluations on safety-related issues. To ensure the homogeneity of clinical data, the study will follow a standard operating procedure (SOP). Specialists will be responsible for data collection, inputting, and cleaning, and follow-up. After all the data have been archived, the researchers will submit the data to the methodology team for statistical analysis. The DSMC is independent of the study sponsors, and there are no conflicts of interest.

### ***Sample size***

The sample size will be calculated using PASS 11.0 (NCSS Statistical and Data Analysis, Kaysville, UT, USA) software.



**Table 1** Checklist for clinical data collection and follow-up plan of enrolled patients

	Baseline			Post-operation					Follow-up				
	Before operation	Operation	POD 1	POD 3	POD 7	POD 30	3 months	6 months	12 months	18 months	24 months	36 months	
Inclusion/Exclusion criteria	x												
Informed consent	x												
Allocation	x												
Demographic information	x												
Laboratory tests	x		x	x			x	x	x	x	x	x	
Operation information		x											
Postoperative recovery outcomes			x	x	x								
Physical examination	x						x	x	x	x	x	x	
Thoracic CT scan	x							x	x	x	x	x	
Abdominal CT scan	x								x	x	x	x	
Upper gastrointestinal radiography	x								x	x	x	x	
Abdominal ultrasound	x						x		x			x	
Gastroscopy	x						x		x			x	
High-resolution esophageal manometry	x								x			x	
24-hour esophageal pH monitoring	x								x			x	
GIQLI and VAS score	x						x	x	x	x	x	x	

x, the need to collect the clinical data. POD, postoperative day; Thoracic CT scan, thoracic computed tomography scan; Abdominal CT scan, abdominal computed tomography scan; GIQLI, gastrointestinal quality of index; VAS, visual analog scale.

Estimates are based on the results of our center's previous research and published literature. The GIQLI score of patients before and after surgery will be the primary outcome used for the sample size calculation.

The hypothesis of the study is that TLSA is superior to TBSA for treating HH. Preliminary results show that the preoperative GIQLI score of the experimental group (TLSA) was  $90.2 \pm 14.3$ , and the postoperative 1-year GIQLI score was  $110.4 \pm 13.7$ . According to the published literature, the preoperative GIQLI score of the control group (TBSA) was  $91.8 \pm 15.1$ , and the postoperative 1-year GIQLI score was  $102.6 \pm 15.0$  (6). Therefore, we presume that the difference in the GIQLI score before and after surgery in the experimental group will be 20.2, while that in the control group will be 10.8, with a standard deviation of 13.0. Setting an  $\alpha=0.025$  level of significance (1 sided), a power of 95%, and a 10% loss to follow-up, we anticipate that 114 patients need to be enrolled; 57 cases in the experimental group and 57 cases in the control group.

### **Statistical analysis**

The results of this trial for efficacy outcomes will be analyzed based on both intention-to-treat protocol and per protocol datasets. SAS 9.2 software will be used to generate the randomization sequence. SPSS version 21.0 (IBM, Armonk, NY, USA) will be used for the statistical analysis. Continuous variables with normal distribution will be described as mean  $\pm$  standard deviation, and independent-samples *t* test will be used for difference tests. Continuous variables with non-normal distribution will be described as the median, and the Mann-Whitney U-test will be used for the difference test. The  $\chi^2$ -test or Fisher's exact test will be used for categorical data. The GIQLI score will be tested by repeated analysis of variance. The  $\chi^2$ -test or Fisher's exact test will be used for adverse events. The Kaplan-Meier method will be used for the survival analysis. The log-rank test will be used to compare the postoperative recurrence rate between the two groups.  $P < 0.05$  will be considered statistically significant.

### **Interim analyses**

Statistical analysis for the primary endpoint will be performed when the total number of enrolled patients reaches 57. The interim analysis will be carried out by an independent statistical team, and the results will be reported to the DSMC. The DSMC will have unrestricted access to

all data, and will discuss the results of the interim analysis and ultimately report to the research group's Efficacy and Safety Evaluation Committee, which will determine whether or not the study can be continued. If the efficacy and safety of the TLSA are lower than those of the TBSA in the interim data results, the clinical trial will be suspended.

