GASTROINTESTINAL SURGERY: EMERGING TECHNIQUES, CONTROVERSIES AND STATE OF ART

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GASTROINTESTINAL SURGERY: EMERGING TECHNIQUES, CONTROVERSIES AND STATE OF ART

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Editorial: Gastrointestinal Surgery: Emerging techniques, controversies and state of art

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Editorial on the Research Topic
Gastrointestinal Surgery: Emerging techniques, controversies and state of art

By Pata F, Rausei S, Scabini S and Pellino G. (2022) Front. Surg. 9: 1033757. doi: 10.3389/fsurg.2022.1033757

> "*The abdomen, the chest and the brain will forever be shut from the intrusion of the wise and humane surgeon.*" Sir John Ericksen, 1837

As other medical fields, surgery is currently undergoing a deep transformation (1): on the one hand, emerging technologies such as robotic, artificial intelligence, machine learning, promise to improve standardization, and effectiveness of diagnosis and treatment, and on the other hand, humanitarian topics such as disparities in equal access to highest quality surgical care worldwide (2), sustainability (3), gender equality, and patient-reported outcomes are increasingly claimed as priorities in the surgical agenda.

As pointed out by Tekkis et al. in their elegant perspective on 3-D printing technology, the adoption of new technologies is not a passive process: effort is needed from the healthcare systems to understand the advantages against the potential economic limits and the need of integration with traditional technology. The reconceptualization and the adoption of new business models may represent the key to overcome these issues.

The technological revolution impacts also on surgical training. Simulation is becoming a mandatory component for trainees in many universities. Evidence of the best training methods require tailored studies as showed by Sahmand et al. in their study on 3D vs. 2D environment for laparoscopic simulation.

The reduced contribution of high-quality trials and structured research programs in surgery in comparison with other medical fields represents a further issue (4), although observational studies may add robust data when randomized controlled trails are not feasible, unethical, or technically challenging (5).

Tousignant et al. identified the main influencers of surgical efficiency and variability in a 5-year robotic sleeve gastrectomy case series: stomach dissection resulted in the Achilles' heel in terms of procedure duration. Although external inference may be limited by the single-center design and the limited numbers of the study, it paves the way to larger cohort studies to confirm these findings and to generate plans to reduce times and costs.

Wang et al. in their meta-analysis on early oral feeding after colorectal surgery—including 1,199 patients—confirmed that early oral feeding may represent a safe option, with reduced length of stay and overall complications, although the higher rate of nasogastric tube reinsertion, a potential source of morbidity, should be taken in account, especially in older patients.

Song et al. focused their attention on the influence of the length of surgical abdominal wound on postoperative recovery. Longer incisions were significantly associated with delay in the first bowel movement, but the effect was not clinically meaningful because this did not change the time of the first passage of flatus, universally recognized marker of postoperative recovery of gut function.

Increasing evidence support the use of indocyanine green fluorescence in oncologic surgery (6, 7), although with a lack of standardization and a quality heterogeneity in several studies (8). Belia et al. provide an overview of the adoption of this technique in the armamentarium of the gastric surgeon. In this field, the equivalence of a totally laparoscopic with the laparoscopic-assisted approach in radical gastrectomy is shown by an interesting retrospective study by Zhong et al.

The deferral of elective procedure during COVID-19 pandemics has been the result of a backlog of millions of surgical procedures, an unexpected challenge for healthcare system worldwide (9). Even in urgent surgery, a shift toward nonoperative management has occurred as revealed by Stavridis et al. in their systematic review on acute cholecystitis management, a similar trend observed in the management of acute appendicitis (10).

The reduced mobility of patients toward high-volume centers during the lockdowns might have suggested alternative surgical strategies to reduce morbidity in low- and medium-volume centers, as proposed by Giuliani et al. in reducing postoperative pancreatic fistula rate after pancreaticoduodenectomy. Albrecht et al. propose the insertion of a negative pressure drainage in the pancreatic duct in the pancreatogastrostomy following pylorus-preserving pancreaticoduodenectomy. The results seem positive, but the small sample (21 patients) and the inherited biases of the design of the study claims caution. On this line, Buonodonno's team describe the preliminary results of a Hub and Spoke learning program in bariatric surgery in a small region of Italy.

Emerging technologies in gastrointestinal surgery are an exciting and tasty topic. We hope with this number to have partially satiated the hunger of the tablemates.

Author contributions

FP, SR, SS, and GP contributed to drafting and writing the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Association of Abdominal Incision Length With Gastrointestinal Function Recovery Post-operatively: A Multicenter Registry System-Based Retrospective Cohort Study

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Objective: To evaluate the influence of the abdominal incision length on the gastrointestinal function recovery post-operatively.

Background: Gut motility recovers more quickly after the minimally invasive laparoscopic surgery compared than after the traditional open surgery; however, whether the minimal abdominal incision contributes to the faster gut motility recovery is controversial and lacks solid clinical evidence.

Methods: A registry-based secondary cohort analysis was conducted to evaluate the association between the abdominal incision length and gut motility recovery post-operatively based on a multicenter, prospective, and observational study of the prolonged post-operative ileus (PPOI) incidence and the risk factors in the patients with the major abdominal surgery. The incision length, in the centimeters, was the exposure. The primary outcome measures were the PPOI incidence and its association with the incision length. The secondary outcome included the days to the first passage of flatus and the days to the first passage of stool.

Results: Overall, 1,840 patients, including 287 (15.7%) patients with the PPOI, were recruited. The PPOI incidence was 17.6% and 13.3% in the long-incision (>18 cm) and short-incision patients (≤18 cm), respectively. The incidence of the PPOI increased by 1.1% (1.0–1.1) by each centimeter increment of the incision length after adjusting for the confounding factors. In comparison to the short-incision patients, the long-incision patients had prolonged passage of stool (4.46 vs. 4.95 days, $p < 0.001$). Each centimeter increment of the incision length contributed to a 2% increased risk of delay in the first bowel movement [hazard ratio (HR) 0.980 (0.967, 0.994)].

Conclusion: A long abdominal incision length independently contributed to the prolonged gut function recovery post-operatively mainly by delaying the time to the first bowel movement, but not influencing the time to first passage of flatus.

Keywords: incision length, prolonged post-operative ileus, gastric surgery, colorectal surgery, pancreas-duodenum surgery

INTRODUCTION

Abdominal alimentary tract surgery results in the post-operative ileus (POI), which is defined as the transient cessation of the coordinated bowel motility after surgery. Resolution of POI is important for shortening the post-operative hospitalization in the era of enhanced recovery after surgery (ERAS). As a minimally invasive modality, laparoscopic surgery greatly enhances the recovery of the patient after surgery. Many studies have shown that the laparoscopic surgery is associated with decreased risk of prolonged ileus (1, 2). Patients have a faster bowel motility recovery and an earlier ability to tolerate an oral diet compared with the traditional open surgery. However, the reason for this benefit remains undefined. It is thought that some advantages of the laparoscopic surgery, including less handling of the intestine and the fine dissection of organs, could contribute to the return of the faster bowel function. The short abdominal incision length is a prominent feature of the laparoscopic surgery compared to the open surgery. Some comparative studies by using the animal models have indicated that the magnitude of the abdominal incision affects the duration of POI (3). The minimal incision independently contributes to the faster bowel motility recovery in the patients with major abdominal surgery that remains controversial. The association of the abdominal incision length with POI needs to be explained.

Patient with the prolonged post-operative ileus (PPOI) cohort study was conducted primarily to investigate the incidence of the PPOI in the patients undergoing open gastrointestinal (GI) surgery. The PPOI was defined as POI lasting longer than the regular resolution period, which is generally the post-operative days 3–4. There are definite PPOI diagnostic criteria based on the systematic review and global survey (4). The PPOI is diagnosed if two or more of the following criteria are met on or after day 4 post-operatively: lack of passage of flatus and/or stool, nausea and vomiting, inability to tolerate oral diet, abdominal distension, and diffuse dilated bowel in a CT scan. The strategy for evaluating the bowel function associated with the PPOI is more comprehensive than the passage of flatus and stool. The PPOI has a profound effect on the course of post-operative recovery. It is recognized as a pathological entity that results in an increased length of the hospital stay and healthcare costs (5).

We designed a retrospective cohort study based on the PPOI registry cohort to investigate the effect of the abdominal incision length on the GI function recovery post-operatively. The variable under study was the abdominal incision length. The PPOI incidence was the primary outcome and the time to the first passage of flatus and the time to the first passage of stool were evaluated as the secondary outcomes.

MATERIALS AND METHODS

Study Design

This study was a secondary analysis of the PPOI cohort. This cohort was part of a prospective, multicenter, and observational cohort study of the PPOI incidence and risk factors in the patients with major abdominal surgery. Overall, 2,083 patients from 22 hospitals in the different areas of China were registered in the dataset. The patient series were consecutively admitted to the hospitals between October 26, 2016, and November 5, 2018. All the patients underwent the open major GI surgery including gastric surgery, colorectal surgery, and pancreaticoduodenectomy surgery. They were followed up after surgery until discharged from the hospitals. A consultant surgeon supervised the data collection at each center ensuring that the data were collected in accordance with the protocol. The final dataset was audited by an independent data validator with 97% ascertainment and 91% data accuracy.

The PPOI cohort was approved by the Ethics Committee of Beijing Friendship Hospital (approve code: 2016-P2-064-01). This cohort was registered on the Chinese Clinical Trial Registry website and the registry ID is ChiCTR-IOC-16009955 (http://www.chictr.org.cn/showproj.aspx?proj=16810).

Exposure Variable

The abdominal incision length was measured in the centimeters by using a sterile ruler after the open abdominal surgery. The patients were divided into a long incision length group (>18 cm) and a short incision length group (≤ 18 cm) according to the mean of all the incision lengths (18 cm). When the logistic regression was performed, the exposure variable incision length acted as a continuous variable. The continuous incision length was recorded as a categorical variable according to the quartile number. Dealing with the categorical incision length could provide the evidence whether there was a linear trend of the odds ratio (OR) across all the four quartiles.

Outcome

The primary outcome was the PPOI incidence after the open abdominal surgery. POI after open abdominal surgery was recognized and it generally returned during the post-operative days 3–4. Delayed recovery of POI has been recognized as a pathological entity and named as the PPOI. The PPOI diagnostic criteria follow the definition proposed by the researchers at the Auckland University, which was determined to be based on the systematic review and global survey (4). The PPOI is diagnosed if two or more of the following criteria are met on or after day 4 post-operatively without prior resolution

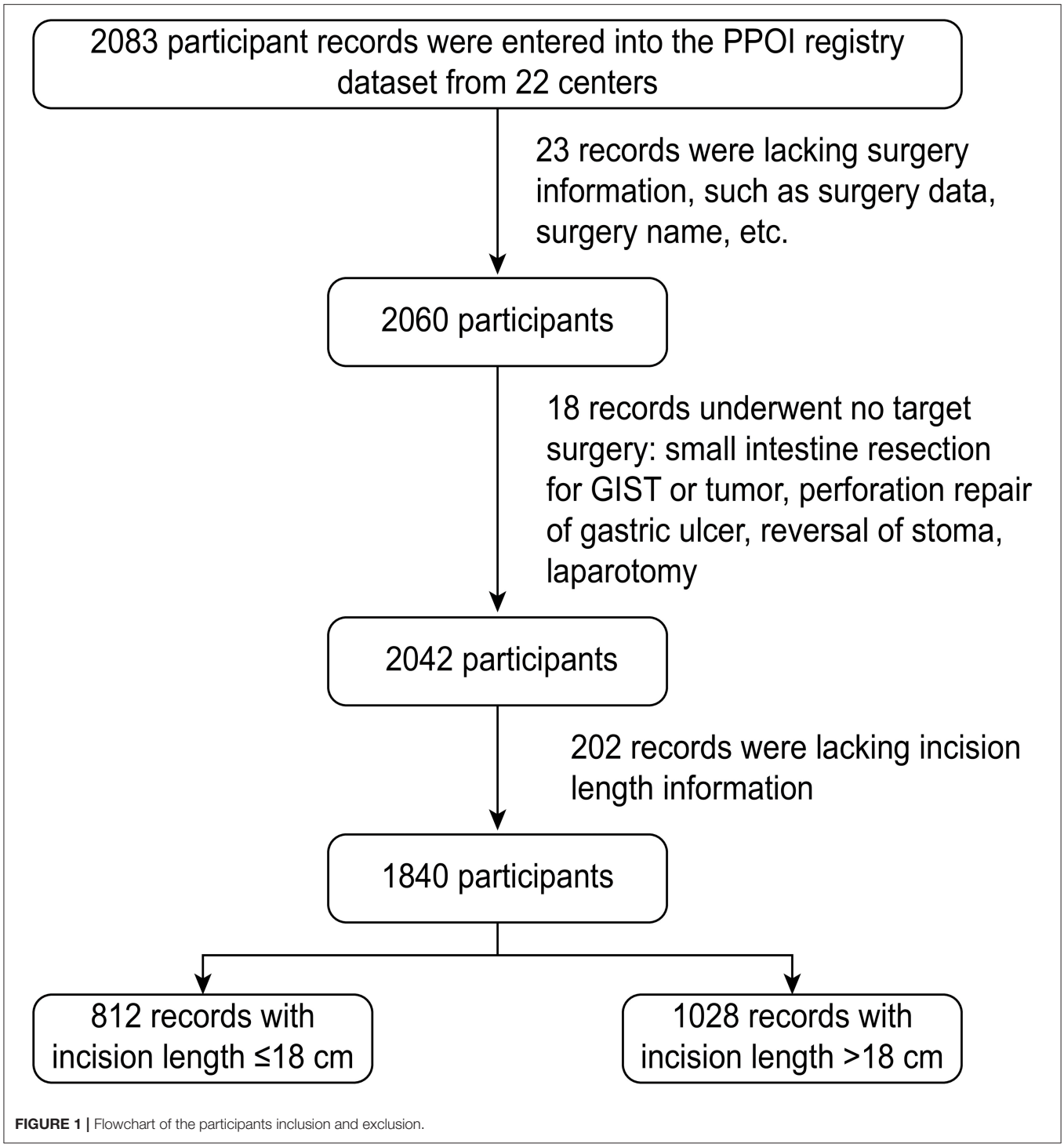

FIGURE 1 | Flowchart of the participants inclusion and exclusion.

of POI: (1) nausea/vomiting over 12 h, whereby nausea was measured on a numerical rating scale with 1 indicating least nausea and 10 indicating severe nausea and a rating score >4 indicated positivity; (2) inability to tolerate an oral diet over 24 h or the diet volume was <25% of the normal volume over the two previous meals; (3) absence of flatus or stool over 24 h and if a stoma was performed, absence of gas or stool in the ostomy bags; (4) abdominal distension defined as an increase in the waist circumference and hollow sound through percussion; and (5) radiological confirmation via CT scan or X-ray showing a dilated fluid-filled stomach or bowel.

The secondary outcomes were the days to the first passage of flatus and the days to the first passage of stool. These two variables were counted as the days from surgery date to the date of first flatus and bowel movement and they are the traditional indicators of the bowel motility recovery.

Covariates

Additional variables that had been previously thought to relate to the bowel motility and the variables that could influence the abdominal incision length were recorded.

The patient variables included the age, sex, body mass index (BMI), primary diagnosis, and the American Society of Anesthesiologists (ASA) grade.

The surgery-related variables included the National Nosocomial Infections Surveillance (NNIS) risk index, specific surgery name, surgical duration (min), blood loss during surgery, blood transfusion during surgery, different centers, year of surgery, and type of abdominal incision. Patients who underwent the Hartmann's procedure, abdominoperineal resection, or wedge resection were recorded as having an anastomosis number of zero. In total, 42 patients did not have anastomosis in our dataset.

Statistical Analysis

The patient characteristics are presented as the mean for the continuous data and count/percentage for the categorical data. A *t*-test (normal distribution) or Kruskal–Wallis rank-sum test (non-normal distribution) for the continuous data and a chi-squared test or Fisher's exact test for the categorical data were used to compare the basal characteristics distribution between the exposure group and the non-exposure group.

Univariate and multivariate logistic regressions were performed to examine whether the abdominal incision length had an independent effect on the PPOI. The covariates such as surgery-related characteristics and the status variables of the patient were included in the regression model for adjustment. The effect estimates are reported as ORs with the corresponding 95% CIs.

The days to the first passage of flatus and the days to the first bowel movement were analyzed by using the Cox proportional hazards regression model. The effect estimates are reported as the hazard ratios (HRs) with the corresponding 95% CIs.

Subgroup analyses were performed for the different centers and years of surgery to demonstrate the possible bias effect. The five largest sample size centers were applied for the subgroup analysis.

The threshold of two-sided statistical significance was set at $p < 0.05$ a priori. All the analyses were performed with SPSS Statistics version 26.0 and R version 4.1.1 (http://www.R-project.org).

RESULTS

The flowchart gives an overview of the inclusion and exclusion criteria of the patient. A total of 2,083 participants from the 22 centers were registered in the PPOI cohort and 243 patients were excluded for the different reasons (**Figure 1**). Overall, 1,840 patients were included in this secondary cohort analysis. During the hospital stay follow-up period, 287 patients developed the PPOI and the PPOI incidence was 15.7%.

All the basal characteristic variables had more than 90% completed data collection (**Table 1**). The included patients were divided into the short-incision group (≤18 cm) and the long-incision group (>18 cm). The patient status-related characteristics, including age, sex, and BMI, were balanced between the long-incision group and the short-incision group (**Table 1**). However, there were more patients with the ASA grade P3 (22 vs. 14.1%) and the fewer patients with the ASA grade P2 (71 vs. 79.9%) in the long-incision group compared with the short-incision group. The NNIS score had a different distribution between the two groups ($p < 0.001$). A total of 30.6% of the 413 patients with the short-incision group had an NNIS score of zero, while 17.5% of the patients with the long-incision group had an NNIS score of zero.

Incision length is dependent on the surgical organ and surgical type. Our data showed that the incision length was closely related to the surgical organ, anastomosis number, and surgical duration (**Table 1**). There were more patients who underwent gastric (42.5 vs. 37.3%) or pancreas–duodenum (35.8 vs. 19.2%) surgery in the long-incision group compared with the short-incision group. A total of 43.5% of the patients with the short-incision group underwent colorectal surgery, while it was 21.7% of the patients with the long-incision group underwent colorectal surgery ($p < 0.001$). The surgical duration in the long-incision group was 231.11 ± 95.43 min, which was longer than the 198.93 ± 82.26 min in the short-incision group ($p < 0.001$). In the long-incision group, 33 and 32.7% of the patients had two and three anastomoses, respectively. The corresponding values were 24.7 and 18.3% in the short-incision group, respectively ($p < 0.001$). In this cohort study, 73.4% of the patients in the short-incision group received patient-controlled analgesia (PCA) compared to 55.4% in the long-incision group ($p < 0.001$).

The primary outcome of the PPOI incidence was 17.6% in the long-incision group and 13.3% in the short-incision group ($p = 0.013$) (**Table 1**). With respect to the secondary outcome, the overall patients delivered the first flatus on the post-operative days 3.47 ± 2.04 and the first bowel movement on the post-operative days 4.73 ± 2.48. In comparison to the patients with the short incisions, those patients with the long incisions had delayed the first passage of stool (4.46 vs. 4.95 days, $p < 0.001$). However, the time to the first flatus was not significantly different between the long- and short-incision groups (3.49 vs. 3.45 days, $p = 0.736$).

The logistic univariate analysis showed that the OR of incision length was 1.06 (95% CI 1.02–1.09) for the PPOI (**Table 2**). The univariate analysis also identified the several risk factors for the PPOI including age, organ surgery, transfusion in surgery, and patient-controlled analgesia. Multivariate logistic regression including all these confounding factors was performed to infer an independent relationship between the incision length and the PPOI. The analysis data showed that the incision length was an independent predictor for the PPOI (OR 1.07, 95% CI 1.03–1.11). The possibility increased nearly 10% by each centimeter increment in the incision length independently.

TABLE 1 | Baseline characteristics of the participants ($n = 1,840$).

	Overall	Data completion	Incision length ≤18 cm	Incision length >18 cm	*p*
N	1,840		812	1028	
Age, mean ± SD, year	60.85 ± 13.25	99.84%	60.24 ± 14.22	61.33 ± 12.42	0.079
Sex (%)		99.89%			0.734
Female	652 (35.5)		292 (36.0)	360 (35.1)	
Male	1,186 (64.5)		520 (64.0)	666 (64.9)	
BMI, mean ± SD, kg/m^2	23.17 ± 3.23	89.51%	23.29 ± 3.27	23.09 ± 3.21	0.211
ASA (%)		98.21%			<0.001
1	114 (6.3)		48 (6.0)	66 (6.6)	
2	1,354 (74.9)		642 (79.9)	712 (71.0)	
3	334 (18.5)		113 (14.1)	221 (22.0)	
4	4 (0.2)		1 (0.1)	3 (0.3)	
5	1 (0.1)		0 (0.0)	1 (0.1)	
NNIS (%)		88.97%			<0.001
0	386 (23.6)		232 (30.6)	154 (17.5)	
1	810 (49.5)		340 (44.8)	470 (53.5)	
2	392 (23.9)		156 (20.6)	236 (26.9)	
3	49 (3.0)		31 (4.1)	18 (2.1)	
Surgery (%)		100.00%			<0.001
Gastric	740 (40.2)		303 (37.3)	437 (42.5)	
Pancreas-duodenum	524 (28.5)		156 (19.2)	368 (35.8)	
Colorectal	576 (31.3)		353 (43.5)	223 (21.7)	
Anastomosis number (%)		91.79%			<0.001
0	41 (2.4)		23 (3.1)	18(1.9)	
1	699 (41.4)		393 (53.5)	306 (32.0)	
2	496 (29.4)		181 (24.7)	315 (33.0)	
3	446 (26.4)		134 (18.3)	312 (32.7)	
4	7 (0.4)		3 (0.4)	4 (0.4)	
Transfusion during surgery (%)		95.54%			0.242
No	1,481 (84.2)		669 (85.4)	812 (83.3)	
Yes	277 (15.8)		114 (14.6)	163 (16.7)	
Surgery duration, mean ± SD, min	216.90 ± 91.24	99.29%	198.93 ± 82.26	231.11 ± 95.43	<0.001
PCA (%)		99.78%			<0.001
No	673 (36.7)		216 (26.6)	457 (44.6)	
Yes	1,163 (63.3)		595 (73.4)	568 (55.4)	
Post-operative transfusion (%)		98.21%			0.996
No	1,626 (90.0)		715 (90.1)	911 (89.9)	
Yes	181 (10.0)		79 (9.9)	102 (10.1)	
Time to first flatus, mean ± SD, days	3.47 ± 2.04	92.01%	3.49 ± 2.00	3.45 ± 2.07	0.736
Time to first bowel movement, mean ± SD, days	4.73 ± 2.48	90.27%	4.46 ± 2.58	4.95 ± 2.38	<0.001
PPOI (%)		99.35%			0.013
No	1,541 (84.3)		700 (86.7)	841 (82.4)	
Yes	287 (15.7)		107 (13.3)	180 (17.6)	

A t-test (normal distribution) or the Kruskal–Wallis rank-sum test (non-normal distribution) was used for the continuous data and a chi-squared test or Fisher's exact test was used for the categorical data.

PCA, patient-controlled analgesia.

Different regression models that adjusted different sets of the confounders confirmed the result regardless of the continuous or categorical incision length (**Supplementary Table 1**).

We were curious about whether the different incision types might have the different influences on the PPOI. Most of the included patients had a vertical incision: upper midline incision ($n = 1,233$), lower midline incision ($n = 264$), incision per right rectus abdominis ($n = 142$), and per left rectus abdominis ($n = 85$). Sixteen patients with subcostal, transverse, or other incisions were ascribed to the miscellaneous surgery. The univariate logistic regression showed that an incision per right rectus abdominis was

TABLE 2 | Univariate and multivariate logistics analysis for the prolonged post-operative ileus (PPOI).

Covariates	Statistics	Univariate		Multivariate	
		OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Incision length, mean ±SD, cm	17.2 ± 4.1	1.06 (1.02, 1.09)	0.0008	1.07 (1.03, 1.11)	0.0002
Age, mean ± SD, year	60.8 ± 13.2	1.02 (1.01, 1.03)	0.0053	1.02 (1.00, 1.03)	0.005
Gender (%)					
Female	652 (35.5%)	Reference			
Male	1,186 (64.5%)	1.07 (0.82, 1.40)	0.6155		
BMI, mean ± SD, kg/m^2	23.2 ± 3.2	1.00 (0.96, 1.04)	0.9121		
NNIS (%)					
0	386 (23.6%)	Reference			
1	810 (49.5%)	1.17 (0.85, 1.65)	0.3435		
2	392 (23.9%)	0.93 (0.62, 1.38)	0.7045		
3	49 (3.0%)	0.37 (0.09, 1.05)	0.1035		
ASA (%)					
1	114 (6.3%)	Reference			
2	1,354 (74.9%)	1.49 (0.85, 2.83)	0.1879		
>3	339 (18.8%)	1.49 (0.80, 2.95)	0.2286		
Surgical organ (%)					
Gastric	740 (40.2%)	Reference		Reference	
Pancreas-duodenum	524 (28.5%)	0.84 (0.62, 1.14)	0.2758	0.80 (0.58, 1.10)	0.170
Colorectal	576 (31.3%)	0.70 (0.51, 0.95)	0.0223	0.68 (0.49, 0.94)	0.023
Surgery duration, mean ± SD, min	216.9 ± 91.2	1.00 (0.99, 1.00)	0.4262		
Transfusion during surgery (%)					
No	1,481 (84.2%)	Reference		Reference	
Yes	277 (15.8%)	1.41 (1.00, 1.95)	0.0425	1.41 (1.00, 1.96)	0.0458
Post-operative transfusion (%)					
No	1,626 (90.0%)	Reference			
Yes	181 (10.0%)	1.09 (0.71, 1.62)	0.6904		
Anastomosis number (%)					
0	41 (2.4%)	Reference			
1	699 (41.4%)	1.08 (0.7, 2.91)	0.867		
2	496 (29.4%)	1.11 (0.48, 3.02)	0.815		
>3	453 (26.8%)	1.14 (0.50, 3.10)	0.773		
PCA (%)					
No	673 (36.7%)	Reference		Reference	
Yes	1,163 (63.3%)	1.28 (0.98, 1.68)	0.0698	1.55 (1.15, 2.09)	0.003
Incision type (%)					
Upper midline	1,233 (71.5%)	Reference		Reference	
Lower midline	264 (15.3%)	0.84 (0.60, 1.15)	0.290	0.57 (0.08, 2.33)	0.490
Right side	142 (8.2%)	0.54 (0.29, 0.93)	0.035	0.36 (0.05, 1.38)	0.197
Left side	85 (4.9%)	0.73 (0.36, 1.35)	0.352	0.53 (0.08, 2.04)	0.421
Year of surgery (%)					
2016	71 (3.9%)	Reference		Reference	
2017	1,439 (78.2%)	1.49 (0.74, 3.41)	0.299	1.69 (0.76, 4.51)	0.237
2018	330 (17.9%)	1.22 (0.57, 2.91)	0.625	1.36 (0.57,3.57)	0.517

less likely to develop the PPOI compared with an upper midline incision (OR 0.54 95% CI 0.29–0.93). However, the multivariate logistic regression demonstrated a non-significant difference among all the four types of the incisions ($p > 0.05$, **Table 2**).

The multivariate logistic regression displayed the several other independent predictors for the PPOI (**Table 2**). The OR of age for the PPOI was 1.02 (95% CI 1.00–1.03). Colorectal (OR 0.68 95% CI 0.49–0.94) and pancreas–duodenum (OR 0.80 95% CI 0.58–1.10) surgery had a lower possibility of developing the PPOI

compared with the gastric surgery. Transfusion during surgery (OR 1.41 95% CI 1.00–1.96) and usage of PCA (OR 1.55 95% CI 1.15–2.09) increased the chance of developing the PPOI.

The secondary outcome analysis showed that the incision length did not have a significant negative effect on the time to the first passage of flatus (HR 0.99 95% CI 0.98–1.01) (**Table 3**). However, a long incision length was independently associated with a prolonged time to the first bowel movement (HR 0.98 95% CI 0.97–0.99) and each centimeter increment of the incision length contributed to a 2% increased risk of delaying the first bowel movement (**Table 4**). A significant relationship existed regardless of the incision type (**Table 4**). The multivariate Cox HR analysis showed several independent risk factors for the delayed passage of stool. Age (HR 0.99 95% CI 0.98–0.99) and the NNIS score were negatively correlated with the time to the first bowel movement (**Table 4**).

Sensitivity analyses were performed for the different centers and years of surgery. Five out of 22 centers recruited more than 100 participants. Logistic regression for the correlation of the PPOI and incision length was applied in the five largest centers. **Figure 2** shows that there was a positive correlation between incision length and PPOI incidence in all five subcenters, but three of them did not reach significance. With respect to the year of surgery of the subgroups, the data showed that the incision length was independently positively related to the PPOI in the 2,017 subgroups (OR 1.06 95% CI 1.03–1.10), which included the largest number of the participants ($n = 1{,}439$). However, the OR did not reach significance in the smallest sample size of 2,016 subgroups (**Figure 2**).

DISCUSSION

This registry system-based, multicenter, and retrospective cohort study revealed that the incision length was independently positively correlated with the PPOI incidence in the patients who underwent the open abdominal surgery. The incision length independently affected the time to the first bowel movement but not the time to the first flatus. Delayed passage of stool post-operatively contributes to the development of the PPOI.

Our data showed that the PPOI incidence associated with the open abdominal surgery was 15.7%. The subgroup analysis of the surgical organ showed a 13.2% PPOI incidence in the colorectal surgery, 15.5% in the pancreas–duodenum surgery, and 17.8% in the gastric surgery. Recently, the GRACE Collaborative Group For Ileus Study reported the proximate PPOI incidence (15.4%) in the colorectal surgery with the same PPOI diagnostic criteria (6).

The etiology of POI is not well-defined and is thought to be multifactorial: surgical stress response, disruption of intestinal continuity, opioid analgesic use, intestinal manipulation, etc. The inhibitory effect of the opioid analgesics on the GI motility has been well-defined (7). Alvimopan, a novel peripherally-acting μ opioid antagonist without inhibition of the central nervous system, can accelerate the GI motility (5). In our dataset, the patient-controlled analgesia comprising mainly the opioid analgesics was an independent risk factor for the PPOI. It was adjusted in the multivariate model for the incision length effect on the GI motility. Intestinal anastomoses disrupted the integrity of the alimentary tract including the physical and electrical continuity. In a murine model of the small bowel resection, the acute disruptions to the interstitial cells of Cajal (ICC) networks, slow waves, and phasic contractions were found (8). Intestinal manipulation is also an important risk factor for POI. Pancreas–duodenum surgery generally has three anastomoses and is thought to receive a greater degree of the intestinal manipulation. Gastric and colorectal surgeries are thought to have fewer anastomoses and the intestinal manipulations. Our data show that gastric surgery had a higher PPOI incidence (17.8%) followed by the pancreas–duodenum surgery (15.4%) and colorectal surgery (13.2%). This result suggests that the disruption of the intestinal continuity might not play an important role in the bowel function recovery.

There are limited studies regarding the effect of the incision length on the gut motility and most of the results come from the animal models. Well-controlled prospective studies in a mouse model show that the longer and deeper abdominal incisions cause more profound inhibition of GI transit and prolong the period of POI (3). A small sample size study with 40 patients who underwent colectomy showed that the transverse incision length correlated with the time to the first bowel sounds and bowel movement but not the time to the first flatus (9).

Our study focused on the association between the incision length and GI motility recovery. We had a relatively large sample size ($n = 1{,}840$) based on a multicenter registry system cohort. The included patients underwent the diverse kinds of the major abdominal surgery including gastric surgery, pancreas–duodenum surgery, and colorectal surgery. The large sample size and diversity of the included patients make the conclusion even more universal. The registry system recorded all the variables that might confound the association between the incision length and bowel function recovery such as anastomosis number, surgical duration, surgical organ, and use of opioid analgesic. All these variables were adjusted in the multimodal regression to give an independent relationship between the incision length and bowel function recovery.

Prolonged post-operative ileus, which is a different pathological entity from POI, was our primary outcome. Our data showed that the abdominal incision length was an independent risk factor for the PPOI. The possibility of developing the PPOI increased 10% by each centimeter increment of the incision length after adjusting for all the kinds of the confounders. With respect to the secondary outcome, our data showed that the incision length was independently related to the days to the first bowel movement. Each centimeter increment of the incision length contributed to a 2% increased risk of delay in the first bowel movement. However, the abdominal incision length did not statistically correlate with the time to the first flatus. We also investigated whether the incision type could have a different influence on the gut motility. Four types of the vertical incisions such as upper

TABLE 3 | Univariate and multivariate Cox analysis for the days to the first flatus.

Covariates	Statistics	Univariate		Multivariate	
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Incision length, mean ± SD, cm	17.1 ± 4.0	0.996 (0.984,1.008)	0.477	0.99 (0.98, 1.01)	0.4962
Age, mean ± SD, years	61.7 ± 11.3	0.997 (0.993,1.002)	0.207		
Gender (%)					
Female	601 (35.6%)	Reference			
Male	1,089 (64.4%)	0.967 (0.875,1.068)	0.507		
BMI, mean ± SD, kg/m^2	23.2 ± 3.2	0.984 (0.968,0.999)	0.038	0.99 (0.97, 1.00)	0.2670
NNIS (%)					
0	361 (23.6%)	Reference		Reference	
1	755 (49.3%)	1.178 (1.039, 1.336)	0.011	1.19 (1.03, 1.38)	0.0178
2	367 (24.0%)	1.028 (0.889, 1.189)	0.706	1.12 (0.93, 1.36)	0.2220
3	48 (3.1%)	1.566 (1.159, 2.117)	0.004	1.81 (1.27, 2.57)	0.0009
ASA (%)					
1	93 (5.5%)	Reference		Reference	
2	1,274 (75.6%)	0.789 (0.639,0.974)	0.027	0.84 (0.66, 1.07)	0.1608
3	318 (18.9%)	0.717 (0.569, 0.903)	0.005	0.71 (0.54, 0.95)	0.0203
Surgical organ (%)					
Gastric	687 (40.7%)	Reference		Reference	
Pancreas-duodenum	475 (28.1%)	1.028 (0.914, 1.156)	0.646	0.91 (0.78, 1.05)	0.2031
Colorectal	528 (31.2%)	1.202 (1.072, 1.346)	0.002	1.12 (0.99, 1.28)	0.0790
Surgery duration, min	213.1 ± 87.5	1.000 (0.999, 1.000)	0.833	1.00 (0.99, 1.00)	0.0582
Transfusion during surgery (%)					
No	1,395 (84.8%)	Reference		Reference	
Yes	250 (15.2%)	0.856 (0.748, 0.980)	0.024	0.93 (0.79, 1.10)	0.3893
Post-operative transfusion (%)					
No	1,508 (90.0%)	Reference		Reference	
Yes	168 (10.0%)	0.831 (0.708, 0.975)	0.023	0.90 (0.74, 1.08)	0.259
Anastomosis number (%)					
0	37 (2.3%)	Reference			
1	650 (40.6%)	0.93 (0.67, 1.30)	0.672		
2	473 (29.5%)	0.94 (0.68, 1.32)	0.736		
>3	442 (27.6%)	0.91 (0.65, 1.27)	0.579		
PCA (%)					
No	576 (34.1%)	Reference		Reference	
Yes	1,113 (65.9%)	0.914 (0.826, 1.011)	0.079	0.91 (0.79, 1.04)	0.1455
Incision type					
Upper midline	1,233	Reference		Reference	
Lower midline	264	1.13 (1.00, 1.28)	0.054	1.18 (0.52, 2.64)	0.691
Right side	142	1.08 (0.90, 1.29)	0.420	1.33 (0.58, 3.02)	0.503
Left side	85	1.39 (1.11, 1.75)	0.004	1.62 (0.76, 3.45)	0.212
Year of surgery					
2016	71	Reference		Reference	
2017	1,439	1.09 (0.85, 1.39)	0.503	1.20 (0.90, 1.61)	0.215
2018	330	1.19 (0.92, 1.55)	0.192	1.54 (1.13, 2.10)	0.007

midline incision, lower midline incision, incision per right rectus abdominis, and per left rectus abdominis constituted 94% of the participants. The results indicated that the gut motility recovery was not significantly different among these four types of the incisions. The negative effect of the incision length on the gut motility recovery existed regardless of the incision type. The bias due to the different hospitals and surgery years was also taken into consideration. Subgroup analyses

TABLE 4 | Univariate and multivariate Cox analysis for the days to the first bowel movement.

