Comparative Study - Retrospective Cohort

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Reappraisal of optimal reconstruction after distal gastrectomy – a study based on the KLASS-07 database

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Backgrounds: This study aimed to compare the incidence of bile reflux, quality of life (QoL), and nutritional status among Billroth II (BII), Billroth II with Braun anastomosis (BII-B), and Roux-en-Y (RY) reconstruction after laparoscopic distal gastrectomy (LDG).

Materials and methods: We reviewed the prospective data of 397 patients from a multicentre database who underwent LDG for gastric cancer between 2018 and 2020 at 20 tertiary teaching hospitals in Korea. Postoperative endoscopic findings, QoL surveys using the European Organization for Research and Treatment of Cancer questionnaire (C30 and STO22), and nutritional and surgical outcomes were compared among groups.

Results: In endoscopic findings, bile reflux was the lowest in the RY group ($n = 67$), followed by the BII-B ($n = 183$) and BII groups ($n = 147$) at 1 year (3.0 vs. 67.8 vs. 84.4%, all $P < 0.05$). The anti-reflux capability of BII-B was statistically better than that of BII, but not as perfect as that of RY. From the perspective of QoL, BII-B was not inferior to RY, but better than BII reconstruction in causing fewer STO22 reflux symptoms at 6 and 12 months. However, only RY caused fewer C30 nausea symptoms than BII at 6 and 12 months, but not BII-B. Nutritional status and morbidities were similar among the three groups, and the operative time did not differ between the BII-B and RY groups.

Conclusions: BII-B cannot substitute for RY in preventing bile reflux, shortening the operative time, or reducing morbidities. Regarding short-term QoL, BII-B was sufficient to reduce STO22 reflux symptoms but failed to reduce C30 nausea symptoms postoperatively.

Keywords bile reflux, Billroth II, Braun, gastric cancer, quality of life, Roux-en-Y

Introduction

Laparoscopic distal gastrectomy (LDG) has become a well-established treatment for early gastric cancer (EGC), with an associated survival rate of up to 90%[1,2]. Consequently, patients with EGC live longer, and the importance of postoperative quality of life (QoL) is also being acknowledged in addition to

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

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oncologic outcomes[3]. Nevertheless, overall survival is inevitably the most important factor when evaluating the results of cancer treatment. Curative distal gastrectomy involves the removal of the pylorus; hence, enterogastric bile reflux is inevitable. Furthermore, bile reflux is a potential risk for malignant changes in the remnant stomach[4]. Gastric cancer in the remnant stomach is detected ~6.8–18.8 years after curative resection for gastric cancer[5]. Furthermore, bile reflux after LDG is considered the main factor influencing postoperative QoL[6], and many patients experience alkaline reflux and malabsorption after LDG. Therefore, surgeons have sought a better reconstruction method that reduces the risk of remnant gastric cancer and provides a better QoL after LDG.

Billroth I (BI) reconstruction is commonly used because of the physiological advantage of the duodenal passages of food[7–10]. However, to ensure a margin of safety, surgeons should inevitably perform Billroth II (BII) or Roux-en-Y (RY) reconstruction if the remnant stomach cannot reach the duodenum due to extensive resection. It has been reported that bile reflux rarely occurs after RY reconstruction; however, it is a time-consuming and complicated procedure with high rates of morbidity[11]. BII reconstruction is popular because of its simplicity, but it leads to frequent bile reflux due to its structural drawback. For this reason, Billroth II with Braun anastomosis (BII-B) was introduced to divert bile reflux, and many surgeons believe that BII-B is a good substitute for RY reconstruction. However, no good-quality randomized controlled trial (RCT) exists, and previous studies did not compare BII, BII-B, and RY reconstruction simultaneously, and analyzed the results of one or two gastrojejunostomies (GJs) with one gastroduodenostomy, or only two GJ procedures without gastroduodenostomy[11–26]. Therefore, in the current era of laparoscopic surgery, the surgeon still performs BII-B with a vague expectation of the effectiveness of bile diversion or performs BII or RY reconstruction according to their preferences.

To address the question of 'Adding Braun anastomosis to BII reconstruction can overcome the shortcomings of BII and eliminate the need for RY reconstruction?', we utilized the multicentre prospectively collected database from 20 institutions in South Korea and compared the postoperative endoscopic findings, QoL, nutritional status, and postoperative morbidities of BII, BII-B, and RY reconstruction after LDG.

HIGHLIGHTS

- In this multicentre database study involving 397 patients, the anti-reflux capability of Billroth II with Braun (BII-B) anastomosis (67.8%) was better than that of Billroth II (BII) (84.4%), but not as good as that of Roux-en-Y (RY) (3.0%) (all $P < 0.05$).
- In terms of quality of life, BII-B caused fewer reflux symptoms than BII. Compared to RY, BII-B did not cause more reflux symptoms (all $P < 0.05$).
- In conclusion, although BII-B is better than BII in relieving reflux symptoms, it cannot replace RY in terms of preventing bile reflux.

Materials and methods

Study design and cohorts

We have followed the STROCSS 2019 guideline for this study (Supplemental Digital Content 1, http://links.lww.com/JS9/B78), and the current study was registered at https://www.researchregistry.com (researchregistry8852)[27]. Since this study originally intended to reappraise the postoperative endoscopic findings (residue, gastritis, bile reflux), QoL, nutritional status, and morbidities of BII, BII-B, and RY reconstruction, we utilized the prospectively collected multicentre database of KLASS-07-RCT, which was designed to analyze the morbidities, QoL, and endoscopic findings of patients within 1 year after LDG. A prospectively collected database of 397 patients who underwent LDG for gastric cancer between January 2018 and October 2020 at 20 institutions in Korea was reviewed. As described in the protocol[28], the inclusion criteria were as follows: (1) histologically proven, clinical stage I gastric cancer; (2) aged 20–80 years; and (3) scheduled for LDG with D1+ or D2 lymphadenectomy. Patients with a history of abdominal surgery, chemotherapy, radiotherapy, incomplete records, conversion to open surgery, or total gastrectomy were excluded from the analysis.

The patient cohorts were divided into three groups, that is, BII, BII-B, and RY, according to the gastrointestinal reconstruction procedure that they underwent. The primary endpoint was to compare the postoperative endoscopic findings (residue, gastritis, and bile reflux) of the three groups at 6 and 12 months postoperatively. The secondary endpoint was to investigate the nutritional status of the patients and differences in QoL associated with the three different reconstruction types using the European Organization for Research and Treatment of Cancer (EORTC) questionnaire. Other parameters evaluated included the clinicopathological demographics of the patients, operative time, reconstructive procedures, number of intraoperative transfusions, length of hospital stay, and postoperative morbidities.

This study was approved by the Institutional Review Board of Korea University Medical Centre (No. X-2020-AN0231) and each participating institution. Informed consent or an equivalent was obtained from all patients included in the study.