### **Patient involvement**

The researchers have played, and will continue to play, an important role in the study design, collection, analysis, and interpretation of data, the writing of the report, and the decision to submit the report for publication.

### **Dissemination plans**

The results will be published in high-quality peer-reviewed journals at the end of study.

### **Trial status**

Version 1.0 of the study protocol was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University in June 2020. The trial was registered in June 2020 on the Chinese Clinical Trial Registry website (<http://www.chictr.org.cn/index.aspx>). We have established the SOP, CRF, and EDC systems for clinical research. In July 2020, we commenced patient enrollment, and the enrollment period is anticipated to conclude in December 2023. Our research currently has 12 enrolled patients, and we plan to publish the research results in May 2024.

### **Discussion**

In the treatment of HH, clinicians are paying increased attention to the improvement of patients' postoperative QOL while pursuing surgical efficacy, for which the protection of the vagus nerve and organ function is particularly important. The terminal branches of the vagus nerve have the peristaltic effect of coordinating the pylorus and duodenum, and can maintain appropriate pyloric tension, prevent gastric emptying disorders, reduce gastric acid secretion, and control gastric acid reflux to a certain extent (12,13). It was confirmed in a previously published study that preservation of the abdominal branches of the vagus nerve significantly improves postoperative gastrointestinal motility and reduces the incidence of gastroparesis in patients with HH (14). The vagus nerve

can directly act on liver cells to promote liver glycogen and protein synthesis, thereby reducing blood sugar and blood lipids, promoting liver cell regeneration, and ultimately controlling blood sugar and blood lipids within the normal range. Hashimoto *et al.* found that the hepatic branch of the vagus nerve plays an important role in the regulation of blood lipids in mice (15). López-Soldado *et al.* found that the impact of liver glycogen regulation on food intake and glucose homeostasis was dependent on the hepatic branch of the vagus nerve; therefore, the hepatic branch of the vagus nerve has certain advantages in postoperative blood glucose and lipid control in patients with diabetes (16). Another study found that vagus nerve injury leads to relative hyperexcitability of the sympathetic nerve, which results in postoperative symptoms of belching, acid reflux, bloating, stomachache, and diarrhea, of which diarrhea is one of the primary factors affecting QOL (17). Furthermore, studies have confirmed that the hepatic branch of the vagus nerve controls movement of the liver and biliary tract (18). When this branch is injured, the gallbladder's peristalsis function decreases, the secretion of bile is restricted, and the secretion of gastrointestinal hormones becomes imbalanced, which increases the risk of gallbladder stones and gallbladder necrosis. Severe cases of inflammation require surgical intervention (18). Therefore, if the hepatic branch of the vagus nerve can be effectively protected during the operation, the incidence of gallbladder stones can be reduced. A meta-analysis found that the incidence of gallstones was lower in patients with gastric cancer who underwent radical gastrectomy with vagus nerve preservation than in those whose procedures did not include vagus nerve preservation (19). Kim *et al.* conducted a prospective, randomized controlled study to examine the effect of vagus nerve preservation on patients' postoperative QOL and found that preservation of the hepatic branch of the vagus nerve can reduce the occurrence of postoperative gallstones, reducing the need for secondary surgery (20).

Although the American Association of Gastrointestinal Endoscopy Surgeons issued guidelines for the diagnosis and treatment of HH in 2013, there are no detailed regulations on how to avoid nerve injury and protect organ function during HH surgery, nor are there any regulations on surgical procedures for HH (5). Moreover, although there have been many studies on the degree of fundoplication, discussion on different surgical approaches is still rare. Consequently, we are conducting the present clinical trial to establish the normative treatment for HH, in an effort to improve patients' QOL.

The main limitation of the present study is that it is a single-center, randomized controlled trial, and the evidence quality is lower than that of a large-sample, multicenter, randomized controlled study. However, our research will provide important data from which to build iterations of the research protocol in the future. We will also enroll more research centers and patients to identify more precise therapies for HH and improve the short- and long-term treatment efficacy for patients with this disease.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol has been approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (L-2020-019). Informed consent will be obtained from each patient. The results will be disseminated to the public through paper in open access journals.

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