Randomised Controlled Trial

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Final results of a randomized controlled trial: comparison of the efficacy and safety between totally laparoscopic and laparoscopic-assisted total gastrectomy for advanced Siewert III esophagogastric junction cancer and upper and middle third gastric cancer

Juan Wang, PhD[a,b], Shushang Liu, MD[a], Haixiang Chen, BSc[c], Jialin Luo, MD[a], Guanghui Xu, MD[a], Xiangying Feng, BSc[a], Xuewen Yang, BSc[a], Jianjun Yang, PhD[a,b,*], Ji Gang, PhD[a,b,*]

Background: This study aimed to compare the efficacy and safety of TLTG with the overlap technique to LATG in patients with advanced Siewert III Esophagogastric Junction Cancer and upper and middle third gastric cancer.

Methods: This single-center RCT enrolled 292 patients with the mentioned cancers, randomly assigned to TLTG overlap ($n = 146$) or LATG ($n = 146$) groups. Data on demographics, pathology, intraoperative variables, postoperative complications, recovery parameters, and 3-year survival were collected. Main outcome: postoperative complications within 30 days. Secondary outcomes: 3-year disease-free and overall survival.

Results: TLTG versus LATG: TLTG had shorter incision, faster flatus/defecation, reduced analgesia, less opioid use, and shorter hospital stay. Similar operation time, anastomosis time, blood loss, and lymph node harvest. TLTG had a lower overall post-op complication rate (P = 0.047) and no significant difference in serious complications ($P = 0.310$). Variances in anastomotic stenosis occurrence at 3 months. No rehospitalization or mortality at 30 days. No significant differences in 3-month disease-free survival ($P = 0.058$) or overall survival ($P = 0.236$).

Conclusion: The overlap method for anastomosis in TLTG is safe and feasible for advanced middle-upper-third gastric cancer, with positive short-term outcomes. This technique has the potential to be the preferred esophagojejunostomy approach in TLTG.

Trial registration: This trial has been registered at Chinese Clinical Trial Registry: ChiCTR1900025667 (registration date: 4 September 2019).

Keywords: gastric cancer, laparoscopic-assisted total gastrectomy, overlap reconstruction, postoperative complications, randomized controlled trial, Siewert III esophagogastric junction cancer, totally laparoscopic total gastrectomy

Introduction

The pioneering work of Kitano *et al*.[1] in introducing laparoscopy-assisted distal gastrectomy has significantly contributed to the increased adoption of totally laparoscopic distal gastrectomy in clinical practice, which has proven to be a secure and efficient treatment method for distal gastric cancer[2–5]. Nevertheless, the adoption of laparoscopic total gastrectomy is limited due to technical complexities, specifically in the intricate creation of an esophagojejunostomy[6–13]. Currently, Siewert classification is commonly used for upper gastric cancer and gastroesophageal junction cancer. According to the position of the tumor center point from the dentate line of the cardia, it is divided into type I (1–5 cm above the dentate line), type II (1 cm above the dentate

[a]Department of Digestive Surgery, The First Affiliated Hospital of Air Force Military Medical University, [b]National Key Laboratory for Integrated Prevention and Treatment of Digestive System Tumors, Xi'an and [c]Medical Record Department, Nanjing Hospital of C.M. Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Nanjing, People's Republic of China

Juan Wang, Shushang Liu, and Haixiang Chen contributed equally to this work.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding authors. Address: Department of Digestive Surgery, The First Affiliated Hospital of Air Force Military Medical University, Xi'an 710032, People's Republic of China. Tel.: +86 298 477 1532. E-mail: jigangfmmu@163.com (J. Gang); Department of Digestive Surgery, The First Affiliated Hospital of Air Force Military Medical University, Xi'an 710032, People's Republic of China. E-mail: yangjj@fmmu.edu.cn (J. Yang).

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line to 2 cm below the dentate line), and type III (2–5 cm below the dentate line). Among them, Siewert III type is classified as gastric cancer and can be treated with radical total gastrectomy. Despite the availability of multiple techniques for completely laparoscopic total gastrectomy, none have gained widespread acceptance[14–16]. During laparoscopic-assisted radical gastrectomy, the reconstruction of the digestive tract is typically achieved through a small incision in the upper abdomen. However, this can present challenges for patients with obesity, a narrow rib arch angle, or high-positioned tumors, often requiring incision extension. This practice may diminish the benefits of minimally invasive surgery and elevate the likelihood of postoperative complications associated with the incision site[17]. In contrast, totally laparoscopic total gastrectomy only requires a 5–6 cm incision. Furthermore, compared to laparoscopy-assisted total gastrectomy (LATG), the anastomosis in totally laparoscopic total gastrectomy benefits from improved magnification and optimal exposure[14,15,18–21]. This method provides enhanced visibility of the lower esophageal area, allowing for precise removal of lymph nodes around the esophagogastric junction and lower esophagus. Significantly, this approach allows for successful implementation even in difficult situations, such as in overweight patients with larger lesions and tumors located higher up[11].

The reconstruction of the digestive tract is a crucial step in the field of completely laparoscopic total gastrectomy (TLTG). One of the many challenges faced in laparoscopic total gastrectomy (LTG) is the complex task of performing an esophagojejunostomy[22,23]. Of particular concern is the risk of anastomotic leakage at the esophagojejunostomy junction, which can have serious and potentially life-threatening consequences. This highlights the utmost importance of identifying the most secure anastomotic approach for the success of TLTG. Following the principles of traditional open surgery, the Roux-en-Y (RY) reconstruction protocol is typically performed after total gastrectomy. Currently, there exists a wide range of methodologies for performing esophagojejunostomy after TLTG. These techniques encompass the circular stapler method for establishing an end-to-side anastomosis between the esophagus and jejunum, the inventive OrVilTM anastomosis method[24,25], the antipuncture approach, and linear approaches, including the functional esophagus-jejunal end-to-end anastomosis (FEEA) and the esophago-jejunal percutaneous side-to-side anastomosis (overlap method)[26–28]. Despite this diverse array of options, a consensus on the most effective modality for esophagojejunostomy in TLTG has yet to be reached, leading to ongoing exploration and investigation[8,29].

