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**EDITORIAL**

Christodoulidis G, Koumarelas KE, Kouliou MN. Pivotal role of exosomes in diagnosis and treatment of esophageal cancer in a new era of precision medicine. *World J Methodol* 2024; 14(1): 90624 [DOI: 10.5662/wjm.v14.i1.90624]

**EVIDENCE REVIEW**

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Koutromanos I, Legaki E, Gazouli M, Vasilopoulos E, Kouzoupis A, Tzavellas E. Gut microbiome in alcohol use disorder: Implications for health outcomes and therapeutic strategies-a literature review. *World J Methodol* 2024; 14(1): 88519 [DOI: 10.5662/wjm.v14.i1.88519]

Joshi AM, Raveendran AV, Arumugam M. Therapeutic role of yoga in hypertension. *World J Methodol* 2024; 14(1): 90127 [DOI: 10.5662/wjm.v14.i1.90127]

Liau MYQ, Toh EQ, Muhamed S, Selvakumar SV, Shelat VG. Can propensity score matching replace randomized controlled trials? *World J Methodol* 2024; 14(1): 90590 [DOI: 10.5662/wjm.v14.i1.90590]

**ORIGINAL ARTICLE****Retrospective Study**

Christodoulidis G, Kouliou MN, Koumarelas KE, Argyriou K, Karali GA, Tepetes K. Billroth II anastomosis combined with brown anastomosis reduce reflux gastritis in gastric cancer patients. *World J Methodol* 2024; 14(1): 89709 [DOI: 10.5662/wjm.v14.i1.89709]

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## Retrospective Study

**Billroth II anastomosis combined with brown anastomosis reduce reflux gastritis in gastric cancer patients**

Grigorios Christodoulidis, Marina Nektaria Kouliou, Konstantinos Eleftherios Koumarelas, Konstantinos Argyriou, Garyfallia Apostolia Karali, Konstantinos Tepetes

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**Abstract****BACKGROUND**

The surgeon performing a distal gastrectomy, has an arsenal of reconstruction techniques at his disposal, Billroth II among them. Braun anastomosis performed during a Billroth II procedure has shown evidence of superiority over typical Billroth II, in terms of survival, with no impact on postoperative morbidity and mortality.

**AIM**

To compare Billroth II *vs* Billroth II and Braun following distal gastrectomy, regarding their postoperative course.

**METHODS**

Patients who underwent distal gastrectomy during 2002-2021, were separated into two groups, depending on the surgical technique used (Billroth II: 74 patients and Billroth II and Braun: 28 patients). The daily output of the nasogastric tube (NGT), the postoperative day that NGT was removed and the day the patient started per os feeding were recorded. Postoperative complications were at the same time noted. Data were then statistically analyzed.

**RESULTS**

There was difference in the mean NGT removal day and the mean start feeding day. Mean total postoperative NGT output was lower in Braun group (399.17 mL *vs* 1102.78 mL) and it was statistically significant ( $P < 0.0001$ ). Mean daily postoperative NGT output was also statistically significantly lower in Braun group. According to the postoperative follow up 40 patient experienced bile reflux and alkaline gastritis from the Billroth II group, while 9 patients who underwent

Billroth II and Braun anastomosis were presented with the same conditions ( $P < 0.05$ ).

## CONCLUSION

There was evidence of superiority of Billroth II and Braun *vs* typical Billroth II in terms of bile reflux, alkaline gastritis and NGT output.

**Key Words:** Billroth II; Billroth II and Braun; Reconstruction techniques; Gastrectomy; Distal gastrectomy

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**Core Tip:** This is a retrospective study to evaluate the efficacy of the addition of Braun enteroenteroanastomosis to Billroth II reconstruction compared to Billroth II alone in terms of the postoperative outcomes of these surgical techniques, following distal gastrectomy. The addition of Braun anastomosis demonstrated superiority in terms of survival without impacting complications or mortality. The study highlights the significance of considering bile reflux and alkaline gastritis in postoperative quality of life after gastrectomy, emphasizing the role of Braun's anastomosis in reducing bile reflux and associated complications.