Operation and gastrointestinal reconstructive procedures

After establishing pneumoperitoneum, LDG was performed according to the Japanese Gastric Cancer Treatment Guidelines[29]. The distal part of the stomach was resected using a linear stapler. After specimen retrieval, either extracorporeal or intracorporeal reconstruction was performed using the BII, BII-B, or RY methods according to the surgeon's preference. In RY, the Roux limb was made after dividing the jejunum 15 cm from the Treitz ligament. Jejunojejunostomy was performed 15–25 cm and 30–40 cm apart from the GJ in BII-B and RY reconstruction, respectively.

Endoscopic findings

Endoscopic examinations were performed twice for all patients at 6 and 12 months after LDG. Prior to designing the current study, prospective collected endoscopic findings from all institutions were already surveyed and analyzed by two expert gastroenterologists in

the main institutions, who were professors with at least 15 years of experience as specialists. They used the RGB (Residual food, Gastritis, Bile reflux) classification to evaluate endoscopic findings and made an interobserver agreement in diagnosis and grading by communicating with the gastroenterologist in each institution through video conference[30]. During endoscopy, the amount and severity of bile reflux were classified based on the extent of the refluxed bile in the remnant stomach. Detailed explanations for the grading system for residual food, gastritis, and bile reflux are described in Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/B79 in the Supporting information. Therefore, two gastroenterologists were blinded to the purpose of the current study.

Quality of life

We reviewed the independently collected QoL data of the cohort that had already been recruited, irrespective of the original purpose of the current study. Patients scheduled to undergo LDG and willing to participate in the EORTC QoL questionnaire survey (C30 and STO22) were included in the study. The QoL survey using the EORTC questionnaire was conducted preoperatively and at 3 months, 6 months, and 1 year postoperatively[28].

The differences in QoL trends over time among the three different anastomotic groups were analyzed using repeated measures analysis of variance (ANOVA), with the preoperative QoL score as the covariate. Analysis of covariance (ANCOVA) was used to compare QoL at certain postoperative time points (3, 6, and 12 months) between the three groups by controlling for the confounding effect of the preoperative QoL score. If the QoL at certain time points (3, 6, or 12 months) was different for the three groups, multiple backward stepwise linear regression analyses were used to determine the most independent risk factors for the differences in QoL for each month, after excluding all possible confounding factors.

Nutritional index

The serum levels of hemoglobin, total protein, albumin, and body mass index (BMI) were measured to evaluate changes in the nutritional status of the three different reconstructive types after LDG. Measurements were performed preoperatively and at 1, 6, 12, 18, 24, 30, and 36 months postoperatively. The differences in nutritional status among the three groups were compared using the same analytical method used for QoL difference analysis.

Statistical analysis

Chi-square ($\chi 2$) or Fisher's exact tests were used for categorical variables. Student's *t*-test or one-way ANOVA was used to compare continuous variables between groups. The Mann–Whitney *U* test was used to compare groups with nonparametric data. Multivariate logistic or multiple linear regression analyses employing backward stepwise selection were performed to identify the most independent factors in determining the incidence of events. All tests were two-sided, and a *P* value <0.05 was considered statistically significant. Statistical analyses were performed using the IBM SPSS Statistics version 25 (IBM Corporation, Armonk, New York, USA).

Results

Baseline characteristics

The clinicopathological characteristics of patients in each group are summarized in Table 1. The BII, BII-B, and RY were performed in 147 (37.0%), 183 (46.1%), and 67 (16.9%) patients, respectively. There were no differences in patient characteristics among the three groups, except for age, comorbidities, and length of the resected distal margin.

Intraoperative outcomes and surgical complications

The operative and reconstructive times were significantly shorter in the BII group than those in the BII-B and RY groups (all $P < 0.05$); however, the operative and reconstructive times did not differ between the BII-B and RY groups. That is, BII-B was as time-consuming as RY reconstruction and required more operative time than BII. The rate of intraoperative transfusion, postoperative morbidities, complication grade according to the Clavien–Dindo classification, and length of hospital stay were not different among the three groups (Table S2, Supporting information, Supplemental Digital Content 2, http://links.lww.com/JS9/B79).

Postoperative endoscopic findings

Bile reflux was significantly lower in the RY group than in the BII-B or BII groups at 6 months (3.0 vs. 67.8%; 3.0 vs. 81.6%, all $P < 0.05$) and 12 months (3.0 vs. 67.8%; 3.0 vs. 84.4%, all $P < 0.001$) postoperatively. Bile reflux was significantly lower in the BII-B group than in the BII group at 6 (67.8 vs. 81.6%, $P = 0.005$) and 12 months (67.8 vs. 84.4%, $P = 0.001$; Table 2).

The frequency of gastritis after RY was significantly lower than that after BII-B or BII reconstruction at 6 and 12 months, but the BII-B group had significantly less gastritis than the BII group at 6 and 12 months (all $P < 0.05$; Table 2). Regarding the grade of gastritis, remnant gastritis was most severe in the BII group, followed by the BII-B and RY groups at 6 and 12 months. The presence and amount of residual food at 6 and 12 months did not differ among the three groups (Table 2 and Fig. 1).

Multivariate logistic regression analysis revealed that BII reconstruction, presence of residual food, and bile reflux were independent risk factors for gastritis at 12 months (all $P < 0.05$; Table 3). At 6 months postoperatively, BII reconstruction and the presence of bile reflux remained independent risk factors for gastritis at 6 months (all $P < 0.05$, Table S3, Supporting information, Supplemental Digital Content 2, http://links.lww.com/JS9/B79).

Quality of life

The trends of QoL items with C30 nausea and STO22 reflux were the best in the RY group, followed by the BII-B and BII groups during the 1-year postoperative period (all $P < 0.05$; Fig. 2). Other aspects of QoL, including global health status, functional and symptomatic scales, were not different among the three groups over 1 year (Fig. S1, Supporting information, Supplemental Digital Content 2, http://links.lww.com/JS9/B79).

Regarding patients' short-term QoL, ANCOVA for each time point (3 months, 6 months, and 1 year postoperatively) revealed that C30 nausea at 6 and 12 months was significantly better in the RY group than in the BII group. However, adding Braun enteroenterostomy did not result in better C30 nausea symptoms than

Table 1

Patient's baseline characteristics among three different reconstruction groups.