Variables	Statistics	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Incision length, mean ± SD, cm	17.1 ± 4.0	0.983 (0.973,0.994)	0.003	0.98 (0.97, 0.99)	0.005
Age, mean ± SD, years	61.69 ± 11.3	0.993 (0.989,0.998)	0.003	0.99 (0.98, 0.99)	0.0078
Gender (%)					
Female	593 (35.7%)	Reference			
Male	1,066 (64.3%)	0.947 (0.856,1.047)	0.289		
BMI, mean ± SD, kg/m^2	23.17 ± 3.2	0.994 (0.978,1.009)	0.429		
NNIS (%)					
0	359 (24.1%)	Reference		Reference	
1	737 (49.4%)	0.850 (0.749,0.964)	0.011	0.91 (0.79, 1.04)	0.1576
2	364 (24.4%)	0.698 (0.603,0.808)	<0.0001	0.76 (0.65, 0.89)	0.0008
3	31 (2.1%)	0.504 (0.348,0.728)	0.000	0.45 (0.30, 0.66)	<0.001
ASA (%)					
1	92 (5.6%)	Reference			
2	1,250 (76.1%)	1.174 (0.950,1.451)	0.139		
3	301 (18.3%)	0.938 (0.743,1.185)	0.593		
Surgical organ (%)					
Gastric	670 (40.4%)	Reference		Reference	
Pancreas-duodenum	479 (28.9%)	1.078 (0.958,1.212)	0.211	1.13 (0.99, 1.30)	0.0772
Colorectal	510 (30.7%)	1.124 (1.001,1.261)	0.048	1.10 (0.97, 1.24)	0.1416
Surgery duration, mean ± SD, min	214.0 ± 89.1	0.999 (0.998,0.999)	<0.0001	1.00 (0.99, 1.00)	0.438
Transfusion during surgery (%)					
No	1,365 (84.7%)	Reference			
Yes	247 (15.3%)	0.885 (0.773,1.014)	0.781		
Post-operative transfusion (%)					
No	1,477 (89.8%)	Reference			
Yes	168 (10.2%)	0.936 (0.798,1.099)	0.420		
Anastomosis number (%)					
0	34 (2.2%)	Reference			
1	634 (40.6%)	0.98 (0.69,1.38)	0.886		
2	453 (29.1%)	0.93 (0.66,1.32)	0.676		
>3	439 (28.1%)	1.01 (0.71,1.44)	0.939		
PCA (%)					
No	573 (34.6%)	Reference		Reference	
Yes	1,085 (65.4%)	1.152 (1.041,1.275)	0.002	1.10 (0.98, 1.24)	0.1122
Incision type					
Upper midline	1,233	Reference		Reference	
Lower midline	264	1.05 (0.93, 1.19)	0.463	0.82 (0.44, 1.52)	0.520
Right side	142	1.20 (1.00, 1.44)	0.043	1.00 (0.54, 1.83)	0.989
Left side	85	0.93 (0.73, 1,19)	0.549	0.76 (0.42, 1.36)	0.352
Year of surgery					
2016	71	Reference		Reference	
2017	1,439	1.18 (0.92, 1.52)	0.187	1.16 (0.89, 1.54)	0.288
2018	330	1.16 (0.88, 1.51)	0.291	1.19 (0.89, 1.60)	0.243

indicated a bit of heterogeneity across the different hospital centers. However, it might be that the small sample size in 2016 resulted in an unreached significant OR of the incision length for the PPOI.

How the abdominal incision trauma negatively affects the bowel function recovery is not well-understood. It has been suggested that an abdominal incision can activate the adrenergic pathway, which inhibits GI transit (3) through a neurogenic pathway at the early post-operative phase. Adrenergic blockade can improve GI transit after laparotomy in the rats. Neurogenic inhibition of the gut motility diminishes more quickly and the global inflammation inhibition results in the gut dysmotility (10).

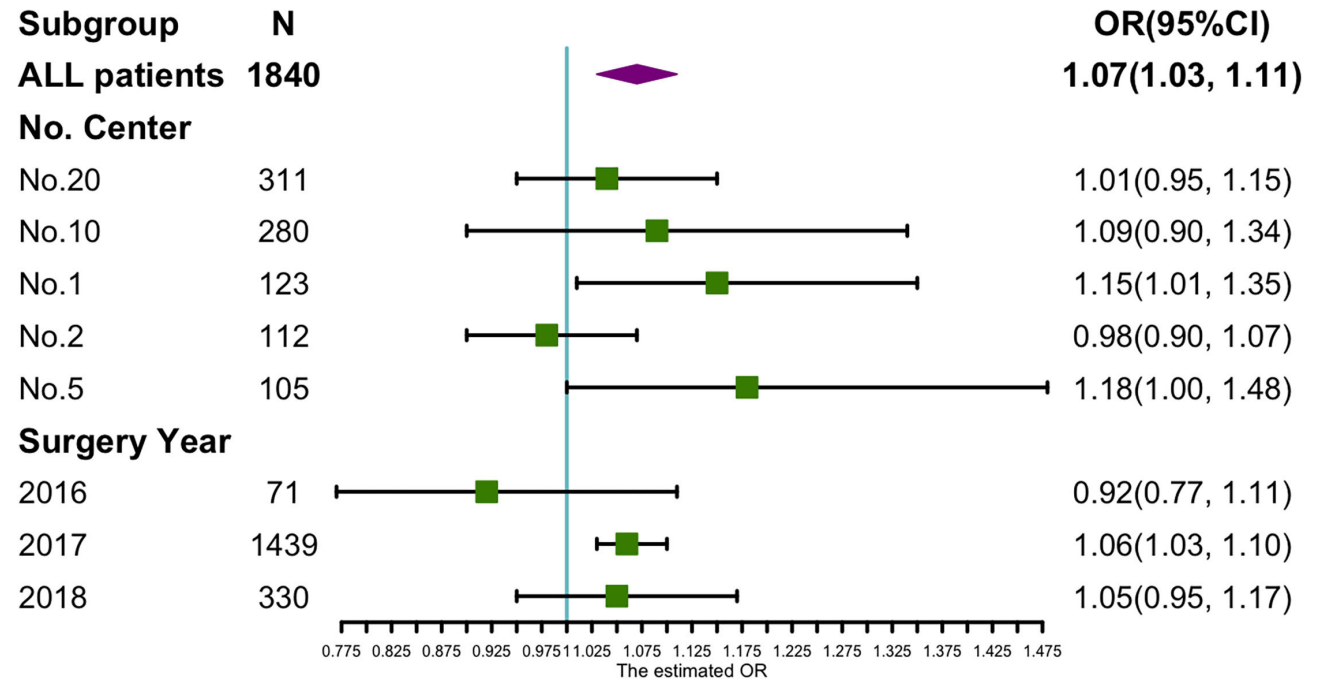

FIGURE 2 | Sensitivity analysis of incision length on PPOI incidence in subgroups of different surgery years and hospital centers.

The peritoneal inflammatory response to an abdominal incision is activated through the neuro-immuno-humoral axis and the inflammatory response retards surgical recovery including prolonged gut motility (11, 12). More specific molecular mechanisms are needed to clarify the detailed relationship between the incision trauma and gut function recovery.

Some limitations of this study should be considered when interpreting the conclusion. This retrospective study was based on a multicenter registry cohort. The missing records might result in the selection bias. A total of 202 patients were excluded because of a lack of the incision length data. We conducted a comparison between the 202 excluded and 1,840 included patients. They were balanced between the age, sex, and BMI. However, there were statistically significant differences among the surgery-related characteristics. This might be the source of the selection bias. In addition, <10% of the data were missing with respect to the secondary outcome of the days to the first flatus and the days to the first bowel movement. Second, since every effort was made to collect the data on the related variables, some confounding covariate data might have been missed. The intestinal inflammatory response following the open abdominal surgery corresponds directly to the gut motility (13). Fluid overload during the perioperative period contributes to the impaired gut motility through edema in the intestinal wall. Electrolyte disturbance involving sodium and potassium also leads to weakened the gut motility (14). All these missed confounding covariates may have influenced the data interpretation. Third, our hospital center subgroup analysis indicated some heterogeneity across the different centers. When considering three out of the five largest sample size centers, it could not be concluded that the incision length was an independent predictor of the PPOI.

CONCLUSION

The abdominal incision length was an independent risk factor for the PPOI. The possibility of developing the PPOI increases 10% by each centimeter increment of the incision length after adjusting for all the kinds of confounders. The incision length was independently related to the days to the first bowel movement but not to the days to the first flatus.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Beijing Friendship Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS, YingY, WG, GJ, and YinmY: drafted the article and revise it critically for important intellectual content. ZZ

made substantial contributions to conception and design and final approval of the article. YingY, WG, GJ, YinmY, LiC, YW, LL, QH, WeiZ, WeimZ, LeC, DX, WT, DY, and WL: made substantial contributions to conception and design and acquisition of data.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.743069/full#supplementary-material

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External Negative Pressure Drainage of the Pancreatic Duct in Pancreatogastrostomy Following Pylorus-Preserving Pancreaticoduodenectomy—Feasibility and Technique

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Albrecht HC, Amling C, Menenakos C and Gretschel S (2021) External Negative Pressure Drainage of the Pancreatic Duct in Pancreatogastrostomy Following Pylorus-Preserving Pancreaticoduodenectomy—Feasibility and Technique. Front. Surg. 8:754288. doi: 10.3389/fsurg.2021.754288

Background: Postoperative pancreatic fistula (POPF) is a major cause of morbidity after pancreaticoduodenectomy. There is no consensus on the best technique to protect the pancreato-enteric anastomosis and reduce the rate of POPF. This study investigated the feasibility and efficiency of external suction drainage of the pancreatic duct to improve the healing of pancreaticogastrostomy.

Methods: Between July 2019 and June 2021, 21 consecutive patients undergoing elective pancreaticoduodenectomy were included. In all patients we performed a pancreaticogastrostomy and inserted a negative pressure drainage into the pancreatic duct. The length and diameter of the pancreatic duct were measured and the texture of the pancreas was evaluated. The daily secretion volume and the lipase value via pancreatic duct drainage were documented. The occurrence of POPF was evaluated.

Results: None of the patients had drainage-related complications. In 4 patients we registered a dislocation of the drainage from the pancreas duct into the stomach. 17/21 Patients showed no signs of POPF. A biochemical leak was measured in one patient. Furthermore, 2 patients had a POPF grade B. In one patient, POPF grade C required reoperation and resection of the remnant pancreas. All 4 cases of POPF met the risk criteria soft pancreas, high volume and high lipase value in the duct drainage.

Conclusion: The insertion of the pancreatic duct drainage was feasible and caused no drainage-related morbidity. POPF-rate was moderate in the risk population of soft pancreas and small duct.

Keywords: pancreaticoduodenectomy, pancreatogastrostomy, postoperative pancreatic fistula, pancreas duct drainage, soft pancreas

INTRODUCTION

Pancreaticoduodenectomy (PD) is the gold standard in the treatment of cancer of the pancreatic head. Although perioperative mortality has decreased significantly, morbidity remains a concern as it can be as high as to 50% (1). Postoperative pancreatic fistula (POPF) is the leading cause of morbidity after PD, with reported incidence of 10 to 35%. (2). According to Daskalaki et al. 19% of fistulas are clinically irrelevant, 70.7% require conservative or interventional treatment (grade B), and severe complications occur in 8.8% (grade C) (3).

Under these terms, different methods and technical versions for the creation of a pancreatic anastomosis—pancreaticojejunostomy (PJ) or pancreaticogastrostomy (PG) have been proposed to avoid anastomotic leak with POPF. Widely used methods include the application of adhesive sealants around the anastomosis, a flap of Ligament teres, the use of transanastomotic stents, drainage and the use of various systemic pharmacological agents (4).

However, no consensus has yet been reached on the best technique to protect the pancreato-enteric anastomosis and reduce the rate of POPF. The following study investigated the feasibility and efficiency of inserting an external suction drain into the pancreatic duct to improve the healing of PG following PD. All studies investigating the impact of duct drainage so far refer only to pancreato-jejunostomy, no data are available for pancreato-gastrostomy.

PATIENTS AND METHODS

Between July 2019 and June 2021, 21 consecutive patients undergoing elective pancreaticoduodenectomy (PD) for benign or malignant pathologies of the pancreas or periampullary region were enrolled in our study.

Surgical Technique

All patients received perioperative antibiotics. After informed consent of the patient, PD was performed as a partial pancreatectomy with pylorus preservation. After resection, the length and diameter of the pancreatic duct was measured to calculate the size of the drainage. The texture of the pancreas (soft/middle/hard) was evaluated and documented by the surgeon. Pancreatic anastomosis was constructed as a pancreaticogastrostomy with the use of monofilament absorbable sutures (in two layers as purse-string seromuscular suture + single button mucosa suture). A pediatric feeding tube made of silastic polyethylene (Vygon, France) with additional lateral holes was inserted into the pancreatic duct for drainage (**Figure 1**). The tube was fixed to the pancreatic stump with a suture (6 × 0 Marlin® rapid, Catgut GmbH, Germany), then the tube was pulled through the ventral incision of the stomach. The incision was closed with a two-layer continuous suture, and the catheter is covered with the gastric serosomuscular layer in a length of 3 cm similar to a Witzel-fistula. The usual single loop reconstruction with bilio-jejunal and pyloro-jejunal anastomosis was then completed. Finally, the drainage of the pancreatic duct was then externalized through a stab incision in the ventral abdominal wall and fixed to the skin to prevent catheter migration. A CT scan of the pancreatic drainage is shown in **Figure 2**. The drainage was connected to a negative pressure suction system (pri-aktive-passiv drainage, Primed medical techniques, Germany). In addition, two Easy Flow drains were placed dorsally to the pancreaticogastrostomy and hepatico-jejunostomy, which are pulled separately left and right through the abdominal wall and fixed to the skin.

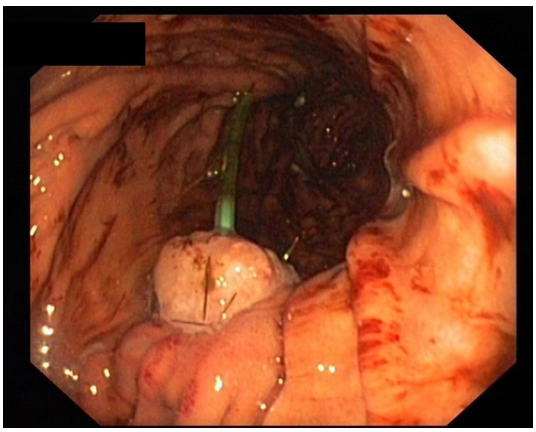

FIGURE 1 | Implanted pancreatic stump with duct drainage.

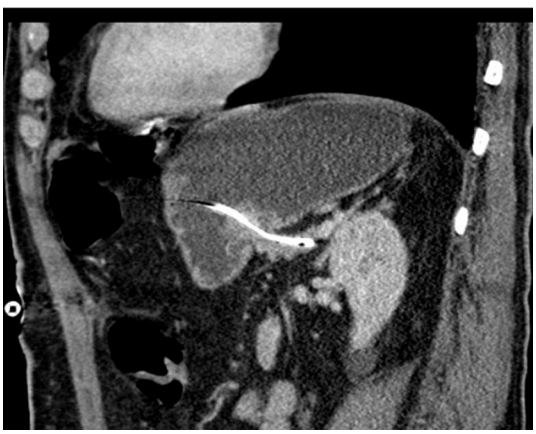

FIGURE 2 | CT image of pancreatic duct drainage in the pancreatic stump and stomach.

Perioperative Management

Enteral nutrition was administered from the first postoperative day through the alimentary limb of a three-lumen nasogastric tube (Freka® Trelumina FR 16/9, Fesenius Kabi, Germany). Additionally, sips of water were given on the first postoperative day. When there was no clinical evidence of leakage in any of the anastomoses, the enteral feeding flow rate was gradually increased to 70 ml/h. A proton pump inhibitor (pantoprazole, Hexal AG, Germany) was administered during

the entire postoperative hospital course. Epidural analgesia was given until 72 h postoperatively. Low molecular weight heparin (Clexane, Sanofi Aventis, Germany) was administered for the prevention of deep vein thrombosis until patients were fully ambulatory.

Several blood values, including serum lipase, protein and albumin, were examined preoperatively. Drainage fluid volume from peripancreatic Easy Flow and pancreatic duct drainage was measured and checked daily. Serum and pancreatic duct-drainage lipase values were measured on postoperative day 3 and 7.

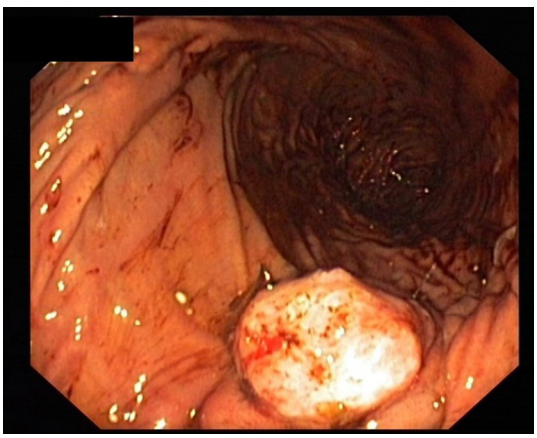

FIGURE 3 | Pancreatic stump after drainage removal.

Peripancreatic Easy Flow drain lipase was measured on postoperative day 3, 5, and 7. The measurement was continued every second day if there were signs of persistent leakage until the drainage was removed. To monitor the inflammatory systemic response, leukocytes and C-reactive protein were measured on the first 3 postoperative days and every third day thereafter (6. /9. /12. etc.). The peripancreatic Easy Flow drains were removed on the 7th postoperative day if there was no evidence of a leakage. However, if there was evidence of leakage or suspected infective complications (fever, leukocytosis and purulent drainage fluid), the peripancreatic drains were left *in situ*. The pancreatic duct drain was removed in most cases between the 6th and 8th postoperative day (**Figure 3**).

In addition, patients were asked about nausea and vomiting during daily rounds and the abdominal status was examined. All possible relevant complications such as anastomosis bleeding, insufficiency of the hepaticojejunostomy or the entero-enterostomy, delayed gastric emptying and reoperation were assessed.

According to the ISGPS 2016 classification, POPF were classified into 3 groups (5).

- Biochemical leak (former Grade A): is defined as a drain output with a persistent amylase/lipase level, which is 3 times higher or more than the upper limit of normal serum amylase/lipase. Biochemical leak has no clinical relevance.

TABLE 1 | Patient demographics, intraoperative data and POPF grading.

	Gender	Age	Diagnosis	Diameter of the pancreatic drainage (ch)	Texture of the pancreatic tissue	Po. days with duct drainage	POPF
1	F	75	IPMN main duct	6	Soft	7	–
2	F	82	Leiomyosarkoma of the retroperitoneum	5	Soft	7	–
3	M	64	Adenocarcinoma of the pancreas	5	Soft	7	–
4	F	81	Adenocarcinoma of the pancreas	5	Soft	7	–
5	M	43	Metasis of a rectal cancer	5	Soft	7 (slipped)	B
6	F	76	Adenocarcinoma of the papilla vateri	5	Soft	20	A
7	M	64	Cholangio–carcinoma	4	Middle	8	–
8	F	74	Inflammatory bile duct stenosis	5	Soft	6	–
9	M	72	Cholangio-carcinoma	6	Soft	7	–
10	M	59	Adenocarcinoma of the pancreas	6	Hard	7	–
11	M	67	Adenocarcinoma of the pancreas	6	Soft	15	B
12	W	56	Adenocarcinoma of the pancreas	8	Hard	7	–
13	M	65	Cholangio-carcinoma	6	Soft	8	–
14	M	58	Adenocarcinoma of the pancreas	6	Soft	20	C
15	W	84	Adenocarcinoma of the pancreas	6	Soft	5 (slipped)	–
16	W	62	Adenocarcinoma of the pancreas	8	Hard	7 (slipped)	–
17	W	69	IPMN main duct	8	Soft	13	–
18	M	70	Ampullary tubulovillous Adenoma with HGIEN	5	Soft	7	–
19	M	66	Adenocarcinoma of the pancreas	6	Soft	7 (slipped)	–
20	W	73	Cholangio-carcinoma	6	Middle	7	–
21	W	78	Adenocarcinoma of the Ampulla vateri	6	Soft	7	–

- Grade B: The Fistula leads to changes in the postoperative Management. The abdominal drain is left for more than 3 weeks or has to be repositioned by endoscopic or percutaneous procedures. It leads to signs of an infection but no organ failure.
- Grade C: Requires a reoperation. It causes systemic infection with single or multiple organ failures up to death.

RESULTS

The insertion of a suction drain into the pancreas duct in pancreatogastrostomy was feasible in all 21 patients. The drainage of the pancreatic duct was well tolerated by all patients and did not result in increased pain levels. We did not observe any complications or discomfort related to the intrapancreatic duct-drain or delayed gastric emptying.

In addition, no wound infection caused by the pancreatic duct drainage or secretion via the drainage channel were detected after removal. The pancreatic duct drain remained at the mean for 7 days (**Table 1**). In patients with manifest fistula, the pancreatic duct drainage was removed when the lipase level of peripancreatic Easy Flow liquid was equal to, lower than, or <3 times the lipase value of the serum and the patient was in stable condition without any clinical sign of abdominal pain. In these patients the duct drain was removed between day 15 and 20. We registered drainage dislocation out of the pancreatic duct into the stomach in 4 patients (between day 5 and 7), which was apparent in a change of the quality of the drain fluid.

12 of the 16 Patients Had a Soft Pancreas Tissue Texture (**Table 1**).

The daily secretion volume via the pancreatic duct drainage was between 0 and 240 ml.

Only in one patient the drain did not extract any fluid at all. The fluid of all other patients was clear and the lipase level ranged between 340 and 42,000 U/L (**Table 2**).

17 of 21 Patients Showed no Signs of POPF. A Biochemical Leak Was Measured in the Case of one Patient. Furthermore, 2 Patients Had a POPF Grade B (**Figure 4**).

POPF grade C was present in one patient requiring re-operation and resection of the remnant pancreas. Unfortunately, this patient died later in the course of acute heart failure with the secondary medical diagnosis of coronary stenosis.

We further had hemorrhage from the lateral part of the pancreatic resection margin in one patient, which could be treated endoscopically. The bleeding was not related to the pancreatic duct drainage.

In all 4 cases of POPF, patients had a soft pancreas, a high volume and a high lipase level in the secretion via the pancreatic duct drainage (**Table 2**; **Figure 5**).

TABLE 2 | Lipase level in serum, peripancreatic- and pancreatic duct drainage (in U/l), secretion volume of the pancreatic duct drainage (in ml) and POPF grading.

Patient	Highest lipase level blood in IE	Lipase level peripancreatic drainage 7th postoperative day in IE	Highest lipase level pancreatic duct drainage in IE	Highest daily volume of secretion in ml	POPF
1	76	18	42,000	200	–
2	192	44	4,062	110	–
3	3	10	10,650	15	–
4	13	10	42,000	120	–
5	609	11,809	42,000	150	B
6	41	14,230	32,899	100	A
7	76	10	23,061	50	–
8	62	67	–	0	–
9	3	10	19,898	10	–
10	3	10	42,000	100	–
11	103	42,000	42,000	170	B
12	3	10	340	10	–
13	87	58	42,000	240	–
14	144	6,776	42,000	150	C
15	22	21	4,905	200	–
16	3	10	4,2000	25	–
17	4	40	42,000	75	–
18	115	10	42,000	200	–
19	33	12	42,000	170	–
20	6	10	42,000	130	–
21	21	10	42,000	75	–

DISCUSSION

Advances in pancreatic surgery techniques and perioperative care have resulted in lower pancreaticoduodenectomy (PD) mortality rates in high-volume expert centers (6). However, morbidity after pancreatic resection remains high. Complications occur in 30–60% of patients after surgery, mainly due to leakage and subsequent fistula at the pancreatic anastomosis (7). There are several reports in the literature of the risk factors that could promote anastomotic leakage (2). Most authors agree that two

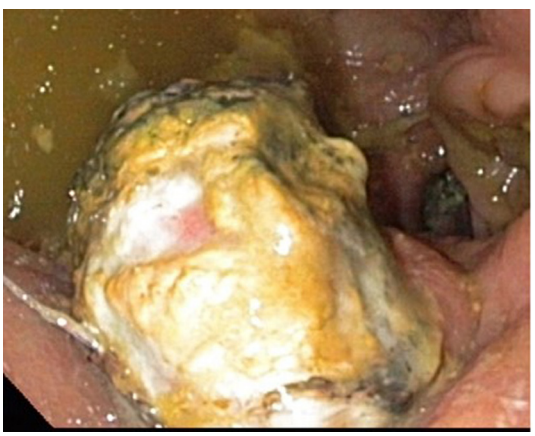

FIGURE 4 | Pancreatic stump of patient 5 (POPF Grade B).

factors play an important role in POPF: first, a soft pancreatic texture and second, an undilated pancreatic duct. Both factors have been most consistently associated with a high rate of POPF (8).

In our study, 16 of the 21 included patients encountered the risk situation of soft pancreatic tissue with a small duct. All 4 cases of POPF were found in these 16 patients of this risk population.

Volume and lipase value in the pancreatic duct drainage secretion had a broad range in our study (**Table 2**). High volume and high lipase value in the duct drainage seem to indicate a high enzymatic activity of the remnant pancreas. In all 4 cases of POPF the latter criteria were seen (**Figure 5**).

The use of pancreatic duct stents and drainages has been discussed in the literature, but the published results are still controversial. **Table 3** provides an overview of the most important studies investigating the role of negative pressure pancreatic drainage in the prevention of pancreatic fistula. In summary, the use of external negative pressure seems to protect more effectively than external drainage with gravity pressure. All these studies refer only to pancreatojejunostomy (9–12).

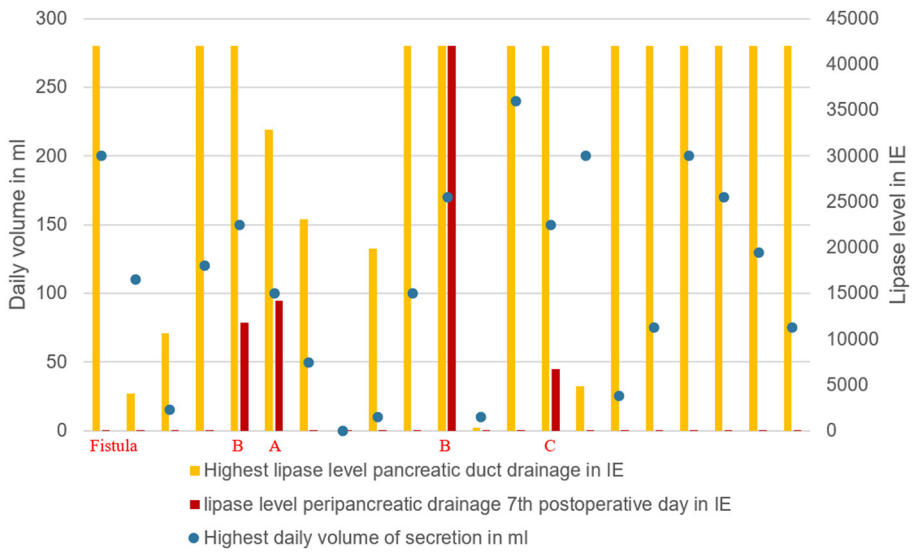

FIGURE 5 | Grade of pancreatic fistula in relation to the highest lipase value and daily secretion volume via pancreatic drainage.

TABLE 3 | Studies reporting pancreatic duct drainage after pancreaticoduodenectomy with pancreaticojejunostomy compared with our results (PRT prospective randomized trial).

References	Type of study	Number of patients	Type of drainage	Pancreatic fistula rate	POPF grade
(9)	PRT	110 (55 vs. 55)	External, negative pressure vs. gravity pressure	25.5 % vs. 43.6 % ($P = 0.045$)	A: 16.4 vs. 32.7 % B: 5.5 vs. 7.3 % C: 3.6 vs. 3.6%
(10)	PRT	76 (41 vs. 35)	External, negative pressure vs. no drainage	69.2 % vs. 70.7 % ($P = 0.922$)	A: 35.9 vs. 13.9 % B: 33.3 vs. 56.8 % p 0.04 C: 0 vs. 0
(11)	Retro-spective	58 (33 vs.25)	External, negative pressure vs. gravity pressure	36.2 % vs. 64 % ($P = 0.026$)	A: 27.2 vs. 24.0 % B + C: 9.0 vs. 40.0 % p 0.012
(12)	Retro-spective	76 (37 vs. 39)	External, negative pressure vs. gravity pressure	9.8 % vs. 31.3 % ($P = 0.018$)	A: 0 vs. 0 % B: 9.8 vs. 14.2 % C: 0 vs. 17.1 %
Gretschel et al. this study	Case series	21	External negative pressure (pancreaticogastrostomy)	19 %	A: 4.8 % B: 9.5 % C: 4.8 %

This study evaluated the implementation of an external pancreatic duct drainage under closed suction with negative pressure in pancreatogastrostomy following PD.

The introduction of a suction drainage into the pancreatic duct was feasible in all patients and did not cause drainage-related morbidity. We registered drainage dislocation into the stomach in 4 patients. This was probably caused by insufficient fixation of the drainage in the soft tissue of pancreas.

Consequently, the correct fixation of the drainage to both the pancreatic stump and the skin must be ensured. One patient with a drainage dislocation developed a POPF grade B.

To what extent the drainage dislocation may have promoted POPF cannot be proven.

The other 3 cases of drainage dislocation did not result in POPF.

In one patient no secretion was found via the pancreatic duct drainage. The phenomenon could have been caused by an incorrect size of the duct drainage or clotted side holes. However, this fact did not affect the regular healing of the anastomosis.

The use of pancreatic ductal drainage did not completely prevent POPF but resulted in a moderate rate of POPF in 4 of 21 patients (19%). In the high-risk population of a soft pancreas with an undilated duct, we saw only one grade C POPF (4.8%) in our feasibility study.

Given the limitations of this feasibility series (limited number of patients, single center study, no control group), however, it cannot be stated to what extent drainage is responsible for the moderate fistula rate in the high-risk population in this study.

The technique is easy to learn and apply and neither leads to a relevant longer operation time nor increases the risk for the patient. It should be emphasized that these are our preliminary results and the first experiences with external drainage under closed suction in pancreatogastrostomy following PD. Our series did not include a control group (no drainage group) and aimed at the evaluation of feasibility of the technique.

CONCLUSION

The applied technique of external pancreatic duct drainage under closed suction with negative pressure in pancreatogastrostomy following PD was feasible without any drainage-related risk for the patient. The use of pancreatic duct drainage resulted in a moderate POPF rate in 4 of 21 patients (19%), with only one POPF grade C (4.8%) in the risk population of a soft pancreas with a non-dilated duct. Motivated by the promising results of our feasibility series, we started a prospective randomized study (registration number DRKS00021634) including one arm with no drainage patients to obtain valid data in a larger cohort.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Brandenburg Medical School (08 April 2019/No. E-01-20181120). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HA, CA, and CM collected and analyzed the data and wrote main parts of the manuscript. SG and HA designed the study and completed the manuscript. All authors meet the criteria of the International Committee of Medical Journal Editors (ICMJE) regarding the definition of authorship.

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Postoperative Outcomes Analysis After Pancreatic Duct Occlusion: A Safe Option to Treat the Pancreatic Stump After Pancreaticoduodenectomy in Low-Volume Centers

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Background: Surgical resection is the only possible choice of treatment in several pancreatic disorders that included periampullar neoplasms. The development of a postoperative pancreatic fistula (POPF) is the main complication. Despite three different surgical strategies that have been proposed–pancreatojejunostomy (PJ), pancreatogastrostomy (PG), and pancreatic duct occlusion (DO)–none of them has been clearly validated to be superior. The aim of this study was to analyse the postoperative outcomes after DO.

Methods: We retrospectively reviewed 56 consecutive patients who underwent Whipple's procedure from January 2007 to December 2014 in a tertiary Hepatobiliary Surgery and Liver Transplant Unit. After pancreatic resection in open surgery, we performed DO of the Wirsung duct with Cyanoacrylate glue independently from the stump characteristics. The mean follow-up was 24.5 months.

Results: In total, 29 (60.4%) were men and 19 were (39.6%) women with a mean age of 62.79 (SD ± 10.02) years. Surgical indications were in 95% of cases malignant diseases. The incidence of POPF after DO was 31 (64.5%): 10 (20.8%) patients had a Grade A fistula, 18 (37.5%) Grade B fistula, and 3 (6.2%) Grade C fistula. No statistical differences were demonstrated in the development of POPF according to pancreatic duct diameter groups ($p = 0.2145$). Nevertheless, the POPF rate was significantly higher in the soft pancreatic group ($p = 0.0164$). The mean operative time was 358.12 min (SD ± 77.03, range: 221–480 min). Hospital stay was significantly longer in patients who developed POPF ($p < 0.001$). According to the Clavien-Dindo (CD) classification, seven of 48 (14.58%) patients were classified as CD III–IV. At the last follow-up, 27 of the 31 (87%) patients were alive.

Conclusions: Duct occlusion could be proposed as a safe alternative to pancreatic anastomosis especially in low-/medium-volume centers in selected cases at higher risk of clinically relevant POPF.

Keywords: pancreatic surgery, pancreatic cancer, low-volume center, pancreatic stump, duct occlusion, COVID-19 pandemic, POPF

INTRODUCTION

Surgical resection is the only possible choice of treatment in several pancreatic disorders, such as malignancies, adenomas, traumas, and severe acute and/or chronic pancreatitis (1). Radical resection is the single most important factor in determining outcomes in patients with pancreatic adenocarcinoma (1–3). Although the surgical context has radically changed in the last 20 years with the advent of new technologies and surgical approaches improving the short-term outcomes in several abdominal surgical fields (4–8), however, the morbidity rate following pancreaticoduodenectomy (PD) remains high, ranging from 30 to 50%, with a mortality rate of 3–5% (9–12). Morbidity in pancreatic surgery is mainly related to the development of a postoperative pancreatic fistula (POPF) (13). According to the International Study Group on Pancreatic Fistula (ISGPF), it is possible to grade POPF based on clinical variables (14). "A grade" fistulas, as called a "biochemical leak" (BL) in update classification, do not need any treatment (currently it is not considered a true pancreatic fistula) and imply no clinical impact. "B grade" fistulas can be managed with medications and only prolong the length of hospital stay in association with a clinically relevant condition. "C grade" fistulas need operative treatment and might be life threatening (12). In high-volume centers for pancreatic surgery, the overall POPF incidence is around 20% (12, 14, 15). Intra-abdominal abscesses, delayed gastric emptying, postpancreatectomy hemorrhage, and sepsis represent additional sources of morbidity. In most cases, however, they occur in association or as a consequence of POPF (16, 17). Advanced age (>75 years), pancreas texture, pancreatic duct diameter, comorbidities, previous endoscopic retrograde cholangiopancreatography (ERCP), duct obstruction, and surgical technique are known risk factors for postoperative morbidity (12, 14, 15, 18–21). The incidence of postoperative complications has a significant impact on the length of hospital stay, costs, quality of life, and chance to start chemotherapy (22, 23). Several different surgical and pharmacological approaches have been proposed to avoid POPF, which might be different depending on the experience and preferences at each center (13, 24). Three main different surgical strategies have been

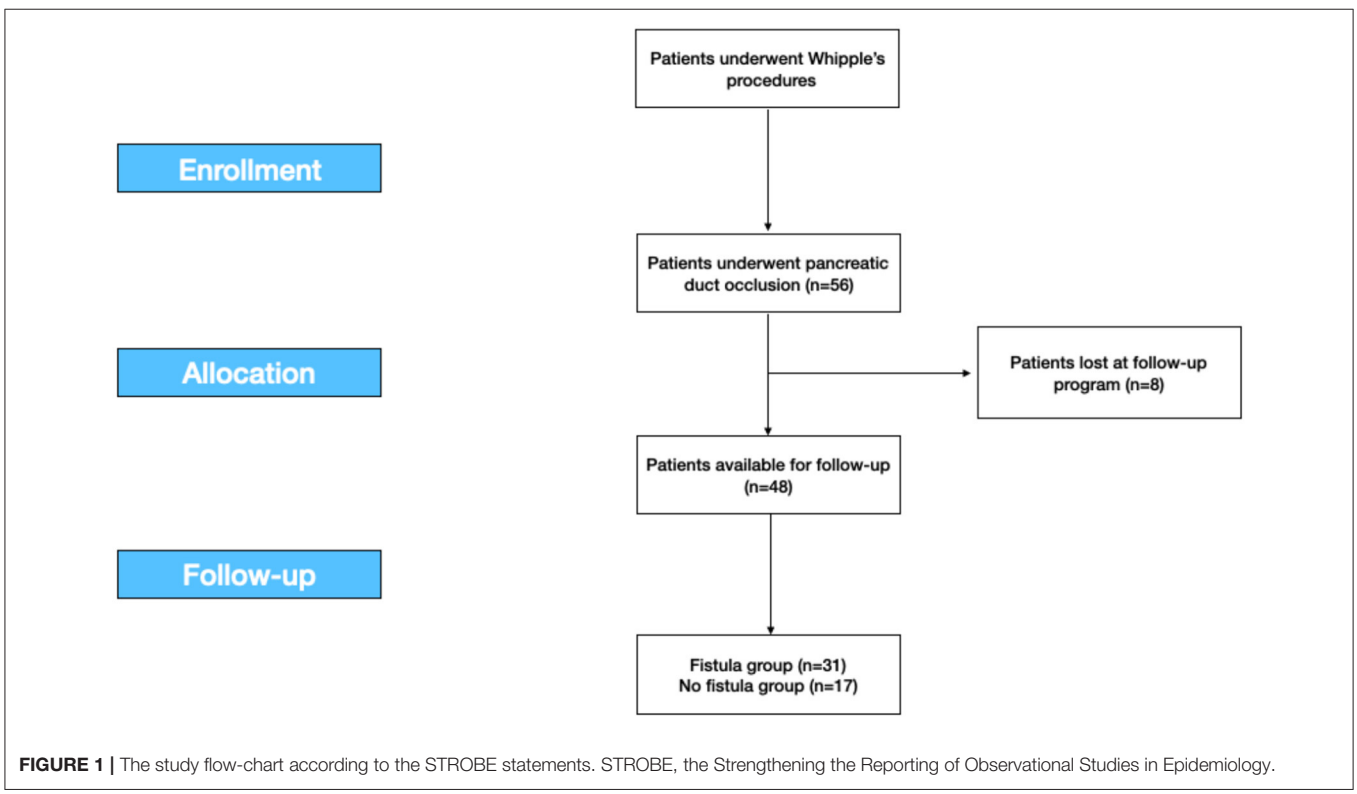

FIGURE 1 | The study flow-chart according to the STROBE statements. STROBE, the Strengthening the Reporting of Observational Studies in Epidemiology.