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## INTRODUCTION

Theodor Billroth (1829-1894) was a prominent figure of surgery during the 19<sup>th</sup> century, being the first to perform a subtotal gastrectomy[1,2]. Among his heritage, Billroth II[1], an operation, in which, after a partial gastrectomy and closure of duodenum stump, a side-to-side anastomosis is performed between jejunum and the greater curvature of the stomach. Although Heinrich Braun (1862-1934), another surgical pioneer, was the first to describe the formation of an ulcer in the jejunum after a gastroenterostomy, he is widely known for the homonymous enteroenterostomy[3]. Braun enteroenterostomy[4], is defined as the anastomosis between the afferent and efferent loops of jejunum, distal to a gastroenterostomy. The purpose of a Braun anastomosis, originally introduced in 1892[5], is to reduce the reflux of bile and pancreatic secretions into the stomach[6], as well as the possibility of ileus[7] and divert oral intake from the afferent limb[8], which is crucial, given the fact that bile reflux is one of the most important factors that determine the postoperative quality of life after gastrectomy[9]. Furthermore, alkaline gastritis is correlated with esophagitis, Barrett's esophagus and with the emergence of metachronous cancer, therefore the management of reflux gastritis is fundamental [10,11]. Due to its alkaline protecting effect, Braun's anastomosis is today widely applied to distal gastrectomy and pancreaticoduodenectomy[5].

Distal gastrectomy[12-14] remains the operation of choice for distal-third gastric cancer, as followed by lower mortality and morbidity rates, higher quality of life and no significant difference as far as long-term survival rates are concerned, compared to total gastrectomy, with the efforts now leaning on maintaining the continuity of the Gastrointestinal tract[15, 16]. Moreover, the surgeon performing a distal gastrectomy, has a variety of reconstruction techniques, Billroth-I, Billroth-II, and Roux-en-Y, each with its respective advantages and disadvantages, at his disposal[5,10-12,16-18]. Among those, Billroth II with or without Braun anastomosis is often preferred worldwide[19]. Braun anastomosis performed during a Billroth II procedure has shown evidence of superiority over typical Billroth II, in terms of survival, with no impact on postoperative complications and mortality[20].

Therefore, this study compared the two above mentioned surgical techniques regarding their postoperative course.

## MATERIALS AND METHODS

For the purpose of this retrospective study, data were collected from patients undergoing distal gastrectomy at the Department of Surgery, University Hospital of Larissa, during 2002-2021. No patients were excluded based on their underlying disease. As far as primary diagnosis is concerned, from the entire sample, 5 patients were diagnosed with gastrointestinal stromal tumor, 6 patients with gastric ulcer, and all the remaining patients suffered from gastric adenocarcinoma. They were then separated into two groups, depending on the surgical technique used (Billroth II: 74 patients, mean age: 70.75 years, 44 male, 30 female; and Billroth II and Braun: 28 patients, mean age: 70.41 years, 21 male, 7 female). As minimum and maximum age in the sample was 42 and 92 years respectively, patients were also divided into two subgroups ( $\leq 67$  years and  $> 67$  years). There was no categorization, on the basis of the way the anastomoses were performed, for example hand sewn or with the use of a mechanical stapler. Demographic data, including age and

gender, the output of the nasogastric tube (NGT), the postoperative day (POD) that NGT was removed, the day the patient started feeding and the total postoperative hospitalization days (PHD) were recorded. Patients on their 5<sup>th</sup> POD underwent gastroscopy in order to investigate any possible development of alkaline gastritis and bile reflux. NGT output was measured on a daily basis at a fixed hour and data were collected until the 10<sup>th</sup> POD. Patients with NGT  $\geq$  10<sup>th</sup> POD or need for NGT reinsertion after 10<sup>th</sup> POD were excluded from the study. Before comparisons between the two surgical techniques were made, the data from each subgroup underwent Shapiro-Wilk test for normality ( $P < 0.05$ ) [21-26]. Due to the fact that normality could not be proven, Mann-Whitney *U* test ( $P < 0.05$ ) was used [27]. Aligned Rank Transform three way ANOVA was then performed (ARTool) for the effects of age, gender and surgical method on hospitalization days and NGT total output, to be examined [28]. All statistical analysis was conducted using IBM SPSS statistics v22 software.