	BII group(1) ($n=147$)	P(1) vs. (2)	BII-B group(2) ($n=183$)	P(2) vs. (3)	RY group(3) ($n=67$)	P(1) vs. (3)
Age, years	63.6 ± 10.5	0.001	60.0 ± 9.9	0.747	60.4 ± 10.2	0.039
Sex						
Male	103 (70.1)	0.347	119 (65.0)	0.767	42 (62.7)	0.344
Female	44 (29.9)		64 (35.0)		25 (37.3)	
Body mass index, kg/m2						
Mean ± SD	24.5 ± 3.2	0.015	23.7 ± 2.9	0.911	23.7 ± 2.5	0.083
Underlying disease						
Hypertension	37 (25.2)	0.796	43 (23.5)	0.508	19 (28.4)	0.619
Cardiovascular	24 (16.3)	0.002	10 (5.5)	0.555	5 (7.5)	0.088
Pulmonary	5 (3.4)	0.779	8 (4.4)	0.620	2 (3.0)	0.874
Neurologic	7 (4.8)	0.225	4 (2.2)	0.389	3 (4.5)	0.927
Hepatic	2 (1.4)	0.825	2 (1.1)	0.797	1 (1.5)	0.939
Diabetes	13 (8.8)	0.850	18 (9.8)	0.643	8 (11.9)	0.468
Renal	3 (2.0)	0.327	1 (0.5)	0.544	0 (0)	0.554
ASA classification						
Grade I	86 (58.5)	0.430	106 (57.9)	0.943	38 (56.7)	0.766
Grade II	49 (33.3)		68 (37.2)		25 (37.3)	
Grade III	12 (8.2)		9 (4.9)		4 (6.0)	
History of previous abdominal surgery	23 (15.6)	0.658	33 (18.0)	0.175	7 (10.4)	0.398
Laparoscopic approach						
Laparoscopy assisted	71 (48.3)	0.580	95 (51.9)	0.255	29 (43.3)	0.555
Totally laparoscopic	76 (51.7)		88 (48.1)		38 (56.7)	
Combined resection						
None	143 (97.3)	0.446	176 (96.2)	0.585	66 (98.5)	0.581
Cholecystectomy	4 (2.7)		5 (2.7)		1 (1.5)	
Other resections	0 (0)		2 (1.1)		0 (0)	
Tumor size, cm (mean ± SD)	2.7 ± 2.2	0.808	2.8 ± 2.2	0.835	2.8 ± 1.7	0.691
D2 dissection	20 (13.6)	0.870	23 (12.6)	0.894	8 (11.9)	0.894
The number of lymph nodes						
Retrieved	41.9 ± 17.1	0.289	39.9 ± 16.7	0.958	40.1 ± 13.7	0.396
Metastasis (median)	0 (0–7)	0.211*	0 (0–15)	0.715*	0 (0–7)	0.589*
Length of resected margin, cm (mean ± SD)						
Proximal	5.8 ± 3.2	0.125	5.3 ± 3.0	0.411	4.9 ± 2.7	0.059
Distal	5.7 ± 3.1	0.149	6.2 ± 2.9	0.061	7.3 ± 4.2	0.009
pT stage						
pT1	126 (85.7)	0.107	171 (93.4)	0.580	64 (95.5)	0.105
pT2	13 (8.8)		8 (4.4)		1 (1.5)	
pT3	4 (2.7)		3 (1.6)		2 (3.0)	
pT4	4 (2.7)		1 (0.5)		0 (0)	
pN stage						
pN0	127 (86.4)	0.926	166 (90.7)	0.276	60 (89.6)	0.386
pN1	13 (8.8)		12 (6.6)		2 (3.0)	
pN2	5 (3.4)		4 (2.2)		4 (6.0)	
pN3	2 (1.4)		1 (0.5)		1 (1.5)	
TNM stage (AJCC 8th classification)						
Stage I	131 (89.1)	0.125	174 (95.1)	0.170	60 (89.6)	0.621
Stage II	14 (9.5)		8 (4.4)		7 (10.4)	
Stage III	2 (1.4)		1 (0.5)		0 (0)	
Stage IV	0 (0)		0 (0)		0 (0)	

TNM stage according to Japanese Classification of the Gastric Carcinoma, 4th edition English.

AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; BII, Billroth II; BII-B, Billroth II with Braun; pN, pathological N; pT, pathological T; RY, Roux-en-Y; SD, standard deviation.

*Derived from Mann -Whitney U test.

pure BII reconstruction over 1 year postoperatively. STO22 reflux symptoms were lower in BII-B and RY patients than in BII patients at 6 and 12 months after controlling for the confounding effects of baseline QoL (all $P < 0.05$; Fig. 2). BII did not achieve a better symptomatic score for any QoL item than BII-B or RY reconstruction.

Multiple linear regression analysis revealed that a lower grade of bile reflux was a common independent factor associated with fewer C30 nausea symptoms at 6 and 12 months. Fewer preoperative C30 nausea symptoms and reconstruction procedures with fewer bile reflux were also associated with fewer C30 nausea symptoms at 6 and 12 months, respectively. Compared with male patients, female patients tended to have more C30 nausea symptoms at 12 months, but this difference was not statistically significant. For STO22 reflux, a lower grade of bile reflux and fewer complaints of STO22 reflux symptoms before surgery were

Table 2

The postoperative endoscopic findings at 6 and 12 months for three different reconstruction groups.

Endoscopic findings	Follow-up	BII group(1) ($n=147$)	P(1) vs. (2)	BII-B group(2) ($n=183$)	P(2) vs. (3)	RY group(3) ($n=67$)	P(1) vs. (3)
Residual food	6 months	57 (38.8)	0.103	55 (30.1)	0.975	20 (29.9)	0.223
	12 months	50 (34.0)	0.341	53 (29.0)	0.339	15 (22.4)	0.109
Gastritis	6 months	125 (85.0)	0.004	131 (71.6)	< 0.001	10 (14.9)	< 0.001
	12 months	125 (85.0)	< 0.001	125 (68.3)	< 0.001	6 (9.0)	< 0.001
Bile reflux	6 months	120 (81.6)	0.005	124 (67.8)	< 0.001	2 (3.0)	< 0.001
	12 months	124 (84.4)	0.001	124 (67.8)	< 0.001	2 (3.0)	< 0.001

BII, Billroth II; BII-B, Billroth II with Braun; RY, Roux-en-Y.

common independent factors associated with fewer STO22 reflux symptoms at 6 and 12 months. Furthermore, a higher grade of food residue based on endoscopic findings at 12 months was linked to worse STO22 reflux symptoms at 12 months. Although not statistically significant, patients with a higher BMI tended to complain of more STO22 reflux symptoms at 6 months (Table 4).

Nutritional status

The nutritional status, including changes in BMI, hemoglobin, protein, and albumin, was not significantly different among the three groups over 3 years postoperatively (Fig. 3).

Late postoperative outcomes

During an average 36-month follow-up period after gastrectomy, the late postoperative outcomes, such as the incidence of dumping syndrome, ulceration, and serum mean corpuscular volume (MCV), an indicator of megaloblastic anemia, were similar among the three reconstructive groups. The incidence of gallstone formation did not differ among the three groups, and only 2 out of 6 patients with gallstones ultimately complained of symptoms and underwent cholecystectomies (Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/B79; Fig. S2, Supporting Information, Supplemental Digital Content 2, http://links.lww.com/JS9/B79).