The conventional method for performing esophagojejunostomy involves a small incision in the upper abdomen, which presents difficulties due to limited visibility and a restricted surgical environment. The intricate manipulation of purse-string sutures and precise placement of the anvil pose significant challenges when performing laparoscopic procedures using the circular stapler method, due to the limited working space. Additionally, the use of circular staplers for esophagojejunostomy increases the risk of stenosis, highlighting the need for a more refined approach[30]. As a result, a growing number of surgeons have turned to total laparoscopic esophagojejunostomy in recent years, enticed by the promise of improved precision and a more controlled surgical environment.

The rise of linear staplers in laparoscopic surgery for constructing esophagojejunostomies marks a significant shift, based on their superior visual clarity compared to traditional circular stapling methods, as well as the creation of a larger anastomotic opening[26,27,31]. In the realm of totally laparoscopic total gastrectomy (TLTG), a significant breakthrough emerged with the inception of the esophago-jejunal percutaneous side-to-side anastomosis, referred to as the overlap method, which was first introduced by Inaba *et al*. in 2010[26]. The innovative approach of TLTG has demonstrated a reduced risk of anastomotic stenosis by eliminating purse-string sutures and anvil insertion. The unrestricted anastomotic diameter, independent of esophageal and jejunal transverse dimensions, serves as a protective barrier against postoperative stenosis. Recent research by Kitagami *et al*. supports the efficacy and safety of TLTG for managing gastric cancer[7,15,27,28]. Although LTG is gaining because of its quicker recovery period and perceived lower invasiveness, the application of the overlap method for reconstruction is restricted to specific institutions and lacks extensive large-scale studies on its efficacy[15,32,33]. The lack of comprehensive clinical randomized controlled trials comparing TLTG with the overlap method to LATG for advanced Siewert III esophagogastric junction cancer and upper/middle third gastric malignancies signified a significant gap in current scientific literature. To address this gap, our single-center, prospective randomized controlled trial aims to compare the effectiveness and safety profiles of TLTG with the overlap method versus LATG in treating advanced Siewert III esophagogastric junction cancer and upper/middle third gastric cancer.

HIGHLIGHTS

- This study is a large sample size randomized controlled trial that compares the feasibility and oncological outcomes of patients who underwent TLTG with the overlap method versus LATG.
- The results of this study indicate that TLTG with the overlap method is a technically safe procedure, as evidenced by acceptable postoperative complications and superior postoperative recovery outcomes.

Patients and methods

This study is a prospective, single-center, single-blind, two-arm randomized controlled trial that has been approved by the Ethics Committee of the First Affiliated Hospital (Xijing Hospital) of Fourth Military Medical University (KY20192093-X-1). The methodology for the ongoing trials was previously published[34]. All participants, as well as their guardians, primary caregivers, and research assistants, have provided written informed consent.

The study included adult patients aged 18–65 diagnosed with advanced Siewert III esophagogastric junction cancer or upper and middle gastric cancer who underwent laparoscopic radical total gastrectomy at Xijing Hospital. Participants were randomly assigned in a 1:1 ratio to the experimental group (TLTG) or the control group (LATG) using a computer-generated randomization scheme. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR1900025667) on 4 September 2019. Surgeons performing the procedures had a minimum experience of 200 cases each in TLTG and LATG. The study primarily focused on postoperative complications occurring within 30 days of surgery, including intra-abdominal hemorrhage, gastrointestinal bleeding, anastomotic leakage, duodenal stump fistula, and other issues. These complications will be classified based on the

Clavien–Dindo system[35]. Secondary endpoints include 3-year disease-free and overall survival rates, with disease-free survival indicating the time from surgery to recurrence or metastasis detection, and overall survival representing the time from surgery to death. The flowchart of this trial is shown in Figure 1. The work has been reported in line with Consolidated Standards of Reporting Trials (CONSORT) Guidelines[36].

The inclusion and exclusion criteria

The inclusion criteria were as follows: 1) age between 18 and 65 years; 2) Siewert type III adenocarcinoma of the esophagogastric junction or gastric cancer of the upper and middle part of the stomach; 3) no neoadjuvant chemotherapy received; 4) feasible to perform D2 radical total gastrectomy (R0 resection), 5) absence of distant metastases and surrounding adjacent organ invasion on preoperative contrast-enhanced computed tomography (CT) chest and abdomen; 6) preoperative staging cT2-4aN0-3M0 (according to AJCC-7th TNM tumor staging); 7) voluntary participation in the study and the provision of informed consent; 8) preoperative Eastern Cooperative Oncology Group (ECOG) score of 0 to 2; 9) preoperative white blood cells (WBC) $\geq 3 \times 10^9$/l, absolute neutrophil count (NEU) $\geq 1.5 \times 10^9$/l, platelet (PLT) $\geq 100 \times 10^9$/l; and 10) preoperative American Society of Anesthesiologists (ASA) score of I–III.

The exclusion criteria were as follows: 1) contraindications for laparoscopic surgery; 2) uncontrolled severe medical diseases, including unstable angina or myocardial infarction within 6 months, congestive heart failure greater than New York Heart Association (NYHA) 2, arrhythmia requiring antiarrhythmic drugs, thrombosis or embolic events within 6 months, severe central nervous system or blood system disease, heart, lung, liver, or kidney dysfunction, immunodeficiency, liver cirrhosis, portal hypertension, or splenomegaly; 3) trauma, fracture, or serious surgery within 6 weeks before the start of the study; 4) autologous bone marrow transplantation or stem cell rescue treatment within 4 months before the start of the study; 5) history of allogeneic organ transplantation; 6) pregnant or lactating women; 7) serious mental illness; 8) history of previous esophageal or gastric surgery; 9) history of other malignant tumors within 5 years; 10) emergency surgery; 11) participating in other clinical trials.