## RESULTS

The study outcomes are displayed in Table 1. The mean PHD for Billroth II was 13.09, while for Billroth II and Braun was 10.17 ( $P < 0.0001$ ). Moreover, there was statistically significant difference between the two methods as far as feeding start day and NGT removal day are concerned ( $P < 0.0001$ ). Data from BII and Braun for NGT removal day follow the normal distribution, but since BII data do not, Mann Whitney was applied. NGT output mean is systematically lower for BII + B group during all POD (Figures 1 and 2). Moreover, patients from BII + B group had their NGT removed by the 6<sup>th</sup> POD due to lack of drainage, while patients from BII group had still an increased drainage volume due to reflux gastritis.

According to the postoperative complications, out of the 74 patients who underwent Billroth II, forty presented with bile reflux and alkaline gastritis (54%), and from the group of patients who underwent BII and Braun these complications were observed in only 9 patients (32%) ( $P < 0.05$ ) (Table 2). These findings were mainly confirmed by the patients gastroscopist report during their postoperative follow-up and the NGT output.

In our study BII outweighed BII and Braun in terms of operation time, with a mean operating time of 226.4 min  $\pm$  41.6 min. for the BII group *vs* a duration of 255.8 min  $\pm$  66.2 min. for the BII and Braun group ( $P < 0.05$ ). However, there were no statistically significant difference in blood loss during surgery (Table 3).

An Aligned Rank Transform three-way ANOVA was conducted and examined the effect of age, gender and surgical method on hospitalization days and NGT total output (Table 4). There was a statistically significant interaction between age and gender in total NGT output ( $P < 0.05$ ) or PHD ( $P < 0.05$ ). Similarly, there was an interaction effect on NGT output or PHD between age and method, gender and method or age, gender, and method ( $P < 0.05$ ). This means that younger and male patients had smaller values of NGT output as well as less hospitalization days. Moreover, whichever of the independent factors were combined with BII and Braun anastomosis had also a better outcome.

Patients on their follow-up were given questionnaires for the postoperative quality-of-life assessing data about patients recovery, in terms of physical, emotional and cognitive behavior. A short analysis of the data acquired indicated that the patients of the two groups had a similar postoperative status.

## DISCUSSION

Gastric malignancies account for 930000 over 1000000 new cases and 700000 deaths annually [15,29]. Gastric cancer is considered the third deadliest, while being the fifth most commonly diagnosed [15]. Considering the progress in earlier diagnosis a more preservative attitude towards distal gastric cancer resection has been recently adopted, since there is no difference regarding long term survival rates between distal and total gastrectomy [12,15]. The extent of the portion of the stomach removed, given adequate oncologic margins ( $\geq 3$  cm for T2 tumors or types 1 and 2 and  $\geq 5$  cm for types 3 and 4) does not constitute a prognostic factor, unlike perigastric lymph node clearance. Regarding lymph node clearance during distal gastrectomy, JGCA recommends D1 or D1+ for cT1N0 and D2 for cT2-T4 tumors [13]. Due to the fact that the most important factor affecting the decision between distal or total gastrectomy is the proximal resection margin, patients suffering from malignancy in the middle part of the stomach can also be submitted to distal gastrectomy, thus counting almost for 23%-70% of all cancer gastrectomies in Europe and Asia [12,30,31]. Although five-year survival rates of gastrectomy range between 33%-50%, patients can suffer from ongoing gastrointestinal symptoms for up to 6 months postoperatively [29,32].

The selection of reconstruction methods following distal gastrectomy presents a significant dilemma. Options such as Billroth I, Billroth II, and Roux-en-Y are available, with the latter gaining prominence in the 1970s and 1980s as a response to the elevated incidence of post-gastrectomy alkaline reflux gastritis [33]. Roux-en-Y exhibits superiority over Billroth II in terms of functional and endoscopic outcomes, attributed to the mitigated risks of gastroduodenal and duodenogastroesophageal reflux (DGER), identified as precipitating factors for malignancy development based on reflux gastritis and esophagitis [7,17,18]. However, Roux-en-Y anastomosis entails certain drawbacks, such as a potential occurrence of Roux stasis syndrome (observed in approximately 0-13% of patients), leading to vomiting, stomach dilation, and prolonged hospitalization [18]. Additionally, the procedure necessitates an extended operation time and is associated with increased intraoperative blood loss and greater postoperative weight loss compared to Billroth II and Braun [10,15]. Billroth II with Braun is often proposed as the primary surgical approach, with Roux-en-Y considered a secondary option in case of Braun's failure [34].