Discussion

In contrast to previous studies that analyzed the results of one or two GJ procedures plus one gastroduodenostomy or only two GJ procedures[11–26], this is the first large-scale study to simultaneously compare the implications of three reconstructive procedures based on the GJ. We utilized a prospectively collected database with endoscopic findings, QoL survey results, and nutritional status of 397 patients from an independent, prospective cohort study conducted to analyze the surgical outcomes and QoL after LDG at 20 institutions in Korea[28]. When the current study was designed, the collection and analysis of data with endoscopic findings and QoL survey for the independent prospective trial were already finished. Moreover, two expert gastroenterologists made an interobserver agreement in the diagnosis and grading of the endoscopic findings before designing the current study. Therefore, with the independence of interpretation of endoscopic findings, QoL data can become unbiased evidence for the current study. Therefore, we believe that our study provided less biased and more objective evidence than previous studies.

Overall survival is the most important issue in the treatment of patients with cancer. Therefore, an ideal gastrointestinal reconstruction procedure should primarily minimize the risk of cancer recurrence in the remnant stomach due to bile reflux. Surgeons can further consider choosing a procedure that does not compromise the postoperative QoL of the patients or their nutritional status. In the current study, the RY method demonstrated the best prevention of bile reflux and gastritis, followed by the BII-B and BII reconstruction. Although adding Braun enteroenterostomy was more advantageous in diverting and reducing bile reflux than pure BII, it could not perfectly prevent bile reflux as in the RY method (Table 2). Previous studies have also reported that RY is superior to BII in terms of preventing bile reflux and gastritis[18,20,22,23,25]. Compared to RY, BII-B reconstruction showed a greater frequency of the occurrence of bile reflux, ranging from 43.4 to 88%[14,15,19,21,26]. One study reported that BII-B was not better in preventing reflux than BII (83.3 vs. 75.9%, $P=0.702$)[26]. These discrepancies can be explained as follows: First, the distances from GJ to Braun enteroenterostomy in BII-B (15–25 cm) were usually shorter than those from GJ to jejunojejunostomy in RY (25–40 cm)[11,14,19,24,26,31]. When Braun anastomosis was performed 15 cm distal to GJ, the incidence of bile reflux was 83.3 and 88%[14,26]. However, the bile reflux was reduced to 43.3–68% when it was located 25 cm below GJ[15,19]. Recently, Yalikun *et al*.[32] reported that the incidence of bile reflux was only 21.4% in patients after distal gastrectomy with modified BII-B, which prolonged the afferent loop from 20 to 35 cm and the efferent loop from 35 to 45 cm. Even in RY, the incidence of bile reflux differed according to the distance from the GJ to the jejunojejunostomy (25 cm, 21.4%; 30–40 cm, 0–8.3%)[11,14,19,26,31]. Second, part of the blood from the proximal artery passes on to the distal artery, even after an arteriovenous fistula is created. Likewise, some bile still flows from the A-loop to the remnant stomach owing to the pressure from the A-loop. Third, the severity of bile reflux varies depending on the direction of the GJ. Interestingly, the incidence of bile reflux after LDG with BII was lower in the antiperistaltic group than in the isoperistaltic group[33]. This can be explained by the mechanism of a physiological barrier in which food stasis arising from antiperistaltic anastomosis acts as a barrier against bile reflux. Similarly, the antiperistaltic direction in the ileocolic anastomosis may behave like a functional pseudo-valve, reducing ileocecal reflux. The theory of a physiologic barrier in antiperistaltic GJ is consistent with the mechanism of 'functional pseudo-valvular mechanism for colonic anastomosis'[33,34]. In the current study, the impact of the peristaltic direction on patient outcomes could not be analyzed because the surgeons unified the direction of the GJ in an isoperistaltic manner prior to patient enrollment.

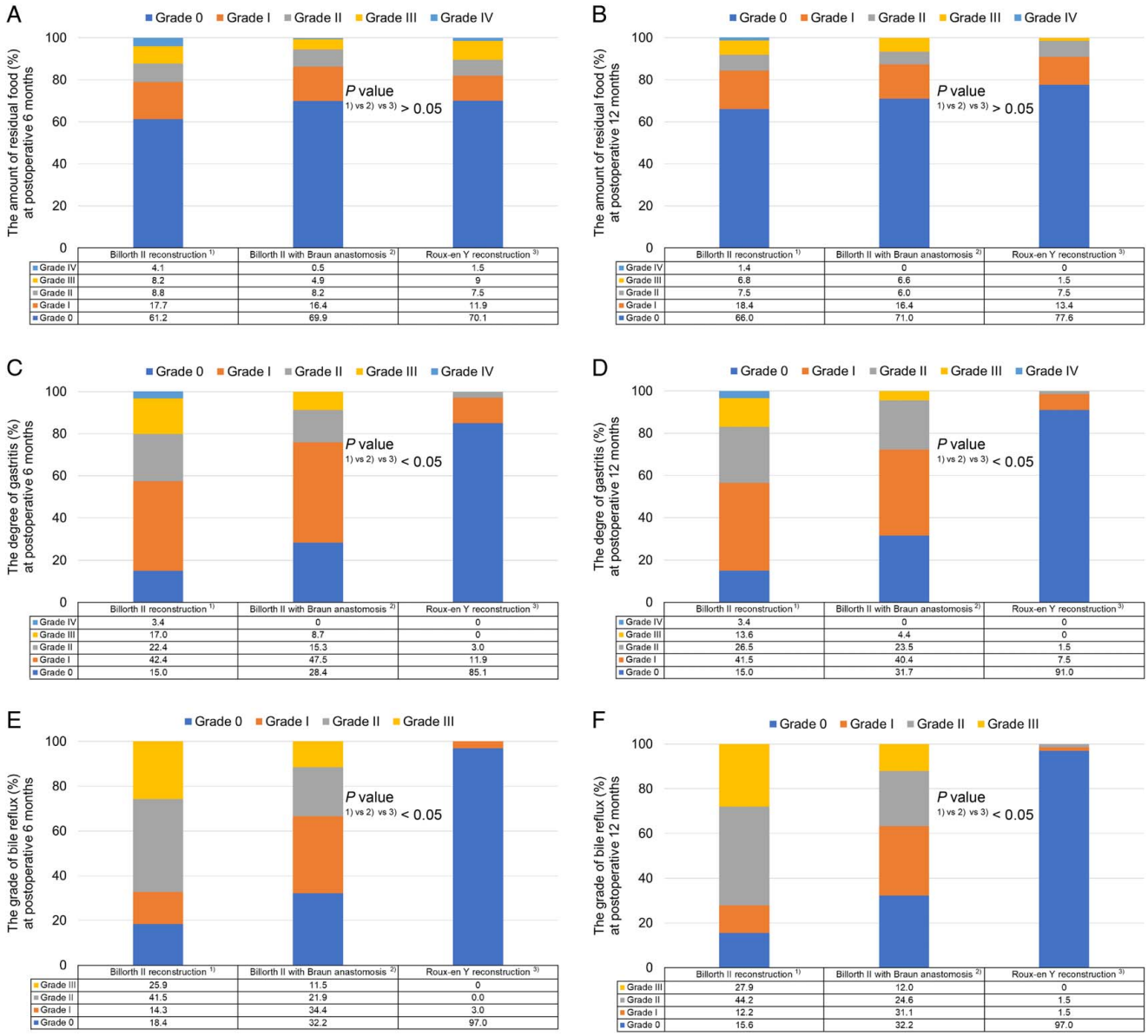

Figure 1. The amount of residual food and degree of gastritis at postoperative 6 and 12 months in the Billroth II group ($n = 147$), Billroth II with Braun group ($n = 183$), and Roux-en-Y reconstruction group ($n = 67$). (A) The amount of residual food at postoperative 6 months. (B) The amount of residual food at postoperative 12 months. (C) The degree of gastritis at postoperative 6 months. (D) The degree of gastritis at postoperative 12 months. (E) The amount of bile reflux at postoperative 6 months. (F) The amount of bile reflux at postoperative 12 months.