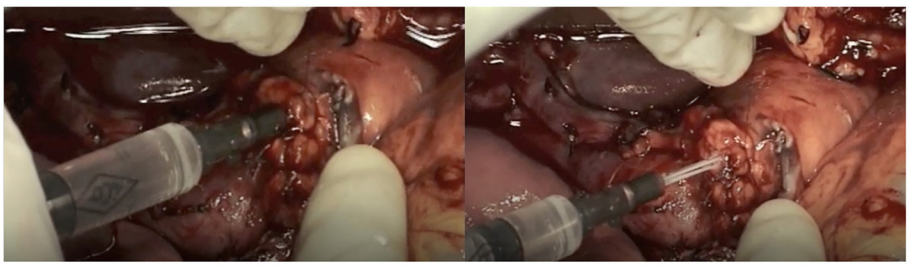

FIGURE 2 | Cyanoacrylate glue injection in Wirsung duct to obtain pancreatic duct occlusion.

proposed to deal with the pancreatic stump following PD—pancreatojejunostomy (PJ), pancreatogastrostomy (PG) and pancreatic duct occlusion (DO)—but none of them has been clearly demonstrated to be superior to the others (25). Despite such detailed reporting of morbidity and mortality following PD, it is still not clear whether is surgeon's experience or hospital volume to rescue patients when a complication occurs (25). If PJ is the procedure of choice in medium-/high-volume centers, DO could be proposed as a safer alternative in medium-/low-volume centers, to reduce the risk of major postoperative complications (26). We decided to review our previous experience in the light of the recent Covid pandemic where, in our country, it has been forced in many regions to displace treatment of oncological patients in low-volume hospitals with limited experience (27, 28). The encouraging results of DO in terms of overall survival, POPF, and "brittle diabetes" are here presented.

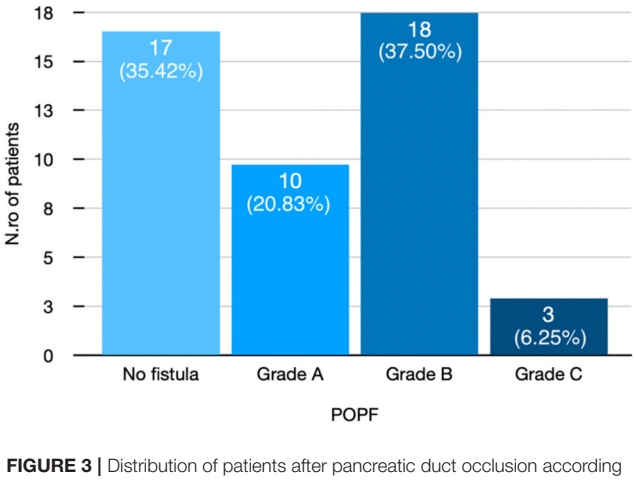

FIGURE 3 | Distribution of patients after pancreatic duct occlusion according to POPF grade. POPF, postoperative pancreatic fistula.

MATERIALS AND METHODS

Study Design

We retrospectively reviewed 56 consecutive patients who underwent Whipple's procedure from January 2007 to December 2014 in a tertiary Hepatobiliary Surgery and Liver Transplant Unit with a low volume of pancreatic resections.

All data were obtained from a prospectively maintained database and analyzed retrospectively. All patients signed a proper informed consent for the scientific anonymous use of clinical data. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the University of Molise (protocol number 10/21, approved date: 12 May 2021).

The follow-up program was performed by clinical exam, CEA, CA19.9 levels, and CT scan every 3 of 6 months after surgery according to Italian guidelines (29).

Eight patients were lost at follow-up, so the analysis on morbidity was conducted on the 48 patients available with a mean follow-up of 25.4 months (**Figure 1**).

In all cases, DO was performed with Cyanoacrylate glue injection.

We recorded data about medical history, body mass index (BMI), American Society of Anaesthesiologists' (ASA) score, preoperative CA19.9, survival, mean operative time, incidence of POPF, the incidence of sepsis, the incidence of postoperative hemorrhage, re-laparotomy rate, hospital stay, incidence of preoperative and postoperative diabetes, 30-day and 90-day postoperative mortality, oncological recurrence, and pancreatic exocrine function.

The pancreatic exocrine function was evaluated by personal or telephonic interviews assessing any substitutive pancreatic enzyme therapy (yes/no) related to steatorrhea/diarrhea since surgery.

This retrospective study was developed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies (**Figure 1**) (30).

Preoperative Workup

Our preoperative workup consisted of total body CT and/or MRI scan for oncological staging and for the exact determination of tumor size and resectability. If total bilirubin was higher than 20 mg/dl, biliary drainage was placed via ERCP in patients whose surgery was not scheduled within 2 wk. A cephalosporin +

TABLE 1 | Baseline characteristics of patients who underwent pancreatic duct occlusion.

	Duct occlusion, =48	Fistula, $n = 31$	No fistula, $n = 17$	*p*-value
Age (yrs)				
Mean (± SD)	62.79 (± 10.02)	62.87 (± 8.23)	62.65 (± 12.96)	*0.9429*
Median	66.00	66.00	66.00	
Range	(34–78)	(44–78)	(34–78)	
Gender, *n* (%)				
Male	29 (60.4)	22 (70.97)	7 (41.18)	*0.0651*
Female	19 (39.6)	9 (29.03)	10 (58.82)	
BMI				
Mean (± SD)	25.27 (± 1.64)	25 (± 1.54)	25.51 (± 1.71)	*0.2968*
Median	25	25	25	
Range	(21–28)	23–28	21–28	
ASA, *n* (%)				
I	1 (2.1)	1 (3.24)	0 (0)	*1.0000*
II	16 (33.3)	12 (38.71)	4 (23.53)	*0.5316*
III	19 (39.6)	12 (38.71)	7 (41.18)	*1.0000*
IV	12 (25.0)	6 (19.34)	6 (35.29)	*0.3002*
Previous procedures, *n* (%)				
ERCP	16 (33.3)	14 (45.16)	2 (11.76)	*0.486*
PTC stent	2 (4.2)	1 (3.22)	1 (5.88)	*1.0000*
Colecistectomy	1 (2.1)	0 (0)	1 (5.88)	*0.3673*
Comorbidities, *n* (%)				
Arterial hypertension	16 (33.3)	10 (32.26)	6 (35.29)	*1.0000*
Diabetes mellitus	10 (20.8)	5 (16.13)	5 (29.41)	*0.2947*
Atrial fibrillation	6 (12.5)	4 (12.90)	2 (6.45)	*1.0000*
HCV positive	3 (6.3)	3 (9.68)	0 (0)	*0.5430*
COPD	3 (6.3)	2 (6.45)	1 (5.88)	*1.0000*
Liver transplantation	1 (2.1)	1 (3.22)	0 (0)	*1.0000*
Cerebral ischemia	1 (2.1)	1 (3.22)	0 (0)	*1.0000*
Pre-operative Ca19.9, U/ml				
Mean, (± SD)	285.14 (± 660.83)	117.79 (±85.29)	787.2 (±1307)	*0.0062*
Median	80.45	80.45	206.85	
Range	(1–2734.10)	(22.4–2431)	(1–2734.10)	

BMI, Body Mass Index; ERCP, Endoscopic Retrograde Cholangiopancreatography; PTC, Percutaneous Transhepatic Cholangiography; COPD, Chronic Obstructive Pulmonary Disease; Ca19.9, carbohydrate antigen 19–9 or cancer antigen 19–9 or sialylated Lewis.

metronidazole was used as infection prophylactic treatment. No patient was allergic to this regimen.

Surgical Technique

We performed a Whipple procedure with an open approach. Gastrectomy was performed using GIA 90 without pylorus preservation.

After pancreatic resection, we performed DO of the Wirsung duct with Cyanoacrylate glue independently from the stump characteristics. In detail, the pancreatic stump was closed with 3/0 polypropylene stitches during glue polymerization while the catheter inserted in the main pancreatic duct for glue injection was simultaneously removed to obtain a complete duct closure (**Figure 2**). No patients underwent vascular resection. We finally performed biliary reconstruction with a Roux-en-Y anastomosis. We always performed a mechanical gastro-jejunal anastomosis.

Two abdominal drainages were placed (one close to the pancreatic remnant and one in the pelvis).

Postoperative Care

All patients stayed at least 1 day in the intensive care unit (range: 1–3 days) and then returned to the ward. Amylase and lipase were routinely monitored in serum starting from postoperative day 3. POPF was defined according to the 2016 update of the International Study Group (ISGPS) (14, 25).

A cephalosporin + metronidazole regimen was adopted when needed. No patient was allergic to this antibiotic regimen and/or presented resistant bacteria. Octreotide 0.1 ml was administered subcutaneously three times a day. In the absence of POPF, patients were allowed oral intake on postoperative day 5.

Complications were graded according to Clavien-Dindo (CD) classification (31).

TABLE 2 | Clinico-pathological data of patients who underwent pancreas duct occlusion included in follow-up program.

	Duct occlusion, $n = 48$	Fistula, $n = 31$	No fistula, $n = 17$	*P*-value
Histological findings, *n* (%)				
Pancreatic adenocarcinoma	24 (50)	14 (45.16)	10 (58.83)	*0.5469*
Ampullary adenocarcinoma	10 (20.84)	6 (19.35)	4 (23.53)	*0.7266*
Bile duct cancer	6 (12.50)	5 (16.14)	1 (5.88)	*0.4022*
Neuroendocrin carcinoma	3 (6.25)	2 (6.45)	1 (5.88)	*1.0000*
Mucinous cystadenoma	3 (6.25)	3 (9.68)	-	*0.5430*
Gallbladder cancer	1 (2.08)	1 (3.22)	-	*1.0000*
Choronic pancreatitis	1 (2.08)	-	1 (5.88)	*0.3542*
Pancreatic texture, *n* (%)				
Soft	33 (68.75)	25 (80.65)	8 (47.06)	*0.0164*
Hard	8 (16.67)	5 (16.13)	3 (16.65)	*1.0000*
Normal	7 (14.58)	1 (3.22)	6 (35.39)	*0.0055*
Pancreatic duct diameter				
Mean, mm	3.98 (± 2.18)	4.25 (± 1.88)	5.00 (± 2.14)	*0.2145*
Range, mm	1–10	3–10	1–8	
≤ 3 mm, *n* (%)	19 (39.58)			
> 3mm, *n* (%)	29 (60.42)			
Hematic amylase, UI/l				
Pre-operative mean (± SD)	178.41 (± 201.37)	202.75 (±236.89)	139.47 (±123.41)	*0.3110*
Post-operative, mean (± SD)	451.31 (± 510.78)	557.37 (±567.52)	246.33 (±298.06)	*0.0413*
7 days p.o., mean (± SD)	74.10 (± 57.44)	88.10 (±60.90)	47.93 (±40.21)	*0.0187*

Statistical Analysis

Descriptive statistics were collected and reported as a whole number (percentage) and mean or median (range). Chi-square test and Fisher exact test including or not Yates' continuity correction, two-by-two cross tables, Student's *t*-test, and ANOVA test were used to compare categorical data and to analyse normally distributed quantitative data.

Differences were statistically significant when *p*-values were <0.05. Statistical analysis was carried out using IBM SPSS Statistics for Macintosh, Version 27.0.

RESULTS

For 8 years, from January 2007 to December 2014, we retrospectively collected data of 56 patients who underwent Whipple's procedure for benign and malignant diseases in a Tertiary Hepatobiliary Surgery and Liver Transplant Unit with a low volume of pancreatic resections. Eight patients (8) were excluded upon they were lost at the follow-up program. Total 48 patients were included (**Figure 1**).

In total, 29 (60.4%) were men and 19 were (39.6%) women with a mean age of 62.79 (SD ± 10.02) years. Thirty-one (64.58%) developed POPF. **Figure 3** shows POPF grade in detail.

Body mass index, ASA score, and other baseline characteristics of patients according to the development of pancreatic fistula are shown in **Table 1**.

Surgical indications were in 95% of cases malignant diseases. Pathological findings according to POPF are depicted in **Table 2**.

TABLE 3 | Perioperative data.

Operative time, min	
Mean (± SD)	358.12 (± 77.03)
Median	360
Range	221–480
Procedures, *n* (%)	
Glubran	48 (100)
Blood trasfusion	
n (%)	6 (12.5)
packed red blood cells, mean (range)	1.5 (1–4)
Hospital stay, days, mean (± SD)	
Fistula group	38 (± 22), (r.:13–115)
No fistula group	17.37 (± 9), (r.:3–45)
p-value	<0.001

Biliary drainage was performed before surgery in 16 (33.3%) patients who underwent ERCP, in one patient (4.2%) who underwent PTC. The incidence of pancreatic fistula after biliary drainage is shown in **Table 1**.

Duct diameter was reported larger than 3 mm in 60% of patients. As depicted in **Table 2**, no statistical differences were demonstrated in the development of POPF according to pancreatic duct diameter groups ($p = 0.2145$).

The soft pancreatic texture was recorded in 68% of cases. As shown in **Table 2**, the POPF rate was significantly higher in the soft pancreatic group ($p = 0.0164$).

The mean operative time was 358.12 min (SD ± 77.03, range: 221–480 min). Six (12.5%) patients needed intraoperative blood cells transfusions (**Table 3**).

TABLE 4 | Short-term and long-term outcomes.

	Duct occlusion, $n = 48$	Fistula, $n = 31$	No fistula, $n = 17$	*P*-value
Clavien-Dindo classification, *n* (%)				
I–II	41 (85.42)	27(87.10)	14 (82.35)	*0.6862*
III–IV	7 (14.58)	4 (12.90)	3 (17.65)	
30-days mortality, *n* (%)	3 (6.45)	2 (6.45)	1 (5.88)	*1.0000*
90-days mortality, *n* (%)	2 (4.16)	2 (6.45)	0	*1.0000*
Short-term outcomes, *n* (%)				
Sepsis	11 (22.92)	9 (29.03)	2 (11.76)	*0.2840*
Post-operative bleeding	10 (20.83)	9 (29.03)	1 (5.88)	*0.0744*
Intraddominal collection	14 (29.17)	14(45.16)	0	*<0.001*
Pleura effusion	2 (4.17)	1 (3.22)	1 (5.88)	*1.0000*
Dehiscence*	2 (4.17)	1 (3.22)	1 (5.88)	*1.0000*
Hemoperitoneum	4 (8.33)	2 (6.45)	2 (11.76)	*0.2300*
Intestinal obstruction	2 (4.17)	2 (6.45)	0	*0.5328*
Stroke	1 (2.08)	1 (3.22)	0	*1.0000*
DIC	2 (4.17)	2 (6.45)	0	*0.5328*
Long-term outcomes, *n* (%)				
Brittle diabetes	8 (16.67)		5 (29.41)	*0.1115*
Octreotide therapy	44 (91.67)	3 (9.68) 31 (100)	13 (76.47)	*0.0122*
Reoperative rate, *n* (%)				
Total	10(20.83)	7 (22.58)	2 (11.76)	
Hemostatis	4 (8.33)	2 (6.45)	2 (11.76)	*0.6073*
Total pancreasectomy	2 (4.17)	2 (6.45)	.	*0.5328*
GI fistula	1 (2.08)	1 (3.22)	.	*1.0000*
Re-anastomosis HJ	1 (2.08)	1 (3.22)	.	*1.0000*
Explorative laparotomy	1 (2.08)	1 (3.22)	.	*1.0000*
Recurrence, *n* (%)	7 (14.58)	6 (19.35)	1 (5.88)	*0.3956*
Follow-up, months				
Mean	24.5	23.5	17.7	
Range	(3–100)	(3–100)	(3–21)	
Overall survival (%)	58.3			

*DIC, disseminated intravascular coagulation; HJ, Hepatico-Jejunostomy;*Dehiscence: 1 Hepatico-jejunostomy; 1 wound.*

TABLE 5 | Mortality rate and cause of death.

	POPF grade	Cause of death
30-days mortality, n.ro		
1	No POPF	Shock-MOFS
1	A grade	MOFS
1	C grade	Stroke
90-days mortality, n.ro		
1	A grade	Hemorrhage-MOFS
1	B grade	MOFS

POPF, postoperative pancreatic fistula.

TABLE 6 | Re-operative rate according to POPF grade and follow-up.

	POPF grade	Follow-up
Hemostasis, n.ro		
1	No POPF	Dead 30 days p.o.
1	No POPF	Alive 12 months p.o.
1	A grade	Dead 7 months p.o.
1	A grade	Alive 78 months p.o.
Total pancreasectomies, n.ro		
1	C grade	Dead 30 months p.o.
1	C grade	Alive 100 months p.o.
GI fistula, n.ro		
1	C grade	Alive 8 months p.o.
Re-anastomosis hepatico-jejunal, n.ro		
1	C grade	Alive 27 months p.o.
Explorative laparotomy, n.ro		
1	C grade	Dead 90 days p.o.

POPF, postoperative pancreatic fistula.

Hospital stay was significantly longer in patients who developed POPF ($p < 0.001$) as described in **Table 3**.

According to the CD classification (31), seven of 48 (14.58%) patients were classified as CD III–IV. Complications, reoperation rate, and whole short-term outcomes that include 30- and 90-day mortality according to pancreatic fistula are extensively described in **Tables 4**–**6** and **Figure 4**.

Eight (16.67%) patients developed brittle diabetes without any statistical relationship to the POPF rate (**Table 4**).

The mean follow-up was 24.5 months (range: 3–100; **Table 4**). The overall survival at the last follow-up was 58.3% (**Table 4**).

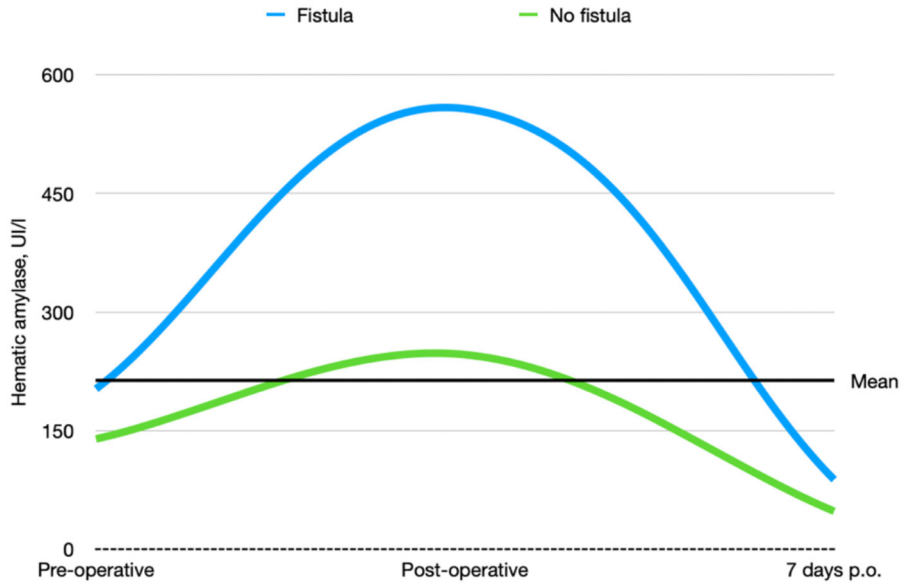

FIGURE 4 | Preoperative, postoperative, and 7-day postoperative hematic amylase trends in patients who underwent pancreatic duct occlusion with and without fistula.

TABLE 7 | Literature summary of pathological findings in pancreatic surgery.

Author	Type	N.ro	Mean Operative Time, min (range)	PA, n (%)	Amp, n (%)	BDC, n (%)	Others, n (%)	Texture soft, n (%)	DD≤3mm, n (%)
Giuliani et al.	DO	48	358 (r.:221–480)	24 (50)	10 (20.8)	6 (12.5)	8 (16.6)	33 (68.7)	19 (39.58)
Mazzaferro et al. (26)	DO	51	480 (r.:400–533)	33 (64.7)	32 (65.3)	6 (10.7)	5 (9.8)	NA	NA
	PJ	49	490 (r.:438–540)	32 (65.3)	4 (8.2)	6 (10.7)	7 (14.3)	NA	NA
Yeo (50)	PG	73	444 (r.:432–456)	40 (55)	7 (10)	6 (8)	4 (5)	16 (22)	3,4 (mean)
	PJ	72	432 (r.:420–444)	40 (56)	11 (15)	7 (10)	7 (9.7)	17 (24)	2,9 (mean)
Duffas (44)	PG	81	≥360 54 (67%) <360 27 (33%)	34 (42)	17 (19)	8 (10)	9 (11)	49 (60)	32 (40)
	PJ	68	≥360 44 (65%) <360 24 (35%)	25 (37)	19 (28)	11 (16)	8 (11.7)	41 (60)	49 (60)
Bassi (51)	PG	69	337.2 (r:336-338)	32 (46)	13 (18.8)	1 (1.4)	24 (34.7)	NA	NA
	PJ	82	353.9 (r: 352-354)	28 (34.1)	11 (13.4)	2 (2.4)	43 (52.4)	NA	NA
Fernàndez-Cruz (52)	PG	53	300 (r.:250-350)	26 (49)	12 (22.6)	8 (15)	10 (18.8)	24 (45)	NA
	PJ	55	310 (r.:250-370)	28 (50.9)	10 (18.1)	7 (12.7)	10 (18.1)	25 (55)	NA

PA, pancreatic adenocarcinoma; Amp, ampullary carcinoma; BDC, bile duct cancer; DD, duct diameter; DO, duct occlusion; PJ, pancreatic-jejunal anastomosis; PG, pancreatic-gastrostomy; NA, not available.

DISCUSSION

Our case series demonstrate that DO might be considered as a safe option to treat pancreatic stump after PD. Evidence supports a strong correlation between surgical outcomes and hospital volume in pancreatic surgery (32–37). Despite these findings during the Covid pandemic period, it was very difficult to provide sanitary migration to high-volume centers (38–40), so also medium- and low-volume centers, which have enough facilities and skills to provide pancreatic surgery, should perform more interventions to answer to the population needs. Our results gained in a Hepatobiliary referral center with a low-volume rate of pancreatic resections may encourage pancreatic resection allowing a reduction of patient mobility. Pedrazzoli et al. in a large systematic review on PD and pancreatic fistula analyzed 162 articles involving 54,232 patients (41). The review shows 4,813 Grade A (8.9%), 4,830 Grade B (8.9%), and 1,872 Grade C (3.5%) POPFs with a mean overall fistula rate of 21.3%. A huge variability of Grades A and B POPFs varied from <2% to more than 20% with a minimum of 0% and a maximum of 42.5% for Grade A and a minimum of 0.7% and a maximum of 33.3% for Grade B POPF. Grade C POPFs arise from 1% to more than 9% with a maximum of 13.6% (41). Di Carlo et al. showed that the DO procedure was feasible and less time-consuming than PJ,

TABLE 8 | Literature summary of complications in pancreatic surgery.

Author	Type	N.ro	P.O. haemorrhage, *n* (%)	SI, *n* (%)	Pneumonia, *n* (%)	Bleeding, *n* (%)	BF, *n* (%)	IA, *n* (%)	DGE, *n* (%)
Giuliani et al.	DO	48	8 (16.67)	4 (8.3)	3 (6.2)	11 (22.9)	1 (2)	14 (29.17)	NA
Mazzaferro et al. (26)	DO	51	7 (13.7)	5 (9.8)	8 (15.7)	7 (13.7)	4 (7.8)	4 (7.8)	8 (15.7)
	PJ	49	5 (10.2)	2 (4.1)	7 (14.3)	5 (10)	7 (14.3)	2 (4.1)	9 (18.4)
Yeo (50)	PG	73	NA	14 (19)	5 (7)	NA	1 (1)	4 (5)	16 (22)
	PJ	72	NA	11 (15)	2 (3)	NA	3 (4)	2 (3)	16 (22)
Duffas (44)	PG	81	13 (16)	NA	NA	13 (16)	6 (7)	11 (14)	NA
	PJ	68	9 (13)	NA	NA	9 (13)	2 (3)	16 (23)	NA
Bassi (51)	PG	69	3 (4)	NA	NA	3 (4)	0	7 (10)	2 (3)
	PJ	82	6 (7)	NA	NA	6 (7)	7 (8.5)	22 (27)	10 (12)
Fernàndez-Cruz (52)	PG	53	1 (2)	3 (8)	2 (4)	1 (2)	0	2 (4)	2 (4)
	PJ	55	1(2)	2 (4)	4 (7)	1 (2)	1 (2)	8 (14)	8 (14)

SI, surgical infection; BF, biliary fistula; IA, intra-abdominal abscess; DO, duct occlusion; DGE, Delayed Gastric Emptying; PJ, pancreatic-jejunal anastomosis; PG, pancreatic-gastrostomy; NA, not available.

TABLE 9 | Literature summary of Clavien-Dindo classification, re-operative rate, POPF and mortality rate in pancreatic surgery.

Author	Type	N.ro	CD I–II, *n* (%)	CD ≥III, *n* (%)	Re-operation rate, *n* (%)	POPF, *n* (%)	Mortality, *n* (%)
Giuliani et al.	DO	48	41 (85)	7 (14)	10 (20.83)	31 (64.5)	5 (10.4)
Mazzaferro et al. (26)	DO	51	15 (29.4)	36 (70.6)	9 (19)	B, C 6 (11.8)	3 (5.9)
	PJ	49	15 (30.6)	34 (69.4)	8 (16.3)	B, C 8 (16.3)	1 (2)
Yeo (50)	PG	73	NA	NA	NA	9 (12)	NA
	PJ	72	NA	NA	NA	8 (11)	NA
Duffas (44)	PG	81	44 (54.3)	37 (45.7)	15 (19)	13 (16)	10 (12)
	PJ	68	38 (55.9)	30 (44.1)	15 (22)	14 (20.5)	7 (10)
Bassi (51)	PG	69	NA	NA	5 (7)	9 (15.8)	0
	PJ	82	NA	NA	5 (6)	13 (15.8)	1 (1)
Fernàndez-Cruz (52)	PG	53	NA	NA	1 (1.8)	A:1 (1,8) B:2 (3.7)	0
	PJ	55	NA	NA	1 (1.8)	B:10 (18.1)	0

CD, Clavien-Dindo Classification; NA, not available.

although it could be associated with higher fistula rates. However, POPF could not be clinically relevant probably due to the absence of a pancreatic enzymes activation (42). In our experience, the overall incidence of POPF was 64%. This observation is consistent with the experience of Tersigni et al. who observed a higher rate of POPF after DO (45.4%) compared to end-to-end PJ anastomosis (15.6%) and to end-to-side PJ anastomosis (11.3%), with a similar incidence of Grade C fistula in all the groups (3.1% after end-to-end PJ anastomosis, 2.3% after end-to-side anastomosis and 3.0% after DO) (43). Consistent with other reports, in our patients a soft pancreatic texture was associated with a significantly higher incidence of POPF (overall 80% of POPF with soft pancreas vs. 16% of POPF with fibrotic pancreas). Moreover, when considering only clinically relevant POPF, we had only two POPFs (4.2%) with fibrotic pancreas vs. 15 POPFs (31.4%) with the soft pancreas ($p < 0.005$). Our incidence of reoperation was quite high 9/48, 18.7% (**Table 4**). It is superimposable to Duffas et al. and Mazzaferro et al. (26, 44). In detail, if we consider patients re-operated due to POPF only in two cases the prognosis was poor. Five re-operated patients had a good prognosis, so we can consider that the stump treatment did not influence the reoperation rate. Four of our patients (8.3%) had a postoperative hemorrhage, and all of them needed to return to the operative room. Interestingly, in only two patients (50%) hemorrhage was a consequence of POPF (all grade A). In the other two cases, the bleeding originated from a small vessel from the portal vein and the gastroepiploic artery. The overall incidence of POPF-related bleeding was 6%, which is in line with other experiences (25). Our length of stay was 38 days in POPF-group, higher than those observed in other experiences (45). More than 90% of patients needed pancreatic enzymes supplementation due to postoperative pancreatic insufficiency. This facet is consistent with other authors (25, 46, 47). However, Tran et al. reported that the need for enzyme supplementation 1 year after surgery was not related to the type of reconstruction (46). In addition, other authors reported that pancreatic exocrine insufficiency might be related to the pancreatic atrophy/fibrosis and preoperative texture than to DO or PJ (25, 46, 47). In our series, 16% of patients developed brittle diabetes, with only 13 patients (27.1%) developing new-onset diabetes. This might confirm that DO has a higher risk of new-onset diabetes, even if only a few patients suffer from uncontrolled diabetes (25,

46, 47). According to Tran et al., the incidence of endocrine insufficiency is significantly higher after DO compared with PJ at 3- and 12-month follow-up after surgery ($p = 0.001$ for both) (46). The overall mortality rate in more than 1,500 PD performed in Italy was reported to be as high as 8.1% (34). Our findings are superimposable to the literature (34), but we would clarify that only two patients who died have developed a clinically relevant fistula. On the other hand, three patients died for cardiovascular causes despite the absence of B or C POPF. We also demonstrated an overall pancreatic surgery-related mortality, which is lower than for low-volume centers (34). It has been suggested that avoiding an anastomosis of the pancreatic duct by means of duct occlusion could minimize anastomosis-related morbidity, especially in low-volume centers (43, 46–48). The aim was to obtain a "*pure*" pancreatic fistula with no activation by bile and/or enteric juice, thereby reducing the risk of life-threatening complications. However, in the experience of a high-volume center, postoperative mortality after PJ seemed to be higher than after DO (43). In a recent prospective randomized control study (26) compared POPF following DO in high-risk patients for pancreatic fistula vs. PJ after PD for low-risk patients for pancreatic fistula, mortality after DO was 5.9% and 2.0% after PJ anastomosis, in our serie 90-day mortality related to significant POPF was (2/48) 4%, so mortality might be considered superimposable with other authors who performed DO (**Table 4**) (49). He et al. (33) analyzed Randomized Controlled Trials (RCTs) and Observational Clinical Studies (OCSs), which were related to different treatments of pancreatic stump and major outcomes after PD or pylorus-preserving PD for malignant or benign pancreatic tumor, chronic pancreatitis, or extra-pancreatic tumors (periampullary, biliary or duodenal). The objective of the meta-analysis was a comparison between PJ and PG using quantitative data on POPF and overall complications. PD without anastomosis or duodenum-preserving pancreatectomy was excluded. We shall underline meta-analysis by He et al. (33) reported a lower mortality index performing PG and PJ, but these data were published by high volume and referral centers for pancreatic surgery. Nevertheless, Duffas et al. reported in their experience an incidence of death after PG and PJ of 12 and 10%, respectively (44). A summary of these findings is depicted in **Tables 7–9**.

It is clear that the outcome of complex surgical procedures may not only rely on technical aspects of surgery but is also affected by resource availability (53, 54). However, some technical aspects can be modified and reduce the risk of life-threatening postoperative complications even in low-/medium-volume centers. Pancreaticoduodenectomy can be safely performed in low-volume centers if amenities and processes typical of high-volume centers can be replicated in specialized units (55, 56). Of note, we represent the only referral center for HPB in a huge geographical region of southern Italy, so the availability of postdischarge home management, financial problems, low human resources and patients wish could affect this outcome. In our opinion, in patients with a higher risk for POPF (soft pancreas, dilated pancreatic duct), DO could be a safer option, ideally suitable in low-volume centers. The ideal concept of reserving pancreatic surgery only to highly specialized centers is probably *utopian*. Geographical limitations, elevated costs for the patients and their relatives, political issues, different regional healthcare systems, and the opposition by medical and surgical staff determine the need to perform this surgery even in academic or tertiary referral hospitals with a limited experience in HPB surgery, but with all the amenities required for very complex surgery (57, 58). So, considering criteria published in the literature (32, 34–36), pancreatic surgery should be centralized, this implies unavoidably an increase of interregional mobility and related healthcare costs, especially for patients from the region of southern Italy. During the Covid-19 pandemic, as we know from the survey written by Aldrighetti et al. on HPB surgery in Italy (27), 72.8% of HPB centers showed a reduction of routine elective operations $\geq$50%, if we combine effects of centralization to the effects of the Covid-19 pandemic we understand how difficult it would be for patients to undergo pancreatic surgery in a quite fast, safe, and effective way (59). In this situation, we decided to analyse our outcomes from a low volume center for pancreatic surgery to overcome the impossibility to send patients to pancreatic surgery referral centers, considering their overload, ensuring to patients a high-quality service at the same time. Our approach led us to guarantee effective treatment and safety procedures during the critical pandemic period. Probably, a surgical alternative such as DO during the phase of PD at higher risk of complications, i.e., the pancreatic anastomosis, could reduce the rates of subsequent morbidity and mortality with similar oncological results.

Limitations

Our study is a retrospective, single-center analysis, we considered consecutive patients who underwent PD and were registered in a prospectively maintained database. We can consider our center as low volume due to the number of PD per year, but we can be supported by high-volume center facilities, including a) being a referral center for hepatobiliary surgery, liver transplantation, advanced colorectal surgery, b) having a dedicated intensive care unit, and c) having interventional radiology and endoscopy available 24 h.

CONCLUSIONS

In conclusion, DO could be proposed as an alternative option to pancreatic anastomosis especially in low-/medium-volume centers. A comparison of DO with other types of pancreatic duct reconstructions should be advisable to draw definitive conclusions, ideally by means of an adequately designed RCT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, with undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Università degli Studi del Molise. The

patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG, FC, and AR: conceptualization. AG and AR: methodology. PA: software. AG, PA, FC, and AR: validation, writing—original draft preparation, and visualization. PA, ALS, MI, AB, MCo, MCa, MB, RV, and AS: formal analysis and investigation, resources, and data curation. PA, FC, and AR: writing—review and editing. GG, BA, and AR: supervision. All authors have read and agreed to the published version of the manuscript.

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Must Clinics Replace 2D by 3D Environments for an Efficient Training of Laparoscopic Novices? A Critical Analysis of the Learning Curve for Basic Skills

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Background and Aims: Published studies repeatedly demonstrate an advantage of three-dimensional (3D) laparoscopic surgery over two-dimensional (2D) systems but with quite heterogeneous results. This raises the question whether clinics must replace 2D technologies to ensure effective training of future surgeons.

Methods: We recruited 45 students with no experience in laparoscopic surgery and comparable characteristics in terms of vision and frequency of video game usage. The students were randomly allocated to 3D ($n = 23$) or 2D ($n = 22$) groups and performed 10 runs of a laparoscopic "peg transfer" task in the Luebeck Toolbox. A repeated-measures ANOVA for operation times and a generalized linear mixed model for error rates were calculated. The main effects of laparoscopic condition and run, as well as the interaction term between the two, were examined.

Results: No statistically significant differences in operation times and error rates were observed between 2D and 3D groups ($p = 0.10$ and $p = 0.72$, respectively). The learning curve showed a significant reduction in operation time and error rates (both p's < 0.001). No significant interactions between group and run were detected (operation time: $p = 0.342$, error rates: $p = 0.83$). With respect to both endpoints studied, the learning curves reached their plateau at the 7th run.

Conclusion: The result of our study with laparoscopic novices revealed no significant difference between 2D and 3D technology with respect to performance time and the error rate in a simple standardized test. In the future, surgeons may thus still be trained in both techniques.

Keywords: learning curve, 2D laparoscopy, 3D laparoscopy, surgical skill, novice

INTRODUCTION

Laparoscopy is a state-of-the-art technique in abdominal surgery clinics today due to the undeniable benefits of its lower invasiveness. A reliable recording of the intraoperative site is essential for successful laparoscopy, and the technical equipment has accordingly improved constantly. Already, the development of high-definition (HD) camera systems with higher resolution, more brightness, and less distortion resulted in measurable technological progress of 2D (two-dimensional) video systems in practice (1). 2D environments were, for a long time, the method of choice, before 3D (three-dimensional) components successively became more established in routine surgery. The first stereoscopic 3D devices were developed in the 1990s, providing a different spatial view of the operation field with improved outcomes for the patient, while the introduction of 4K monitors for 2D laparoscopy with 4-fold higher resolution as compared to 2D/HD led to a further improvement of the monoscopic view. Today, high-resolution 2D or 3D video systems are an integral part of, basically, all modern operating theaters, and clinics currently often use both in parallel.

Experienced surgeons often prefer monoscopic special features to gain a three-dimensional impression despite the lacking stereoscopic view in 2D systems (2), especially if they experience side effects like eye strain, vertigo, or discomfort under 3D vision technologies (3). A stereoscopic view might, nevertheless, be beneficial due to an improved depth perception, and many studies, indeed, demonstrate advantages of 3D over 2D/HD systems, which are reflected in a reduced performance time and lower number of errors in daily clinical practice.

Comparative studies of 2D and 3D laparoscopy already date back to the 1990s (4). Buess et al. showed 1996 an error reduction of 43% and a 32% reduced performance time under 3D as compared to a 2D view (5). While the benefits of 3D environments in practice are evident, the question remains if a costly technical change from 2D to 3D is really required to improve the acquisition of basic laparoscopic skills in a standardized training setting. If the superiority of 3D systems is demonstrable in the learning curve of inexperienced medical students, a direct entry into 3D laparoscopy should be recommended to enable faster integration into a clinical daily routine.

MATERIALS AND METHODS

Sample Size Calculation and Endpoints

In a pilot study using the 2D technique, test persons ($n = 3$) started on average with 224 s in Experiment 1 and ended, on average, at 152 s in Experiment 10.

We defined a 15% reduction in time (23 s) for 3D compared to 2D technique as a meaningful improvement. With an estimated standard deviation of 26 s in the pilot study, a group size of 22 test persons per group is required to achieve a power of 80% by assuming the usual alpha-level of 5%.

For this prospective, randomized controlled study, 45 laparoscopic novices were recruited. All the participants were students of the Brandenburg Medical School Theodor Fontane, the Brandenburg University of Applied Sciences, or other training facilities.

All the participants were surveyed in a questionnaire with respect to gender, wearing of glasses, video gaming frequency, dominant hand or university affiliation, and randomly assigned to 2D ($n = 22$) and 3D ($n = 23$) groups. Only the participants with a normal or corrected-to-normal vision were selected. All the participants completed the tasks using 2D and 3D monitors at the same setting and on the same day.

For this investigation, the Karl Storz SZABO-BERCI-SACKIER laparoscopic box trainer was used, holding a 10-mm camera port and two 5-mm working ports in a triangle position. The technical specifications of the applied imaging system were as follows: 3D video endoscope IMAGE 1 S 3D with TIPCAM 1 S 3D LAP (10-mm diameter, 30° optics); connect module: IMAGE1 S CONNECT and IMAGE1 S 3D-LINK (Karl Storz SE & Co. KG, Tuttlingen, Germany); 32" 3D monitor EJ-MDA32 (Panasonic Canada Inc., Ontario, Canada). The mode change from 2D to 3D was done at the video endoscope.