A retrospective analysis involving 720 patients with gastric malignancy from 1997-2011 suggested that Billroth II and Braun may enhance lifespan without escalating postoperative complications and mortality rates [20]. The literature, including a Randomised Clinical Trial and a prospective randomized trial, underscores the comparable acceptability of

**Table 1 Study outcomes**

	Operation	n	Mean	SD	P value
Postoperative hospitalization days	Billroth II	74	13.09	1.41	< 0.0001
	Billroth II + Braun	28	10.17	2.01	
Feeding start day	Billroth II	74	6.33	0.66	< 0.0001
	Billroth II + Braun	28	5.17	0.41	
NGT removal day	Billroth II	74	4.31	0.31	< 0.0001
	Billroth II + Braun	28	4.00	0.67	
NGT output (day 0)	Billroth II	74	183.56	56.29	< 0.0001
	Billroth II + Braun	26	73.64	25.70	
NGT output (day 1)	Billroth II	72	265.80	50.08	< 0.0001
	Billroth II + Braun	26	168.18	76.95	
NGT output (day 2)	Billroth II	61	234.59	44.82	< 0.0001
	Billroth II + Braun	21	85.56	43.08	
NGT output (day 3)	Billroth II	49	280.00	57.76	< 0.0001
	Billroth II + Braun	16	47.14	17.82	
NGT output (day 4)	Billroth II	30	251.67	70.48	< 0.0001
	Billroth II + Braun	12	136.00	93.25	
NGT output (day 5)	Billroth II	21	234.62	65.08	< 0.0001
	Billroth II + Braun	7	116.67	92.80	
NGT output (day 6)	Billroth II	13	322.50	76.11	< 0.0001
	Billroth II + Braun	1	0	NA	
NGT output (sum)	Billroth II	74	1102.78	203.94	< 0.0001
	Billroth II + Braun	28	399.17	140.18	

NGT: Nasogastric tube; NA: Not available.

**Table 2 Postoperative complications**

Postoperative complications	Billroth II	Billroth II with Braun	P value
Bile reflux	40	9	0.048
Alkaline gastritis	40	9	0.048
Anastomotic bleeding	2	1	0.820
Anastomotic fistula	1	1	0.470

Billroth II and Braun to Roux-en-Y gastrojejunostomy, emphasizing the significance of considering operation time and blood loss in critically ill patients during the selection of the appropriate procedure[10,15,17]. However, a prospective randomized trial exhibited statistically significant differences in favor of Roux-en-Y regarding the degree and extent of gastritis and bile reflux, though no distinctions were observed in the overall Gastrointestinal Quality of Life Index score [17,35,36].

The application of Braun anastomosis in pancreaticoduodenectomy (PD) has garnered substantial attention, with studies indicating its potential benefits. Comparative analyses between Child non-Braun and Child Braun cohorts revealed statistically significant reductions in DGER rates in the Braun group, positioning Braun enteroenterostomy as a significant independent factor in mitigating DGER[37]. These findings align with similar results in pylorus-preserving pancreatoduodenectomy, affirming the advantageous role of Braun anastomosis in minimizing postoperative DGER incidence[38]. A recent meta-analysis of ten studies comprising 1614 patients reported no significant differences in mortality, intraoperative blood loss, postoperative pancreatic fistula, bile leakage, gastrointestinal hemorrhage, intra-abdominal abscesses, wound complications, and overall hospital stay between Braun PD and typical PD. Nevertheless, the Braun group exhibited lower rates of reoperation, morbidity, clinically relevant DGER, postoperative NGT