Like as in the endoscopic findings, the trends of C30 nausea and STO22 reflux symptoms during the postoperative 1 year were the best in the RY group, followed by those in the BII-B and BII groups. From the patients' perspectives at certain time points, RY reduced both C30 nausea and STO22 reflux symptoms at 6 and 12 months compared to BII. Although BII-B failed to achieve fewer C30 nausea symptoms at 6 and 12 months than BII, it provided fewer STO22 reflux symptoms at 6 and 12 months than BII reconstruction. BII could not achieve any benefits in terms of C30 nausea and STO22 reflux symptoms postoperatively. In the current study, fewer postoperative reflux symptoms were commonly determined by a lower grade of bile reflux (Fig. 2 and Table 4). Previous studies demonstrated that the stronger anti-reflux capability of RY reconstruction contributed to fewer nausea and reflux symptoms[12–14,17,26]. Bile reflux into the remnant stomach and gastroesophageal reflux of gastric acid or intestinal contents are regarded as two important factors that contribute to reflux oesophagitis after distal gastrectomy[16,17,26]. Gastric acid secretion is regulated by the contact of digestive contents with the duodenum[11,35]; bile reflux into the remnant stomach can be considered a major risk factor for worse esophageal reflux symptoms in GJ-based reconstruction. Reflux symptoms may not be solely explained by the bile reflux grade. Our results showed that fewer preoperative reflux symptoms and lower food residue grades resulted in fewer postoperative reflux symptoms. Additionally, a lower BMI tended to contribute to

Table 3

Univariate and multivariate logistic regression analysis for variables causing gastritis at postoperative 12 months.

	Univariate analysis			Multivariate analysis		
Variables	***B***	**OR (95% CI)**	***P***	***B***	**OR (95% CI)**	***P***
Age, years (per one-year increase)	0.010	1.010 (0.990–1.031)	0.329			
Sex, male (vs. female)	0.365	1.440 (0.935–2.218)	0.098			
Body mass index, kg/m2 (per increase)	−0.031	0.969 (0.640–1.469)	0.884			
ASA classification						
Grade II vs. I	0.491	1.634 (0.820–3.256)	0.977			
Grade III vs. I	0.086	1.089 (0.098–12.135)	0.977			
Totally laparoscopic (vs. laparoscopy assisted)	−0.031	1.007 (0.640–1.469)	0.969			
Combined resection	0.448	1.565 (0.417–5.880)	0.507			
Reconstruction procedures						
Billroth II with Braun anastomosis (vs. Billroth II)	−0.813	0.443 (0.254–0.773)	0.004	−0.632	0.531 (0.286–0.987)	0.046
Roux-en-Y reconstruction (vs. Billroth II)	−4.056	0.017 (0.007–0.045)	<0.001	−2.459	0.085 (0.030–0.245)	<0.001
The size of tumor (centimeters, per one-year increase)	−0.051	0.950 (0.863–1.046)	0.300			
The number of retrieved lymph nodes (per increase)	−0.001	0.822 (0.986–1.011)	0.822			
Depth of invasion						
pT2–4 vs. pT1	0.320	1.377 (0.643–2.947)	0.410			
Lymph node metastasis						
pN1–3 vs. pN0	−0.334	0.716 (0.377–1.359)	0.307			
Presence of residual food at 12 months	0.755	2.129 (1.301–3.483)	0.003	0.667	1.948 (1.027–3.692)	0.041
Presence of bile reflux at 12 months	3.177	23.985 (13.896–41.397)	<0.001	2.328	10.260 (5.706–18.450)	<0.001
Reconstruction procedures * presence of bile reflux						
BII with Braun anastomosis * presence of bile reflux	1.460	4.305 (2.544–7.283)	<0.001			
Roux-en-Y reconstruction * presence of bile reflux	−0.249	23.985 (0.048–12.596)	0.861			

Covariates were age, sex, body mass index, American Society of Anaesthesiologists classification, totally laparoscopic approach, combined resection, reconstruction procedures, size of tumor, score of remnant food material, presence of bile reflux, pathologic T and N stages. The result was obtained after adjusting the confounding effect of the multicenter.
TNM stage according to Japanese Classification of the Gastric Carcinoma, 4th edition English.
ASA, American Society of Anaesthesiologists; BII, Billroth II; OR, odds ratio; pN, pathological N; pT, pathological T.

fewer reflux symptoms at 6 months ($P = 0.058$; Table 4). BMI ≤ 23.7 kg/m2 was reportedly associated with the resolution of reflux symptoms after anti-reflux surgery[36]. Delayed gastric emptying progressively reduces pressure on the esophagogastric junction and aggravates reflux symptoms[37]. QoL is a relative multidimensional concept that reflects the ratio between expectations and the present status of an individual. The innate subjective perceptions of symptoms inherent to each patient may be associated with postoperative reflux symptoms[38–40]. The BII-B group tended to have the least preoperative reflux symptoms (Fig. 2) and BMI (23.7 kg/m2), similar to that of the RY (23.7 kg/m2) but smaller than that of the BII group (24.5 kg/m2) (Table 1). Although reflux symptoms can be caused by the physical retrograde movement of the gastric contents, nausea is an unpleasant sensation triggered by diverse emetic stimuli through the nervous system. Gastric luminal irritants, such as bile salts, have been reported as chemical stimuli that affect the unpleasant sensation of nausea[41–43]. Understandably, RY reduced bile reflux by 97% and resulted in fewer nausea symptoms than BII. However, despite preventing bile reflux by only 22.4%, BII-B failed to yield