Performance Task

For our investigations, the standard task "peg transfer" of the laparoscopy boxtrainer "LuebeckToolbox" (6) was used, in which white and blue sleeves in mixed positions have to be sorted according to color in two boxes with a hinged lid. In the beginning, all instruments are placed in the upper left and right corners. Time measurement was started, and the first sleeve was grasped with the instrument in the dominant hand. After opening the lid of the diagonally opposite box with the non-dominant hand, sleeves had to be transferred into the box, followed by closing the lid again. The next sleeve was transferred into the other box with the non-dominant hand in the same manner. Lost sleeves had to be picked up again, and all lids had to be closed before the next sleeve could be transferred. After all sleeves had been color sorted appropriately into the boxes, instruments were brought back into the neutral position (**Figure 1**). Time measurement was stopped and an error log was created. To determine the learning curve, the exercise was carried out 10 times. Performance time and the error rate of the 10 trials were recorded.

Statistical Analysis

Baseline characteristics between participants of the two experimental groups were compared using the Fishers exact test for categorical variables and independent samples *t*-test for age. Normality distribution assumption was checked graphically and by Shapiro–Wilk test for performance times stratified by the laparoscopic group and trial.

Primary endpoints were operation times, and error rates were deemed as secondary endpoints. To analyze operation times, a two-way repeated measurements ANOVA with the effect of trail (that is the repeated measurement factor) and the main effect of

Abbreviations: AIC, Akaikes Information Criterion; 2D, two dimensional; 3D, three dimensional; DFG, German association of research; GLMM, generalized linear mixed model; HD, high definition; RMSA, root-mean squared error.

FIGURE 1 | A practice module "Pack your luggage" of the Luebeck Toolbox: Open-box and sorting sleeves according to color.

laparoscopic condition (2D vs. 3D) was performed. Furthermore, the interaction between condition and trial was entered to assess whether learning curves differ between conditions. Differences in operating times between laparoscopic conditions would result in a significant main effect of that factor. If the participants showed a steeper learning curve in one laparoscopic condition, this would result in a significant interaction effect between time and condition.

Post-hoc tests for the repeated measurement factor were performed using pairwise dependent *t*-tests with Bonferroni–Holm adjustment to control for alpha-failure inflation due to multiple comparisons. In a sensitivity analysis, *post-hoc* comparisons were additionally stratified by laparoscopic condition.

Error rates were described descriptively and compared between laparoscopic conditions by the Mann–Whitney test. To take longitudinal data structure and discrete nature of error counts into account, a generalized linear mixed model (GLMM) with negative binomial residual distribution (due to substantial overdispersion) and log-link was performed. The main effects of laparoscopic condition and repeated measurement and interaction between both were entered as predictors. Model performance was assessed by Akaikes Information Criterion (AIC), root-mean-squared error (RMSA), and pseudo-R^2 (Nagelkerke). A hypothesis for effects on error rates was analogous with operation times. Trial effects in the GLMM were reported by exponentiated model coefficients and their 95% confidence intervals. For the trial factor, the first trial was set as the reference category. For a graphical presentation of error rates, displaying mean or median values is inadequate, and would result in substantial loss of information. Therefore, failure rates in each trial were depicted by density plots (also known as violin plots), stratified by laparoscopic condition. Solid and dashed lines in the plot represent median and lower/upper quartiles, respectively. The mean error rate in each trial is depicted by the black dot within the violin.

According to the training instructions (http://www.luebeck-toolbox.com/training.html), two types of errors were recorded: dropping the sleeve between grasping and placement in the box (drop sleeve errors) and incomplete closure of the box (open box errors). The number of errors was compared for each type between the two laparoscopic modes using the Mann–Whitney test.

Data were stored in Microsoft Excel, and analyses were performed with R (version 4.1.1, R Foundation for Statistical Computing, Vienna). Values of $p < 0.05$ were considered statistically significant.

TABLE 1 | Background of the participants.

	2D group ($n = 22$)	3D group ($n = 23$)	*P*-value
Gender (male/female)	14:8	15:8	0.912
Right-/left-hander	21:1	20:3	0.608
Spectacle wearer (yes/no)	10:12	11:12	0.873
Prospective career in medicine/technology/other	9:6:7	9:8:6	0.963
Active video gamer Regular/past/no	7:5:10	11:3:9	0.492

Statement of Ethics

Written informed consent was obtained from those who agreed to participate. The article is excempted from ethical committee approval since that has not been necessary according to recommendation of the DFG (German association of research—"Deutsche Forschungsgesellschaft"). Neither there have been any risks during the performance task nor any unclear examinations or operations at the patients.

RESULTS

The age range of the participants was 18–35 years, with a mean age of 24. ± 3.3 years in the 2D group and 23.4 ± 2.9 years in the 3D group ($p = 0.83$). Both groups did not significantly differ with respect to gender, wearing of glasses, frequency of video gaming, dominant hand, and university affiliation (**Table 1**). The mean values of time required to perform each of the 10 test runs showed no significant difference between the 2D/HD and 3D groups (**Figure 2**).

Operating Times

Operation times were reasonably normally distributed; however, the Mauchly test revealed a violation of the sphericity assumption ($p < 0.001$) so that a Greenhouse–Geisser correction was applied ($\varepsilon_{GG} = 0.428$). The ANOVA showed a highly significant and strong effect of time [$F_{(3.85,161.7)} = 155.9$, $p < 0.001$, $\eta_g^2 = 0.554$]. With mean operating times of 251 s (SD = 67.9 s) in the first trial dropping to 123 s (SD = 23.9 s) in the 10th trial. The between-subject main effect of the laparoscopic condition failed to reach significance [$F_{(1,42)} = 2.79$, $p = 0.10$, $\eta_g^2 = 0.042$]. However, descriptively comparing operation times between laparoscopic conditions at each single trial showed slightly shorter operation times in the 3D condition for each and every comparison (see **Figure 2**). The interaction between laparoscopic condition and trial was not significant all [$F_{(3.85,161.7)} = 0.342$, $p = 0.84$, $\eta_g^2 = 0.003$].

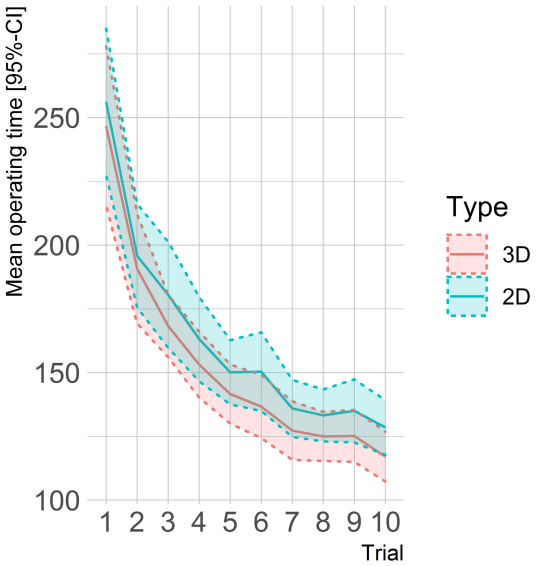

FIGURE 2 | Mean operating time and 95% confidence bands.

As the main effect of laparoscopic condition was not significant, *post-hoc* tests of the trial effect on operation time were assessed in a pooled analysis. Adjusted pairwise *t*-tests showed no substantial time improvements from the 7th trial onward ($p_{\text{adjusted}} > 0.11$, with the exception of a significant difference between 7th and 10th trials, $p_{\text{adjusted}} = 0.004$). Additionally, we performed the *post-hoc* tests stratified by laparoscopic condition, mainly resulting in the same time effects as in the pooled analysis.

Error Rates

Distribution of errors (see **Figure 3**), within each trial and across all trials, was heavily right-skewed. Within each trial, the number of errors ranges between 0 and 5, with a median of 0 errors (IQR: 0–1). The overall number of errors, summarized across all trials, ranges between 1 and 24, with a median of 6 (IQR: 3–6). Stratified by laparoscopic condition, the participants showed a median of 5.5 errors (IQR: 3.3–7.8) in the 2D condition and 6. errors (IQR: 3–12.5) in the 3D condition, indicating no significant differences between groups ($p_{\text{MW-Test}} = 0.72$, $d = 0.11$).

The GLMM ($AIC = 1{,}059$, $RMSE = 1.02$, $R^2_{\text{Nagelkerke}} = 0.17$) only showed a significant time effect ($p < 0.001$). Neither laparoscopic condition ($\beta = -0.15$, $SE = 0.42$, $p = 0.72$) nor the interaction between condition and trial ($p = 0.83$) was significantly associated with error rates. A significant error reduction (compared to the first trial) was observed from the 5th trial onward [$b_{5.trial} = 0.32$, 95%-CI: (0.14, 0.67), with a minimum failure rate in the 7th trial ($b_{7.\text{trial}} = 0.16$, 95%-CI: (0.06, 0.39)].

Two types of errors (drop sleeve errors and open box errors) were recorded. The error rate of the 10 test runs is depicted in **Figure 4**. Because error types did not differ significantly ($p = 0.0715$) between the laparoscopic modes, the errors were subsequently analyzed together.

DISCUSSION

The current state-of-the art operating theaters are 3D/HD, 2D/HD, and 2D/4K systems, whereby 4K resolution monitors introduced a few years ago definitely brought about an improvement of the visual orientation at the operation site (7). Many studies in the past comparing the surgical performance of these different visualization systems, however, yielded quite heterogeneous results, which are, apparently, also dependent on the laparoscopic tasks to be performed and/or the skills of the respective surgeon.

A systematic review by Sørensen et al. in 2016 assessing 31 randomized studies demonstrated a certain advantage of 3D laparoscopy over 2D/HD in primarily simulated settings (3). The operating time under 3D vision was significantly reduced in 71% of the randomized controlled trials, the error rate is 63%. A systematic review of laparoscopic cholecystectomy by Komaei et al. showed a significant advantage of 3D laparoscopy in 60% with respect to operating time (8), while two recent clinical studies comparing 2D/HD vs. 3D laparoscopic right hemicolectomy detected no significant difference with respect to intra- and postoperative complications and confirm equivalent patient outcomes (9, 10). When interpreting the results for the different technologies, many factors besides the technological improvements over the years have been taken into account, e.g., if the participants in these studies were laparoscopic novices or experienced surgeons. Harada et al. reported that expert laparoscopic surgeons, despite very good experiences with 3D/HD systems, still see an advantage in the 2D/4K technology for tasks in narrow spaces (7).

Our study was mainly aimed to assess and to question previous study findings as an essential part of the research in this field. The replication of data increases the acceptance of previous studies but also promotes critical discussion as a part of a modern error culture. The common goal is the optimal training of young surgeons. Which practical implementations should we draw to provide an efficient clinical training for future surgeons inexperienced in laparoscopic techniques? And are the frequently stated advantages of 3D technologies so convincing that 2D technologies should not be used in the future, even though this would require a complete and costly exchange of the clinical equipment? To answer these questions, our study was accordingly limited to laparoscopic novices in a standardized box trainer setting.

The Luebeck Toolbox is an established training tool for basic minimally invasive surgery skills (11). The participants were asked to perform a simple test, the "peg transfer" of the "Luebeck Toolbox" in 10 replicates. Measurements were operating time and number of errors, both target criteria in the comparison of 3D and 2D laparoscopy for everyday clinical practice. Mean values of test times did not significantly differ between 2D/HD and 3D groups. In the first test runs, a similar learning curve with significance ($p < 0.05$) was demonstrable for both groups. From

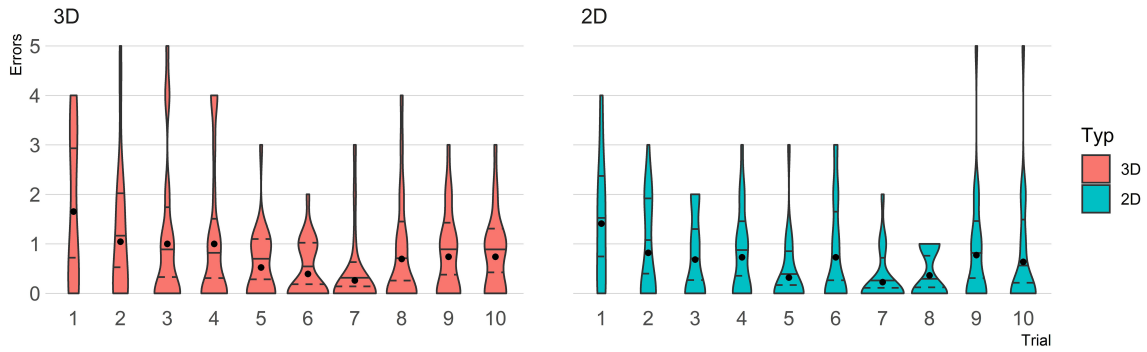

FIGURE 3 | A density plot of error rates.

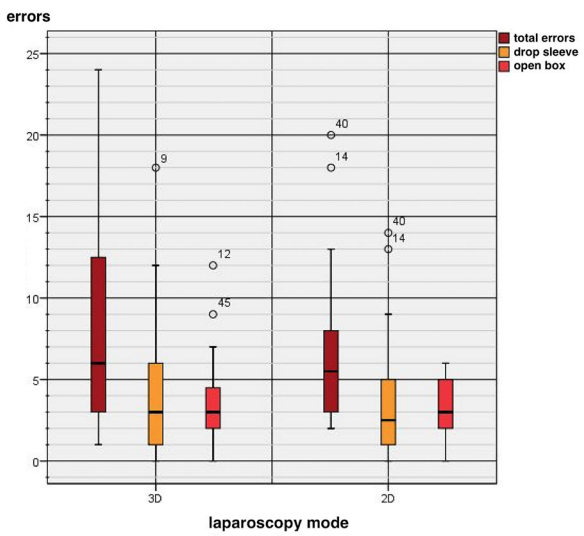

FIGURE 4 | Comparison between two-dimensional (2D) and three-dimensional (3D) systems regarding technical errors.

the 5th attempt in the 2D group and from the 6th attempt in the 3D group onward, no significant difference could be detected anymore. In pairwise comparisons, the operating time was no longer significantly reduced after the 7th attempt. With respect to the error rate, no significant difference between the 2D and 3D groups was observed.

Two types of error (drop sleeve errors and open box errors) did not differ significantly between the laparoscopic modes.

Our results are, partially, in contrast to other studies, thus confirming the divergence of current studies, comparing the benefits of 3D vs. 2D techniques with respect to a reduction of performance time and better performance. Poudel et al. demonstrated in a similar investigation with 44 students per group a significant advantage of the 3D group in operation time and the error rate (12). A comparable result was obtained in a study with 50 novices by Schoenthaler et al. (13). Despite the dominance of 3D laparoscopy in many studies, one-third of the studies found no significant differences in 2D applications, and, apparently, many medical students experience difficulties when switching to 2D devices after having been trained in 3D environments, which is reflected by poorer performance (12, 14). Thomaschewski et al. reported comparable learning curves in confined spaces for 3D and 2D/4K resolution (15), indicating that both systems are equally suited.

The findings of this study demonstrate that laparoscopy novices perform simple tasks without any differences between 2D/HD and 3D techniques concerning learning speed and the error rate. We currently see no need to exchange existing 2D equipment in clinics for training purposes, especially if an upgrade to 2D/4K resolution is possible. For more challenging tasks in simulated settings or the improvement of surgical performance in daily clinical practice (which was not assessed here), 3D systems may yield better results than 2D/HD systems.

Strengths and Limitations of the Study

Our study has a number of important strengths. The study participants were medical students who were prepared for practical surgical activities with this exercise according to their study progress. Therefore, the validity of the generalization of the results to other medical students with this level of training can be assumed. The clear and standardized execution of the experiment by means of the scientifically evaluated Luebeck toolbox provides a high degree of objectivity, validity, and comparability. The replication of data increases the acceptance of previous studies, but also promotes critical discussion as a part of a modern error culture.

Finally, our study was a non-industry-funded trial. Our study and the results have scientific integrity and independence. Probst et al. show that studies with industry funding lead to exaggerated positive reporting of outcomes. They reported in the analysis of

165 randomized controlled trials about a positive outcome in 76.5% of industry-funded trials and in 38.% of non-industry-funded trials (16).

The following are limitations of the study. It is unclear whether results of our study using Luebeck toolbox are transferable to the operation room. Our students were novices with no experience in laparoscopic surgery. It is questionable whether our results are transferable to experienced surgeons.

Our study design included 10 trials to record the performance time and the error rate. We performed a sample size calculation and endpoints. In our pilot study using the 2D technique, test persons ($n = 3$) started, on average, with 224 s in Experiment 1 and ended, on average, at 152 s in Experiment 10.

We defined a 15% reduction in time (23 s) for 3D compared to 2D technique as a meaningful improvement. With an estimated standard deviation of 26 s in the pilot study, a group size of 22 test persons is required to achieve a power of 80% by assuming the usual alpha level of 5%. Laubert et al. reported a median of approximately 32 repetitions to reach expert performance (experienced surgeons with a least 500 minimally invasive surgeries) of 72 s. Therefore, it cannot be ruled out that continuing the task might potentially result in a significant difference in later trials. However, the most important learning curve differences were reported in the early trials (11).

CONCLUSIONS

The results of our study with laparoscopically inexperienced students revealed no significant differences with respect to performance time and the error rate between 2D/HD and 3D technology for a simple standardized task. Both techniques are thus equally suited for the training of future surgeons, and we see no need to exchange existing 2D systems in clinics. With its critical analysis, the study provides a knowledge gain on this topic, supports a differentiated view, and reflects the daily praxis in German clinics where both technologies successfully exist in parallel.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS, CD, AG, CH, and RM contributed to conception or design of the work, data analysis and interpretation, critically revised the article, and finally approved the version to be published. CD, AG, and CH contributed to data collection. MS, CD, and RM drafted the article. All authors contributed to the article and approved the submitted version.

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Facilitating the Adoption and Evolution of Digital Technologies Through Re-conceptualization

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Background: The NHS has been making steps toward greater efficiency and cutting costs to maintain quality of care despite constraints, but without innovation the NHS will not be able to meet its increasing financial demands. The purpose of this article is to analyse a single potentially transformative technology's path of adoption in the NHS [3D printing (3DP)].

Methods: Analysis of 3DP and its current value propositions. Re-conceptualization of the technology to gain insights into these value propositions and identify the capabilities it may provide. Analysis of previous business models to identify where this value is not fully captured and development of a new business model, followed by exploration of benefits and potential limitations of this new model.

Results: 3D printing applications can be broadly categorized into anatomical modeling, implants, and tools. Conceptualizing 3D imaging using the layered architecture model suggests the potential of 3DP to evolve the current imaging and modeling infrastructure of the NHS, and as such should be adopted to facilitate this potential.

Conclusion: 3D printing is an innovation with large potential for generativity, and it is important that it is integrated at a level that could both stimulate and communicate its benefits. Re-conceptualization identified a backbone within the NHS that could facilitate it as a point of entry, and the most successful installations have been through this channel. However, progress on the frontier is currently limited by both physical and organizational boundaries, the resolution of which is paramount for the current and future success of this technology.

Keywords: 3D printing, imaging, innovation, healthcare system, layered modular architecture

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INTRODUCTION

The NHS is a publicly funded organization responsible for maintaining the physical and mental wellbeing of the UK population. Thirteen percent of all jobs in the UK are in the health and care sector (1), a large fraction of which are encompassed by the NHS. In order for it to perform at such size and scope, a bureaucratic structure has been established, resulting in structural inertia and

barriers to the development and implementation of new technology. This resistance is observed to a greater extent in the NHS than its international equivalents (2), likely due to being compounded by a continuous increase in financial constraint. The NHS has been making steps toward greater efficiency and cutting costs to maintain quality of care despite constraints, but without innovation the NHS will not be able to meet its increasing financial demands (2). As such, addressing its uptake of digital technology is of paramount importance to stimulate innovation and ensure its continued survival.

We analyse a single potentially transformative technology's path of adoption in the NHS [3D printing (3DP)]. Following an outline of the current value propositions, we present a re-conceptualized view of 3DP to gain insights into these value propositions and identify the capabilities it may provide. Following this we analyse previous business models to identify where this value is not fully captured. Finally, we present and explore a new business model to identify its benefits and potential limitations.

3D Printing in Healthcare, the Point of Entry

3D printing, a type of additive manufacturing, is the process of translating computer aided design models to produce 3D objects through the addition of material layer-by-layer (3). This definition highlights the duality of 3DP as both a digital and physical innovation, being the software that translates 3D models into commands for the printing apparatus and as the apparatus itself, with Polykarpou et al. (4) attributing this to Jones and Rose's (5) bridging of the digital and physical domains. As such, a more expanded view of 3DP (**Figure 1**) is a process that derives from a sequence of prior innovations within the digital domain, namely scanning and imaging.

In the context of medicine, scanning and imaging have fully penetrated the NHS, with extensive use of X-rays, ultrasound scans, and magnetic resonance imaging amongst others to create digital models of patients. Bailey et al. (6) highlights the benefits of virtual modeling, enabling virtual teams and remote control, e.g., radiology departments diagnosing patients and advising procedure without examination, as well as simulation, such as a surgery team planning an operation in advance by interacting with the model, as well as use in educating medical students (7). Alongside the benefits come limitations. Practitioners need to be trained to interpret the scan as well as identify where it may not be an accurate representation of reality. Furthermore, they only have access to the digital information provided. Zuboff (8) highlighted the struggles of carrying out this "informated work," an observation which despite improvements in training and modeling, remains present today. Beyond professional use, another implication is that for the patient, who likely has little skill in interpreting scans, thus contributing to the continuous ethical struggle of acquiring true patient consent for procedures and prescriptions. 3D printing has been introduced to healthcare on the foundation of 3D imaging in part as a means of reducing the limitations of virtual models as well as to introduce new capabilities.

VALUE PROPOSITIONS OF 3D PRINTING

Despite an enormous variety of current applications for 3DP, most can be categorized into three groups: anatomical modeling, implants and tools. The proposed benefits of all these vary, however are encompassed by four main categories: clinical application, patient orientation, education, and logistical improvement.

3D Modeling has been introduced as a means to counteract the limitations of digitized work whilst preserving its benefits. The printing of previously digitized models minimizes the degree of "informated work" required, aiding doctors in planning complex surgery (9), whilst increasing the range of remote planning. The proposed benefit is a more efficient use of operating time with cost reduction implications (10, 11). The same principle has been applied to educating patients, aiding in obtaining informed consent (9), as well as in clinical training. However, despite a vast array of articles detailing the surgical application of these benefits to their own niches (12), few have focused on communicating their financial value.

3D printing implants partly offer value through similar means. The development of patient specific surgical guides for implants in maxillofacial surgery have been shown to reduce operation times, with international data suggesting 33% reductions and £1,500 equivalent savings per operation (13). The value propositions of the implants themselves are mostly linked to aesthetic functionality, longevity and simplicity in procedure. Whilst the latter two can be linked to financial benefit through costs of replacements and errors, the tangible value of marginally improved aesthetic outcomes to a hospital is less direct. Social factors influence individual's decisions under bounded rationality (14), exemplified by IT investments improving hospital reputation through media attention (15), which in turn carries benefit in the form of referral, opportunities, funding, etc. Along similar lines, patient orientated products such as implants and 3D models for communication serve to improve the reputational value of the hospital that adopts them.

Newer implants explore the use of a 3D-printed mesh with cell-culture injection, as well as the direct printing of cell layers in the form of "bio-inks." These have been used to make patient specific tissues such as skin (16), larger tissues such as knee menisci (17) and, though still in its infancy, organ printing such as ovaries. If clinical viability were established however, the logistical and reputational advantage of donor waiting-list management and transportation cost-saving would be considerable.

The proposed advantages of tools vary with the level of integration. At the procedural level, custom tools could enable better surgical outcomes, malfunction reduction, and cost savings in atypical anatomical situations e.g., laparoscopic trocars for children (18).

On the hospital level, there is an opportunity for hospital equipment design, customization, and optimization for various efficiency improvements (4) which could be amplified on an NHS scale with plaformization, amplifying innovation through the generativity a distributed innovation network provides (19). This maneuver has the possibility of generating a threat of vertical

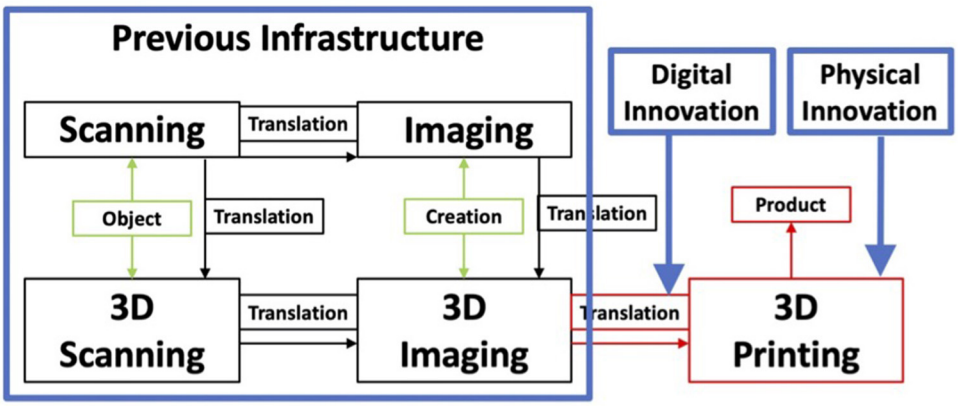

FIGURE 1 | 3D printing as development of its predecessors, and segmentation according to observations by Polykarpou et al. (4).

integration to NHS suppliers, increasing the buyer power of the NHS (20), potentially driving down the cost of externally sourced equipment.

DISCUSSION

Re-conceptualization of 3D Printing

Our conceptualization of 3DP is a development of Polykarpou et al. (4), which highlighted the bridging of the physical and digital domains, but also separately emphasized the creation of a physical domain and reliance on a previous infrastructure. These three separate observations were combined to develop **Figure 1**.

However, analyzing the value propositions of 3DP in healthcare has shown a huge variation in applications, all stemming from an initial process innovation. This presents another key feature of 3DP, its ability to facilitate generativity, which may not be emphasized enough in previous conceptualizations. The origin of this generativity can be explained by integrating 3DP with its precursor (**Figure 2**).

Conceptualizing 3D imaging using the layered architecture model suggests a large degree of modularity through independent layer development. Layered modular architectures possess the intrinsic capability of stimulating generativity (21), evidenced by the plethora of applications of 3D imaging through innovations in all layers. If 3DP is conceptualized as an innovation in the service and device layers of 3D Imaging's architecture, then it can be conceptualized as a product of the architecture's modularity, and so be subject to the same modularity, thus explaining the origin of the generativity observed so far. This conceptualization shows the potential of 3DP to evolve the current imaging and modeling infrastructure of the NHS, and as such should be adopted to facilitate this potential. However, this is not fully appreciated in previous adoption models.

Traditional Model of Adoption and Diffusion

Gartner's Hype cycle for Healthcare Providers, 2018 (22) segments 3DP into the products of its generativity. What this suggests is that 3DP is not viewed as a singular entity to be adopted but rather as a collection of separate innovations to be chosen and developed independently of each other.

The structure of the NHS encourages further segmentation, with the categories above further categorized according to niches. This is due to the NHS being highly decentralized with control over hospital funding in individual areas largely conducted by 135 Clinical Commissioning Groups (CCGs). The variation in demography across the UK results in a heterogeneity of need for different innovations between and within CCGs, encouraging innovation to be managed in niches where it is most needed. In theory, this makes adoption of technology easier, and has enabled many improvements since its introduction in 2012, an example being improved mental health care[1]. However, the large degree of organizational complexity that decentralization has brought (23) has increased the number of barriers through which knowledge would need to be exchanged, as well as amplifying the "dysfunctions" in knowledge communication across these barriers. A particular disruption of relevance is "audience learning" (24), highlighted practically as the establishment of a CCG "fortress mentality" (25), where providers prioritize their own area pressures over collaborating with other providers for greater goals, reducing the diffusion of knowledge, and by extension, innovation.

For 3DP in particular, a hospital identifies its individual needs and is provided 3DP for use in a niche that needs addressing, with a simultaneous clinical study for efficacy. However, whilst evidence of efficacy is considerable, the overall 3DP-process is often slow (26), limiting the number of patients it can help in a given time period. Furthermore, evidence of financial benefit to hospitals is scarce, and with a lack of use in surrounding departments to demonstrate further application and cost justification, the technology is not given the opportunity to grow due to concern over financial risk. Attempts to address the issues brought up are also slow. In 3D modeling, the bottleneck is

[1] Available online at: http://445oon4dhpii7gjvs2jih81q.wpengine.netdna-cdn.com/wp-content/uploads/2016/09/NHSCC_Support-from-the-start_final.pdf (accessed August 03, 2019).

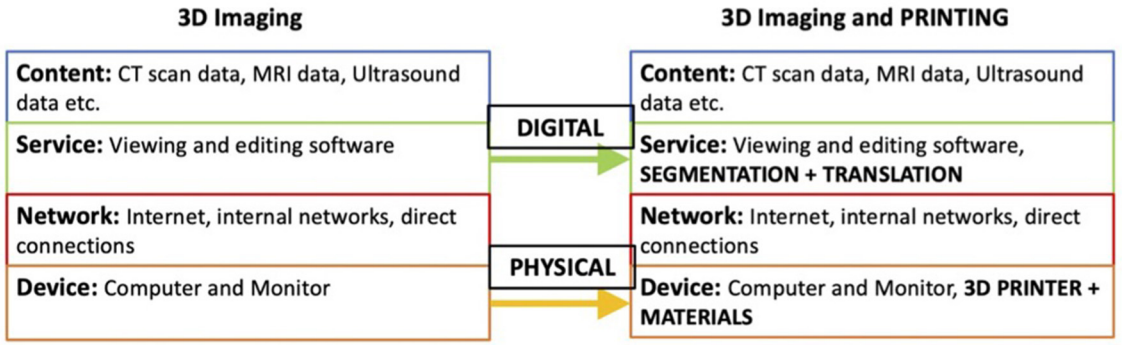

FIGURE 2 | Innovation in the service and device layers of 3D Imaging's layered modular architecture.

the need to segment scans into specific sections for printing. This is currently done manually, taking up to 6 h. Solutions involving the hiring of technicians (27) and segmentation though machine learning have been proposed (28), however without sufficient financial evidence to justify a technician or sufficient past cases to serve as a source of information for learning, optimization to increase efficiency cannot occur.

Overall, the traditional approach prevents 3DP from integrating with and building on its previous infrastructure, thus failing to communicate all of its value, resulting in a decreased interdepartmental reach as well as reduced process improvement. In essence this is a case of "role constrained learning" amplified by the bureaucratic inflexibility of the NHS with regards to changing structure to facilitate evolution. This in turn has contributed to its lack of diffusion (learning under ambiguity), with much of the diffusion that does occur due to acknowledgment of the reputational value of digital innovation. Adoption for the sake of reputation however is usually superficial, thus expressing the same limitations in growth potential as the pioneers, and consequently is not developed further.

Novel Adoption Approach

For 3DP's integration into the NHS to be successful, a business model would not only need to firstly facilitate 3DP's potential for generativity, but also present a value proposition that attends to the dysfunctions in knowledge transfer created by the structure of the NHS. These two are not mutually exclusive, as generativity is itself a value which can be communicated.

Radiology (imaging) exists interdepartmentally in many hospital settings, enabling multiple parties to benefit within the hospital. If 3DP lies on the same modular architecture, and is also integrated at such an interdepartmental level, it would be poised to evolve to benefit all departments in a similar manner. If all departments were provided with 3DP, setting up a distributed network, generativity would theoretically be maximized.

However, a successful business model creates, delivers and captures value (29), and in a hospital setting value exists on two levels, one for a subgroup of patients, the other for all patients under the hospitals care. Therefore, a medical business model has the added requirement of balancing one with the other. A 3DP installation would be costly and demand organizational shift, the consequences of which may affect patient care in other areas. As such, the marginal benefit (in terms of delivering value and stimulating generativity) of adding a printer must be compared to its cost. Interdepartmentalization not only stimulates generativity (creating value), but also increases the size of the patient subgroup (delivering more value), thus enabling the perceived marginal benefit of installing a small number of 3DP's to rise above their cost. Perceived cost to hospitals has decreased further from a more evolved study of 3DP's benefits, with much change in the tone of systematic reviews from Diment et al. (12) showing an uncertainty of wider application due to lack of non-anecdotal evidence, to Emile and Wexner (30) amongst others clarifying such uncertainty. Whilst this still may not communicate much financial value, based on reports from medical professionals, it communicates clinical efficacy to surrounding medical professionals, reducing "role constrained learning" and decreasing the projected costs of organizational resistance, as well as improving hospital reputation.

However, despite the changes in perceived benefit from the re-conceptualization and perceived cost from research, hospitals can often only justify the purchase of a few printers, and thus the service installed, whilst interdepartmental, is centralized, a compromise that maximizes generativity whilst minimizing cost. This is evidenced by Cambridge University Hospitals' (CUH) successful centralized 3DP service (27). Cambridge University Hospital takes the reunification of 3DP further, constructing 3D models, tools, and implants interdepartmentally, further increasing potential generativity and the size of the patient subgroup.

Limitations of a Centralized 3D Printing Department

3D Printing requires the entry of new staff, materials and devices whilst also integrating with hospital infrastructure. It also requires skills independent of other roles within healthcare, such as an understanding the 3DP process, segmentation, and materials (27). Most 3DP hubs hire specialized technicians to fill these knowledge demands, creating differences in knowledge (explicit and tacit) between technicians and hospital staff. This creates a new boundary

of knowledge and dependence, increasing the complexity of technician interactions (31) and potentially limiting productivity if this complexity cannot be overcome. With centralized, interdepartmental 3DP services these boundaries exist between all the departments spanned, amplifying complexity further. Barrett et al. (32) highlights how even a three-way interaction involving technicians for new hospital equipment can create damaging relationships, through neglect and strain. There is direct 3DP evidence of this in Polykarpou et al. (4) where failure to communicate across the pragmatic boundaries (33) between the new technicians and the incumbent engineers resulted in neglect toward the engineers and strain in the relationship between the two, ultimately contributing to a halt of the expansion of the 3DP department into workshop space under protest of the engineers.

3D printing's properties as a physical innovation adds another layer of complexity to its adoption. This is demonstrated most obviously through an interdepartmental positioning to stimulate generativity, but also logistically with the identification of areas to be repurposed for its implementation. Without sufficient attention to the relative importance of place to the relevant parties involved, growth may be limited (4).

Resolving organizational issues as they arise is a challenge, however there are a few methods to aid in resolution. Firstly, another contributor to complexity at boundary relations is novelty. If 3DP is conceptualized and integrated in a similar manner to its predecessor—radiology, then the novelty of the interaction may be reduced. However, there is a clear difference in the skills required to carry out the two functions, and as 3DP grows it will need to interact with departments previously alien to radiology or with renewed importance, such as materials procurement and surgical teams. Novelty is therefore still expected. Another potential means of resolving barriers is with boundary spanners. Given the context of the NHS and the requirement of boundary spanners to be knowledgeable and respected by both communities (34), prime targets would be the passionate physicians who attempted to integrate 3DP in the traditional approach, displaying sufficient knowledge in both peripheries. Alternatively, an increased focus on educating young doctors of the benefits of 3DP may create boundary spanners for the future. As 3DP becomes increasingly relevant with new discoveries and improvements such as the advent of organ printing, overcoming these organizational boundaries will be crucial to their implementation and effect. Should they be addressed and solved at a time of relative simplicity, the core infrastructure of the NHS will be more accommodating of the discoveries of the future.

CONCLUSION

We have analyzed a case of technological implementation in the NHS where growth was limited by the channel of introduction. 3D printing is an example of an innovation with large potential for generativity, and it was important that it was integrated at a level that could both stimulate and communicate its benefits. Re-conceptualization identified a backbone within the NHS that could facilitate it as a point of entry, and the most successful installations have been through this channel. However, progress on the frontier is currently limited by both physical and organizational boundaries, the resolution of which is paramount for the current and future success of the innovation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

NT: conception, design of work, review, analysis, interpretation of findings, drafting, and revision of manuscript. RR-S: conception of work, interpretation of findings, drafting, and revision of manuscript. GP and CK: interpretation of finding and revision of manuscript. All authors have provided approval for publication and agree to be accountable for all aspects of the work.

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REVIEW
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Impact of Early Oral Feeding on Nasogastric Tube Reinsertion After Elective Colorectal Surgery: A Systematic Review and Meta-Analysis

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Background: Colorectal cancer is a common malignant tumor appearing in the gastrointestinal tract. Surgical resection is recognized as the best means to improve patient survival. However, it is controversial whether early oral feeding (EOF) after elective colorectal resection demonstrates safety and efficacy in concerned clinical outcomes.

Methods: We searched PubMed, Embase, Cochrane Library, and CNKI from inception to September 2021. Two authors independently screened the retrieved records and extracted data. EOF was defined as feeding within 24 h after surgery, while traditional oral feeding (TOF) was defined as feeding that started after the gastrointestinal flatus or ileus was resolved. The primary outcome was nasogastric tube insertion, and the secondary outcomes were the length of hospital stay and total complications. Categorical data were combined using odds ratio (OR), and continuous data were combined using mean difference (MD).

Results: We screened 10 studies from 34 records after full-text reading, with 1,199 patients included in the analysis. Nasogastric tube reinsertion (OR 1.69; 95% CI 1.08 to 2.64, p=0.02) was more frequent in the EOF group, and older ages (>60 years) were associated with higher risk of nasogastric tube reinsertion (OR 2.05; 95% CI 1.05 to 3.99, $p = 0.04$). Reduced length of hospital stay (MD −1.76; 95% CI −2.32 to −1.21; p<0.01) and the rate of total complications (OR 0.49; 95% CI 0.37 to 0.65, p<0.01) were observed in EOF compared with TOF.

Conclusions: EOF was safe and effective for patients undergoing elective colorectal surgery, but the higher rate of nasogastric tube reinsertion compared with TOF should not be ignored.