Surgical intervention/treatment protocols

The experimental group received TLTG. For TLTG, all the anastomoses were performed laparoscopically. Jejunojejunostomy (Y anastomosis) were performed before esophagojejunostomy. The jejunum was intracorporeally transected at a point 20 cm distal to the ligament of Treitz using a 60 mm Endo-GIA linear stapler. At ~55 cm distal to the planned site for esophagojejunostomy, a side-to-side jejunojejunostomy were performed using a 60 mm linear stapler. The entry point was closed with an extracorporeal interrupted hand-sewn technique using absorbable monofilament sutures. The jejunal mesenteric defect were closed to prevent internal herniation. The duodenal and distal jejunal staple lines were reinforced with interrupted 4–0 absorbable sutures. A small hole was made 6 cm distal to the stapler line on the antimesenteric side of the jejunal limb, while another small hole was made on the left wall of the esophageal stump. One limb of the 45 mm linear stapler was inserted into the esophageal stump using the nasogastric tube as a guide and another limb of the liner stapler was placed in the jejunal limb. The forks of the stapler were closed and fired to construct a Roux-en-Y side-to-side esophagojejunal anastomosis. After the hemostasis at the anastomosis site was confirmed, the entry hole was closed by continuous full-thickness hand suturing using a 3–0 barbed suture. The D2 lymph node

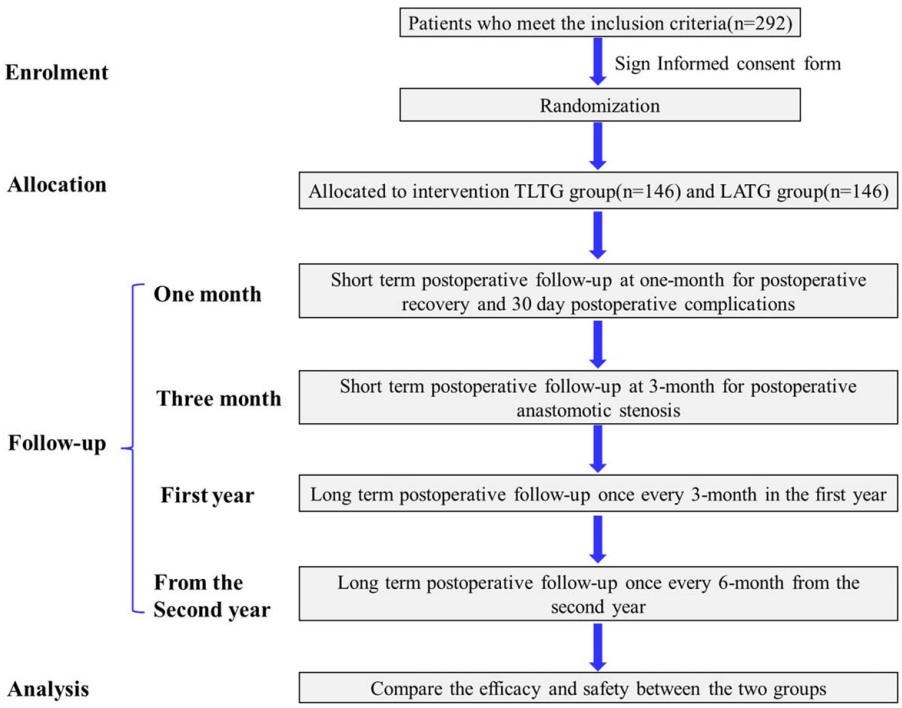

Figure 1. Flowchart of patient enrollment.

dissection was performed and the whole stomach and the lower esophagus were fully mobilized. The esophagus and the duodenum were transected using a 60 mm linear stapler. The resected specimen was removed through the umbilical port site by extending the incision. The right diaphragmatic crus and the ventral side of the esophageal hiatus were partially divided to widen the surgical field for reconstruction, if necessary.

The patients in the control group were receive LATG. The procedure for radical D2 lymphadenectomy and the complete mobilization of the stomach were the same as that used in the overlap group. The esophagojejunal anastomosis were performed with the traditional open Roux-en-Y anastomosis technique using a circular stapler. An 8–10 cm incision was made in the upper abdomen. Purse-string sutures were placed 2–3 cm away from the upper edge of the tumor and the esophagus and the duodenum were routinely transected. The anvil of the circular stapler was inserted into the esophageal stump. The jejunum was extracorporeally transected 25 cm distal to the ligament of Treitz. Then, a Roux-en-Y end-to-side esophagojejunal anastomosis were constructed with the circular staplers. Finally, a jejunojejunal side-to-side anastomosis were made about 55 cm below the esophagojejunostomy using a hand sewn method extracorporeally.

Sample size estimation

In our central database, which includes data from 2268 individuals who underwent radical total gastrectomy, the documented incidence of postoperative complications was 19.9%. For the experimental group, we estimated an incidence rate of 8%. The study parameters were selected to facilitate a noninferiority analysis with a specified noninferiority margin of 20% ($\alpha = 0.05$, $\beta = 0.20$, power of 80%). Following rigorous calculations, a sample size of 132 per group was determined, totaling 264 participants. To accommodate a potential 10% attrition rate, the study will recruit 292 participants (146 in each group) in line with established guidelines[34].

Statistical analysis

Data will be presented as mean ± SD or numerical values with corresponding percentages. The study will include detailed information on enrolled, excluded, completed, and lost to follow-up subjects, providing a clear overview of each group's status in the analytical dataset. Comprehensive comparisons will be conducted across various domains, including baseline characteristics, intraoperative parameters, and postoperative histopathology, to assess equivalence between the two cohorts. Statistical analysis will involve the use of *t*-tests for continuous variables, χ^2 tests for overall complication rates, and the Wilcoxon rank sum test for laboratory parameters, intraoperative metrics, and postoperative histopathological characteristics. Survival analysis will be performed using the Kaplan–Meier method, with the Log-Rank test for evaluating differences in survival outcomes. SAS 9.4 software or a newer version will be used for statistical analyses, with all *P*-values calculated based on a two-tailed approach and a significance level of $P < 0.05$.

Results

Demographic and clinicopathological characteristics of the enrolled patients

A total of 292 participants were evenly distributed, with 146 individuals in each group. All 292 procedures were performed accurately without intraoperative complications or the need for open surgery. R0 resection was achieved successfully for all patients. Analysis revealed no significant differences between the groups in various parameters, including gender distribution ($P = 0.496$), age ($P = 0.901$), ASA score ($P = 0.408$), differentiation ($P = 0.637$), tumor site ($P = 0.125$), Lauren classification ($P = 0.323$), T pathological stage ($P = 0.798$), N pathological stage ($P = 0.092$), clinical staging ($P = 0.866$), comorbidities (diabetes, $P = 0.238$; hypertension, $P = 0.756$; respiratory, $P = 0.876$; cardiovascular, $P = 0.152$), tumor complications (bleeding, $P = 0.607$; obstruction, $P = 0.643$), laboratory values (serum albumin, $P = 0.385$; hemoglobin, $P = 0.619$), BMI ($P = 0.414$), and tumor size ($P = 0.293$). Clinical and pathological characteristics are summarized in Table 1.