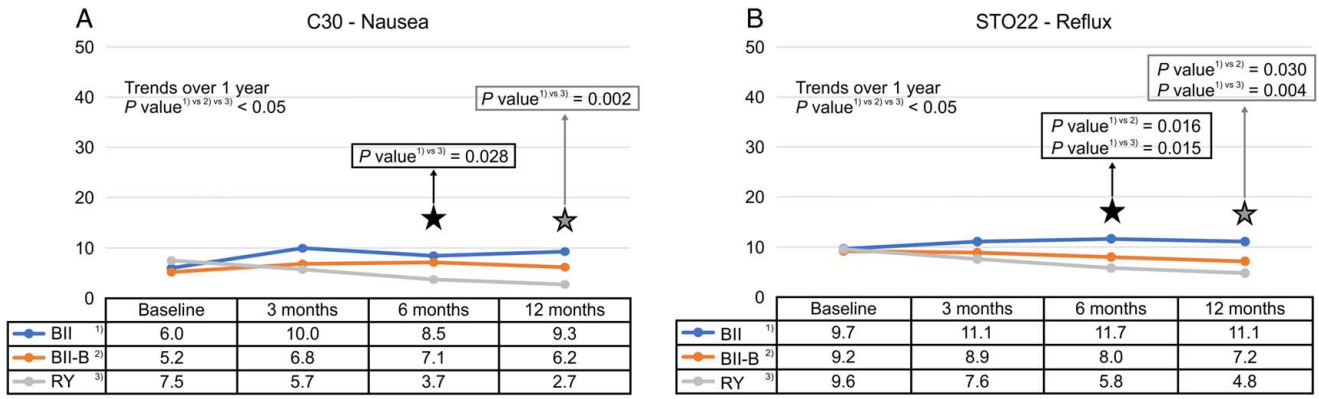

Figure 2. Quality of life (QoL) measurements of the Billroth II (BII) group ($n = 147$), Billroth II with Braun anastomosis (BII-B) group ($n = 183$), and Roux-en-Y reconstruction (RY) group ($n = 67$) using the Korean version of the European Organization for Research and Treatment of Cancer (EORTC) questionnaire. (A) C30 nausea. (B) STO22 reflux.

Table 4

Linear regression analysis for variables determining the differences in the symptom scale at postoperative 6 and 12 months by backward stepwise methods.

		Unstandardized coefficient			
Symptom scale	**Variable factors**	**B**	**Standard errors**	**Standardized coefficient**	***P***
C30 nausea (6 months)	C30 nausea (preoperative)	0.187	0.06	0.142	0.005
	Grade of bile reflux[a] (from 0 to 3)	3.401	0.790	0.216	< 0.001
C30 nausea (12 months)	Grade of bile reflux[a] (from 0 to 3)	6.135	0.758	0.496	< 0.001
	Male (vs. female reference)	− 2.453	1.327	− 0.087	0.065
	Reconstruction methods[b] (from 1 to 3)	− 3.061	1.196	− 0.157	0.011
STO22 reflux (6 months)	Grade of bile reflux[a] (from 0 to 3)	3.033	0.574	0.256	0.002
	Body mass index	0.397	0.209	0.091	0.058
	STO22 reflux (preoperative)	0.221	0.048	0.243	< 0.001
STO22 reflux (12 months)	Grade of bile reflux[a] (from 0 to 3)	4.327	0.555	0.364	< 0.001
	Presence of residual food in endoscopy (12 months)	1.605	0.692	0.108	0.021
	STO22 reflux (preoperative)	0.199	0.047	0.197	< 0.001

[a]Grade of bile reflux = 0, absence of bile; 1, tinged to small amount (< 1/3) of bile in remnant stomach; 2, moderate amount (≥ 1/3 to <2/3) in remnant stomach; 3, large amount (≥ 2/3 to entire extent) in remnant stomach. Grade of bile reflux 0 is the reference group.

[b]Reconstruction methods = 1, Billroth II anastomosis; 2, Billroth II with Braun anastomosis; 3, Roux-en-Y reconstruction. Reconstruction method 1 is the reference group.

Covariates were age, sex, body mass index, American Society of Anaesthesiologists classification, laparoscopic approach (totally laparoscopic vs. laparoscopy assisted), combined resection, reconstruction procedures, size of tumor, number of retrieved lymph nodes, score of remnant food material, grade of bile reflux, preoperative quality of life score, and pathologic T and N stages.

pT, pathological T.

fewer nausea symptoms than BII (Table 2). In this study, postoperative nausea symptoms were commonly determined based on the bile reflux grade. In line with reflux symptoms, preoperative nausea symptoms were found to be associated with nausea symptoms at 6 months. Interestingly, female patients tended to exhibit increased nausea at 12 months ($P = 0.065$; Table 4). Female sex has been reported to predict a higher incidence of postoperative nausea sensation after surgery[44,45]. Considering