Keywords: early oral feeding, elective colorectal surgery, nasogastric tube reinsertion, systematic review, meta-analysis

INTRODUCTION

Colorectal cancer occupies approximately 10% of all diagnosed cancers, significantly contributing to cancer-related deaths worldwide (1). Although early colorectal cancers could be appropriately managed through endoscopic resection techniques (safer and less expensive than surgery), many patients with confirmed colorectal cancer are still referred for surgery, combined with chemoradiotherapy (2). However, the complications following traditional colorectal cancer surgery occur in 20–30% of cases, with an average postoperative hospital stay of 8–12 days (3).

A multimodal rehabilitation strategy was initiated to reduce the stress of surgery and then developed into Enhanced Recovery After Surgery (ERAS). The ERAS programs have been shown to be safe and beneficial in patients undergoing colectomy, gastrectomy, pancreatic resections, pelvic surgery, etc., and become a standard in preadmission, preoperative, intraoperative, and postoperative periods to not only reduce patients' complications and enhance fast recovery but also save public resources (4, 5). A reasonable feeding protocol is considered an effective way to reduce the length of hospital stay, despite sometimes being identified as a potential factor triggering postoperative complications. In 2017, the ERAS Study Group, which was established in 2001, recommended early intake of oral fluids and solids—a type of early oral feeding (EOF)—to support energy and protein supply and reduce starvation-induced insulin resistance (6).

In past decades, the passage of flatus or bowel movements, which signals the resolution of postoperative ileus, indicates that starting an oral diet is safe. Recent studies, however, question traditional oral feeding (TOF) by indicating that the routine use of a nasogastric tube (NGT) after elective colorectal surgery, which is used in decompression of the gastrointestinal tract and prevention of pulmonary complications, may not be necessary (7–9). With its advantage of improving prognosis without obvious adverse events, EOF was introduced for upper gastrointestinal surgery and rapidly extended to other surgeries (10). However, owing to not meeting the energy target requirement, many of the patients had to receive NGT reinsertion. Therefore, it is necessary to prove the EOF protocol as safe and feasible to implement by clinicians with regards to LOS, postoperative complications, and NGT reinsertion.

The present study aimed to conduct a systematic review and meta-analysis, evaluating the associations between the timing of oral intake and length of hospital stay or postoperative complications after colorectal surgery. Besides, the specific objective was to explore NGT reinsertion by subgroup analysis considering distinct ages.

METHODS

Selection Criteria

The inclusion and exclusion criteria were determined before performing the study. Studies were considered eligible when: (1) The type of feeding was oral, in which EOF was defined as feeding within 24 h after surgery while TOF was defined as feeding that started after the gastrointestinal flatus or ileus was resolved, (2) the data of NGT reinsertion after elective colorectal surgery were provided, (3) studies were completed before September 2021 with a structured dataset. Studies were excluded for involving a rapid rehabilitation program transcending EOF or TOF. We did not limit the age and sex in these studies as long as there were no severe complications before surgery.

Two reviewers independently screened the eligibility of retrieved articles. Disagreement in study selection was resolved by group discussion and arbitrated by a third reviewer.

Search Methods

Databases including PubMed, Embase, Cochrane Library, and CNKI were searched from the earliest datasets of each to September 2021. There was no language restriction. Review articles were manually searched to identify additional studies. Article titles and abstracts were screened, and full texts were reviewed independently by two reviewers. The search string used the following keywords and was modified for each: ("colorectal surgery OR colorectal resection" [MeSH]) AND ("oral intake OR oral feeding" [MeSH]) AND ("nasogastric tube reinsertion" [MeSH]).

Data Extraction and Outcomes

Two reviewers independently reviewed selected studies and extracted data; once discrepancies appeared, reviewers discussed and resolved them through repeatedly referring to the original articles. We attempted to contact the study authors for additional information when any significant information was missed.

Primary outcome was nasogastric tube reinsertion. Secondary outcome measures included: (1) length of hospital stay and (2) total postoperative complications. All outcomes mattered clinically in the context of elective colorectal surgery. We also conducted a subgroup analysis of the data on NGT reinsertion by distinct ages.

Assessment of Risk of Bias

Two review authors independently evaluated the risk of bias for each study, using the revised risk of bias tool (RoB 2.0). We judged each potential source of bias as high, low, or some concerns, using the criteria for the following domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result.

Data Analysis

We selected the RevMan 5.3 software from Cochrane Collaboration Network to conduct a meta-analysis. Odds ratio (OR) and weighted mean difference (WMD) were used for dichotomous and continuous outcomes, respectively. Both datasets were presented by a 95% confidence interval (CI). Before the meta-analysis, we evaluated potential heterogeneity among the included studies in two steps. First, we checked whether the studies adopted similar designs by examining the participants included, interventions and controls used, and the outcomes, to ensure that the studies were methodologically and clinically homogeneous. The statistical heterogeneity was explored using I^2 statistics. We recognized I^2<50% as low and I^2>50% as high heterogeneity among the selected studies. The causes of

heterogeneity should be analyzed by sensitivity analyses. We conducted a subgroup analysis of patients aged over 60 vs. <60 (referring to the age in EOF) through the mean ages reported in the articles, and another subgroup analysis was performed for major complications vs. minor complications.

RESULTS

Characteristics of Studies

A total of 10 records were identified from PubMed, Cochrane Library, Embase, and CNKI. A total of 759 studies remained after excluding duplicate records. Overall, 34 studies remained after screening titles and abstracts. The remaining 10 studies were screened for quantitative synthesis by reading full texts (**Figure 1**). There was no limitation in language. Only randomized controlled trials (RCTs) were included. The selected trials included a total of 10 studies and 1,199 patients. Among the included 10 studies from 1995 to 2013, four studies involved patients over 60 years in the EOF group and six <60 years. The site of diagnoses, type of surgery, feeding time, age, and gender are listed in **Table 1**. Five studies were classified as low risk of bias, and the other five studies were classified with some concerns (**Supplementary Figure 1**).

Description of Results

NGT Reinsertion

All data in the selected studies were presented in forest plots. We found that the NGT reinsertion rate was higher in the EOF group than in the TOF group (odds ratio [OR] 1.689; 95% confidence interval [CI] 1.08–2.64; $p = 0.02$; $I^2 = 0\%$) (**Figure 2**). This result showed a significant difference between EOF/TOF and NGT reinsertion after elective colorectal surgery. In addition, subgroup analysis was performed to explore the different effects of oral intake patterns in distinct ages.

Subgroup Analysis

There were four studies involving 677 patients with mean ages over 60 and 522 patients with mean ages <60. EOF was 2.05-fold more likely to be associated with an NGT reinsertion than TOF with low heterogeneity (OR 2.05; 95% CI 1.05 to 3.99; p=0.04; I^2 = 0%). No significant difference was found in regard to the NGT reinsertion between EOF and TOF in the group <60 years old (OR 1.44; 95% CI 0.79 to 2.63; $p = 0.24$; $I^2 = 0\%$) (**Figure 3**).

Length of Stay

Nine of ten studies provided the data of LOS and demonstrated significant heterogeneity (WMD −1.76; 95% CI −2.32 to −1.21; p<0.01; $I^2 = 96\%$). Given that LOS varied in the included studies,

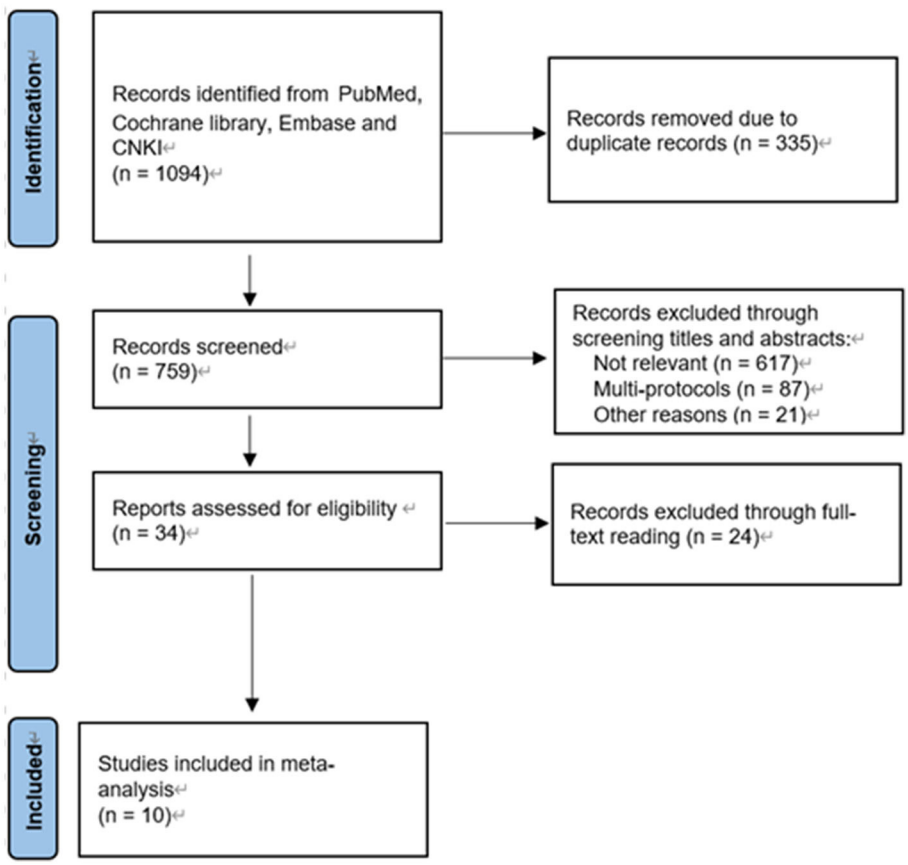

FIGURE 1 | Flow diagram of study selection.

TABLE 1 | Characteristics of the included studies.

Study	Year of publication	Country	diagnosis	Feeding time of TOF	EOF cases	EOF age (mean)	EOF number of males	TOF cases	EOF age (mean)	EOF number of males
Chen et al. (11)	2010	China	100% malignant	UPOF	160	61.2	92	160	58.3	95
Dag et al. (12)	2011	Turkey	100% malignant	UPOF	99	62	52	100	61	61
Feo et al. (13)	2004	Italy	100% malignant	UPOF	50	67.6	NR	50	67.6	NR
Hartsel et al. (14)	1997	America	64% malignant	AROI	29	66	NR	29	68	NR
Lucha et al. (15)	1997	America	Not reported	AROI	26	51	17	25	51	16
Nakeeb et al. (9)	2009	Egypt	100% malignant	AROI	60	52.3	39	60	56.3	42
Reissman et al. (16)	1995	America	Not reported	AROI	80	51	34	81	56	43
Stewart et al. (17)	1998	Australia	Not reported	UPOF	40	58	19	40	59	18
Wang et al. (18)	2013	China	100% malignant	UPOF	24	56.3	20	24	54.3	13
Yang et al. (19)	2010	China	100% malignant	UPOF	32	57.2	20	30	59.5	23

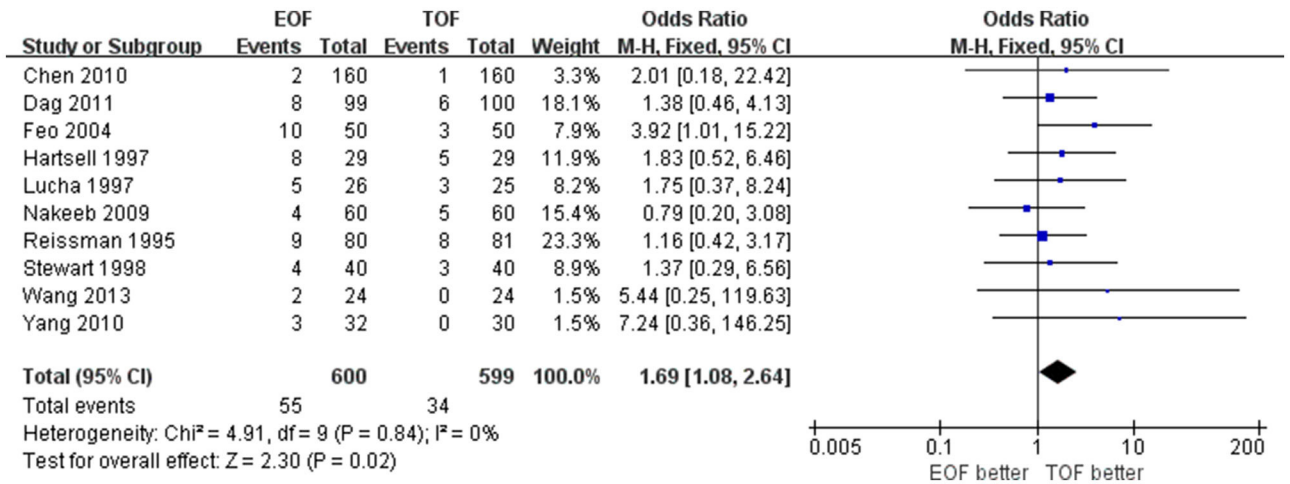

FIGURE 2 | Forest plots of nasogastric reinsertion. All of the included studies were synthesized.

we conducted a sensitivity analysis, presenting that the median LOS was shorter in the EOF group of the studies before 2010 with low heterogeneity (WMD −0.62; 95% CI −0.67 to −0.56; $p<0.01$; $I^2 = 0\%$) (**Figure 4**).

Total Complications

All 10 studies accessed the data concerning total complications, which were synthesized in forest plots. There was a significant difference between the EOF group and the TOF group with low heterogeneity (OR 0.49; 95% CI 0.37 to 0.65; $p<0.01$; $I^2 = 48\%$) (**Figure 5**). Subgroup analysis showed that EOF was associated with a lower rate of major complications (OR 0.57; 95% CI 0.34 to 0.95; $p = 0.03$; $I^2 = 0\%$) (**Figure 6**).

DISCUSSION

Although surgical resection is a primary option to treat colorectal cancer, it also triggers significant postoperative complications and deaths. In traditional postoperative management, patients undergoing colorectal surgery have nasogastric tubes inserted to avoid the oral intake of fluids or nutrients until the postoperative ileus (POI) is resolved. As an important part of the ERAS protocol after colorectal resection, EOF was proposed for postoperative management and presented clear benefits and safety (3, 20). However, it is still controversial whether EOF could improve prognosis without adverse events. Although a recent meta-analysis (21) pooled present clinical trials and provided extensive evidence advocating EOF, the evidence seems inadequate. Many studies other than colorectal surgery were included in the meta-analysis, for example, upper gastrointestinal surgery and small bowel resection.

Admittedly, it was reported that nasogastric tube removal in the immediate course after elective colorectal surgery could improve the rehabilitation of gastrointestinal functions and prevent postoperative infections, thus benefiting patients with shorter LOS and lower postoperative complications (22). Moreover, in a retrospective study involving 1,561 patients (23), the authors suggested that a perioperative strategy with no use of NGT, which could provide a higher tolerance rate of early intake, was proven safe and effective for postoperative rehabilitation. However, some studies emphasized a negative

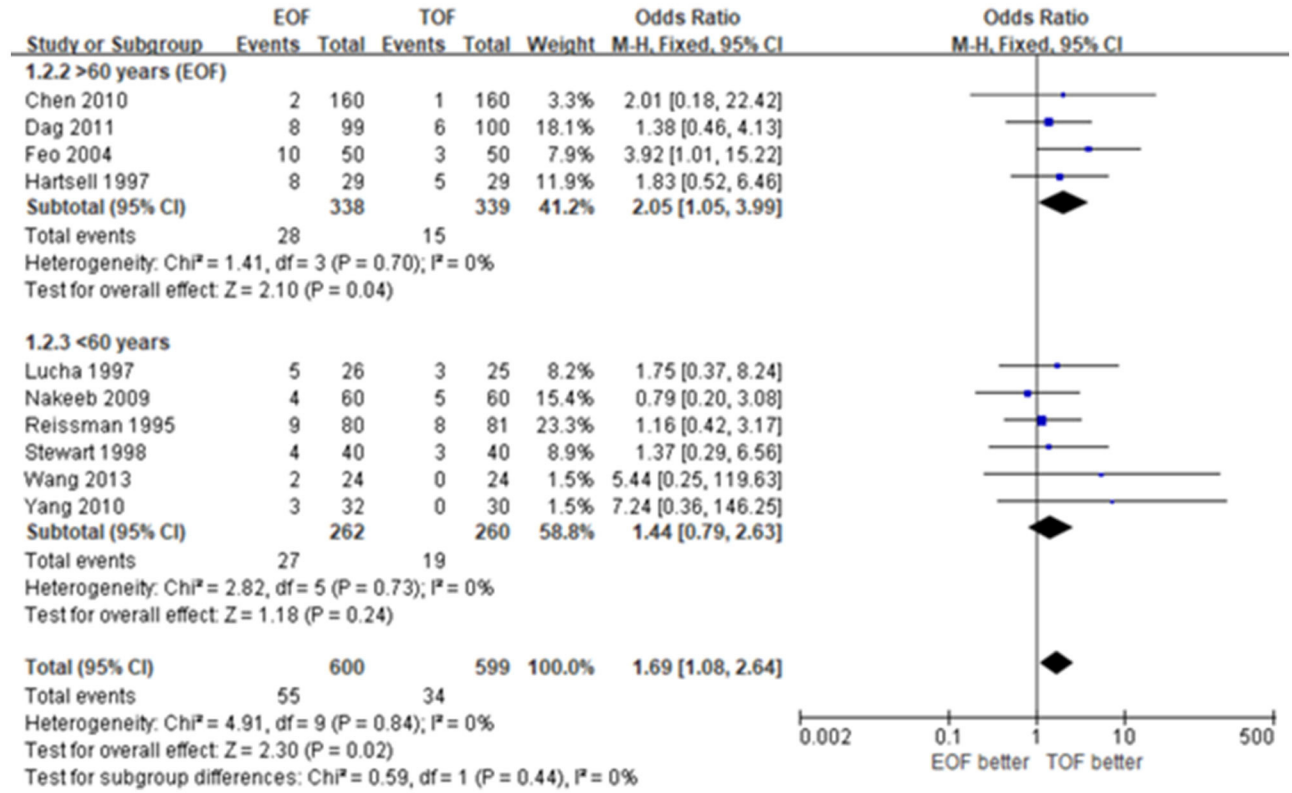

FIGURE 3 | Forest plots of nasogastric reinsertion. **(A)** Patients over 60 years. **(B)** Patients <60 years.

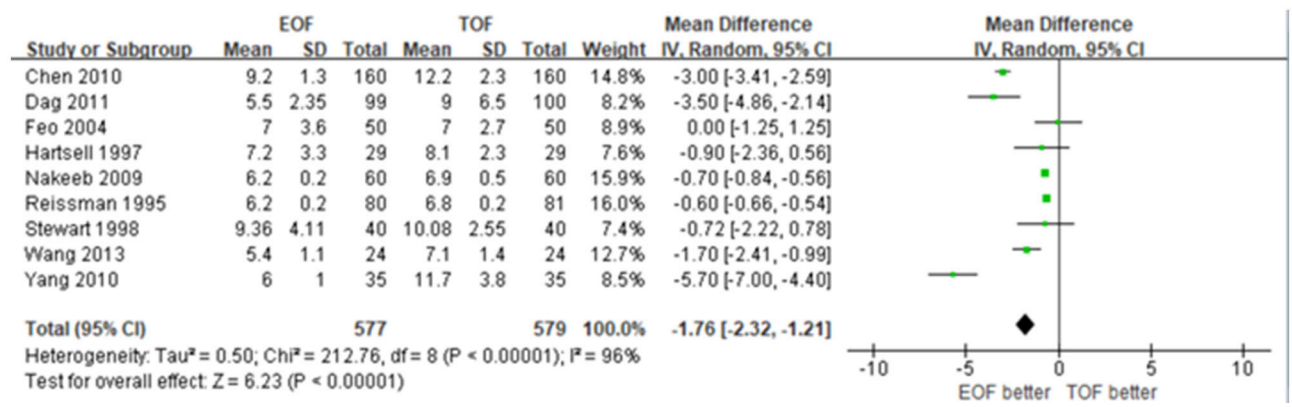

FIGURE 4 | Forest plots of length of hospital stay.

impact on patients' recovery that early feeding exerted. Li conducted a meta-analysis evaluating anastomotic leakage rate after esophagectomy (24). It concluded that the EOF group was more likely to be associated with anastomotic leakage in that type of open surgery. Early feeding without NGT insertion could not trigger any severe complications but postoperative vomiting, for which the surgeon would suspend the EOF protocol (25). These facts indicated that the EOF protocol should be further improved.

In our meta-analysis, we focused on the problem of NGT reinsertion that the EOF protocol may give rise to. On one hand, although the patient accepted EOF at first, surgeons had to reinsert nasogastric tubes and restart tube feeding in response to certain adverse events or according to the patient's requirement. On the other hand, surgeons might apply the strategy of NGT reinsertion once POI has not been resolved within a reasonable period after colorectal surgery, which challenges 25% of the patients (26). Wolthuis proposed NGT reinsertion as the most

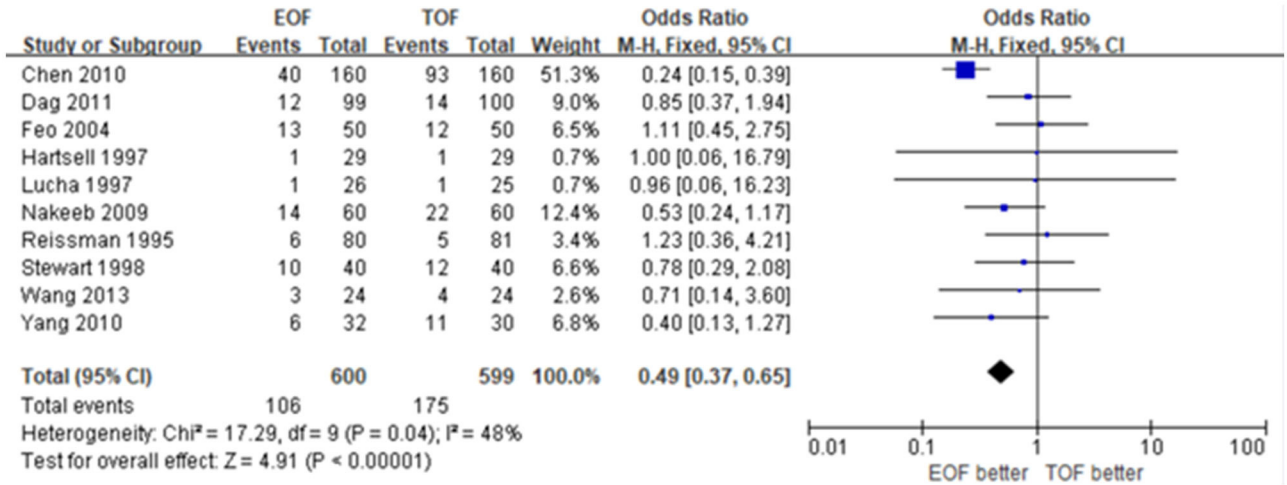

FIGURE 5 | Forest plots of total complications.

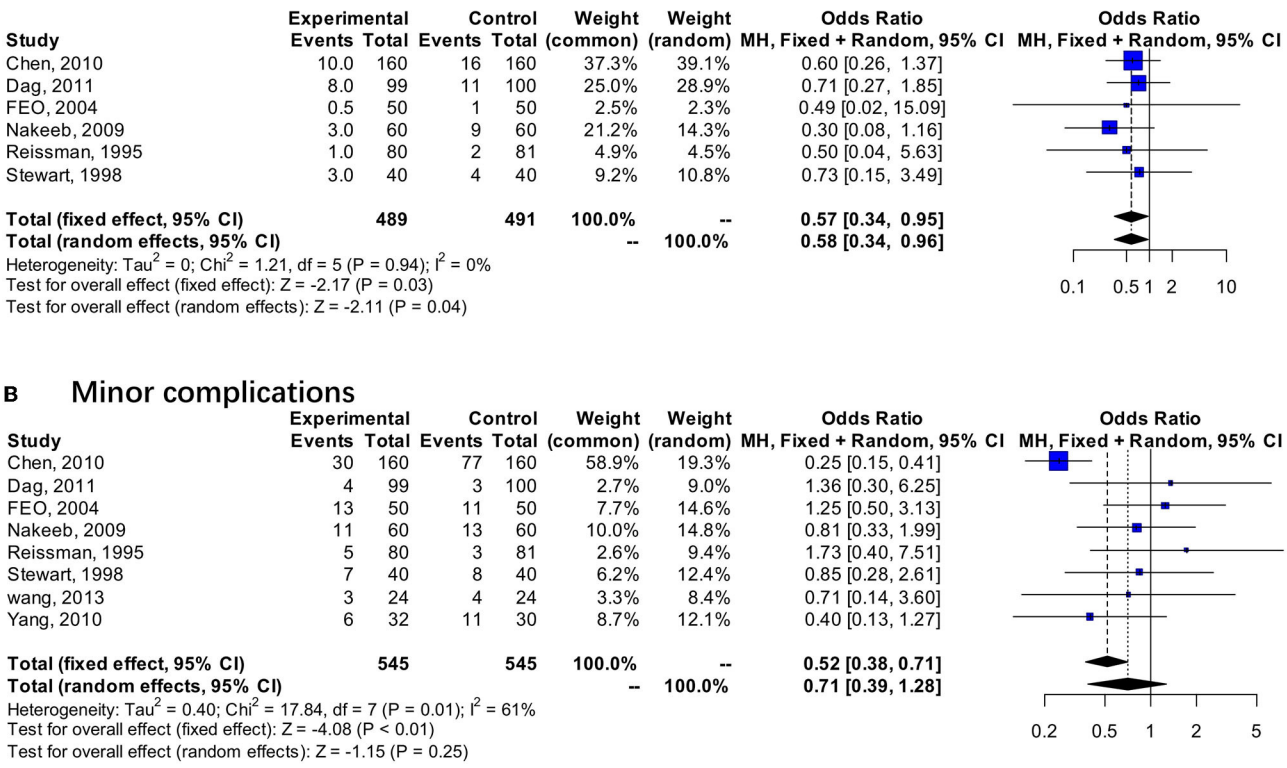

FIGURE 6 | Forest plots of total complications. **(A)** Major complications. **(B)** Minor complications.

significant sign of prolonged POI (despite an overestimation of ileus rates), which affects LOS and postoperative complications (27). Therefore, it is inferred that NGT reinsertion is a sign effectively reacting to the patient's recovery. In our study, NGT reinsertion was 1.7-fold more likely to happen in the EOF group than in the TOF group. In the following subgroup analysis, we found that EOF was more associated with NGT reinsertion in the subgroup of older patients. Since NGT reinsertion can make patients uncomfortable and initiate an infection, surgeons should be more conservative about the timing and tolerance

of oral intake and more cautious about the EOF protocol for older patients.

However, the results of our study did not infer that EOF should not be performed, instead, we recommended EOF since we observed shorter LOS and lowered complications in the EOF group, consistent with previous findings (28, 29). Shorter LOS and lower complication rates were associated with healthcare expenditures, which was definitely beneficial to patients and healthcare facilities. We assumed that the higher rate in NG tube reinsertion might be correlated with an unmet nutritional requirement, which indicates that the EOF protocol, especially the formula of diets, needs further improvement and more studies.

However, LOS presented a varied result with high heterogeneity, possibly because the surgical method and postoperative recovery have progressed year after year. Therefore, we conducted a sensitivity analysis and found that distinct publications periods may be the source of heterogeneity. The studies published before 2010 presented 0.62 days of LOS shorter in the EOF group with low heterogeneity. Thus, although EOF was deemed safe and effective for feeding nutrition under the ERAS protocol, LOS was inevitably extended once NGT reinsertion or other adverse events happened.

There were several limitations in our study. Firstly, although only RCTs were included in this study, the definition of EOF and TOF, the timing of feeding initiation, and the amount of oral intake differed in selected studies, thus inevitably resulting in bias. Secondly, as mentioned above, NGT reinsertion might be beneficial to relieving the problem of POI, thus trading off the impact of EOF to LOS and complications and finally making the results weaker. Thirdly, the outcome data were not comprehensive enough. Detailed information about NGT reinsertion was missing, e.g., the success rate of NGT reinsertion. These drawbacks are expected to be addressed in well-designed multicenter RCTs in the future. Fourth, we did not use the 2020 PRISMA guideline to guide our study, since the study were performed several steps before we found out that the 2020 PRISMA guideline was released. We believed that the results were not biased by this point, because we conformed to the previous PRISMA version.

All participants received laparotomy, and the EOF feeding time was on the first postoperative day. UPOF refers to the feeding time would not start until passage of flatus. refers the feeding time started after resolution of operative ileus.

CONCLUSIONS

EOF resulted in a high incidence of NGT reinsertion despite a reduction in length of hospital stay and postoperative complications in patients with elective colorectal surgery.

AUTHOR CONTRIBUTIONS

YC and XH contribute to selecting the topic. HW and SL contribute to organizing literature and extracting data. JJ contributes to supervising the process and statistics. YWu and YWa contribute to drafting the manuscript. YZ, ZW, and DW contribute to the revision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.807811/full#supplementary-material

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A Hub and Spoke Learning Program in Bariatric Surgery in a Small Region of Italy

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Background: Metabolic and bariatric surgery (BS) are considered life-changing and life-saving treatments for obese patients. The Italian Society of Obesity Surgery (SICOB) requires at least 25 operations per year to achieve the standard of care in the field. Despite the increasing need to treat obese patients, some small southern regions of Italy, such as Molise, do not have enough experience in bariatric procedures to be allowed to perform them. Therefore, our aim was to run a Hub and Spoke Program with a referral center in BS to treat obese patients and provide a proper learning curve in BS in Molise.

Methods: In 2020, the "A. Cardarelli Hospital" in Campobasso, Molise, started a formal "Learning Model of Hub and Spoke Collaboration" with the Hub center "Ospedale Del Mare", Naples. A multidisciplinary approach was achieved. Patients were supervised and operated under the supervision and tutoring of the referral center. We retrospectively reviewed our prospectively collected database from February 2020 to August 2021 in order to analyze the safety and effectiveness of our learning program.

Results: In total, 13 (3 men and 10 women) patients underwent BS with the mean age of 47.08 years and a presurgery BMI of 41.79. Seven (53.84%) patients were the American Society of Anesthesiologist (ASA) II, and 6 (46.16%) patients were ASA III. Twelve (92.31%) procedures were laparoscopic sleeve gastrectomies, 1 (7.69%) patient underwent endoscopic BioEnterics Intragastric Balloon (BIB) placement. One (8.33%) sleeve gastrectomy was associated to gastric band removal. Mean surgical time was 110.14 ± 23.54 min. The mean length of stay was 4.07 ± 2.40 days. No Clavien-Dindo ≥ III and mortality were reported. The follow-up program showed a mean decrease of 11.82 in terms of body mass index (BMI) value. The last 5 procedures were performed by the whole equips from "A. Cardarelli" under external tutoring without any impact on complication rate.

Conclusion: The setup of a proper Hub and Spoke Program may allow to perform BS to provide the standard of care. This approach may reduce health costs and related patient migration.

Keywords: bariatric surgery, Hub and Spoke, sleeve gastrectomy, BioEnterics Intragastric Balloon, metabolic surgery, obesity

INTRODUCTION

The WHO has estimated that 1.9 billion adults worldwide are overweight and 650 million are obese (1). In Italy, as reported by Global Obesity Observatory, the overall percentage of patients with body mass index (BMI) > 30 kg/m^2 is across 12 and 10% for men and women over 18 years old, respectively (2). Despite it being a high percentage, it is lower than the mean value of European states (2). In particular, in Molise, a small region of Italy, the overall percentage of obesity is over 14% in both genders: one of the highest national values (3). In literature, it is clearly described a link among obesity and hormonal, endothelial and inflammatory level alterations (4, 5), and pieces of evidence regarding the association between the increased BMI and carcinogenesis (6–8).

The metabolic and bariatric surgery (BS) showed to be the most successful treatment for weight loss and to reduce the patients' comorbidities due to obesity (9, 10).

Bariatric surgery and many other elective surgical services had to deal with the widespread postponements in many parts of the world during the Coronavirus Disease-2019 (COVID-19) pandemic (11, 12). Nevertheless, the surgical treatment of obesity cannot be defined as *"elective"* (13), because nowadays it is considered a life-changing intervention and a life-saving surgery, improving health, quality of life, and long-term survival (11).

Therefore, "A. Cardarelli Hospital" in Campobasso (Molise) started a "Teaching/Learning Model of Hub and Spoke Collaboration" among some referral centers for bariatric, colorectal, and liver surgery (14), in order to reduce patient migration offering the best standard of care to people for all the surgical specialties. The learning programs allow to guarantee effective treatment and safety procedures in patients with morbid obesity also during the critical pandemic period as reported in minimally invasive approaches performed in complex surgery (15–18).

Hub and Spoke Programs have already demonstrated a great impact on regional health programs avoiding health migration, reducing costs, and decreasing the waiting times for surgery (15, 19, 20).

Our study aimed to evaluate the safety and effectiveness of the Hub and Spoke Bariatric Learning Program in a small Italian region analyzing all the peri-, intra-, and postoperative outcomes and the BMI reduction, Total Weight Loss (%TWL), and Excess Weight Loss (%EWL) after 30 and 90 days from surgical procedures, in order to reduce the health system costs and patients migration.

MATERIALS AND METHODS

Hub and Spoke Program

Due to the limited number of inhabitants, Molise does not offer a formal plan specialized in the treatment of obese patients. Consequently, the General Surgery Unit of "A. Cardarelli Hospital", in Campobasso, Italy, started a partnership with the BS unit of "Ospedale del Mare", Naples, Italy, directed by Prof. Pietro Maida.

Following the BS guidelines, provided by the Italian Society of Obesity Surgery (SICOB) (21), a multidisciplinary team (MDT) has been setup. Bariatric surgeons, dieticians, nutritionists, psychologists, and anesthetists collaborate and discuss all the cases.

All patients were operated under the supervision and tutoring of the referral center surgeon. The surgeons involved in the Hub and Spoke Learning Program moved from Molise to Naples one time per month during the learning period to be properly trained before surgery.

Methods

We retrospectively reviewed our prospectively collected database from February 2020 to August 2021 according to STrengthening the Reporting of OBservational studies in Epidemiology (22). The elective BS was interdicted in the months between March and June 2020 and from November 2020 to May 2021 due to the COVID19 pandemic period in order to reduce in-hospital viral transmission and related postoperative pulmonary complications. The goal was to preserve the hospital workers and to better care for patients affected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, and to have more beds for patients.

We included all obese patients (BMI > 30 kg/m^2) (23) who underwent BS at "A. Cardarelli Hospital" in that period. No exclusion criteria were chosen. Under the supervision of MDT, all patients underwent a 3-week very low-carbohydrate ketogenic diet program before surgery (10). Before the admission in the surgery unit, all patients performed a molecular rhino-pharyngeal swab to verify the negativity to SARS-CoV-2 infection. According to SICOB guidelines, all patients, before surgery, performed dietary and psychological evaluation, routine blood samples, chest-XR and ECG, and esophagogastroduodenoscopy (EGDS). All patients carried out an oral glucose tolerance test (OGTT) and glycosylate hemoglobin test (HbA1c).

The serum levels of triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and total cholesterol were measured on a preoperative day, subsequently at 90 days after surgery.

TABLE 1 | Baseline characteristics of patients.

Variables	N. (%) and/or Mean ± SD
Age (years)	47.08 ± 7.54
Gender	
Male	3 (23.08)
Female	10 (76.92)
ASA	
II	7 (53.84)
III	6 (46.16)
Comorbidities	
Hypertension	11 (84.61)
Gastritis	11 (84.61)
Diabetes Mellitus	4 (30.76)
Hypothyroidism	3 (23.08)
Esophagitis	2 (15.38)
SARS-CoV-2 swab positivity	0 (0)

SD, standard deviation.

TABLE 2 | Intraoperative and postoperative course.

Variables	N. (%) and/or Mean ± SD
Intraoperative course	
Surgical approach	
VLS	12 (92.31)
EGDS	1 (7.69)
Type of surgery	
LSG	12 (92.31)
BIB	1 (7.69)
Associated procedures to LSG	
Gastric band removal	1 (8.33)
Mean operative time (minutes)	110.14 ± 23.54
Postoperative course	
Clavien-Dindo classification	
I	3 (23.07)
II	1 (7.69)
≥III	0 (0)
TPN	1 (7.69)
PONV	3 (23.07)
Length of stay (days)	4.07 ± 2.40

SD, Standard Deviation; VLS, Video-laparoscopy; EGDS, esophagogastroduodenoscopy; LSG, Laparoscopic Sleeve Gastrectomy; BIB, BioEnterics Intragastric Balloon; TPN, Total Parenteral Nutrition; PONV, Postoperative Nausea and Vomiting.

In selected cases, spirometry, echocardiogram, and perioperative Continuous Positive Airway Pressure (CPAP) were performed. The intraoperative risk was evaluated with the American Society of Anesthesiologist (ASA) score (24).

An Enhanced Recovery After Surgery (ERAS) program was used to achieve a rapid recovery of patients' conditions (25–27).

Postoperative complications were assessed according to the Clavien-Dindo classification (28). Follow-up was planned at 30 and at 90 days after surgery.

Due to the COVID-19 pandemic, telemedicine has been used in some cases to perform a follow-up and prescribing therapies by means of communication technologies (29).

All individuals included in this study signed informed consent for the scientific anonymous use of clinical data. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the University of Molise (protocol number 10/21, approved date: May 12, 2021).

Technical Notes

Sleeve Gastrectomy

Antibiotic prophylaxis was performed 30 min before intervention [ceftriaxone 2 g intravenous (i.v.)]. No patients presented allergy to the prophylactic regimen. Due to the intimate correlation between obesity and thrombotic risk, all patients were subjected to antithrombotic therapy (30, 31). All operations were performed through a minimally invasive approach under general anesthesia. A nasal-gastric tube was placed after anesthesia, and it was removed on postoperative day 3. A urinary catheter was placed according to the expected procedure length.

The tutor, and operating surgeon, stood to the patient's right, the assistant on the left side. The abdomen was insufflated to 12 mmHg to achieve pneumoperitoneum, and 5 ports were located.