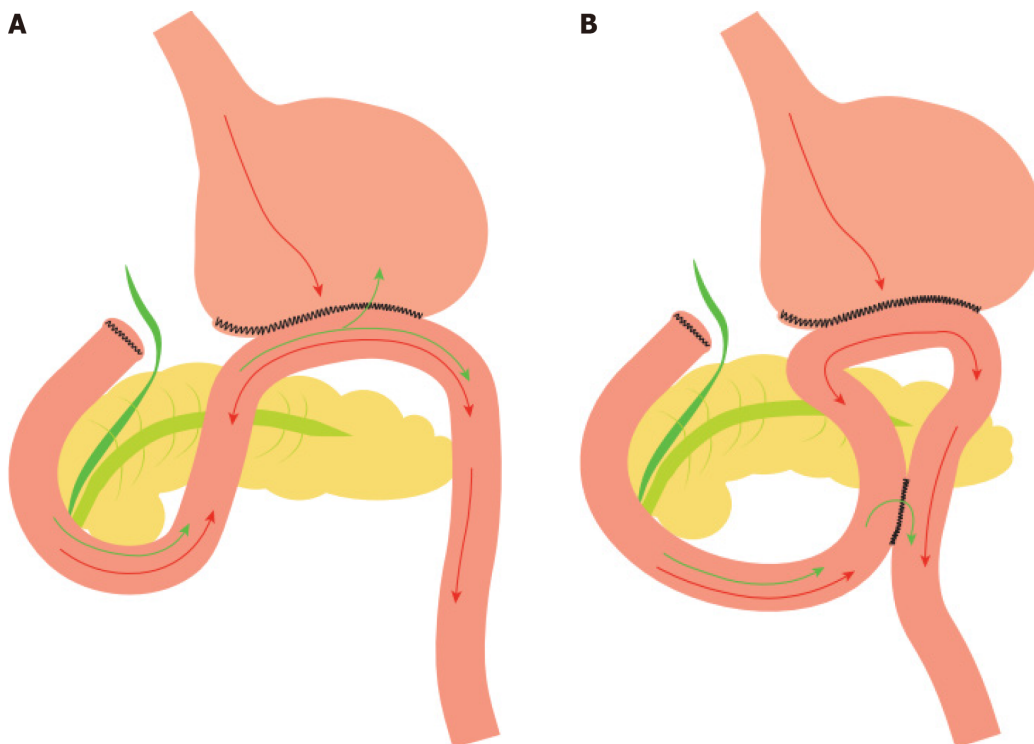
**Table 3 Patients' characteristics**

Characteristics	Billroth II	Billroth II and Braun
Age	70.75	70.41
Gender		
Male	44	21
Female	30	7
Operation time (min)	226.4 ± 41.6	255.8 ± 66.2
Blood loss (mL)	175.4 ± 121.3	148.7 ± 96.8

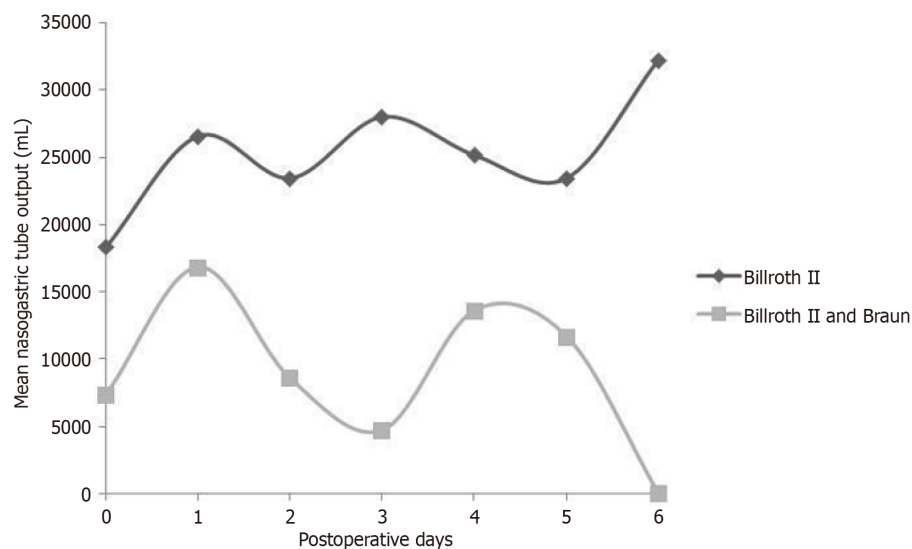
**Table 4 Aligned Rank Transform three-way ANOVA results (*P* < 0.05)**

	NGT output (sum)	Postoperative hospitalization days
Age	0.929	0.339
Gender	0.325	0.093
Method	0.170	0.469
Interaction age and gender	0.861	0.288
Interaction age and method	0.946	0.635
Interaction gender and method	0.579	0.177
Interaction age, gender, and method	0.983	0.998

NGT: Nasogastric tube.