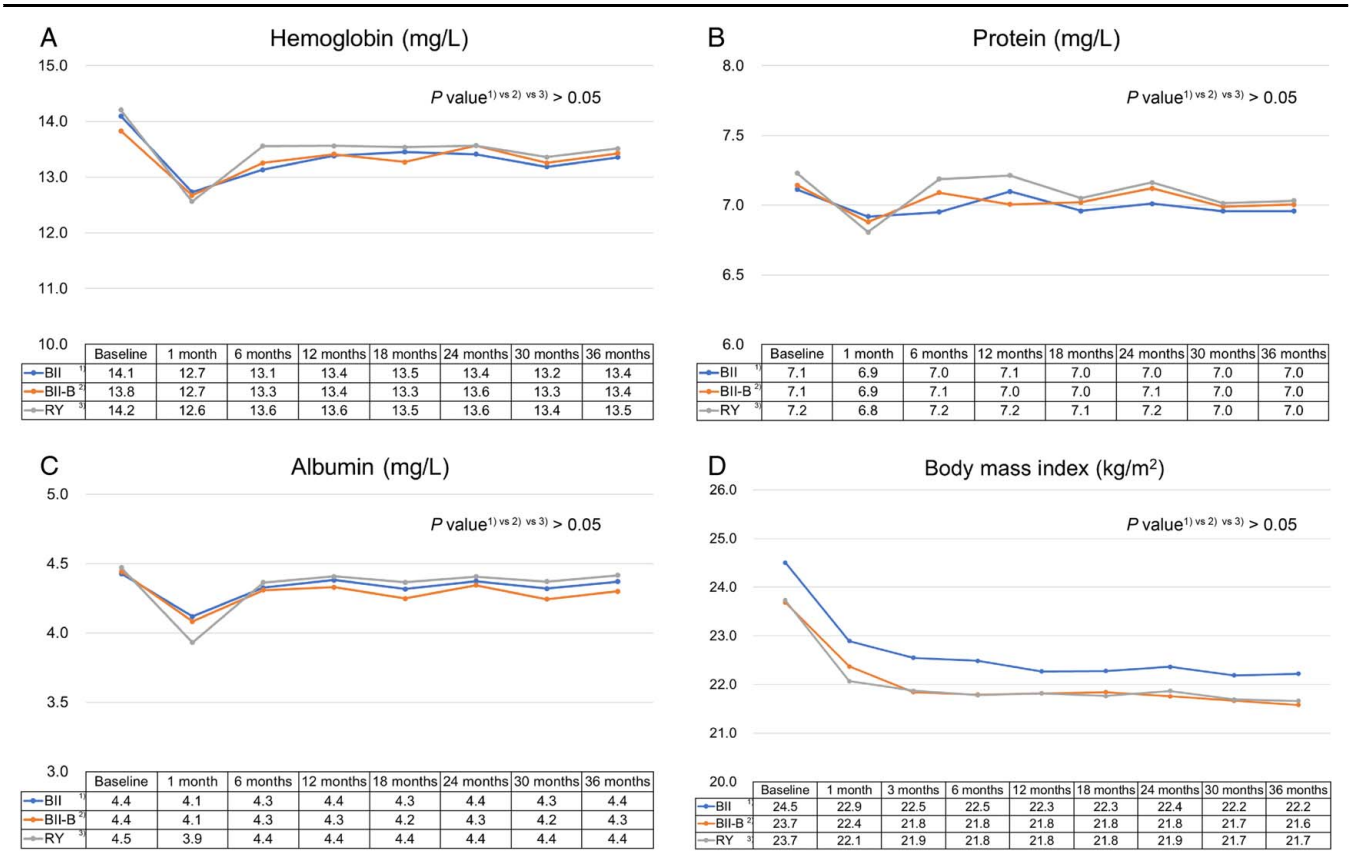

Figure 3. The nutritional status of hemoglobin, total protein, albumin, and body mass index of the Billroth II (BII) group ($n = 147$), Billroth II with Braun anastomosis (BII-B) group ($n = 183$), and Roux-en-Y reconstruction (RY) group ($n = 67$). (A) The serum level of hemoglobin (mg/l). (B) The serum level of protein (mg/dl). (C) The serum level of albumin (mg/dl). (D) The body mass index (kg/m2).

these factors, not only the severity of bile reflux but also other factors can affect postoperative nausea or reflux symptoms in a complex manner. Other aspects of QoL, including global health status and functional and symptomatic scales, were not affected by different reconstruction procedures.

Duodenal food passage, remnant stomach volume, delayed gastric emptying, and bypassed limb length have been recognized as indicators of nutritional status after distal gastrectomy. Since the majority of iron absorption occurs in duodenal enterocytes[7,9,46], BI patients reportedly have higher hemoglobin levels and lower weight loss than BII or RY patients[46–49]. Regarding remnant stomach volume, total gastrectomy causes more weight loss than distal gastrectomy[46]. However, the residual volume showed no positive impact on nutritional outcomes in patients after distal gastrectomy. Because diet recovery in these populations was mainly achieved by increased motility of the small bowel[50], the population in the current study did not undergo gastroduodenostomy; hence, nutritional status could be affected by delayed gastric emptying or bypass limb length. Gustavsson *et al*.[51], suggested that limb length >40 cm is a high-risk factor for Roux stasis. In our study, the RY limb length was standardized at 30–40 cm, and only one patient (1.5%) in the RY group experienced delayed emptying. The grade of residual food and the incidence of delayed emptying were similar among groups (Fig. 1 and Table S2, Supporting information, Supplemental Digital Content 2, http://links.lww.com/JS9/B79). While large deviations in the bypassed limb length (100–200 cm) have a significant impact on weight loss in bariatric populations[52], a relatively small deviation in limb length might have no impact on the nutritional status of patients with gastric cancer. Our study showed similar changes in nutritional parameters among the three groups over 3 years (Fig. 3), which was consistent with previous RCTs comparing the results of BII and RY reconstruction[53].

The late postoperative outcomes were similar among the three reconstructive procedures (Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/B79 and Fig. S2 in Supporting information, Supplemental Digital Content 2, http://links.lww.com/JS9/B79). However, the incidence of dumping syndrome within 3 years tended to be lower in the RY reconstruction group than in the BII reconstruction group, without statistical significance ($P = 0.093$; Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/B79). Previous studies, including meta-analyses, have also reported that RY is more effective in reducing dumping syndrome than other procedures[14,54,55] because it diminishes jejunal contractions and interrupts migration of the motor complex, which may ultimately slow down the flow of chyme through the Roux limb[54,56,57]. We were unable to investigate the incidences of iron deficiency, vitamin B_{12} deficiency, or megaloblastic anemia. All patients in this study had their duodenum (where most of the iron is absorbed) bypassed, and their fundus (in which the parietal cells produce intrinsic factor [IF]) preserved. For efficient vitamin B_{12} absorption, it should be attached to IF and recognized by receptors on enterocytes in the ileum, which is the main absorption site for the vitamin B_{12}–IF complex. The serum MCV and hemoglobin levels were similar between the groups. Therefore, the incidence of anemia may follow a similar pattern[7,9,46,58,59]. Gallstone formation after gastrectomy is usually explained by the destruction of the vagal nerves and the exclusion of the duodenum, which leads to changes in cholecystokinin secretion, ultimately decreasing gallbladder contraction. Therefore, complete amputation of the vagal trunk with esophageal or hepatoduodenal lymphatic dissection can increase the incidence of gallstones. The population in the current study underwent LDG with sacrificing pylorus, and the proportion of D2 dissections was similar among the three groups (Table 1). Only 2 of 397 patients (0.5%) required cholecystectomy for symptom aggravation, which is similar to the results of a previous study (0.5%), suggesting that prophylactic cholecystectomy may be unnecessary[60]. In addition to the severity of bile reflux, various factors, including acid secretion, local ischemia, anastomotic tension, *Helicobacter pylori* infection, smoking, and non-steroidal anti-inflammatory drug (NSAID) use, have been mentioned as aetiologies of ulceration after gastrectomy. Only one patient (0.2%) with a history of continued smoking and NSAID medication after surgery had developed ulceration at the 1-year follow-up. Considering that the incidence was negligible, the impact of reconstruction might not be great, but long-term follow-up is necessary for exact comparison[61–68].

As previously demonstrated[14,15,19,21,26], RY is better than BII-B at preventing bile reflux and gastritis (Table 2). One year postoperatively, RY showed the best trends in QoL outcomes regarding nausea and reflux symptoms, followed by BII-B and BII reconstruction (Fig. 2). Nevertheless, many surgeons are hesitant to perform RY reconstruction. They considered RY to be more complicated than BII-B because RY requires an additional jejunal division, which may increase morbidity. However, RY reportedly has no specific disadvantage compared with BII-B, except for a longer operative time and Roux stasis[19,21,69]. In the present study, all surgeons routinely closed Peterson's space during RY reconstruction. The rate of postoperative complications including internal hernia, Roux stasis, and reconstructive and operative times, were not different between the RY and BII-B groups (Table S2, Supporting information, Supplemental Digital Content 2, http://links.lww.com/JS9/B79). Unfortunately, BII-B failed to alleviate the time-consuming labor of RY and required more operative time than pure BII reconstruction. This is probably because BII-B and RY reconstructions equally required jejunojejunostomy, and RY required only an additional procedure to close Peterson's space after jejunal division. Therefore, if the RY limb length was standardized at 30–40 cm and the RY was performed by a skilled surgeon, there would be no differences in the operative time, morbidities, or Roux stasis between BII-B and RY reconstruction.