We used the reverse Trendelenburg position to facilitate the fall of the transverse colon and small intestine toward the pelvis. We did a complete mobilization of the greater curvature of the stomach proximally to His' angle. After identification of pylorus, the first operating surgeon identified the site of transection 5–6 cm proximal to the pylorus. We conducted the dissection along the greater curvature at the stomach mid-body. A linear stapler was used to complete the dissection, after the introduction of a blunt-tipped bougie dilator (32). To avoid technical drawbacks, methylene blue dye was used to perform a leak test during surgery. The peritoneal drainage tube was inserted, and it was removed when the peritoneal drainage volume was <20 ml/die.

During the procedure, we preserved the splenic vessels and avoided an extreme splenic traction. Postoperative Nausea and Vomiting (PONV) and prophylaxis were performed using double metoclopramide (10 mg/2 ml) injections (33). A liquid diet was ongoing on postoperative day 3. After 2 weeks, patients were encouraged to eat a semi-solid diet and were progressively advanced with a normal diet over the following 2–4 weeks.

In the absence of clinical signs of the leak, stenosis, and other complications, we scheduled discharge.

BioEnterics Balloon Placement

After patients' sedation with midazolam or propofol, we performed an upper gastrointestinal endoscopy in order to exclude eventual pathologies. The BioEnterics Balloon (BIB) insertion and the postoperative treatment were performed according to other experiences available in the literature (34). A liquid diet was ongoing on postoperative day 3, solid on postoperative day 10.

Follow-up was scheduled 1 week after BIB positioning and every 3 weeks for a 6-month period. At the end of 6 months, after sedation, we removed the BIB through a single-channel endoscope and dedicated device.

Statistical Analysis

All quantitative data are reported as mean ± SD.

The difference between preoperative BMI, 30 days and 3-month BMI from surgery was analyzed to evaluate the success of the surgery. Weight loss was also calculated as %TWL during follow-up. The %TWL value was estimated through the formula: [(initial weight – current weight)/(initial weight)] × 100.

The excess weight loss (%EWL) was estimated using the formula: (weight loss/baseline excess weight) × 100, the weight loss is the preoperative weight – initial weight loss. The baseline excess weight is represented by the initial weight – ideal weight (X), and where $X = 25 \times m^2$. An ideal BMI (25 kg/m^2) was used to calculate the X.

A two-tailed $p < 0.05$ was established as statistically significant. IBM Statistical Package for the Social Sciences (IBM SPSS®) was used to analyze data.

RESULTS

A total of 13 (3 men and 10 women) patients who were included in our study underwent BS between February 2020 and August 2021.

The mean age was 47.08 years ± 7.54 with a mean BMI, before surgery, of 41.79 ± 6.02.

Regarding ASA score 7 (53.84%), patients were ASA II and 6 (46.16%) patients were ASA III.

The most frequent comorbidities were hypertension (84.81%), gastritis (84.61%), and diabetes mellitus (30.76%). No patient was found positive at SARS-CoV-2 molecular swab. Baseline characteristics of patients are depicted in **Table 1**.

All procedures were performed laparoscopically. Twelve (92.31%) procedures were sleeve gastrectomies (LSG) and 1 (7.69%) patient underwent endoscopic BIB placement. One (8.33%) LSG was associated to gastric band removal.

All surgical operations were performed under general anesthesia, except for the placement of BIB.

Mean surgical time was 110.14 ± 23.54 min. No hiatal hernia was found or repaired. No Intensive Care Unit (ICU) admission was reported.

Clavien-Dindo I-II complications were observed in 4 out of 13 patients: we reported 3 (23.07%) cases of PONV and 1 (7.69%) patient, after LSG, required Total Parental Nutrition (TPN) during hospitalization.

The mean length of stay was 4.07 ± 2.40 days. No mortality was reported.

Surgical characteristics and postoperative course are shown in **Tables 2**, **3**.

The follow-up rates were 100% at 30 and 90 days.

BMI, %TWL, and %EWL trends are shown in **Figure 1**.

DISCUSSION

Our study demonstrates the safety and the efficacy of the bariatric procedures, mainly LSG, performed in a peripheric center when involved in a Hub and Spoke Program.

Analyzing our results concerning preoperative patient characteristics, they are superimposable to other relevant casistics from referral centers for BS (35). All the patients have at least one comorbidity in addition to obesity. The most common comorbidities were hypertension and diabetes as reported in the literature (36–39).

Patients who underwent BS in our center were all ASA II and III. It is clear that high-volume centers can report more variability patients' ASA scores due to the greater number of cases (40, 41). The absence of ASA I patients might influence the postoperative data analysis.

Concerning intra-operative courses, all the procedures were performed through a laparoscopic approach following the standard of care for referral bariatric centers in the USA (42). No conversion or re-intervention is reported.

It can also be speculated that the number of the complications reported is higher than reported by a referral center (30 vs. 5–15%, respectively) (43, 44), but we shall underline that we reported only Clavien-Dindo I or II complications treated in conservative approach.

Furthermore, the small sample size influenced the complication rate. No patient presented the complications reported as serious as an anastomotic leak, cardiac, genitourinary, hemorrhagic, neurologic injuries, obstruction, postoperative shock, pulmonary, splenic injury, thromboembolic event, wound infection, and reoperation (42, 45–48). No patients needed ICU stay.

Moreover, this finding may benefit from the small sample size, but it is also due to a careful selection of cases, which were always discussed with the Hub MDT.

Moreover, a proper step by step learning curve of the whole team was established to achieve the best results as described in Vitiello et al.'s experience (35).

The mean hospital stay is higher than the length of stay (LOS) reported in the literature for a high-volume center for LSG (35, 49–51). As known, LOS may be influenced by modifiable and non-modifiable factors (52).

In our case, most of the factors that affect LOS cannot be modified, such as age, BMI, ASA, and creatinine.

As reported by Tholey et al. (53), the ASA score > 2 was a significant predictor of an LOS longer than 48 h, probably due to the greater risk of even mild complications.

Among the non-modifiable factors, there are also the socio-economic conditions and the geographical distance between little towns and the Cardarelli Hospital.

In Molise, it might be difficult for many patients to undergo 1-day hospital service before and after surgery, forcing them to hospitalize these patients and frail and lonely patients (54).

We are aware that center volume correlates to results (55–58), but in a moment in which health migration constitutes a risk for the population due to the COVID19 pandemic (59, 60), a Hub and Spoke Program for elective BS may offer patients the chance

TABLE 3 | Outcomes after 90 days from BS.

	Pre-operative measurement, Mean ± SD	90-day post-operative measurement, Mean ± SD	*P*-value
N. of patients	13	13	
Weight (kg)	112.22 ± 22.48	80.47 ± 16.91	**0.0004**
Height (cm)	164.00 ± 9.07		
BMI (kg/m^2)	41.79 ± 6.02	29.97 ± 4.44	**<0.0001**
Serum lipid profile			
Total cholesterol (mmol/L)	194.22 ± 21.34	173.82 ± 18.57	**0.0157**
LDL (mmol/L)	130.00 ± 21.12	118.30 ± 16.32	0.1271
HDL (mmol/L)	39.57 ± 6.54	41.56 ± 5.49	0.4090
Triglyceride (mmol/L)	120.44 ± 26.00	92.73 ± 29.12	**0.0172**
Other parameters			
Glycemia (mg/dL)	107.36 ± 42.89	102.42 ± 31.75	0.7414
Hb (g/dL)	13.15 ± 1.21	12.81 ± 1.67	0.5578
eGFR* (ml/min/1.73 m^2)	103.05 ± 12.65	102.71 ±10.09	0.9402

*SD, Standard Deviation; BMI, Body Mass Index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Hb, hemoglobin; eGFR, estimated Glomerular Filtration Rate. *eGFR was calculated according to CKD-EPI formula. Bold values are statistically significant findings.*

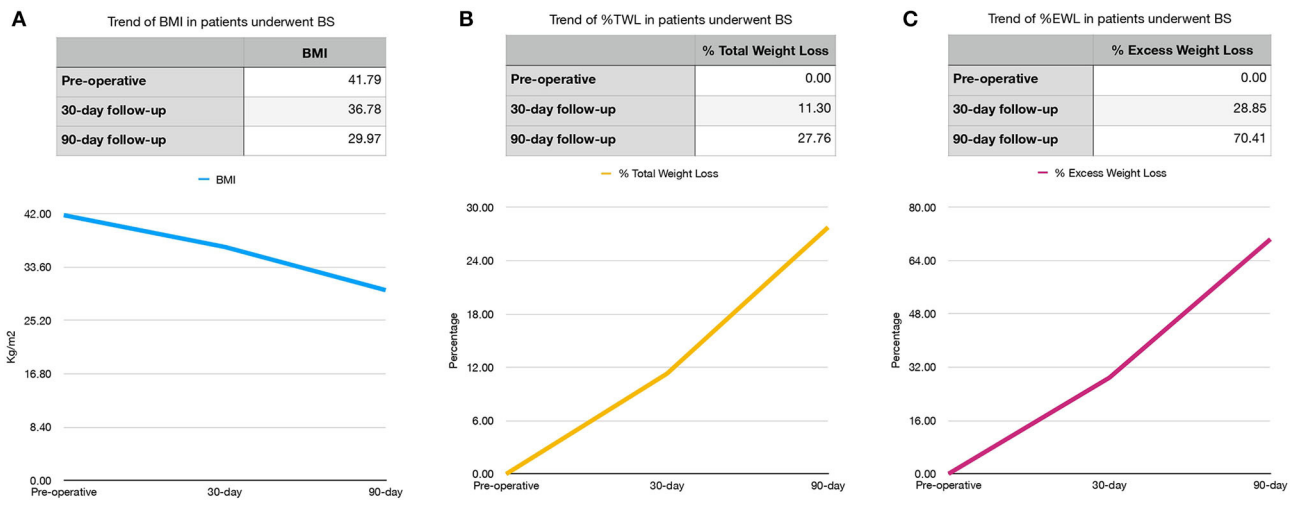

FIGURE 1 | Preoperative, 30- and 90-day BMI **(A)** and %TWL **(B)** and %EWL **(C)** trends in bariatric surgery (BS) patients. BMI, body mass index (kg/m^2); %TWL, Total Weight Less; %EWL, Excess Weight Loss.

to be treated in the safest and most effective way without the costs and risks of health migration (20).

The chance to be treated in their own region is also important for the families of the patients because in the COVID19 pandemic period, it was even more difficult to assist patients far from home (61).

Therefore, we can affirm that our approach has led us to guarantee effective treatment and safety procedures also during the critical pandemic period, as reported by Bonalumi et al. in cardiac and vascular surgery during the COVID19 pandemic (62). Moreover, Ceccarelli et al. have been experienced the safety of this program in liver surgery and concluded that it may allow patients to undergo a suitable standard of care for complex surgery (20).

Furthermore, our Hub and Spoke Learning Program aims precisely to improve the capacity and experience of the surgical team in order to best manage all the modifiable factors reported by Meneveau et al. with a consequent reduction of complications and hospital stay (52).

During the follow-up, our patients had a consistent reduction in BMI and our findings were in line with results from referral centers for BS (35, 51, 63).

Our aim is to share the first report of a successful Hub and Spoke Program, which allowed to best manage patients from a small region of Italy, where it is very difficult to reach all the standards of care for the most frequent surgical pathologies, but where health migration should be reduced respecting the rules of the best surgical practice.

Limitations

The major drawback of our study is the small number of patients enrolled in the study. However, we would like to share our successful experience to encourage the application of Hub and Spoke Programs, which are up to now the best way to reduce health mobility and consequent health costs for patients coming from small regions achieving the best standard of care.

CONCLUSION

Our pilot study has the aim to demonstrate the effectiveness of Hub and Spoke Learning Program to reduce migration and costs ensuring the standard of care in BS, especially in laparoscopic sleeve gastrectomy. Our program is still being continued and we are enrolling even more patients which can undergo BS for the first time in their region. Our further goals are represented by the improvement of outcomes, even more autonomous patient management and the possibility to propose all types of interventions in our hospital.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, with undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Molise. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB, PA, and AR: conceptualization. PA and AR: methodology and writing—review and editing. PA, MC, and RV: software. PA, MC, AS, RV, MB, and AR: validation, writing—original draft preparation, and visualization. MC, AS, RV, GD, GG, CL, MB, DE, and LS: formal analysis and investigation, resources, and data curation. PM, BA, GG, and AR: supervision. All authors have read and agreed to the published version of the manuscript.

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SYSTEMATIC REVIEW
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Selective Hepatic Vascular Exclusion versus Pringle Maneuver in Major Hepatectomy: A Systematic Review and Meta-Analysis

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Objectives: Mortality and morbidity following hepatic resection is significantly affected by major intra-operative blood loss. This systematic review and meta-analysis evaluates whether selective hepatic vascular exclusion (SHVE) compared to a Pringle maneuver in hepatic resection reduces rates of morbidity and mortality.

Methods: A systematic review and meta-analysis were conducted according to the PRISMA guidelines by screening EMBASE, MEDLINE/PubMed, CENTRAL and SCOPUS for comparative studies meeting the inclusion criteria. Pooled odds ratios or mean differences were calculated for outcomes using either fixed- or random-effects models.

Results: Six studies were identified: three randomised controlled trials and three observational studies reporting a total of 2,238 patients. Data synthesis showed significantly decreased rates of mortality, overall complications, blood loss, transfusion requirements, air embolism, liver failure and multi-organ failure in the SHVE group. Rates of hepatic vein rupture, post-operative hemorrhage, operative and warm ischemia time, length of stay in hospital and intensive care unit were not statistically significant between the two groups.

Conclusion: Performing SHVE in major hepatectomy may result in reduced rates of morbidity and mortality when compared to a Pringle maneuver. The results of this meta-analysis are based on studies where tumors were adjacent to major vessels. Further RCTs are required to validate these results.

Clinical Trial Registration: PROSPERO (CRD42020212372) https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=212372.

Keywords: pringle, selective hepatic vascular exclusion (SHVE), hepatectomy, liver resection, Systematic (Literature) Review

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INTRODUCTION

Over the past two decades, improvements in safety have allowed hepatic resection to play a significant role in the management of benign and malignant hepatobiliary disease (1–4). Due to the liver's specialized blood supply, major intra-operative hemorrhage can significantly affect morbidity and mortality (5, 6). Most hepatic resections require vascular occlusion, especially where tumors are sizeable or lie close to major vessels.

The Pringle maneuver, first described in 1908 as a technique to minimize blood loss during hepatic surgery, is the most common technique of vascular occlusion in surgical practice (7–9). It involves clamping of the hepatoduodenal ligament and occluding the portal triad, which minimizes the blood inflow into the liver via the portal vein and hepatic artery. Blood outflow from the liver is not affected, therefore Pringle maneuver cannot prevent backflow bleeding from the hepatic veins. Furthermore, if the tumor lies close to the inferior vena cava or at the confluence of one or more of the major hepatic veins, major hemorrhage as well as air embolism can occur, as a result of injury of these vessels. Total hepatic vascular exclusion (THVE) was developed in an attempt to reduce these complications, occluding both hepatic inflow and outflow by performing a Pringle maneuver and clamping the inferior vena cava (IVC) above and below the liver (10–12). However, this causes significant hemodynamic disturbance due to the interruption of venous blood flow in the IVC (13, 14).

Selective hepatic vascular exclusion (SHVE) is a newer technique which involves clamping the hepatic veins without clamping the IVC (15, 16). This can control hepatic inflow and outflow, preserving caval flow and therefore avoiding major hemodynamic disturbance. SHVE is not widely used by surgeons despite the theoretical advantage it offers, as it is technically challenging and can be complicated by laceration of the hepatic veins during dissection resulting in major hemorrhage.

The safest type of vascular occlusion to perform in hepatectomy remains a contested topic of discussion. The aim of this systematic review and meta-analysis is to compare morbidity and mortality between SHVE and Pringle maneuver in major hepatectomy surgery.

METHODS

Study Design

This systematic review and meta-analysis was registered at PROSPERO (CRD42020212372). It was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data Sources and Search Strategy

The following electronic databases were searched: MEDLINE/PubMed (1946 to June 2021), EMBASE (1947 to June 2021), Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) from The Cochrane Library (2020, Issue 7) on 26 June 2021. This was done by two independent authors (SM, MT). A combination of medical subject headings (MeSH) and free-text terms were used to form the search strategy for each database. This is displayed in Supplementary Table S1 (Online Resource 1).

In order to identify relevant studies that did not get included in the initial database searches, the reference lists of selected articles were examined. The World Health Organization International Clinical Trials Registry, ClinicalTrials.gov, ISRCTN Register and PROSPERO were also searched to identify any unpublished studies.

Study Selection

Our inclusion criteria included: randomized controlled trials (RCTs) or comparative observational studies in the English language; human studies; studies including patients aged 18 years or older of any gender; studies where a hepatectomy was performed; studies where a Pringle maneuver was performed for hepatic inflow occlusion in the SHVE group.

Our exclusion criteria included: non-English studies; non-medical, non-human studies; studies in patients under the age of 18 years old and conference abstracts, editorials, expert opinion, case reports and non-comparative observational studies.

The studies that were identified by the initial search strategy were reviewed by two independent authors (RV, MT). Duplicated were removed. Rayyan software was used to screen titles and abstracts of identified studies for inclusion into the review (17). If the study abstract was not sufficient to make a decision for inclusion, the full paper was screened. Any conflicts that arose were resolved through discussion, and a third author (MD) made the final decision where necessary.

Data Extraction

The data was extracted from studies using an electronic data extraction spreadsheet. This was done by two independent authors (SM, MCS). Any conflicts that arose were resolved through discussion, and a third author (MD) made the final decision where necessary. Collected data included: study-related data, patient demographics, peri-operative management and relevant outcome measures.

Outcome Measures

Intra-operative outcome measures included: operative time (minutes), warm ischemia time (minutes), blood loss (milliliters), patients requiring blood transfusion, blood transfusion (units), air embolism and hepatic vein rupture.

Post-operative outcome measures included: overall mortality, intra-operative mortality, in-hospital mortality, overall complication rate (%), hospital stay (days), intensive care unit (ICU) stay (days), post-operative hemorrhage, liver failure and multi-organ failure.

Where studies reported outcomes as median with range, the mean and standard deviation were estimated using the validated method described by Hozo et al. (18).

Assessment of Risk of Bias

Risk of bias was assessed by two independent authors (SM, MCS). This was carried out using the revised Cochrane risk-of-bias tool (RoB 2) for RCTs and the Cochrane Risk Of Bias In Non-Randomized Studies – of Interventions tool (ROBINS-I) for non-randomized studies. Where there were disagreements between the two authors, this was discussed and the final decision was made by a third independent author (MD).

Data Synthesis and Statistical Analysis

The software Review Manager (RevMan) (The Cochrane Collaboration; Version 5.3.5, The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data synthesis (19). This was done by one independent author (MB) who entered the extracted data into the software. A second independent author (MD) then reviewed the entered data.

To estimate treatment effects, relevant outcome parameters that were extracted from the included studies were assessed. For dichotomous variables, the Mantel-Haenszel method was used to pool the odds ratio (OR). For continuous variables, the mean difference (MD) was calculated between the two groups (20). A forest plot was generated for each outcome measure with 95% confidence intervals (CIs) and its associated p-value. Statistical significance was defined as $p < 0.05$.

The Cochran Q test (χ^2) was used to assess the heterogeneity between studies. This was then further quantified by generating an inconsistency statistic (I^2) for each outcome measure. Low heterogeneity was defined as an I^2 of 0–50% and fixed-effects modelling was used. Conversely, high heterogeneity was defined as an I^2 of 51–100% and random-effects modelling was used.

To explore potential sources of heterogeneity, sensitivity analyses were carried out. For each outcome parameter with high inter-study heterogeneity, individual studies were removed and the analysis would be repeated to assess that study's contribution to the overall effect size and heterogeneity. In order to explore potential changes in the effect size, subgroup analyses of the RCTs and observational studies were carried out.

The independent (unpaired) samples t-test was performed on the Pringle and SHVE groups to assess statistical significance between patient demographics. This was done using the software IBM SPSS Statistics (IBM Corp; Version 23.0, Armonk, NY, USA) (21). Statistical significance was defined as $p < 0.05$.

RESULTS

Study Selection

The literature search identified 2,411 studies, which became 1,267 following removal of duplicated studies. Abstracts were then assessed for eligibility and 1,253 studies were excluded. From the remaining 15 studies, six met the inclusion criteria. Therefore the study population for this systematic review is comprised of three RCTs, two retrospective cohort studies and one case-control study reporting a total of 2,238 patients. PRISMA flowchart is demonstrated in **Figure 1**.

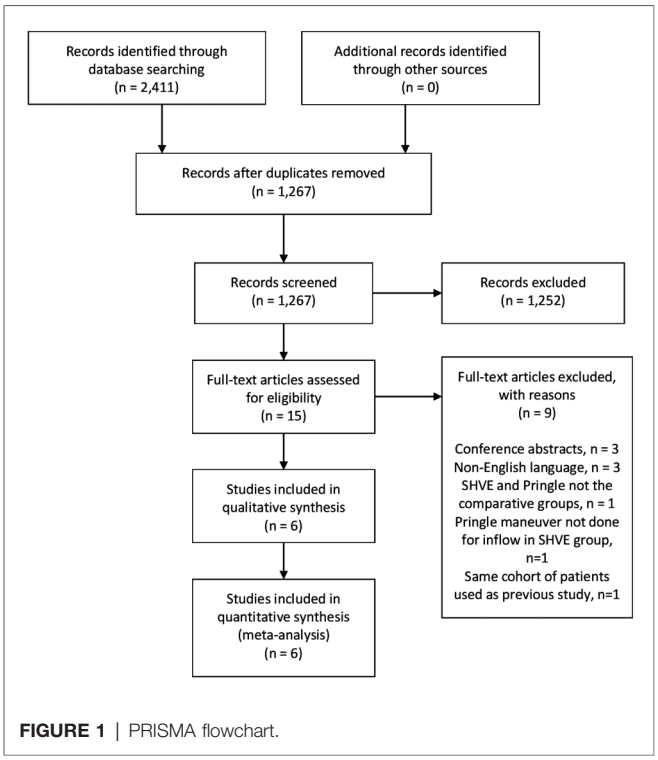


FIGURE 1 | PRISMA flowchart.

Study Characteristics

All studies were published between the years 2003 and 2019. One study was undertaken in Greece (22), four in China (23–26) and one in Thailand (27). All RCTs were single-center studies. Study durations ranged from 11 to 96 months. In total, there were 1,288 patients in the Pringle group and 950 in the SHVE group. Study characteristics are presented in **Table 1**.

Baseline demographics of the study populations are presented in **Table 2**. There was no statistically significant difference in the mean age and gender between the Pringle and SHVE groups. Tumor size, number of patients with cirrhosis (including Child-Pugh Grade) and hepatitis B status were only reported in a few of the studies, but where they were reported, they were comparable across the two groups. The extent of tumor invasion of the hepatic veins was reported by the four studies from China and remained comparable across the two groups (23–26). These studies only selected patients with tumors encroaching on the hepatic veins. Zhou et al. (23) and Tongsiri et al. (27) reported the number of hepatic veins involved rather than named veins therefore it was not possible to assess whether there were differences between the Pringle and SHVE groups.

Other than one study that solely looked at outcomes in hemangioma (25), malignancy was the most common indication for resection, and hepatocellular carcinoma (HCC) accounted for the majority of malignant lesions in both groups. The number of patients with HCC were similar across the two groups. The most commonly performed resections were right and left hepatectomy, with very few numbers reported for the various segmentectomies, and this remained comparable across the two groups. All studies reported the use of a clamp-crushing technique for liver resection, except Tongsiri et al. which used ultrasonic dissection (27), and all studies used additional polypropylene 3-0 and 4-0 sutures for hemostasis.

TABLE 1 | Summary of characteristics of included studies.

Author	Year	Journal	Country	Study design	Retrospective or prospective	Study period	Study duration (months)	*n*, total	*n*, Pringle	*n*, SHVE
Smyrniotis et al.	2003	World Journal of Surgery	Greece	RCT	Prospective	1995–2002	84	110	55	55
Zhou et al.	2008	European Journal of Surgical Oncology	China	Case-control	Retrospective	2000–2005	58	235	110	125
Zhang et al.	2012	British Journal of Surgery	China	Cohort	Retrospective	2003–2010	84	1420	870	550
Yang et al.	2014	American Surgeon	China	Cohort	Retrospective	2003–2011	96	273	153	120
Si-Yuan et al.	2014	International Journal of Surgery	China	RCT	Prospective	2008–2010	24	160	80	80
Tongsiri et al.	2020	Journal of The Medical Association of Thailand	Thailand	RCT	Prospective	2018–2019	11	40	20	20

RCT, randomized controlled trial; SHVE, selective hepatic vascular exclusion.

TABLE 2 | Baseline patient demographics of included studies.

Author	Average age (years)		*n*, male		Tumour size (cm)		*n*, cirrhosis		*n*, Child-Pugh Grade A		*n*, Child-Pugh Grade B		*n*, HBsAg + ve	
	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE
Smyrniotis et al.	62	61	44	43	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Zhou et al.	52.3	51.6	77	86	11.8	12.4	65	74	102	113	8	12	71	90
Zhang et al.	53	51	630	406	8.6	8.9	604	393	580	379	24	14	621	427
Yang et al.	41.9	45.8	62	41	12.9	14.2	2	1	N/R	N/R	N/R	N/R	N/R	N/R
Si-Yuan et al.	48.3	49.2	63	61	8	8.2	48	50	43	45	5	5	N/R	N/R
Tongsiri et al.	57.4	61.1	4	11	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	1	0
Independent samples t-test	$p = 0.840$		$p = 0.743$		$p = 0.758$		$p = 0.776$		$p = 0.771$		$p = 0.780$		$p = 0.815$	

Statistical significance defined as $p < 0.05$.
HBsAg, hepatitis B surface antigen; N/R, not reported.

Two studies performed a continuous Pringle maneuver for all patients in both groups (22–25) and Tongsiri et al. performed intermittent Pringle maneuver for both groups (27). Si-Yuan et al. performed a continuous Pringle maneuver for the SHVE group only (26) and two studies performed a continuous Pringle maneuver either if the liver was cirrhotic (24) or developed cirrhosis (23) in both groups. Zhang et al. (24) and Yang et al. (25) converted to THVE in the Pringle group in 34 and 11 patients respectively. Si-Yuan et al. converted to THVE in one patient in the SHVE group as the tumor had invaded the IVC (26). Tongsiri et al. converted two patients in the SHVE group to Pringle (27). All studies described clamping the right, middle and left hepatic veins in all cases regardless of the type of resection. Operative techniques are presented in Supplementary Table S2 (Online Resource 1).

Data Synthesis

Hemorrhage and Transfusion

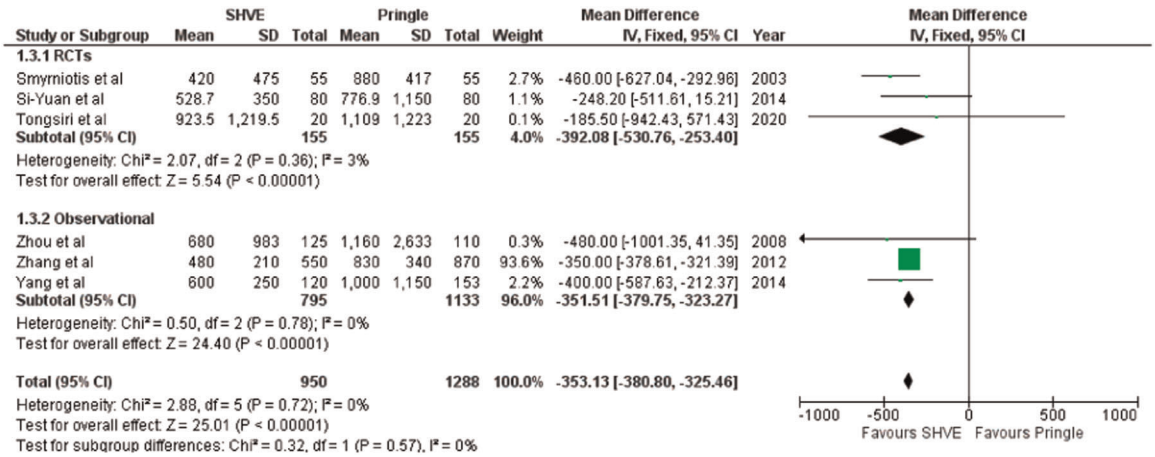
The pooled analysis demonstrated a statistically significant decrease in blood loss (MD: −353.13, 95% CI: −380.80–−325.46, $p < 0.00001$); number of patients requiring blood transfusion (OR: 0.31, 95% CI: 0.20–0.50, $p < 0.00001$); and number of units transfused (MD: −1.59, 95% CI: −1.70–−1.49, $p < 0.00001$) in the SHVE group compared to the Pringle group. Forest plots for these outcomes are presented in **Table 3**. Rates of post-operative hemorrhage remained similar between the two groups (OR: 0.55, 95% CI: 0.17–1.78, $p = 0.32$). This is presented in Supplementary Figure S3 (Online Resource 1). Heterogeneity between studies for blood loss ($I^2 = 0\%$, $p = 0.72$); units of blood transfused ($I^2 = 0\%$, $p = 0.48$); and rates of post-operative hemorrhage ($I^2 = 22\%$, $p = 0.27$) was low. There was high heterogeneity between studies for number of patients requiring blood transfusion ($I^2 = 74\%$, $p = 0.004$).

Morbidity and Mortality

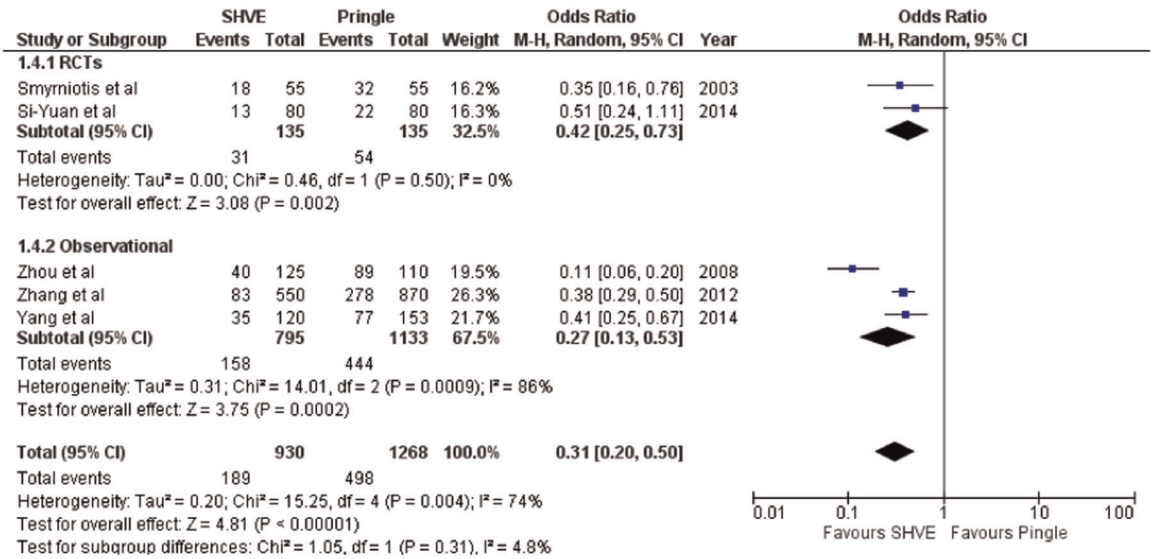
There was a statistically significant decrease in overall mortality (OR: 0.12, 95% CI: 0.03–0.55, $p = 0.005$) and in-hospital mortality (OR: 0.09, 95% CI: 0.01–0.68, $p = 0.02$) in the SHVE group compared to the Pringle group. Heterogeneity remained low between the studies for both overall mortality ($I^2 = 0\%$, $p = 0.81$) and in-hospital mortality. ($I^2 = 0\%$, $p = 0.41$).

TABLE 3 | Forest plots comparing primary and secondary outcomes in Pringle and selective hepatic vascular exclusion.

Blood loss



Patients requiring transfusion



Units of blood transfused

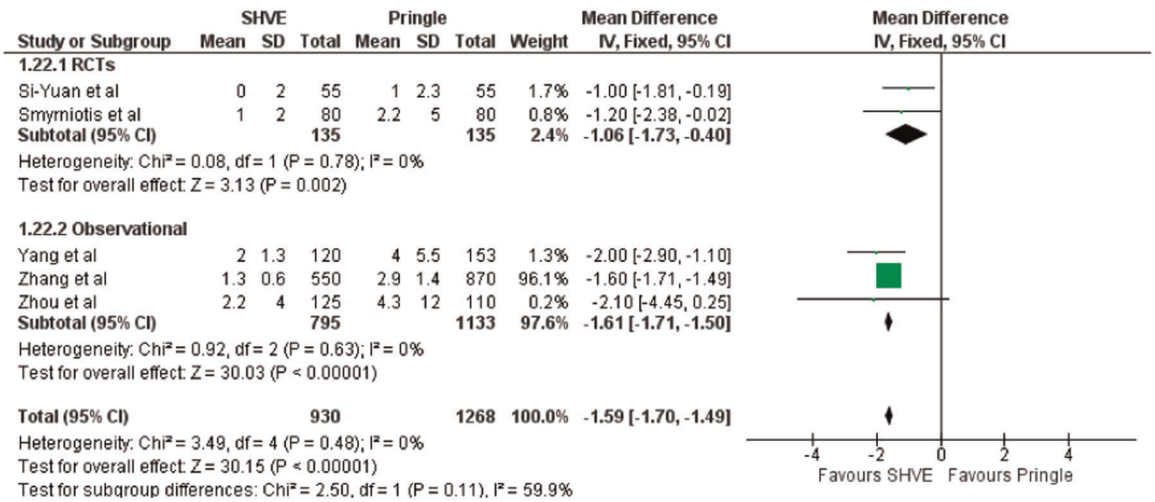


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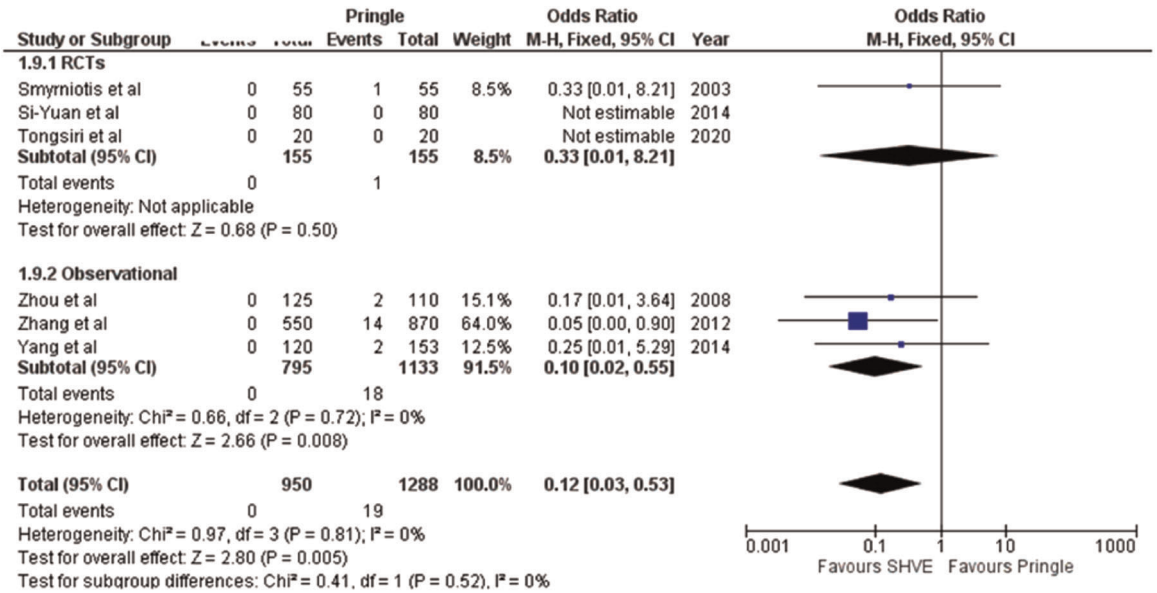
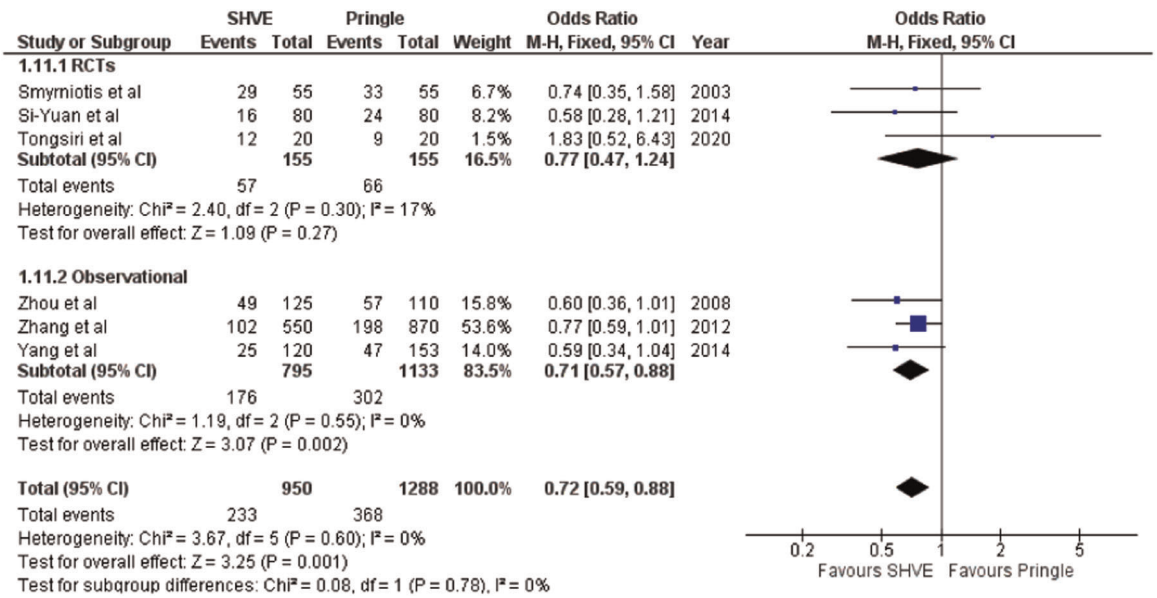
TABLE 3 | Continued

Overall mortality



Overall complications



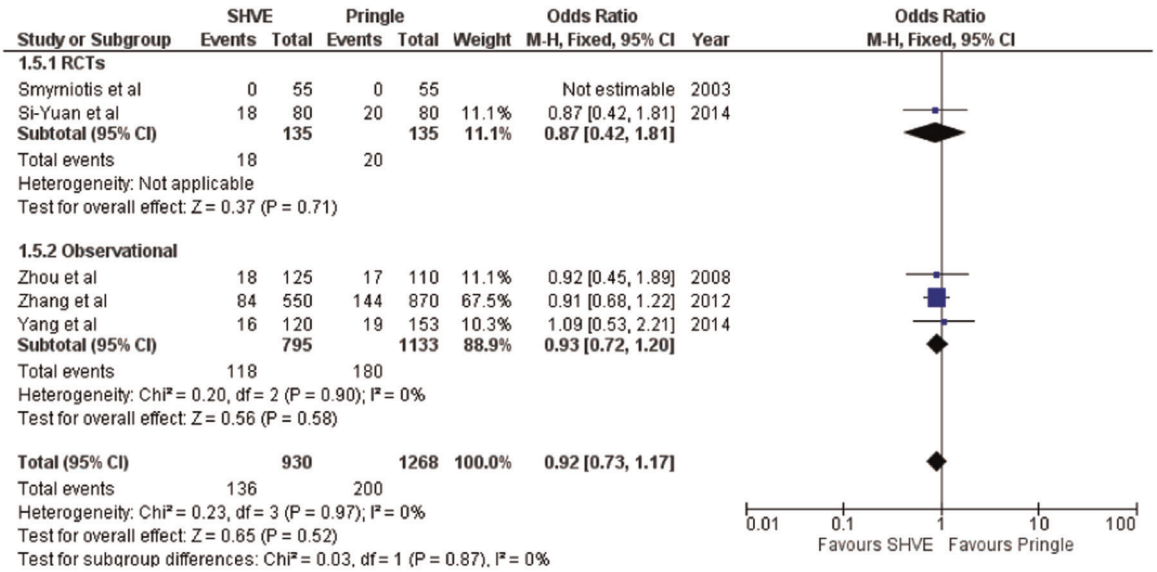
(*continued*)

The forest plot for overall mortality is presented in **Table 3**. In-hospital mortality is presented in a forest plot in Supplementary Figure S4 (Online Resource 1).