Perioperative surgical outcomes

In the field of intraoperative results, a thorough evaluation was conducted, which included the duration of the operation, the time for esophagojejunostomy anastomosis, the amount of blood loss during surgery, the number of lymph nodes retrieved, and the size of the incision. All of these factors were carefully recorded and thoroughly examined. Remarkably, there were no notable distinctions between the two cohorts regarding the average operation time ($t = 1.499$, $P = 0.135$), time to perform esophagojejunostomy anastomosis ($t = 1.309$, $P = 0.192$), amount of blood loss during surgery ($t = 0.407$, $P = 0.684$), and total count of retrieved lymph nodes ($t = 1.406$, $P = 0.161$). In the TLTG cohort, a portion of patients required blood transfusions, with seven individuals (4.79%) receiving this treatment. In the LATG cohort, this number increased to nine patients (6.16%). Nonetheless, there was no statistically significant disparity between the two cohorts ($\chi^2 = 0.264$, $P = 0.607$). Notably, the average incision length in the TLTG cohort was significantly shorter than that in the LATG cohort ($t = 43.38$, $P < 0.0001$). None of the surgeries necessitated a transition to alternative laparoscopic anastomosis techniques or open surgical interventions. A detailed comparison of the surgical outcomes for patients in both groups is clearly delineated in Table 2.

Postoperative recovery outcomes

The assessment of postoperative recuperation involved a thorough examination of various factors, including the interval until the initial instance of flatulence or bowel movement, the length of time pain medication was used, the use of opioids, and the duration of hospitalization after surgery. As demonstrated in Table 3, significantly, the TLTG cohort exhibited a notably reduced time to initial flatus or bowel movement in comparison to the LATG group ($t = 12.11$, $P < 0.0001$). Additionally, the TLTG group demonstrated a significantly shorter period of postoperative pain relief compared to the LATG group ($t = 13.47$, $P < 0.0001$). Notably, a subset of patients (2.74%) in the LATG group required opioid administration, while no such intervention was necessary for the TLTG cohort. Furthermore, there was a noticeable difference in opioid usage, with the TLTG group requiring significantly less administration compared to the LATG group ($\chi^2 = 4.056$, $P = 0.044$). Moreover, the TLTG cohort exhibited a significantly shorter postoperative hospitalization period compared to the LATG group ($t = 3.494$, $P = 0.0006$), highlighting a faster recovery trajectory in the former. A detailed

Table 1

Comparison of demographic and clinicopathologic characteristics.

Clinicopathologic characteristics	TLTG group ($n=146$)	LATG group ($n=146$)	P	χ^2
Sex			0.496	0.463
Male	128	124		
Female	18	22		
Age	58.19 ± 5.43	58.12 ± 4.91	0.901	0.124
ASA score			0.408	0.685
I	80	87		
II	66	59		
Differentiation			0.637	0.902
I	35	35		
II	67	60		
III	44	51		
Tumor site			0.125	0.723
Siewert III Esophagogastric Junction	81	9		
Upper and middle third	65	11		
Lauren classification			0.323	2.258
Intestinal type	34	45		
Diffuse type	68	64		
Hybrid type	44	37		
T pathological stage			0.798	0.451
T2	52	50		
T3	59	56		
T4	35	40		
N pathological stage			0.092	6.438
0	35	31		
1	37	57		
2	41	32		
3	33	26		
Clinical stage			0.866	0.288
I	16	14		
II	62	66		
III	68	66		
Comorbidity				
Diabetes	24	17	0.238	1.390
Hypertension	24	26	0.756	0.097
Respiratory	24	25	0.876	0.025
Cardiovascular	28	19	0.152	2.054
Tumor complications				
Bleeding	7	9	0.607	0.264
Obstruction	9	11	0.643	0.215
Serum albumin (g/l)	42.61 ± 7.73	41.85 ± 7.21	0.385	0.871
Hemoglobin (g/l)	124.70 ± 19.71	125.90 ± 20.52	0.619	0.497
BMI	24.61 ± 2.27	24.31 ± 2.24	0.414	0.819
Tumor size (diameter, cm)	3.74 ± 1.57	3.93 ± 1.54	0.293	1.055

ASA score, American Society of Anesthesiologists score.

analysis of postoperative recovery outcomes for patients in both groups can be found in Table 3.

Postoperative complications

Table 4 summarizes postoperative complications in the TLTG and LATG groups, with 6.16 and 13.01% of patients developed postoperative complications, respectively. The TLTG group had a significantly lower postoperative complication rate than the LATG group ($P=0.047$). Severe complications (Clavien–Dindo grade >III) occurred in three TLTG and six LATG patients, showing no significant difference ($P=0.310$). Effective management strategies were employed for all postoperative

Table 2

Comparison of perioperative surgical variables between TLTG group and LATG group.

Surgical variable	TLTG group	LATG group	P	t
Operation time (minutes)	278.4 ± 54.36	287.90 ± 53.40	0.135	1.499
Time to perform esophagojejunostomy anastomosis (minutes)	48.32 ± 8.76	49.69 ± 9.12	0.192	1.309
Estimated blood loss (ml)	299.30 ± 212.00	309.20 ± 204.50	0.684	0.407
Total number of harvested lymph nodes	39.57 ± 5.83	40.50 ± 5.49	0.161	1.406
Incision length (cm)	5.01 ± 0.82	9.01 ± 0.76	< 0.0001	43.38

Table 3

Comparison of postoperative recovery outcomes between TLTG group and LATG group.

Surgical variable	TLTG group	LATG group	P	t/χ^2
The time to first flatus or defecation (hours)	54.91 ± 9.51	67.28 ± 7.87	< 0.0001	12.110
Days of administration of analgesics	1.59 ± 0.68	2.76 ± 0.80	< 0.0001	13.470
Administration of opioid	0	4	0.044	4.056
Duration of postoperative hospitalization (d)	6.40 ± 3.95	8.62 ± 6.61	0.0006	3.494

Table 4

Comparison of postoperative complications between TLTG group and LATG group.