**Figure 1 Billroth II and Braun figure.** A: Billroth II; B: Billroth II and Braun.



**Figure 2** Mean daily nasogastric tube output.

reinsertion, and vomiting[6].

Our study, albeit contributing valuable insights, is not without limitations. It bears the inherent biases of a retrospective, non-randomized trial conducted over a nineteen-year span, during which accumulated experience may have exerted an influential role. Notably, the study group lacked stratification based on anastomosis techniques (manual suturing or the use of a stapling device), surgery type (open *vs* laparoscopic) and the specific disease leading to gastrectomy, the latter due to a constrained sample size. The uneven distribution of participants between the two groups may introduce non-homogeneity biases. It is pertinent to acknowledge that gastric reflux was not quantitatively assessed using imaging methods, such as radionuclide biliary scanning. Despite these limitations, the existing literature supports the utility of Braun anastomosis, emphasizing the exigency for well-designed randomized controlled trials to further delineate its merits.

## CONCLUSION

In conclusion, there were evidence of superiority of Billroth II and Braun against typical Billroth II, in terms of bile reflux, alkaline gastritis and NGT output. These results were statistical significant, eventhough the several study limitations. The need for randomized controlled trials is highlighted.

## ARTICLE HIGHLIGHTS

### Research background

The study focuses on comparing two reconstruction techniques, Billroth II and Billroth II with Braun anastomosis, commonly used after distal gastrectomy, examining their impact on postoperative outcomes. The retrospective study collected data from patients undergoing distal gastrectomy, dividing them into two groups based on the reconstruction technique used. The significance of our research lies to the close follow-up in accordance with the gastroenterologists to confirm the diagnosis of alkaline reflux gastritis.

### Research motivation

The research is motivated by the debate on the optimal reconstruction technique following distal gastrectomy for gastric cancer. The study aims to contribute valuable insights by comparing the postoperative outcomes of the two reconstruction methods, Billroth II and Billroth II with Braun anastomosis, in order to inform clinical decision-making and potentially improve patient outcomes in the treatment of distal gastric cancer.

### Research objectives

To evaluate and compare the postoperative course of patients undergoing distal gastrectomy with either Billroth II or Billroth II with Braun anastomosis. Specific outcomes under scrutiny involve factors such as postoperative hospitalization days (PHD), feeding initiation, nasogastric tube (NGT) removal, and the occurrence of complications like bile reflux and alkaline gastritis, aiming to discern potential advantages between the two reconstruction techniques.

### Research methods

The study employed a retrospective design, collecting data from patients who underwent distal gastrectomy at the Department of Surgery, University Hospital of Larissa, spanning from 2002 to 2021. Patients were categorized based on the reconstruction technique used (Billroth II or Billroth II with Braun), and statistical analyses, including Mann-Whitney *U* test and Aligned Rank Transform three-way ANOVA, were performed to assess variables such as PHD, feeding start day, NGT removal, and complications.

### Research results

The research revealed that distal gastrectomy with Billroth II and Braun anastomosis demonstrated superiority over typical Billroth II in terms of postoperative outcomes. Statistically significant differences were observed, including shorter PHD, earlier feeding initiation, quicker NGT removal, and a lower incidence of complications such as bile reflux and alkaline gastritis, highlighting potential benefits of the Billroth II and Braun anastomosis technique in the surgical management of distal gastric cancer.

### Research conclusions

In conclusion, the study suggests evidence of the superiority of Billroth II with Braun anastomosis over typical Billroth II in the context of distal gastrectomy for gastric cancer. Despite inherent limitations in the retrospective design, the findings emphasize the potential benefits of the specific reconstruction technique, such as reduced postoperative complications and improved outcomes.

### Research perspectives

Future research should focus on addressing limitations such as sample size constraints, variations in surgical techniques, and the absence of quantitative assessments for gastric reflux, aiming to provide more conclusive evidence on the optimal reconstruction method for enhanced postoperative outcomes in patients with distal gastric cancer.

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## FOOTNOTES

**Author contributions:** Tepetes K and Christodoulidis G designed the study; Christodoulidis G, Kouliou MN, Koumarelas KE, and Karali O collected the data; Kouliou MN, Koumarelas KE, and Karali O wrote the manuscript; Argyriou K performed the statistical analysis and contributed to the analysis; Tepetes K, Christodoulidis G, and Argyriou K supervised the report.

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