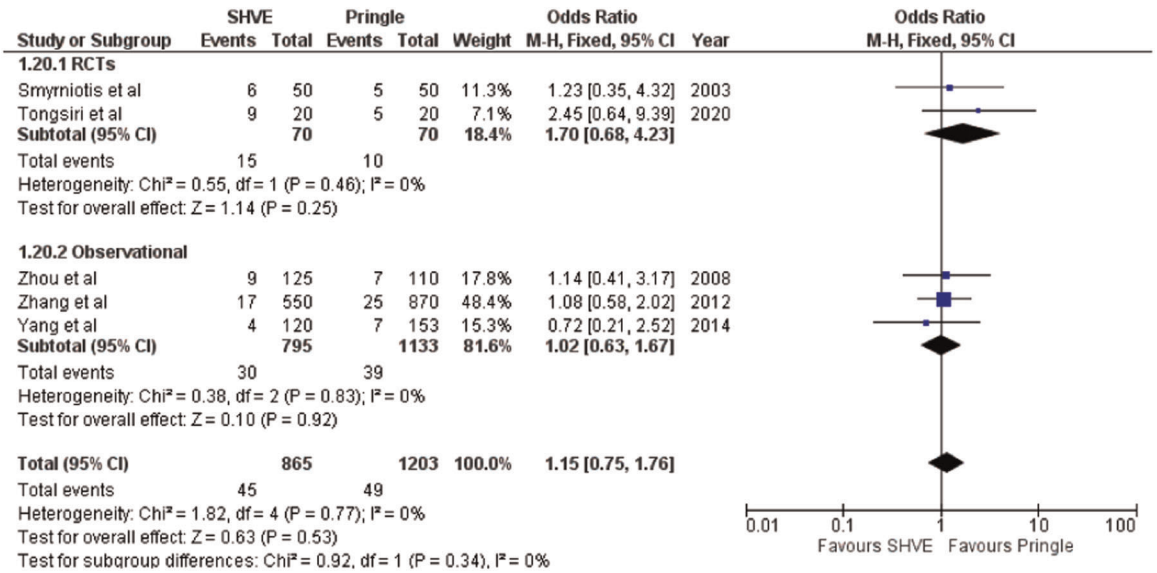
The meta-analysis of complication rate demonstrated a statistically significant decrease in the SHVE group compared to the Pringle group (OR: 0.72, 95% CI: 0.59–0.88, $p = 0.001$) with low heterogeneity ($I^2 = 0\%$, $p = 0.60$). There was no statistically significant difference in hepatic vein rupture (OR: 0.92, 95% CI: 0.73–1.17, $p = 0.52$) or bile leak (OR: 1.15, 95% CI: 0.75–1.76, $p = 0.53$) between the two groups. Heterogeneity was low for both hepatic vein rupture ($I^2 = 0\%$, $p = 0.97$) and bile leak ($I^2 = 0\%$, $p = 0.77$). There was a statistically significant decrease in air embolism (OR: 0.08, 95% CI: 0.02–0.36, $p = 0.0008$); liver failure (OR: 0.31, 95% CI: 0.12–0.81, $p = 0.02$); and multi-organ failure (OR: 0.15, 95% CI: 0.03–0.83, $p = 0.03$) in the SHVE group compared to the Pringle group. Heterogeneity between studies for air embolism ($I^2 = 0\%$, $p = 0.97$); liver failure ($I^2 = 0\%$, $p = 0.98$); and multi-organ failure ($I^2 = 0\%$, $p = 0.78$) remained low. The forest plots for these outcomes are presented in **Table 3**.

TABLE 3 | Continued

Hepatic vein rupture



Bile leak



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Duration of Surgery and Hospital Stay

There was no statistically significant difference in warm ischemia (MD: −0.84, 95% CI: −2.18–0.51, $p = 0.22$) or operative time (MD: 6.44, 95% CI: −2.65–15.54, $p = 0.16$) in the SHVE group compared to the Pringle group. Heterogeneity was high for both warm ischemia time ($I^2 = 69\%$, $p = 0.01$) and operative time ($I^2 = 84\%$, $p < 0.00001$).

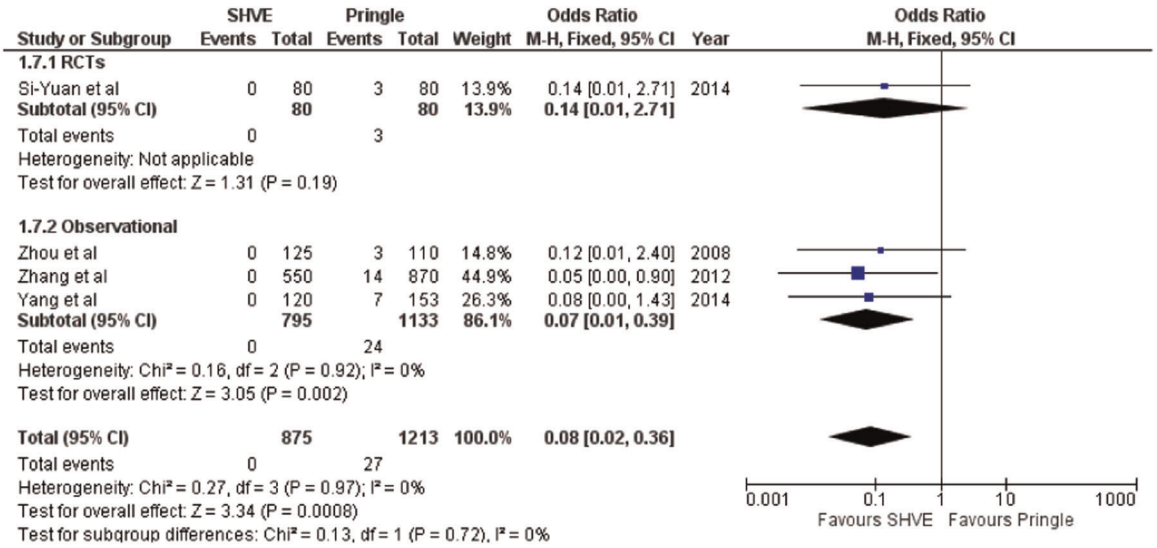
Similarly, there was no statistically significant difference in length of stay in hospital (MD: −3.04, 95% CI: −8.06–1.98, $p = 0.24$) or ICU (MD: 0.66, 95% CI: −0.53–1.86, $p = 0.28$) in the SHVE group compared to the Pringle group. Heterogeneity was high for both hospital stay ($I^2 = 99\%$, $p < 0.00001$) and ICU stay ($I^2 = 99\%$, $p < 0.00001$). The forest plots for these outcomes are presented in Supplementary Figures S5–S8 (Online Resource 1).

Sensitivity and Subgroup Analysis

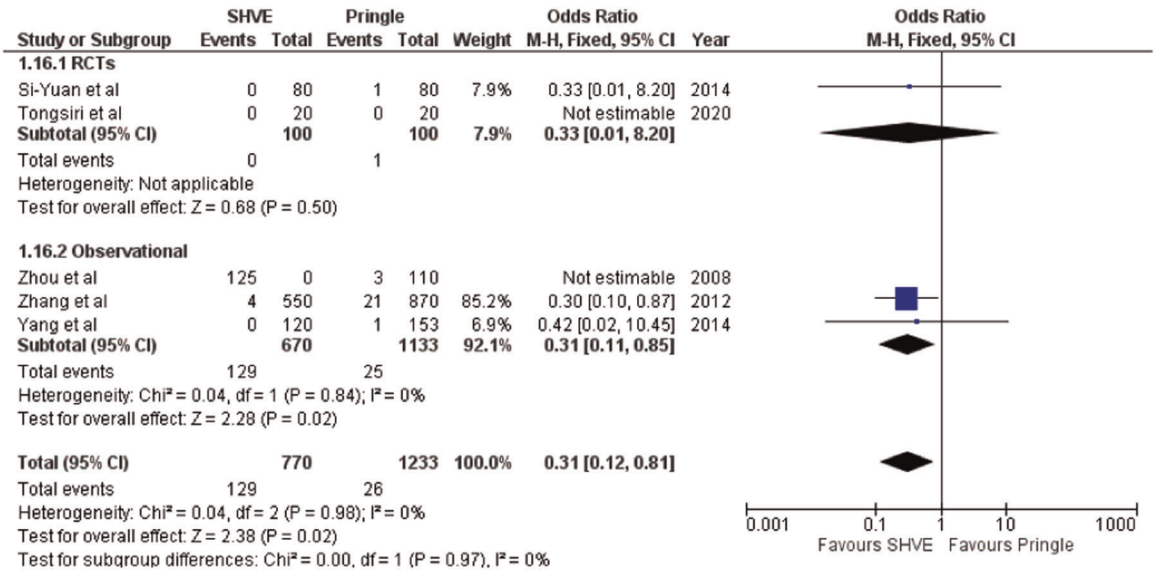
Random-effects modelling was applied to patients requiring transfusion, operative time, warm ischemia time, ICU stay and hospital stay due to the high heterogeneity between studies. This did not affect the pooled effect size or heterogeneity. Sensitivity analyses were also performed. Excluding the Si-Yuan study resulted in the operative time becoming significantly shorter in the Pringle group, excluding the Si-Yuan study resulted in warm

TABLE 3 | Continued

Air embolism



Liver failure



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ischemia time became significantly shorter in the SHVE group and excluding the Zhang study resulted in the hospital stay becoming significantly shorter in the SHVE group.

Subgroup analyses separating RCTs from observational studies had no effect on the meta-analysis of all outcomes, except complication rate which did not show a significant difference between the SHVE and Pringle groups in RCTs alone and hospital stay which became significantly reduced in the SHVE group.

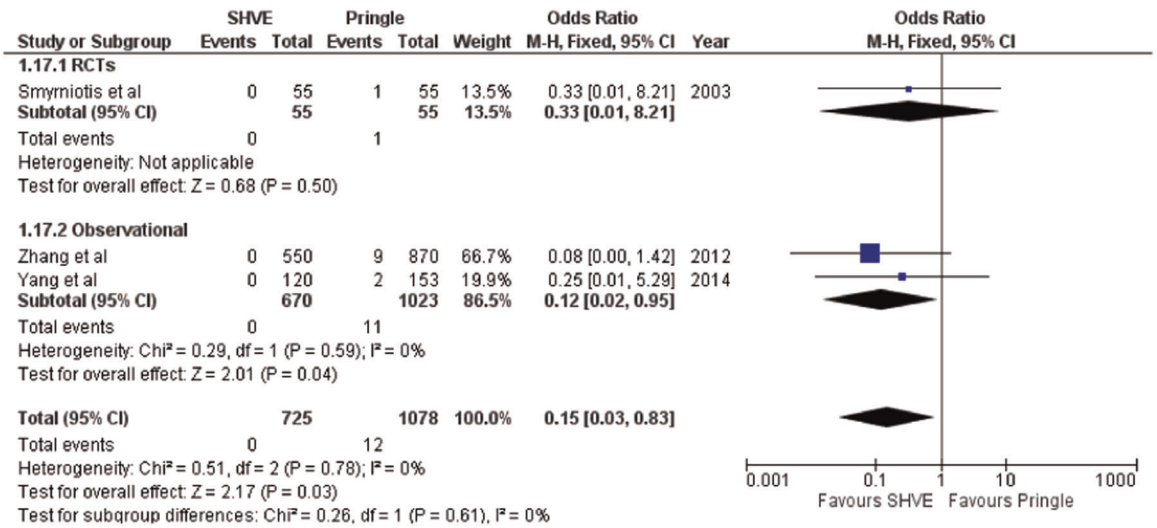
Methodological Quality of Included Studies

Overall, risk of bias was low for all randomized controlled trials included in this review. Double blinding was not possible as surgeons knew whether they were performing performed SHVE or Pringle maneuver. Since knowledge of assigned intervention did not affect objectively measured post-operative endpoints, this did not add risk of observer bias. Additionally, there was no bias from missing outcome data and any deviations from intended interventions were equally distributed between both groups. Measurement of outcomes and reporting of results did not confer a significant risk of bias.

Overall, risk of bias was moderate for all observational studies. This was mainly due to issues with confounding bias as studies did not account for important variables or make reasonable adjustments to prevent this. All studies were found to have moderate risk of bias in the selection of reported

TABLE 3 | Continued

Multi-organ failure



CI, confidence interval; M-H, Mantel-Haenszel test; RCT, randomized controlled trial.

results. Zhang et al. and Yang et al. had serious issues with deviation from intended interventions. The risk of bias assessment of both RCTs and observational studies is presented in Supplementary Figure 9 (Online Resource 1).

DISCUSSION

Mortality following major hepatic resection has markedly improved in recent years due to advancements in surgical and anesthetic techniques (1–4). Resection of tumors lying adjacent to the hepatic veins can result in major hemorrhage or venous air embolism. Therefore, hepatic vascular control has been recognized as an important aspect of reducing morbidity in these patients. Whilst portal triad clamping (Pringle maneuver) can control hepatic inflow, it does not prevent backflow from the hepatic veins. THVE may prevent massive bleeding from lacerated veins but causes significant hemodynamic disturbance due to obstruction of blood returning via the IVC. SHVE combines the advantages of both the Pringle and THVE techniques, reducing blood in the hepatic field whilst maintaining caval flow (7–14).

This systematic review and meta-analysis was conducted to compare the mortality and morbidity when using SHVE versus a Pringle maneuver in hepatectomy. Meta-analysis of the data revealed significantly decreased rates of mortality, overall complications, blood loss, blood transfusion rates, units of blood transfused, air embolism, liver failure and multi-organ failure when performing SHVE compared to a Pringle maneuver. The heterogeneity between studies for all these outcomes except blood transfusion rates were low suggesting that these outcomes are robust and reliable. Rates of hepatic vein rupture, post-operative hemorrhage, operative time, warm ischemia time, hospital stay and ICU stay were not statistically significant between the two techniques. All of these outcomes, except for hepatic vein rupture, had high heterogeneity between studies.

The results of this study are consistent with a meta-analysis reported in 2008 comparing techniques of vascular exclusion with Pringle (28). The study by Smyrniotis et al. (22) reported a subgroup analysis of SHVE versus Pringle and showed a significant decrease in blood loss and patients requiring blood transfusion in the SHVE group. There are no registered ongoing trials comparing SHVE to Pringle. Therefore, this review remains the most up to date review of the evidence.

Three of the studies in this review, including one RCT, selected patients who had tumors lying adjacent to the major hepatic veins (24–26). These studies were included the most frequently in the meta-analyses for all outcomes and therefore it is likely that these results suggest that SHVE may be a more appropriate technique to perform in this population of patients.

Limitations

This review is limited largely by heterogeneity of included studies. Several selection bias can be identified: status of the liver pre-operatively, number and location of resected liver nodules, continuous versus intermittent Pringle maneuver, transection techniques and peri-operative chemotherapy. As chemotherapy affects the quality of the liver parenchyma and subsequently the blood loss, the lack of this information increases the heterogeneity in the results.

Although SHVE describes the technique of hepatic outflow occlusion, there are different methods in which inflow occlusion can be performed. In this review, studies were only included if they performed a Pringle maneuver as part of the hepatic inflow. This minimized the heterogeneity between the studies, but in doing so, reduced the number of good quality studies that could be included in this review. Further studies with a standardized definition of SHVE are required.

This review demonstrated that rates of hepatic vein injury during both liver parenchymal and hepatic vein dissection remains comparable between Pringle and SHVE techniques. However, the studies included reported three different methods for outflow occlusion (ligation, clamping and tourniquet). Although different outflow occlusion techniques increases heterogeneity amongst the studies, this had no effect on rates of hepatic vein laceration.

SHVE is not widely practiced as it is considered technically challenging owing to the difficulty in isolating the major hepatic veins from the vena cava and the risk of injury associated with it. In clinical practice, SHVE is is much less reproducible than the Pringle maneuver, especially in centers with low volume and experience. SHVE has also become less practiced since the publication of many of these studies, partly due to the advance of the laparoscopic approach. Due to the difficulty in comparing existing variables and the low numbers of studies included in this review, wider conclusions for clinical practice cannot be drawn.

CONCLUSION

This systematic review and meta-analysis of best available evidence revealed that performing SHVE in major hepatectomy resulted in a lower overall mortality, lower complication rates including air embolism and liver failure and lower amounts of blood loss and transfusion requirement. The results of this meta-analysis are based on few high-quality studies where tumors were adjacent to major vessels, which seems the most suitable situation to utilize this technique. Due to the limitations of this review, it is difficult to draw conclusions for clinical practice. Larger studies are required to identify which groups of patients, tumors and types of resection benefit the most from the use of SHVE.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

Conception and design: TS, MS, MT. Literature search and study selection: MT, RV. Data extraction: SM, MS. Methodological appraisal: SM, MS. Statistical analysis: MB, MD, SM. Writing of the article: SM, MS. Critical revision of the article: All authors. Final approval of the article: All authors. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.860721/full#supplementary-material.

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How to Identify the Indications for Early Intervention in Acute Necrotizing Pancreatitis Patients: A Long-Term Follow-Up Study

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Aim: To explore the indications for early intervention in patients with acute necrotizing pancreatitis (ANP) and evaluate the effect of early intervention on the prognosis of ANP patients.

Methods: The clinical data of patients with ANP who underwent general surgery at Xuanwu Hospital of Capital Medical University from January 1, 2014, to December 31, 2020, were collected retrospectively. The patients were followed-up every 6 months after discharge, and the last follow-up date was June 30, 2021.

Results: A total of 98 patients with ANP were included in the study. They were divided into an early group (n= 43) and a delayed group (n = 55) according to the first percutaneous drainage (PCD) intervention time ($\leq$ 4 weeks or $>$ 4 weeks). Body temperature, inflammatory factor levels, and the number of patients with persistent organ failure (POF) were higher in the early group than in the delayed group. After the minimally invasive intervention, the body temperature and inflammatory factors of the two groups decreased significantly, most patients with POF improved, and the number of patients with reversal of POF in the early group was higher than that in the delayed group. Although the patients in the early group required more surgical intervention than those in the delayed group, there was no significant difference in mortality, incidence of postoperative complications, total length of hospital stay, or operation cost between the two groups. During long-term follow-up, there was no significant difference in the incidence of short-term and long-term complications and overall survival between the two groups.

Conclusions: Compared to patients in the delayed group, early intervention did not affect the prognosis of patients with ANP. It may be more suitable for patients with ANP with deterioration [such as POF or infected pancreatic necrosis (IPN)].

Keywords: acute necrotizing pancreatitis, percutaneous drainage, infected pancreatic necrosis, persistent organ failure, complications

INTRODUCTION

Acute pancreatitis (AP) is a common acute surgical condition of the abdomen. Although 80% of AP patients have mild self-limited disease, 20% of patients develop pancreatic necrosis and progress to acute necrotizing pancreatitis (ANP), and approximately one-third of patients with infected pancreatic necrosis (IPN) have significantly increased mortality (1, 2).

After the Dutch pancreatitis study group proposed and confirmed the effectiveness and safety of "step-up" minimally invasive intervention in the treatment of IPN (3), this strategy has become the preferred intervention recommended by current guidelines (4, 5). Specific measures were as follows: (1) for patients with suspected or confirmed IPN, timely antibiotic treatment should be administered in the early stage (≤4 weeks), and the intervention time should be postponed to 4 weeks after the onset of the disease, when the pancreatic necrosis is encapsulated and the boundary with the surrounding normal tissue is clear; and (2) percutaneous drainage (PCD) or endoscopic drainage (ED) of pancreatic necrotic tissue and effusion were performed to control infection. Video-assisted debridement (VAD) or endoscopic necrosectomy (EN) was performed according to the patient's condition, and laparotomy was performed when necessary.

In a recent international survey on the diagnosis and intervention time of IPN for patients diagnosed with IPN, although 55% of pancreatic experts supported antibiotic treatment first and puncture treatment after necrosis wrapping, but 45% of pancreatic experts still believe that minimally invasive intervention should be performed immediately after the diagnosis of IPN (6). Recently, a multicenter Randomized Controlled Trial (RCT) study published by the Dutch pancreatitis study group found that although early intervention did not benefit IPN patients more than delayed intervention, early intervention was an effective treatment option for IPN patients with clinical deterioration, but there was no clear indication of patients suitable for early intervention (7).

Therefore, by comparing the effects of different timing of PCD intervention on the long-term prognosis of ANP patients, this study clarified the indications for early PCD intervention in ANP patients and provided a reference for clinicians in the treatment of ANP.

METHODS

Study Design

This study retrospectively collected the clinical data of patients with AP during general surgery at Xuanwu Hospital of Capital Medical University from January 1, 2014, to December 31, 2020, using the case database of Xuanwu Hospital of Capital Medical University. All patient data were anonymously analyzed using an electronic data acquisition system without informed consent. This study was reviewed and approved by the Ethical Review Committee of Xuanwu Hospital of the Capital Medical University (No. 2020092). A detailed flowchart of the process is shown in **Figure 1**.

Inclusion and Discharge Criteria

The inclusion criteria of patients were as follows: (1) ANP patients with pancreatic and/or peripancreatic necrosis confirmed by imaging examination (enhanced CT, MRI, etc.); (2) patients were treated with the "step-up" intervention strategy; and (3) the case data and follow-up data are complete.

The exclusion criteria were as follows: (1) mild AP (MAP) without pancreatic necrosis and/or peripancreatic necrosis; (2) ANP patients with conservative treatment or "one-step" intervention strategy; (3) ANP patients requiring emergency surgery; (4) patients with chronic pancreatitis, acute attack, or recurrent acute pancreatitis (RAP); and (5) patients with incomplete case or follow-up data.

Observation Indicators

The primary outcome of this study was number of surgical interventions and in-hospital mortality in both groups. The secondary outcomes of this study were the number of patients with persistent organ failure (POF), duration of nutritional support, type of nutritional support, operation cost, short-term postoperative complications (such as abdominal bleeding, gastrointestinal obstruction, gastrointestinal fistula, etc.), length of stay in the intensive care unit (ICU), total length of hospital stay, long-term complications during follow-up [incision hernia, pancreatic pseudocyst, RAP, pancreatic exocrine dysfunction (PEI), pancreatic endocrine dysfunction, chronic pancreatitis, pancreatic tumor, other gastrointestinal symptoms, etc.], quality of life score [Short Form-36 (SF-36), Euroqol-5 dimensions (EQ-5D) rating scales], and pain score (Izbicki pain score). The definitions of the relevant observation indicators used in this study are listed in **Table 1**.

Patient Management

According to current international guidelines (5), patients were given standard treatment measures such as fluid resuscitation, analgesia, inhibition of pancreatic enzyme secretion, and early enteral nutrition after admission. Antibiotic treatment was administered only to patients with suspected or confirmed infections. Laboratory and imaging examinations were performed regularly to observe changes in the patient's condition. If the patient's condition improved, the current treatment was continued. If the patient's condition worsened, a multidisciplinary team (MDT), including pancreatic surgeons, anesthetists, intensivists, and imaging specialists, collaborated and evaluated the patients and took individualized treatment measures. Patients with deterioration organ failure (OF) or new onset OF (NOF) were provided with relevant organ support therapy [continuous pumping of vasoactive drugs, mechanical ventilation therapy (MVT), continuous renal replacement therapy (CRRT), etc.]. Patients with suspected or confirmed IPN were empirically given third-and fourth-generation cephalosporins or carbapenem antibiotics according to previous research results, which were then replaced with sensitive antibiotics according to the results of the pathogen drug sensitivity test (10).

The indications for "step-up" intervention in ANP patients were as follows: (1) after conservative treatment, the patient's

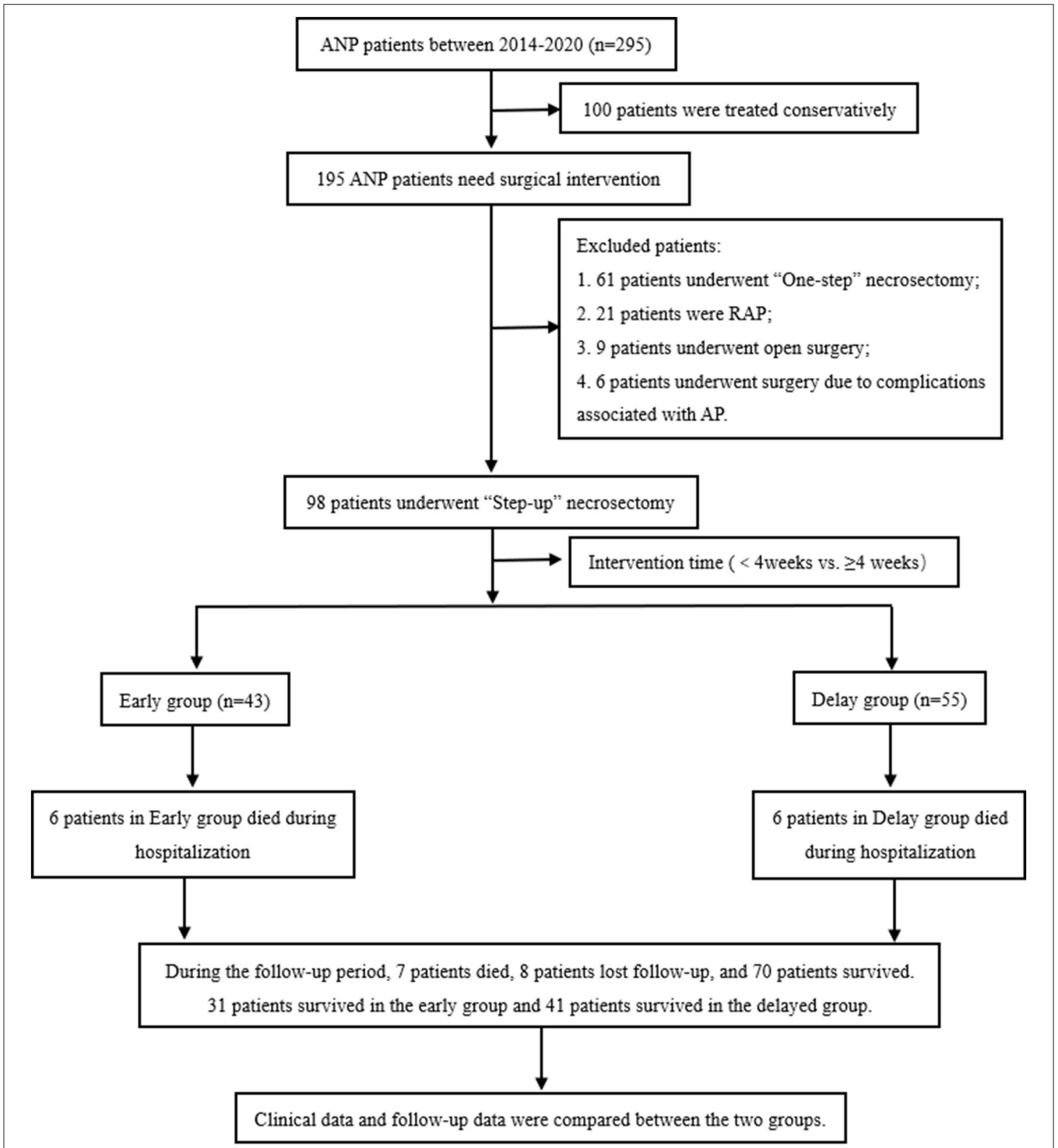

FIGURE 1 | Flow chart of patient enrollment and follow-up. ANP, acute necrotizing pancreatitis; AP, acute pancreatitis; RAP, recurrent acute pancreatitis.

condition had no significant improvement or had continued deterioration (NOF or increased temperature and inflammatory indicators, etc.); (2) the presence of IPN was confirmed; and (3) Patients develop pancreatic pseudocyst (PP) or walled-off necrosis (WON), and the range of necrosis in patients was enlarged, resulting in compression symptoms of surrounding organs (such as digestive tract or biliary tract obstruction). Pancreatic surgeons in our center have rich experience in

TABLE 1 | Definitions of the observation indicators.

Observation indicators	Definition
Acute pancreatitis (5)	Fulfillment of two of the following three criteria: (1) acute onset of epigastric pain radiating to the lower back; (2) blood amylase and/or lipase levels >3 times higher than normal; and (3) imaging examination (e.g., abdominal ultrasound, enhanced CT, and MRI) revealing typical findings of acute pancreatitis.
Necrotizing pancreatitis (8)	Presence of varying density shadows in the pancreatic parenchyma on contrast-enhanced CT, with no enhancement in the pancreatic parenchyma in the early stages of disease. The degree of pancreatic necrosis in necrotizing pancreatitis patients was divided into <30%, 30–50%, and > 50%.
Infected pancreatic necrosis (5)	Fulfillment of either of the following two criteria: (1) abdominal enhanced CT scan displaying the "bubble sign" in pancreatic and/or peripancreatic tissues; (2) development of positive pancreatic necrotic bacterial or fungal cultures with fine-needle aspiration (FNA) or other micro-invasive procedures.
Organ failure	
Pulmonary failure	PaO_2/FIO_2 <300, or need for mechanical ventilation.
Circulatory failure	Circulatory systolic blood pressure <90 mmHg, despite adequate fluid resuscitation, or need for inotropic catecholamine support.
Renal failure	Creatinine level ≥177 umol/L after rehydration or new need for hemofiltration or hemodialysis.
New-onset organ failure	First onset of organ failure requiring intervention at any time in a 24 h period.
Multiple organ failure	Number of organs in failure ≥2.
Surgical complications	
Intraabdominal hemorrhage	Persistent bleeding fluid in the drainage tube or around the wound, requiring surgical, radiologic, or endoscopic intervention.
Gastrointestinal fistula	Secretion of fecal material from a percutaneous drain or inflow into the necrotic cavity, either from small or large bowel; confirmed by endoscopy, imaging or during surgery.
Gastrointestinal obstruction	Gastrointestinal symptoms (e.g., abdominal distention, abdominal pain, dyspepsia, etc.) caused by pressure on surrounding organs by pancreatic necrotic material.
Pancreatic fistula	Amylase content in drainage tube or exudate around wound ≥3 times the serum amylase level.
Abdominal compartment syndrome	An increase in intra-abdominal pressure (≥20 mmHg) caused by various factors leading to the dysfunction of digestive, circulatory, respiratory and urinary systems.
Long-term complications	
Incision hernia	After patient discharge, the full-thickness abdominal wall is discontinuous and abdominal contents bulge, with or without obstruction
Pancreatic pseudocyst (2)	Mature, encapsulated collection(s) of fluid with a well-defined wall outside the pancreas, homogenous fluid density, no solid component
Recurrent pancreatitis	A history of two or more episodes with and interval of at least 3 months
Pancreatic exocrine dysfunction	Clinical symptoms were improved by oral pancreatic enzyme use for more than 6 months, with no need to take this drug before the onset of AP
Pancreatic endocrine dysfunction	New onset diabetes after pancreatitis, need oral hypoglycemic drugs or insulin therapy for at least 6 months
Chronic pancreatitis (9)	Patients experience abdominal pain, weight loss, diabetes, and fatty diarrhea, endosonography/CT/MRI imaging shows dilated main duct and side branches, intraductal calcifactions, parenchymal calcifications. The symptoms did not occur before the onset of AP

laparoscopic necrotic tissue debridement, "PCD + VAD" was often used for intervention, and the specific intervention steps have been described in detail in previous studies (11).

Patients in the early group received PCD treatment within 4 weeks of onset, and patients in the delayed group received PCD treatment 4 weeks after onset. After PCD intervention, clinicians determined the next treatment strategy by observing whether the patients' clinical symptoms improved (such as reversal of OF, decrease in body temperature, decrease in inflammatory factors, and reduction of pancreatic necrosis on CT). If the patient's condition improved, current treatment was continued. If the patient's condition deteriorated, VAD treatment was performed. Representative images are shown in **Figure 2**.

Follow-Up

After the patient was discharged, clinicians mainly followed-up the patients through inpatient visits, outpatient visits, telephone, e-mail, and other means. The follow-up period was 6 months. The follow-up mainly included physical examination (whether there was an incision hernia), laboratory examination (such as routine blood tests, biochemistry, and fecal elastase-1), and imaging examination (enhanced CT to evaluate whether there were morphological changes in the pancreas). In addition, patients completed the SF-36, EQ-5D, and Izbicki pain scales to facilitate the evaluation of their recent quality of life. The last follow-up date in this study was June 30, 2021.

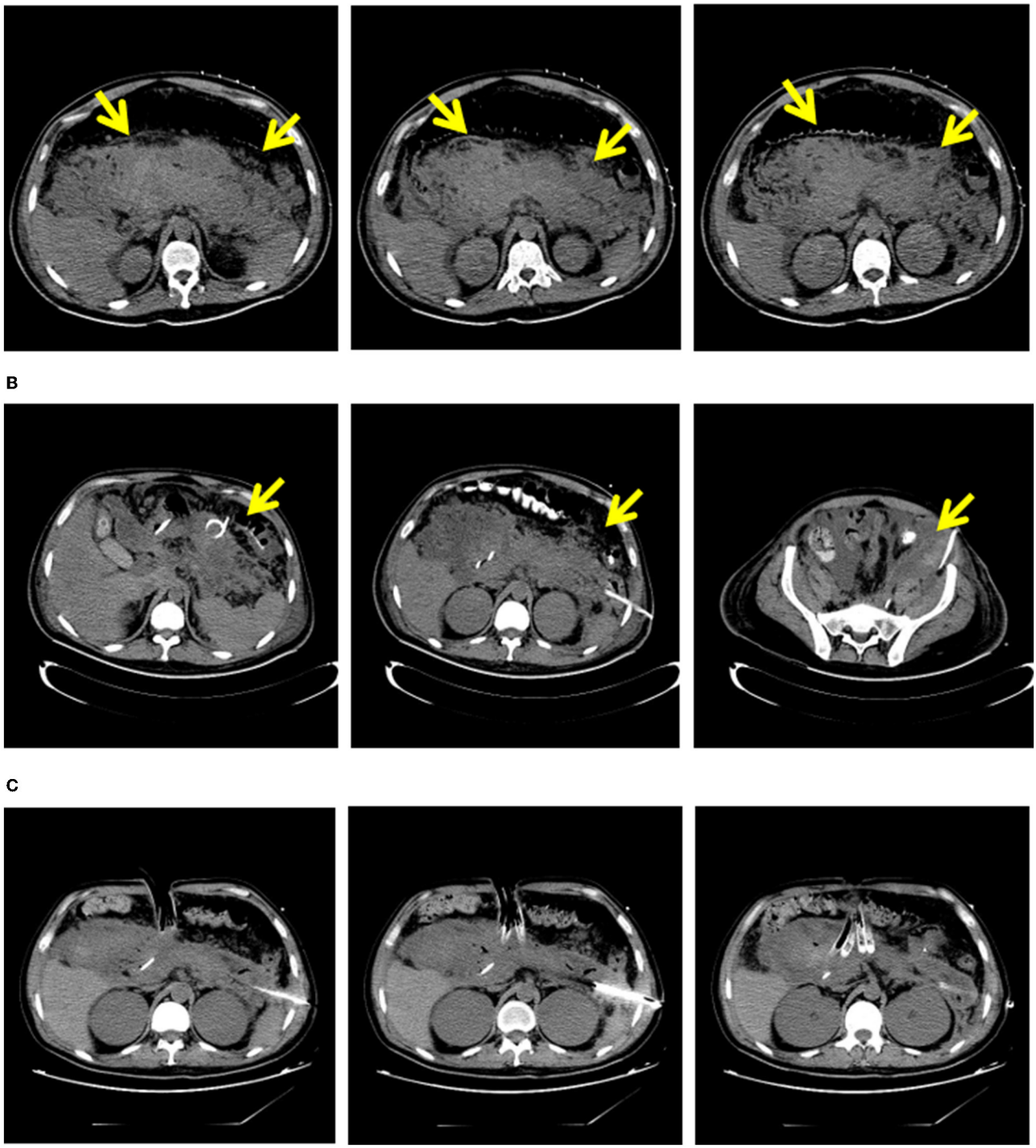

FIGURE 2 | "Step-up" strategy in 32-years-old male with necrosing pancreatitis. **(A)** In 10 days of the onset of patients with pancreatic necrosis area. **(B)** Areas of pancreatic necrosis after PCD. **(C)** Areas of pancreatic necrosis after VAD. PCD, percutaneous catheter drainage; VAD, video assisted debridement.