Complications	TLTG group ($n=146$)	LATG group ($n=146$)	P	χ^2
All postoperative complications	9 (6.16%)	19 (13.01%)	0.047	3.950
Clavien–Dindo grade >III	3 (2.05%)	6 (4.11%)	0.310	1.032
Anastomosis leakage	0	6 (4.11%)	0.013	6.126
Duodenal stump leakage	2 (1.37%)	3 (2.05%)	0.652	0.203
Pancreatic fistula	2 (1.37%)	3 (2.05%)	0.652	0.203
Intra-abdominal hemorrhage	2 (1.37%)	3 (2.05%)	0.652	0.203
Abdominal infection	4 (2.74%)	12 (8.22%)	0.040	4.232
Pulmonary infection	5 (3.42%)	4 (2.74%)	0.735	0.115
Wound infection	0	3 (2.05%)	0.082	3.031
Wound dehiscence	0	2 (1.37%)	0.156	2.014
Ileus	2 (1.37%)	3 (2.05%)	0.652	0.203
Unplanned secondary surgery	3 (2.05%)	6 (4.11%)	0.310	1.032
Rehospitalization	0	0	–	–
30-day mortality	0	0	–	–
Gastrointestinal bleeding	0	0	–	–
Chyle leakage	0	0	–	–
Pleural effusion	0	0	–	–
Pulmonary embolism	0	0	–	–
Thrombosis	0	0	–	–
Embolism	0	0	–	–
Deep vein thrombosis	0	0	–	–

complications. The distribution and analysis of the main complications were shown in Figure 2.

Specifically, esophagojejunal anastomotic leakage was observed in six patients in LATG group but none in the TLTG group ($P = 0.013$). One patient was managed by endoscopic treatment with a self-expanding metal stent, three patients were managed by reoperation and other two patients were recovered by conservative treatment. Duodenal stump leakage affected two patients (1.37%) in the TLTG group and in three patients (2.05%) in the LATG group ($P = 0.652$). Two patients in the TLTG group and two patients in the LATG group were successfully managed by surgical treatment (duodenal tube decompression, abdominal lavage, and tube drainage), the other one patient in the LATG group was cured by conservative treatment. Pancreatic fistula was observed in two patients (1.37%) in the TLTG group, and in three patients (2.05%) in the LATG group ($P = 0.652$). Except for one case in TLTG group who underwent surgical treatment, the remaining four cases were cured through conservative treatment. Abdominal hemorrhage was observed in two patients (1.37%) in the TLTG group, and in three patients (2.05%) in the LATG group ($P = 0.652$). One patient in TLTG group and two patients in LATG group were managed conservatively by blood transfusion, while other one patient in TLTG group and one patient in LATG group were treated by reoperation. In the TLTG group, four patients (2.74%) developed abdominal infection, while 12 patients (8.22%) in the LATG group encountered this complication ($P = 0.040$). Treatment involved reoperation for three patients in TLTG group and five patients in LATG group, and drainage with anti-infection medication for the remaining one patient in TLTG group and seven patients in LATG group. Pulmonary infection occurred in five patients in TLTG group (3.42%) and four patients in LATG group (2.74%) ($P = 0.735$), all nine patients managed successfully with conservative methods such as anti-infection and promotion of sputum excretion. In the TLTG group, there were no patient developed wound infection or wound dehiscence, while in the LATG group, there were three and two patients occurred wound infection or wound dehiscence, respectively. Patients with wound dehiscence were cured by reoperation, while patients with wound infection were cured conservatively. Ileus was observed in two patients (1.37%) in TLTG group and three patients (2.05%) in LATG group ($P = 0.652$), all of these five patients underwent reoperation. There was no significant difference in unplanned secondary surgeries between the two groups ($P = 0.310$). All patients with complications were successfully managed. Here, the incidence of some complications such as duodenal stump leakage ($P = 0.652$), pancreatic fistula ($P = 0.652$), abdominal bleeding ($P = 0.652$), pulmonary infection ($P = 0.735$), wound infection ($P = 0.082$), wound dehiscence ($P = 0.156$), and ileus ($P = 0.652$) showed no significant variance between the two groups, while notable differences were seen in the incidence of esophagojejunal anastomotic leakage ($P = 0.013$) and abdominal infection ($P = 0.040$) between the two groups. Additionally, there was no occurrence of gastrointestinal bleeding, chyle leakage, pleural effusion, pulmonary embolism, thrombosis, embolism, and deep vein thrombosis in both groups of patients after surgery. The patient's complications and management were summarized in Table 5. There were no instances of rehospitalization in either group. Additionally,