In Japan, perhaps for this reason, the most common method of reconstruction after distal gastrectomy was BI (77%), followed by RY (21%) and BII (0.7%)[8]. While Kitano *et al*. first introduced laparoscopy-assisted distal gastrectomy (LADG) for EGC patients in 1991, the Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) group performed LADG later than Japanese surgeons, and the KLASS 01 trial started enrolling EGC patients since 2006[1,70]. In addition, the trend to perform totally laparoscopic procedures seems to have encouraged Korean surgeons to perform easier and faster anastomosis[1]. In Korea, except for BI (63.4%), the most frequently adopted reconstruction was BII (33.1%), while RY had a frequency of only 3.3%[10]. Pursuing convenience for ease and speed, rather than oncological safety, cannot be justified. Therefore, some researchers have suggested that BII reconstruction should not be considered to reduce the potential risk of cancer recurrence in the remnant stomach. In terms

of objective evaluation of the anti-reflux capacity through endoscopic findings, BII-B could better prevent bile reflux than BII but was far from the ideal capability of RY. Additionally, BII-B did not guarantee a shorter operative time or fewer morbidities than RY. From the perspective of patient experience, BII-B was not inferior to RY but better than BII reconstruction in causing fewer reflux symptoms at 6 and 12 months. RY caused fewer nausea symptoms than BII at 6 and 12 months postoperatively, but not BII-B. Therefore, we recommend that surgeons consider RY for oncologic safety and at least BII-B, not BII, for reduced reflux symptoms (Table 2, Fig. 2, and Fig. S3, Supporting information, Supplemental Digital Content 2, http://links.lww.com/JS9/B79). It takes about 6.8–18.8 years for metachronous cancer to develop in the remnant stomach after curative gastrectomy. As old age, longer operative time, and underlying disease can increase postoperative morbidities[5,71,72], BII can be suggested in elderly patients with severe comorbidities and short life expectancy.

This study had several limitations. First, this collateral study was designed after the prospective collection of multicentre cohort data for the KLASS-07 clinical trial[28]. Since the collected cohort mainly consisted of data related to postoperative morbidities and endoscopic findings within 1 year, the analyses for disease-free or overall survival could not be performed. Second, we could only investigate differences in QoL during postoperative 1 year. The reflux of bile acids can damage the gastric mucosa and potentiate the development of gastritis, gastric ulcers, and reflux oesophagitis, which may worsen over time, ultimately affecting patients' long-term QoL. Considering that bile reflux caused by anatomical alterations is permanent, specific QoL items affected by bile reflux are also expected to be poor even after 1 year. Compared to other anastomotic procedures, RY reconstruction has been reported to provide better long-term QoL to patients after LDG by reducing bile reflux[16,73–75]. Since aging is associated with inevitable time-dependent changes in the adaptive capacity of the gastrointestinal tract, the assessment of gastrointestinal physiology-related QoL requires several years of observation. Therefore, a limitation of this study was that the difference in long-term QoL due to the reconstructive procedure could not be analyzed. In contrast, most QoL related to surgical procedures was mainly determined during the early recovery period[76] and remains stable after the first year following surgery. QoL usually returns to the baseline level ~1 year after gastrectomy[77]. Analyses of QoL over multiple time points during the first year among the three groups were expected to compensate for these limitations. Third, because of the retrospective nature of the current study and surgeon's preferences for specific reconstruction methods, the population of each group was not evenly distributed when divided according to the method of reconstructive procedures. Considering that the cohort was operated by surgeons with annual experience of > 30 gastrectomies, the impact of the surgeon's experience on the reconstruction procedure is expected to be insignificant. Fourth, we could not recommend an optimal Roux limb length for RY reconstruction. The surgeons participating in the current study reached a consensus to perform jejunojejunostomy 30–40 cm apart from the GJ before the patients were enrolled from 20 institutions in South Korea. Accordingly, we could not analyze the impact of variations in limb length on the frequency of bile reflux, Roux stasis, or QoL differences. However, our results showed that RY with an alimentary limb of 30–40 cm provided negligible incidence of bile reflux, fewer nausea and reflux symptoms without Roux stasis, and fewer nutritional problems. Therefore, jejunojejunostomy 30–40 cm apart from the GJ may be appropriate for RY reconstruction. Future well-designed RCTs are expected to resolve these issues and limitations.

Conclusion

In conclusion, as per the experience of the patients' short-term QoL, BII-B was not inferior to RY in providing fewer STO22 reflux symptoms than BII reconstruction. Only RY reduced both C30 nausea and STO22 reflux symptoms compared with BII. Similarly, from the perspective of surgeons who objectively evaluate the reflux-preventing capacity, BII-B is not an alternative to RY reconstruction. Bile reflux can potentiate cancer recurrence in the remnant stomach, and Braun anastomosis cannot divert as much bile as RY and fails to shorten operative time or reduce morbidity. Hence, RY reconstruction is recommended during curative distal gastrectomy. However, QoL symptoms after distal gastrectomy cannot be solely explained by bile reflux grade and may be associated with various factors. In addition, BII showed the benefit of shortened operative time compared with BII-B or RY reconstruction. Because increased operative time is associated with the risk of complications, BII reconstruction can be performed in a limited manner in older patients with gastric cancer who have a short life expectancy. If the purpose was to prevent bile reflux, BII-B was unlikely to have a significant effect. Therefore, it is necessary to clinically apply appropriate reconstructive methods that consider various factors such as subjective preoperative QoL symptoms, remaining life expectancy, and BMI. Considering that continued bile reflux caused by anatomical alterations will have a long-term impact on patient lives, future large-scale RCTs are expected to provide unbiased evidence of the long-term endoscopic findings, QoL, nutritional status, complications, and survival data of the patients.

Ethical approval

All procedures were performed in accordance with the ethical standards of the Responsible Committee on Human Experimentation (Institutional and National) and with the Helsinki Declaration of 1964 and later versions. This study was approved by the Institutional Review Board of Korea University Medical Center (No. X-2020-AN0231).

Consent

Written informed consent was obtained from the patient for the 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

S.-H.P., H.H., and S.P.: conceptualization; S.-H.P., H.H., H.S.C., B.K., and K.-S.Y.: formal analysis; S.-H.P. and S.P.: funding acquisition; S.-H.P., H.H., and S.P.: methodology; S.P.: project administration; and S.-H.P. and H.H.: writing – original draft. All authors were involved in data curation; investigation; resources; software; supervision; validation; visualization; and writing – review and editing.

Conflicts of interest disclosure

All authors have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: https://www.researchregistry.com
2. Unique identifying number or registration ID: research registry8852.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/registernow# home/registrationdetails/643a61e208740f00295d6808/.

Guarantor

The Guarantor, Sungsoo Park, accepts full responsibility for the work and/or the conduct of the study, has access to the data, and controls the decision to publish.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to governmental policy regarding individual information but are available from the corresponding author upon reasonable request.

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