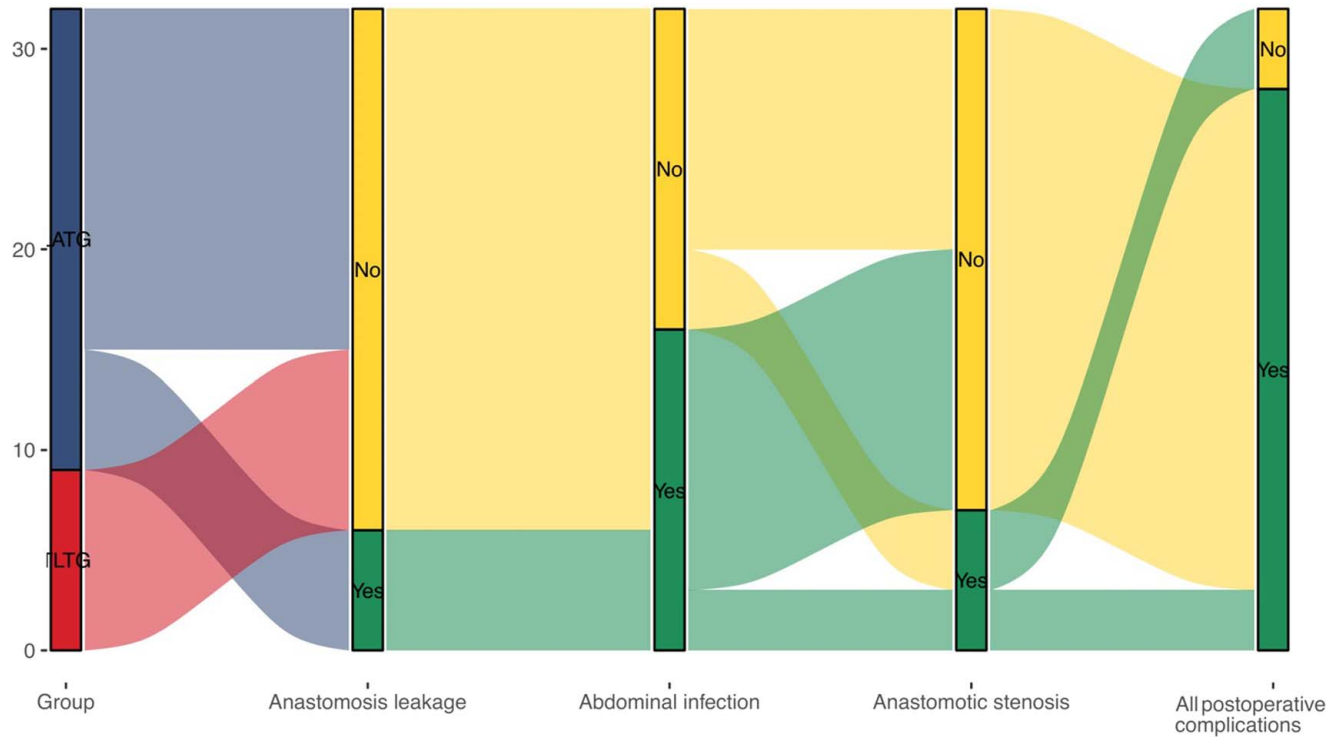

Figure 2. Distribution of different complications in two groups of patients with complications.

Table 5

The patient's complications and treatment.

Case	Sex	Age	Group	Type of complication	Clavien–Dindo classification	Treatment	Hospital days
1	M	65	TLTG	Pancreatic fistula, abdominal and pulmonary infection, ileus	4	Operation	20
2	M	64	TLTG	Abdominal bleeding	2	Conservative	13
3	M	62	TLTG	Pancreatic fistula, abdominal infection	2	Conservative	20
4	M	58	TLTG	Duodenal stump leakage, abdominal bleeding and infection, ileus	4	Operation	33
5	M	64	TLTG	Duodenal stump leakage and abdominal infection	3A	Operation	28
6	M	65	TLTG	Pulmonary infection	2	Conservative	15
7	M	58	TLTG	Pulmonary infection	2	Conservative	10
8	M	62	TLTG	Pulmonary infection	2	Conservative	11
9	M	57	TLTG	Pulmonary infection	2	Conservative	13
10	M	55	LATG	Duodenal stump leakage and abdominal infection	2	Conservative	17
11	M	64	LATG	Abdominal bleeding	2	Conservative	11
12	F	59	LATG	Pulmonary infection	2	Conservative	15
13	M	58	LATG	Duodenal stump leakage, abdominal and pulmonary infection, ileus	3A	Operation	36
14	M	58	LATG	Duodenal stump leakage, abdominal infection, ileus	3A	Operation	36
15	M	64	LATG	Anastomosis leakage, abdominal infection	2	Conservative	26
16	M	62	LATG	Wound infection	2	Conservative	13
17	M	62	LATG	Abdominal bleeding	2	Conservative	12
18	M	63	LATG	anastomosis leakage, abdominal infection	3A	Operation	45
19	M	61	LATG	Anastomosis leakage, abdominal infection and bleeding, wound dehiscence	4	Operation	35
20	M	52	LATG	Anastomosis leakage, abdominal infection	3A	Operation	38
21	M	62	LATG	Anastomosis leakage, abdominal infection	2	Conservative	17
22	M	65	LATG	Pulmonary infection, wound dehiscence, ileus	3A	Operation	26
23	M	58	LATG	Wound infection	2	Conservative	10
24	M	64	LATG	Pancreatic fistula, abdominal infection	2	Conservative	15
25	M	63	LATG	Pulmonary infection	2	Conservative	13
26	M	58	LATG	anastomosis leakage, abdominal infection	2	Conservative	16
27	F	46	LATG	Pancreatic fistula, abdominal infection	2	Conservative	16
28	M	60	LATG	Pancreatic fistula, abdominal infection, wound infection	2	Conservative	25

there were no reported deaths within 30 days following surgery in either group.

Long-term follow-up outcomes

In terms of long-term postoperative follow-up outcomes, it is important to highlight that none of the patients in the TLTG group exhibited anastomotic stenosis, whereas seven patients in the LATG group encountered this complication by 3-months follow-up. This variation was determined to be statistically significant with a *P*-value of 0.007 (Table 6). At the 1-year follow-up after surgery, 19 patients in the LATG group had anastomotic stenosis, while none of the patients in the TLTG group had anastomotic stenosis. The difference between the two groups was statistically significant ($P < 0.0001$, Table 6). At the 2-year follow-up after surgery, 28 patients in the LATG group had anastomotic stenosis, while none of the patients in the TLTG group had anastomotic stenosis. The difference between the two groups was also statistically significant ($P < 0.0001$, Table 6).

Furthermore, in terms of the long-term nutritional status of enrolled patients after surgery, we use body weight changes to reflect the enrolled patient's long-term nutritional status. We found that there was no statistically significant difference between the two groups of enrolled patients in the average weight change at 1-year ($P = 0.143$, Table 6) and 2-year ($P = 0.486$, Table 6) follow-up after surgery, respectively.

Survival outcomes

At the data cut-off point on 2 January 2024, the median follow-up duration stood at 41 months (range: 6–51). Within this timeframe, the TLTG cohort exhibited a median DFS of 40 months, while the LATG cohort reported a median DFS of 39 months. In terms of OS, the TLTG group demonstrated a median OS of 41.5 months, slightly higher than the LATG group's median OS of 41 months. The DFS rate for the TLTG

Table 6

Comparison of long-term follow-up outcomes between TLTG group and LATG group.

Long-term follow-up outcomes	TLTG group	LATG group	*P*	t/χ^2
Anastomotic stenosis 3 months after surgery	0	7 (4.79%)	0.007	7.172
Anastomotic stenosis 1-year after surgery	0	19 (4.79%)	< 0.0001	20.322
Anastomotic stenosis 2-year after surgery	0	28 (4.79%)	< 0.0001	30.970
The average weight change at 1-year	1.27 ± 1.03	1.46 ± 1.03	0.143	1.469
The average weight change at 2-year	3.78 ± 0.70	3.72 ± 0.58	0.486	0.699

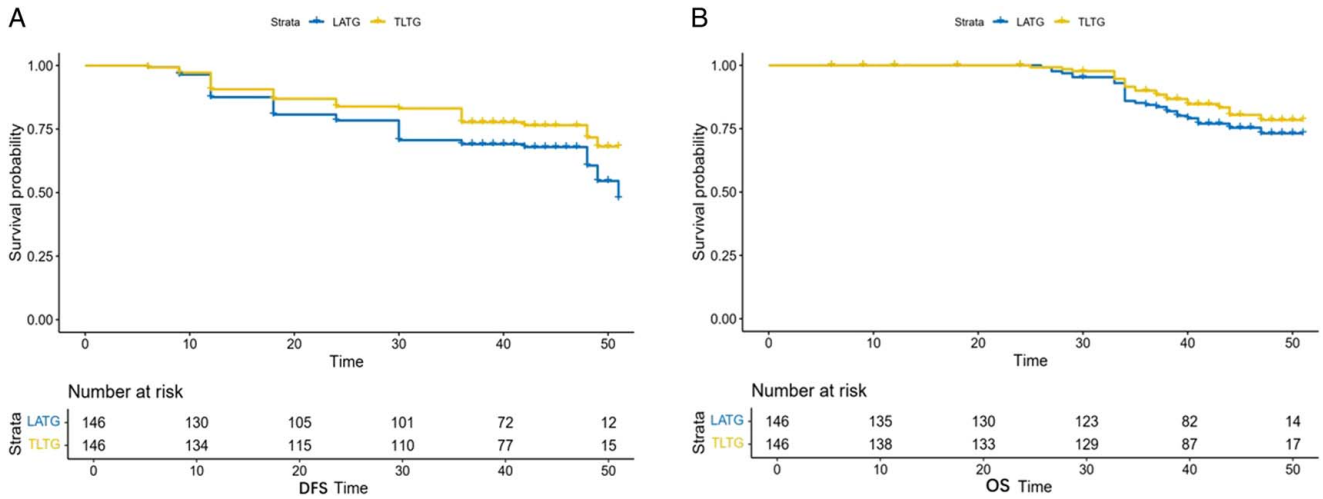

Figure 3. The disease-free survival and overall survival of the patients in TLTG and LATG groups. A. Disease-free survival. B. Overall survival.

group was 76.71%, compared to 67.12% for the LATG group, although statistical significance was not reached ($P = 0.058$). Similarly, the OS rate for the TLTG group was 84.25%, while the LATG group reported an OS rate of 79.45%, with no statistically significant differences between the two cohorts ($P = 0.236$). Figure 3 visually represents the DFS and OS outcomes for both groups.

Discussion

In this study, we found that among individuals diagnosed with advanced Siewert III esophagogastric junction cancer and upper/middle third gastric cancer, TLTG had significantly shorter incision length, initial flatus or bowel movement, postoperative pain relief time, and postoperative hospital stay, significantly reduced the opioid usage, overall postoperative complications, postoperative abdominal infections, anastomotic fistula, and anastomotic stenosis compared to LATG. In addition, the TLTG and LATG group had similar operation time, esophagojejunal anastomosis time, intraoperative blood loss, intraoperative blood transfusion, total count of retrieved lymph nodes, incidence of severe postoperative complications, long-term postoperative nutritional status, and long-term postoperative survival outcomes.

The lead surgeon in this study performs >200 gastric cancer operations per year. Given the collective expertise and experience of the surgical team at this establishment, the research found no substantial variance in surgical duration between TLTG and LATG. Nonetheless, during the initial introduction of TLTG at our facility, the surgical duration was notably lengthier compared to LATG. Consequently, extrapolating the conclusions of this study to low-volume facilities or less experienced surgeons may pose challenges. Furthermore, this study yielded favorable surgical and oncological results, indicating that TLTG is safe and feasible. Prior investigations from Japan and Korea have highlighted that TLTG is a reliable and efficient procedure with favorable short-term results[7,37], which aligns with our own results. The advantage of TLTG in terms of incision length also reflects that compared with LATG, TLTG is more minimally invasive.

In terms of postoperative recovery, the TLTG group had a faster recovery compared to the LATG group, which benefits from the smaller incision that resulting in less postoperative pain and the fewer analgesics use. The mild postoperative pain also indirectly promotes earlier postoperative gastrointestinal function recovery, thereby shortening the hospital stay after surgery. Essentially, TLTG, as a more minimally invasive surgical approach, reduces the stress state of patients after surgery and lower the intensity of their postoperative inflammatory response. All of this accelerate the rapid recovery of patients after surgery.

Numerous studies have demonstrated that the overlap method results in a low occurrence of anastomotic-related complications and satisfactory short-term outcomes in terms of postoperative complications[27,38,39]. Our study indicates that compared to LATG, TLTG does not increase the incidence of severe complications and reduces the overall incidence of postoperative complications. Further analysis of the main postoperative complications revealed that TLTG mainly reduced the incidence of anastomotic leakage and associated abdominal infections. Surgeons often prioritize the safety of anastomosis, especially in the context of total gastrectomy. Anastomosis leakage is a critical complication that can result in prolonged hospitalization, higher medical expenses, increased risk of anastomotic stenosis, need for reoperation, and in severe cases, patient mortality. It can also have a long-term impact on prognosis[40–42]. The nationwide internet-based database of Japan reported that in 2011, the occurrence of anastomotic leakage following total gastrectomy was 4.4% (881 out of 20,011)[43]. A separate study spanning from 1997 to 2016 revealed a slightly higher incidence of anastomosis leakage at 6% (58 out of 969)[42]. According to Schietroma *et al.*[44], the incidence of Anastomosis leakage was reported to be as high as 14.6%. In this trial, no patients in the TLTG group experienced anastomotic leakage, while 4.11% of patients in the LATG group did. This indicates that despite its complexity, TLTG does not elevate the likelihood of postoperative complications and can be considered a safe surgical approach. Additionally, the LATG group had longer incisions compared to the TLTG group, potentially increasing the likelihood of wound complications. During the study, it was observed that five patients in the LATG group experienced

wound complications, while none of the patients in the TLTG group did. Although the difference was not statistically significant, this indicates that TLTG may result in a lower occurrence of wound complications compared to LATG. While the overlap operation may present certain specific complications, such as the development of esophageal submucosal pseudocanals, none of the participants in this trial experienced this particular condition.

In terms of long-term outcomes, there was no significant difference in nutritional status and postoperative survival between the two groups. It may due to that both groups underwent total gastrectomy although the reconstruction methods of the digestive tract were different. The significant difference in postoperative anastomotic stenosis between the two group may be due to the difference between linear anastomosis and tubular anastomosis.

The standard approach for open total gastrectomy involves utilizing a circular stapling device for esophagojejunal anastomosis. This method was also initially used for esophagojejunostomy after TLTG[45,46]. However, there are certain technical challenges associated with performing laparoscopic esophagojejunal anastomosis using a circular stapling device. Performing a purse-string suture in the esophagus and inserting an anvil head is a challenging task when using laparoscopy. Additionally, the esophagus is shortened and retracted into the chest after being transected, which further complicates the procedure. The limited field of view provided by laparoscopy makes it difficult to manipulate the circular stapler. Furthermore, reinforcing the anastomotic line through laparoscopy is a demanding task. Ultimately, utilizing circular staplers for esophagojejunal anastomosis carries a high risk of stenosis[30]. The prevalence of these issues is heightened in individuals with obesity compared to those with a lower BMI. Research has shown that the rate of anastomotic stenosis with circular staplers ranges from 3.2 to 21%, while the leakage rate ranges from 1.7 to 6.0%[23,30].

According to Schneider *et al*., utilizing a linear stapler for constructing an esophagojejunostomy is simpler, even in high mediastinal locations, and eliminates the need for thoracotomy, compared to using a circular stapler. Their research additionally revealed that the caliber of the anastomotic stoma created using the linear stapler technique was notably greater in comparison to that formed through the circular stapler approach[47]. In addition, a wide linear-stapled anastomosis can be achieved regardless of the esophageal caliber. The use of a linear stapler during the procedure has been shown to have a low risk of anastomotic stenosis[12,27,31]. Furthermore, studies have found that the blood supply to the staple line remains at safe levels when performing a side-to-side esophagojejunostomy using a linear stapler, such as the overlap method, resulting in a reduced risk of anastomotic leakage[48]. The overlap technique is a commonly utilized approach for reconstructing the esophagojejunal anastomosis in TLTG. This method effectively mitigates tension in the anastomosis, thereby reducing the mesentery division. This secures additional jejunum length for anastomosis[37,49]. The procedure involves the use of a linear stapler for the anastomosis, thus requiring adequate dissection around the abdominal esophagus. Ensuring an adequate hiatus space and proper esophageal length for stapler placement is crucial to prevent complications such as anastomosis issues and hiatal hernia. Excessive hiatus dissection can create tension in the esophagus, potentially leading to complications. Our study results highlight the superior effectiveness of TLTG with the overlap technique in mitigating complications associated with esophagojejunal anastomosis when compared to LATG. In the standard LATG procedure, an extracorporeal anastomosis is established through an incision of 8–10 cm in the mid-upper abdomen. In cases where patients have a higher BMI, it may be imperative to extend the incision to optimize visibility and ensure a safer surgical field. Additionally, performing an extracorporeal esophagojejunostomy in a limited space can be challenging, particularly when suturing the anastomosis during surgery. In instances where there is a limited length of exposed esophagus, the risk of anastomotic fistula may be heightened due to increased tension and peristalsis of the jejunum. Through the utilization of TLTG, the esophagojejunal anastomosis is conducted with complete laparoscopic visualization, offering a more thorough surgical outlook and reducing anastomotic tension. In comparison to LATG, TLTG is characterized as a less invasive and traumatic surgical approach, as highlighted by Kim *et al*.[19]. Although TLTG has demonstrated enhanced early surgical outcomes, the broader acceptance of esophagojejunostomy poses challenges. In practice, employing a linear stapler for intracorporeal anastomosis is often deemed more practical than utilizing a circular stapler for extracorporeal anastomosis[50].

To ensure the success of safe and efficient TLTG with overlap reconstruction, several key factors must be emphasized. Firstly, the surgeon needs to master the technique of laparoscopic suturing. Secondly, adequate mobilization of the lower esophagus by at least 5 cm is essential to reduce tension at the esophagogastric anastomosis site. Thirdly, positioning the jejunum on the left side of the esophagus is preferred to facilitate anastomosis construction in the limited mediastinal space. Using a 45 mm linear stapler for the esophagojejunal anastomosis is recommended. Reinforcing the stapled anastomotic line with continuous sutures using a double-ended barbed wire is vital to minimize the risk of anastomotic leakage. Finally, when inserting the 45 mm linear stapler into the esophageal stump, guidance from a nasogastric tube is necessary, and caution must be taken to avoid inadvertently pinching the tube during the stapler firing process.

Our study has limitations, being conducted at a single center, potentially limiting generalizability. The short follow-up period necessitates future studies to report outcomes beyond this timeframe, including a 5-year follow-up. Surgical procedures were performed by skilled surgeons at a high-volume institution, suggesting limited applicability to less experienced surgeons or smaller facilities. Despite these constraints, our research provides valuable insights into the safety and positive outcomes of TLTG with the overlap method in patients with advanced Siewert III esophagogastric junction cancer and upper-middle-third gastric cancer.

This study represents a significant randomized controlled trial comparing the feasibility and oncological efficacy of TLTG with the overlap technique versus LATG. Our findings support TLTG with the overlap method as a technically secure approach, with favorable postoperative complication rates and improved recovery outcomes.

Conclusion

In conclusion, utilizing the overlap method in TLTG for esophagojejunal anastomosis proves to be a safe and effective approach, yielding better postoperative outcomes compared to

LATG in patients with advanced upper-middle third gastric cancer. Our results validate the advantages of TLTG with the modified overlap technique, including accelerated bowel recovery, reduced incision length for decreased pain, shorter hospital stays, and a lower incidence of anastomotic leakage.

Ethical approval

This a prospective, single center, single-blind, two-arm randomized controlled trial was approved by the Ethics Committee of the First Affiliated Hospital (Xijing Hospital) of Fourth Military Medical University (KY20192093-X-1).

Consent

Written informed consent was duly acquired from each participant, as well as their guardians, primary caregivers, and research assistants. Fully informed written consent was documented in the paper. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

J.W.: conceptualization, data curation, methodology, funding acquisition, and writing – original draft; S.L.: software, investigation, and project administration; H.C. and J.L.: investigation and project administration; G.X.: project administration; X.F. and X.Y.: supervision and validation; J.Y.: formal analysis and project administration; G.J.: conceptualization, methodology, resources, and writing – review and editing.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

This trial has been registered at Chinese Clinical Trial Registry: ChiCTR1900025667 (registration date: 4 September 2019).

Guarantor

Gang Ji and Jianjun Yang are corresponding authors.

Data availability statement

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Provenance and peer review

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