Statistical Analysis

In this study, Excel 2018 (Microsoft, Redmond, CA, USA) was used to record the clinical data of patients (SPSS 23.0, IBM Corp, Armonk, NY, USA), and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA) was used for statistical analysis. The Shapiro–Wilk test was used to evaluate whether the study

TABLE 2 | Baseline characteristics of acute necrotizing pancreatitis patients.

Characteristics	Early group ($n = 43$)	Delay group ($n = 55$)	*P* value
Gender [*n* (%)]			0.31
Male	28 (65.12)	41 (74.55)	
Female	15 (34.88)	14 (25.45)	
Age [year (mean ± SD)]	44.88 ± 13.70	46.66 ± 14.36	0.538
BMI	23.92 ± 3.94	24.45 ± 4.02	0.521
Etiology [*n* (%)]			0.555
Gallstones	21 (48.84)	29 (52.73)	
Hyperlipidemia	17 (39.53)	16 (29.09)	
Alcohol abuse	0 (0)	2 (3.64)	
Others	5 (11.63)	8 (14.55)	
Systemic disease			0.376
Hypertension	14 (32.56)	8 (14.55)	
Coronary heart disease	3 (6.98)	3 (5.45)	
Diabetes	7 (16.28)	8 (14.55)	
others	23 (53.49)	31 (56.36)	
ASA [score, median (range)]	1 (1–2)	1 (1–3)	0.606
Admission temperature [°C (mean ± SD)]	37.23 ± 1.09	36.74 ± 0.57	0.048*
CTSI [score, median (range)]	8 (4–10)	8 (2–10)	0.495
Extent of necrosis [*n* (%)]			0.603
<30%	12 (27.91)	20 (36.36)	
30–50%	16 (37.21)	20 (36.36)	
>50%	15 (34.88)	15 (27.27)	
Degree of less-enhanced necrotic area [HU (mean ± SD)]	17.76 ± 8.29	17.11 ± 9.70	0.728
Transfer time [days (mean ± SD)]	6.09 ± 2.81	16.75 ± 12.32	0.001*
Transfer [*n* (%)]	33 (76.74%)	45 (81.82%)	0.374
Admission laboratory indicators [mean ± SD]			
WBC (×109/L)	11.46 ± 6.95	10.36 ± 4.75	0.355
Percentage of neutrophils (%)	83.96 ± 9.08	77.99 ± 7.81	0.017*
Hb (g/L)	88.13 ± 21.79	109 ± 35.51	0.019*
Hct (%)	27.69 ± 6.08	30.80 ± 7.58	0.031*
Alb (g/L)	28.12 ± 4.34	29.83 ± 6.29	0.28
CRP (mg/L)	306.15 ± 213.85	175.88 ± 119.01	0.001*
PCT (ng/ml)	1.75 ± 1.35	1.16 ± 1.01	0.02*
IL-6 (pg/ml)	326.36 ± 214.14	203.3 ± 173.34	0.002*

BMI, body mass index; ASA, American Society of Anesthesiologists; CTSI, computer tomography severity index; WBC, white blood cell count; Hb, hemoglobin; Hct, hematocrit; CRP, C-reactive protein; Alb, albumin; PCT, procalcitonin; IL-6, interleukin.
**P < 0.05.*

TABLE 3 | Intervention indications of the two groups.

Characteristics	Early group ($n = 43$)	Delay group ($n = 55$)	*P*-value
Primary indications for intervention [*n* (%)]			
Infection	37 (86.05)	31 (56.36)	0.002*
Gastric outlet obstruction	3 (6.98)	16 (29.09)	0.009*
Abdominal pain	0 (0)	4 (7.27)	0.129
Other indications	3 (6.98)	4 (7.27)	0.955
Initial intervention time [days (mean ±SD)]	15.26 ± 7.08	50.86 ± 19.58	0.001*
Initial intervention [*n* (%)]			
PCD	9 (20.93)	8 (14.55)	0.433
Endoscopic transluminal drainage	0 (0)	1 (1.82)	0.374
Subsequent intervention [*n* (%)]			
VAD	33 (76.74)	43 (78.18)	0.805
Open necrosectomy	1 (2.33)	3 (5.45)	0.629

PCD, percutaneous drainage; VAD, video-assisted debridement.
**P < 0.05.*

data fit the normal distribution. Data with normal distribution were expressed as mean ± standard deviation (M ± SD), and the differences between groups were analyzed using the independent sample t-test. Data with skewed distribution were presented as median (range), and between-group differences were analyzed using the rank sum test. Quantitative data are presented as rates, and differences between groups were analyzed using the chi-square test or Fisher's exact probability method. The Kaplan-Meier method was used for survival analysis. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 98 patients with ANP were included in this study, including 69 men and 29 women, with an average age of 45.88 ± 13.95 years. There were 50 cases of biliary pancreatitis, 33 of hyperlipidemic pancreatitis, two of alcoholic pancreatitis, and 13 of other causes (eight of pancreatitis after ERCP, four of unknown cause, and one of traumatic pancreatitis). Patients with ANP were divided into an early group ($n = 43$) and a delay group ($n = 55$) according to the time from the onset of ANP to the first intervention (≤4 weeks or >4 weeks).

Baseline Data

There were no significant differences between the two groups in terms of sex, age, etiology, body mass index (BMI), American Society of Anesthesiologists (ASA) score, number of combined systemic diseases, or degree of pancreatic necrosis. In terms of admission laboratory indicators, the percentage of neutrophils (83.96 ± 9.08 vs. 77.99 ± 7.81%, $P < 0.05$), C-reactive protein (CRP) (306.15 ± 213.85 vs. 175.88 ± 119.01, $P < 0.05$), procalcitonin (PCT) (1.75 ± 1.35 vs.

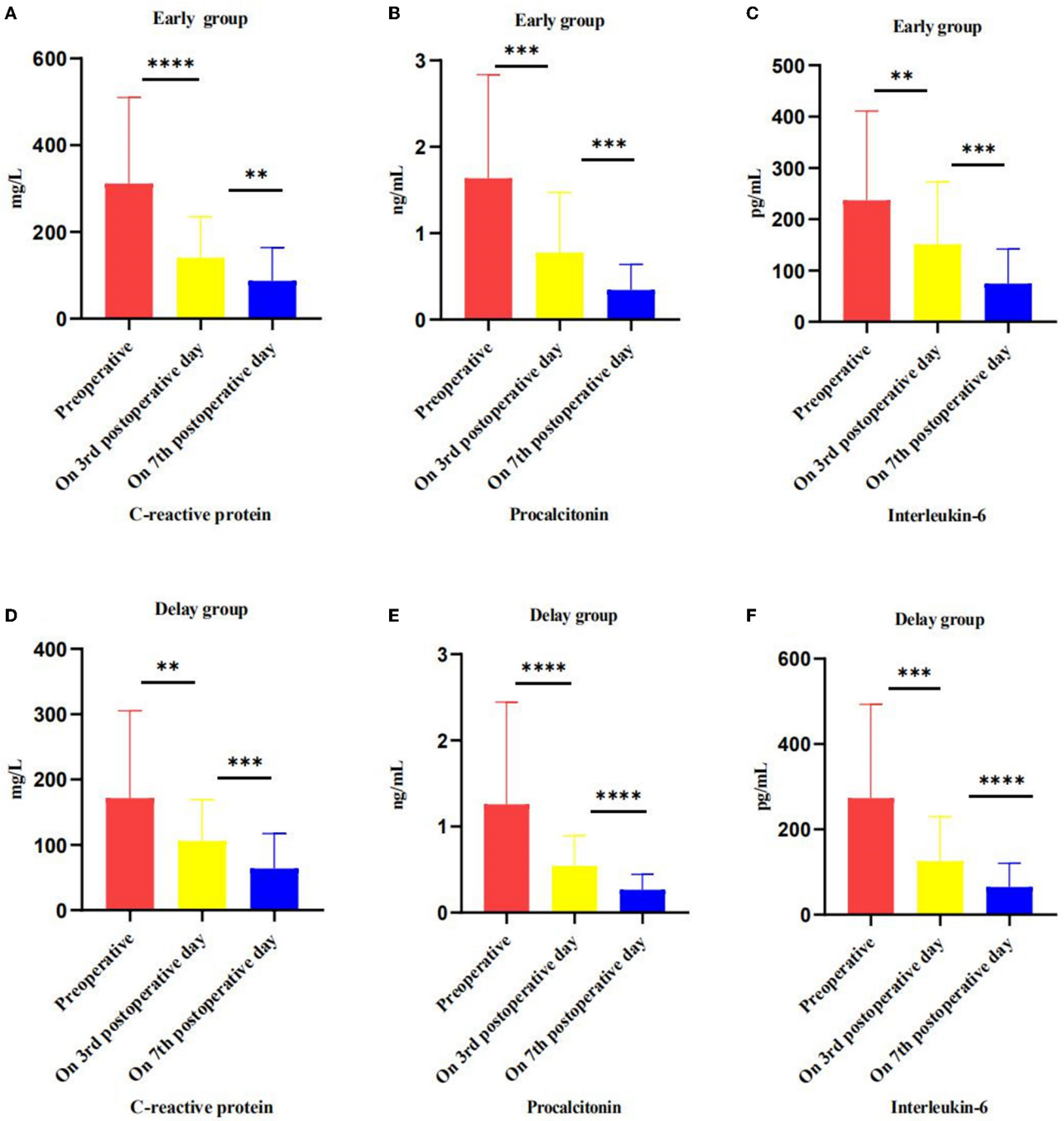

FIGURE 3 | Effect of intervention on inflammatory markers, preoperative, postoperative, and pre-discharge comparison. **(A–C)** In the early group, the level of CRP, PCT and IL-6 change trend in preoperative, on 3 and 7 postoperative days. **(D–F)** In the delayed group, the level of CRP, PCT and IL-6 change trend in preoperative, on 3 and 7 postoperative days. *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$; ****$P < 0.001$.

1.16 ± 1.01, $P < 0.05$) and interleukin-6 (IL-6) (326.36 ± 214.14 vs. 203.3 ± 173.34, $P < 0.05$) in the early group were higher than those in the delay group. In addition, the hemoglobin level in the early group was lower than that in the delay group (88.13 ± 21.79 vs. 109 ± 35.51, $P < 0.05$) (see **Table 2**).

Intervention Indication

The main reason for intervention in the early group was IPN (86.05 vs. 56.36%, $P < 0.05$), while the main reasons for intervention in the delayed group were IPN and digestive tract obstruction (6.98 vs. 29.09%, $P < 0.05$). The time of first intervention in early group was earlier than that in delay group

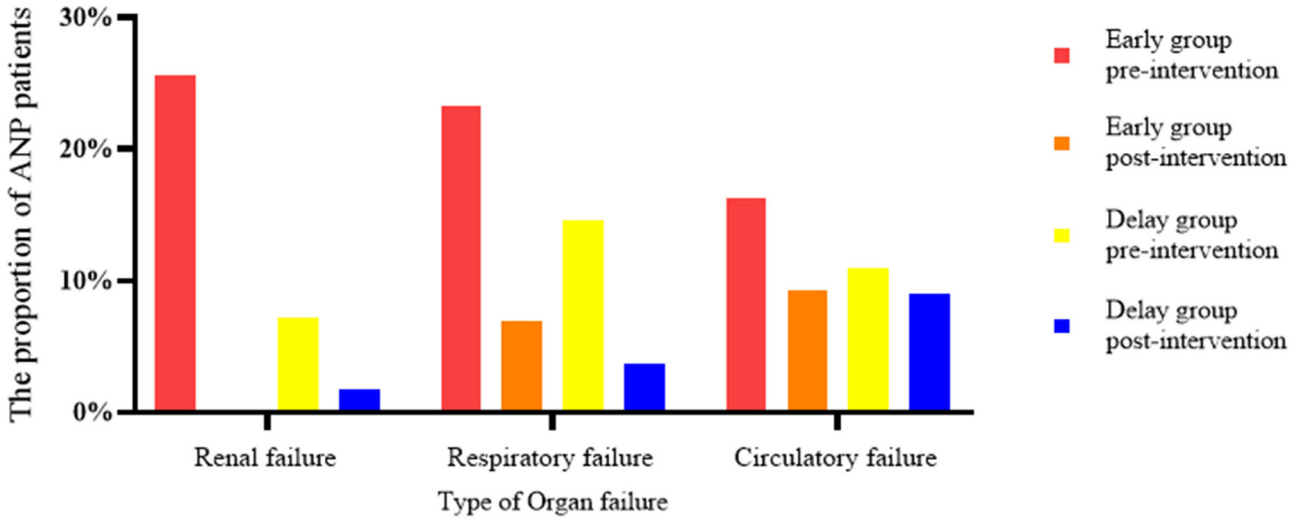

FIGURE 4 | Effect of interventions on organ failure, comparing early vs. delay group. In the early group, the proportion of patients with renal failure decreased from 25.58 to 0%, that of patients with respiratory failure decreased from 23.26 to 6.98%, and that of patients with circulatory failure decreased from 16.28 to 9.30%. In the delayed group, renal failure decreased from 7.27 to 1.82%, respiratory failure decreased from 14.55 to 3.67%, and circulatory failure decreased from 10.91 to 9.09%.

(15.26 ± 7.08 days vs. 50.86 ± 19.58 days, $P < 0.05$). he number of patients who improved after PCD treatment only (20.93 vs. 14.55%, $P > 0.05$) and the number of patients needing VAD treatment (76.74 vs. 78.18%, $P > 0.05$) were similar between the two groups. In addition, one patient in the early group and three patients in the delay group required open necrosectomy (2.33 vs. 5.45%, $P > 0.05$) (**Table 3**). Although the level of preoperative inflammatory factors (CRP, PCT, IL-6) in the early group was higher than that in the delayed group ($P < 0.05$), the level of inflammatory factors in both groups decreased significantly after the intervention. The results are presented in **Figure 3**.

Clinical Outcomes

In terms of clinical outcome, POF was more common in patients in the early group (44.19 vs. 18.18%, $P < 0.05$); however, most of the patients in the two groups had reversed OF after the intervention (**Figure 4**). Although patients in the early group needed minimally invasive intervention more than patients in the delay group [2 (1–7) vs. 2 (1–5), $P < 0.05$], the number of patients in the two groups that needed combined nutritional support (74.42 vs. 65.45%, $P > 0.05$), the duration of enteral nutritional support (22.12 ± 17.30 days vs. 26.87 ± 25.25 days, $P > 0.05$), length of parenteral nutrition support (27.54 ± 22.35 days vs. 29.61 ± 28.51 days, $P > 0.05$), operation cost (26,498 ± 9022.98 vs. 27131.92 ± 8918.18, $P > 0.05$), incidence of postoperative complications (18.60 vs. 18.18%, $P > 0.05$), length of ICU stay (25.32 ± 24.18 days vs. 30.88 ± 29.51 days, $P > 0.05$), total length of hospital stay (40.28 ± 27.52 days vs. 47.76 ± 32.51 days, $P > 0.05$), and mortality during hospitalization (13.95 vs. 10.91%, $P > 0.05$) were not significantly different (**Table 4**).

Follow-Up

During the follow-up period, seven patients died, eight patients were lost to follow-up, and 71 patients survived. Among them, three patients died, three patients were lost to follow-up, and 31 patients survived in the early group; in the delayed group, four patients died, five patients were lost to follow-up, and 40 patients survived. The overall survival rates of the two groups were 91.18% (31/34) and 90.91% (40/44), respectively (**Figure 5**).

There were no significant differences in the follow-up time (42.83 ± 25.74 vs. 41.74 ± 27.09, $P > 0.05$), pancreatic pseudocyst (8.11 vs. 4.08%, $P > 0.05$), incisional hernia (5.41 vs. 4.08%, $P > 0.05$), recurrent acute pancreatitis (24.32 vs. 8.16%, $P > 0.05$), new onset pancreatic endocrine insufficiency (29.73 vs. 14.28%, $P > 0.05$), pancreatic exocrine insufficiency (13.52 vs. 16.33%, $P > 0.05$), and chronic pancreatitis (2.70 vs. 6.12%, $P > 0.05$) (**Table 5**).

In the quality-of-life rating scale, there was no statistically significant difference in the SF-36 physical or mental health score, EQ-5D health status score, or Izbicki pain score between the groups (**Table 6**).

DISCUSSION

There has always been controversy over the timing of intervention with "step-up" strategies. Some pancreatic experts supported antibiotic treatment first and puncture treatment after necrosis wrapping, these experts believe that: (1) in the early stage of the disease, the boundary between the scope of pancreatic necrosis and normal tissue is blurred. Early intervention causes great trauma to patients and is more prone to postoperative complications. (2) Some patients can improve after conservative treatment with antibiotics without intervention. Other pancreatic experts still believe that minimally invasive intervention should be performed immediately after the diagnosis of IPN (6). They considered that: (1) the concept of "delayed intervention" comes from the era of open surgery, and it is controversial whether it is applicable to the current

TABLE 4 | Comparison of clinical outcomes between two groups.

Characteristics	Early group ($n = 43$)	Standard group ($n = 55$)	*P* value
Primary composite outcomes			
Mortality [*n* (%)]	6 (13.95)	6 (10.91)	0.76
Secondary outcomes			
Persistent organ failure	19 (44.19)	10 (18.18)	0.007*
Single organ failure	10 (23.26)	2 (3.64)	
Multiple organ failure	9 (20.93)	8 (14.55)	
Renal failure	11 (25.58)	4 (7.27)	0.022*
Respiratory failure	10 (23.26)	8 (14.55)	0.302
Circulatory failure	7 (16.28)	6 (10.91)	0.552
Nutritional support [*n* (%)]			0.383
Only parenteral nutrition	11 (25.58)	19 (34.55)	
Enteral and parenteral nutrition	32 (74.42)	36 (65.45)	
Duration of nutritional support [days (mean ± SD)]			
Parenteral nutrition	27.54 ± 22.35	29.61 ± 28.51	0.685
Enteral nutrition	22.12 ± 17.30	26.87 ± 25.25	0.795
Number of operations [time median (range)]	2 (1–7)	2 (1–5)	0.03*
Surgical complications [*n* (%)]			0.794
Intraabdominal hemorrhage	2 (4.65)	4 (7.27)	
Gastrointestinal fistula	2 (4.65)	2 (3.64)	
Gastrointestinal obstruction	2 (4.65)	4 (7.27)	
Others	2 (4.65)	0 (0)	
Operation cost (RMB)	26,498 ± 9,022.98	27,131.92 ± 8,918.18	0.749
ICU stay [days (mean ± SD)]	25.32 ± 24.18	30.88 ± 29.51	0.844
Total hospital stay [days (mean ± SD)]	40.28 ± 27.52	47.76 ± 32.51	0.211

ICU, intensive care unit.
*$P < 0.05$.

era of minimally invasive surgery (12); and (2) in the era of minimally invasive approach, PCD is not technically difficult, and in other abdominal cases requiring PCD, drainage before necrotic wrapping has been a very common practice (13). Theoretically, timely drainage of pancreatic necrotic tissue rich in inflammatory factors is conducive to reducing systemic inflammatory response syndrome (SIRS), avoiding further clinical deterioration, and improving the prognosis of patients. In addition, PCD can reduce abdominal pressure and the risk of abdominal compartment syndrome. Furthermore, early PCD intervention can control the source of infection and speed up the encapsulated necrotic tissue (14).

By comparing the clinical data of patients in the early and delayed groups, this study defined the indications for early PCD intervention in patients with ANP. Compared with delayed intervention, early intervention did not increase mortality, incidence of postoperative complications, operation cost, or length of hospital stay. In the long-term follow-up, the overall survival and long-term complication rates of the two groups were similar. It has been further confirmed that early PCD intervention is an effective and safe treatment strategy for ANP patients with deterioration (such as POF or IPN) in the early stages of the disease.

Previous studies have pointed out that 18% of ANP patients were diagnosed with IPN (bubble sign) 3 weeks before the onset, 43% developed package necrosis 3 weeks before the onset, and have intervention indications in the early stage of the disease (15). In a large-scale multicenter study of the Dutch pancreatitis study group, the early group received PCD intervention within 24 h, and the delayed group received PCD intervention as late as 4 weeks after onset on the basis of antibiotics, and 39% of patients in the delayed group improved after conservative treatment with antibiotics, confirming the effectiveness of antibiotics in IPN patients. Although the comprehensive complication index score and mortality of the two groups were similar, it did not prove the superiority of early intervention in the treatment of patients with IPN. It is only suggested that early PCD intervention can be considered for IPN patients with rapid clinical deterioration (7). In this study, patients in the early group received PCD intervention after the failure of conservative antibiotic treatment. The first PCD intervention in most patients in the early group was between 2 and 3 weeks after onset. In addition, only 18.37% of patients with ANP showed improvement after PCD intervention. This is lower than the 35–51% reported by other research institutes (3, 7, 9, 16, 17). It may be that our hospital is one of the largest acute pancreatitis diagnosis and treatment centers in northern China. Approximately 80% of patients were referred from other hospitals, and some patients were referred to our hospital after the PCD intervention failed, and the condition was relatively serious. We believe that for ANP patients with suspected or confirmed IPN, the timing of early intervention should be determined according to the changes in the patients' condition after conservative treatment with antibiotics.

Although the current guidelines recommend that patients with ANP with suspected or confirmed infection should be treated conservatively with antibiotics, some patients still deteriorate after conservative treatment, suggesting that conservative treatment may not be applicable to all patients with IPN (5). In the expert consensus of the American Gastroenterology Association on the management of pancreatic necrosis, PCD should be considered when patients are suspected of having IPN and conservative treatment fails (18). A retrospective study based on a prospective database pointed out that in ANP patients, although early intervention is conducive to reducing the inflammatory response and improving it compared with delayed intervention, it is considered that early intervention is more suitable for ANP patients with IPN and/or POF (17). A single center RCT study of the Chinese acute pancreatitis clinical trial group found that early intervention may benefit ANP patients with POF (14), and further multicenter studies were conducted to clarify the early intervention indications of ANP patients (19). In this study, the body temperature and inflammatory factor levels of patients in the early group were significantly higher than those in the delayed group, suggesting that patients in the early group had more SIRS

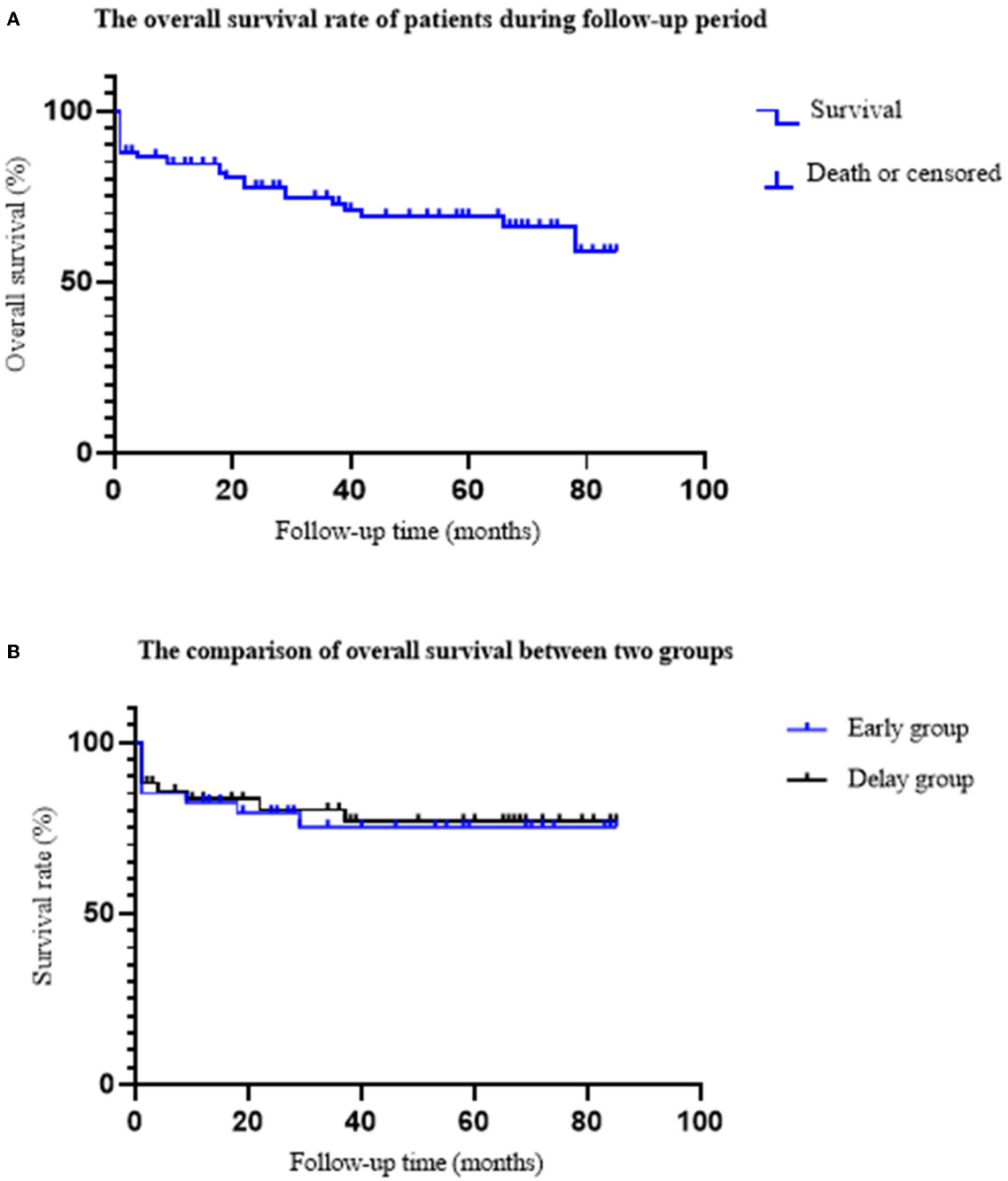

FIGURE 5 | The comparison of overall survival rate between two groups. **(A)** The overall survival rate of ANP patients. A total of 19 patients died, eight patients were lost follow-up, and 71 patients survived. The average follow-up time was 40.17 ± 26.36 months. **(B)** The comparison of the overall survival rate between the two groups. In the early group, nine patients died; six patients died during hospitalization, and three patients died during follow-up. In the delayed group, 10 patients died; six patients died during hospitalization and four patients died during follow-up. The overall survival rates of early group and delayed group were 91.18 and 90.91%, respectively ($P = 0.967$).

caused by ANP. With the extension of SIRS duration, patients are more likely to have OF and IPN, and sepsis caused by IPN may induce or aggravate OF, resulting in an increased risk of disease deterioration and death (20–22). In our study, about 44.19 and 86.05% patients in the early group have POF and IPN, respectively, which were significantly higher than those in the delayed group, also supporting this opinion. After PCD intervention, the inflammatory factor levels of ANP patients decreased significantly, and most patients with POF were successfully separated from organ support treatment. The

TABLE 5 | The long-term complication between the two groups during the follow-up period.

Characteristics	Early group ($n = 31$)	Delay group ($n = 40$)	*P* value
Follow-up time (months)	42.83 ± 25.74	41.74 ± 27.09	0.858
Long-time complications [*n* (%)]			
Pseudocyst	3 (9.68)	2 (5)	0.647
Incision hernia	2 (6.45)	2 (5)	0.792
Recurrent pancreatitis	9 (29.03)	4 (10)	0.062
New onset endocrine insufficiency [*n* (%)]			0.104
Oral medication	9 (29.03)	6 (15)	
Insulin	2 (6.45)	1 (2.5)	
Pancreatic exocrine insufficiency [*n* (%)]			0.946
Diet adjustment	1 (3.23)	0 (0)	
Enzyme use	5 (16.13)	8 (20)	
Chronic pancreatitis [*n* (%)]	1 (3.23)	3 (7.5)	0.627
Pancreatic cancer [*n* (%)]	0 (0)	0 (0)	0
Clinical symptoms [*n* (%)]			0.268
Bloating	3 (9.68)	5 (12.5)	
Weight loss	6 (19.35)	2 (5)	

TABLE 6 | Quality of life rating scale during the follow-up period of surviving acute necrotizing pancreatitis patients.

Rating scale (mean ± SD)	Early group ($n = 31$)	Standard group ($n = 41$)	*P*-value
SF-36 Physical health score[a]	40.54 ± 7.58	37.00 ± 13.89	0.18
SF-36 Mental health score[a]	45.03 ± 8.45	40.91 ± 15.24	0.157
EQ-5D based health status score[b]	71.40 ± 13.99	67.79 ± 25.99	0.463
Lzbicki pain score[c]	17.31 ± 13.85	13.47 ± 12.83	0.207

[a] *SF-36, Short Form-36. The SF-36 physical and mental health scores range from 0 to 100. The higher the score, the better the quality of life.*

[b] *EQ-5D, Euroqol-5 dimensions. The scores also range from 0 to 100, and the higher the score, the better the health.*

[c] *The higher the Izbicki pain score, the more severe is the discomfort. The Izbicki pain score scale includes four parts (ranging from 0 to 100 per part); the sum of the values of the four parts is divided by 4.*

number of patients with OF remission in the early group was greater than that in the delayed group, suggesting that early PCD intervention is conducive to controlling SIRS and reversing OF.

In terms of clinical outcomes, the overall mortality of patients in this study was 12.24%, which is similar to the mortality reported in endoscopic or surgical early intervention ANP studies in recent years (7.8–30%) (7, 14, 17). Although there was no significant difference between the two groups in terms of the length of nutritional support, incidence of postoperative complications, operation cost, length of ICU stay and mortality. But the number of surgical interventions in the early group was greater than that in the delayed group, combined with the patient's admission condition and the number of patients with POF was more than those in the delayed group, affect the rise of the number of interventions.

Through the long-term follow-up of patients with ANP after discharge, it was found that there was no significant difference in the overall survival rate and the incidence of long-term complications (incision hernia, new pancreatic endocrine insufficiency, PEI, etc.) between the two groups. This further confirms that early PCD intervention is safe and effective for patients with ANP. Previous studies have reported that IPN intervention may cause damage to adjacent pancreatic tissues, resulting in a decline in the pancreatic reserve and secretion function; 21% AP patients have RAP, and ∼8% of RAP patients progress to chronic pancreatitis (CP) (23), 27% have PEI, and 37% have new pancreatic endocrine insufficiency during follow-up (24, 25). This aggravates the medical burden on patients and affects their quality of life. A study by Firkins et al. (26) confirmed that age (50–64 years old), male sex, low economic level, Elixhauser comorbidity index $\geq$ 3 points, components of metabolic syndrome, severe AP (SAP), and RAP are risk factors for pancreatic endocrine dysfunction, while alcoholic etiology, SAP, or ANP are high-risk factors for PEI (23, 25). Sanchez et al. (27) found that triglyceride levels were positively correlated with the risk of RAP by retrospectively collecting clinical data of patients with AP in the United States. Therefore, clinicians should strengthen the publicity and education of AP-related complications, closely monitor AP patients with high-risk factors (such as laboratory examination and imaging evaluation), and follow-up regularly to prevent and delay the occurrence of long-term complications of AP.

However, this study also has some limitations: firstly, this was a retrospective study and some of the patients were referred from other hospitals. The reason for an early or late intervention is not clear, clinical indicators were affected by the details of the clinical data at the time of referral, and there may be some statistical bias. Secondly, the first PCD intervention in some patients was performed in other hospitals. The clinical experience and operation level of pancreatic surgeons in different hospitals may also affect patient prognosis. Third, we did not compare the effect of endoscopic intervention on patients with necrotizing pancreatitis.

CONCLUSIONS

Compared to delayed intervention, early intervention did not affect the prognosis of patients with ANP. For ANP patients with deterioration (such as POF) in the early stages of the disease, early intervention may be more suitable than conservative treatment. In view of the complex and changeable condition changes of ANP patients, further

multicenter clinical trials with large sample sizes are needed to verify and identify the potential beneficiaries of early intervention.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

FL designed and performed the research. YD and Y-LF carried out the studies and participated in collecting data. YG, WM, YQ, and Y-LF performed the statistical analysis and participated in its design. JL, FC, and ZZ wrote the manuscript. FL revised the manuscript. All authors read and approved the final manuscript.

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COVID-19 and Acute Cholecystitis Management: A Systematic Review of Current Literature

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Introduction: Since the beginning of the COVID-19 pandemic, many patients with clinically acute presentations have been approached differently. The fear of viral transmission along with the short period of study made patients delay their hospital visits and doctors reassess the approach of certain acute situations. This study aimed to assess the changes in the management of patients with acute cholecystitis before and during COVID-19.

Methods: A systematic review of the literature using PubMed (MEDLINE), Scopus, and ScienceDirect databases was performed until 01 September 2021. Totally, two kinds of studies were included, those assessing the management of acute cholecystitis during COVID-19 and those comparing the periods before and during the pandemic. The outcomes recorded include management approaches, complications, and mean length of stay.

Results: A number of 15 eligible articles were included in the study. During the pandemic, six studies revealed a shift toward conservative management of acute cholecystitis and five of them reported that conservative management was opted in 73% of the patients. On the contrary, data from all studies revealed that the surgical approach was preferred in only 29.2% of patients. Furthermore, when comparing the periods before vs. during COVID-19, the conservative approach was reported in 36.3 and 43.2% before vs. during COVID-19, respectively, whereas surgical intervention was performed in 62.5% of patients before COVID-19 and 55.3% during the pandemic. The length of stay was delayed when a non-surgical approach was selected in most studies. Complications, mainly classified by the Clavien-Dindo scale, were higher in the pandemic period.

Conclusion: A tendency toward more conservative approaches was observed in most studies, reversing the previously used surgical approach in most cases of acute cholecystitis. In most of the examined cases during the COVID-19 pandemic, antibiotic treatment and percutaneous cholecystostomy were much more considered and even preferred.

Keywords: acute cholecystitis, COVID-19, antibiotics treatment, conservative treatment, percutaneous cholecystostomy

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INTRODUCTION

Acute cholecystitis is an emergency condition, most commonly the result of gallbladder disease, and is usually presented with right upper abdominal pain, pain in the right shoulder, nausea, vomiting, and occasionally fever. During 2012, in the United States, it was the sixth most common gastrointestinal and pancreatic diagnosis from emergency department visits, accounting for a total of 651,829 emergency department visits and 389,180 hospital admissions, amounting to 0.7 per 100,000 mortality rate (1).

According to the World Emergency Surgery Association (WSES) (2) and the Tokyo Guidelines (3), early laparoscopic surgery is the gold standard and should be performed as soon as the diagnosis is made and the choledocholithiasis risk is evaluated. This approach results in a shorter length of stay (LOS), fewer complications in comparison to late cholecystectomy, and generally decreased recurrence rates. Patients who are at high risk of morbidity or mortality should undergo conservative treatment and in case of failure, percutaneous cholecystostomy (PC) could serve as an alternative (2, 3).

During 2019, a new coronavirus named SARS-CoV-2 was identified. The related disease had a great social and financial global impact and was soon recognized as a pandemic (4). During such times, the worldwide healthcare systems and the management of surgical interventions were compromised. Due to the increased rate of hospitalizations, many organizations amended their guidelines to limit admission rates, so that they could free up space for possible patients infected with COVID-19 and limit patient exposure in a heavily infected environment. Based on this, organizations such as the British Intercollegiate General Surgery Guidance (BIGSG) (5), the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) (6), and the European Association for Endoscopic Surgery (EAES) (7) have stated that a more conservative approach to surgery, which means antibiotic therapy, PC, and "watchful waiting," is preferred, whenever possible, in acute cholecystitis (5–7). On the other hand, WSES highly suggests that laparoscopic cholecystectomy should remain the standard of care even in the setting of the COVID-19 pandemic and warns against the excessive use of PC (8).

The rationale for this study is that no systematic review currently examines the shift toward a more conservative approach in the management of acute cholecystitis and the related outcomes in the COVID-19 era. This research aims to assess the impact of COVID-19 on acute cholecystitis management and its treatment.

METHODS

A systematic review of the literature was performed. The studies evaluating the management of acute cholecystitis during the COVID-19 period, as well as those comparing COVID-19 and non-COVID-19 periods, were included. Case reports, case series, abstracts, congress proceedings, and non-English language reports were excluded from our review. Studies with less than 15 patients were also excluded. The outcome measures taken into consideration were the rates of different management strategies during both the pandemic period and as a comparison between COVID-19 and pre-COVID-19 period. The rates of complications and mean LOS during those periods were also examined.

Literature Search

The two independent researchers (SK and LI) performed a literature search using PubMed (MEDLINE), Scopus, and ScienceDirect on 01 September 2021. The search terms used were "COVID-19" OR "SARS-CoV-2" AND "Acute Cholecystitis." Review articles were hand-searched to identify any remaining studies. The preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines (**Figure 1**) were followed (9). A registered review protocol was not used; however, the search strategy of one database (PubMed) is reported in the **Supplementary Material**.

Data Collection and Analysis

The same two independent researchers screened titles and abstracts produced through our search strategy, and full texts of relevant articles were obtained. Eligibility was independently assessed by each author. One of the senior authors acted as a mediator whenever there was a disagreement between the two main reviewers with regards to the inclusion or exclusion of a paper. The quality of each study was assessed using the Oxford level of evidence (10). Data retrieved from each paper included the country and duration of the study, the type of study, the level of evidence, the patient number, the age, and the gender. Primary outcomes consisted of types of management of acute cholecystitis during the COVID-19 period and comparison of different treatments during the COVID-19 and pre-COVID-19 period. Secondary outcomes consisted of complication rates and mean LOS between those periods. Excel® (Microsoft, Redmond, WA, USA) was used for data handling and analysis. Each author was independent and blinded at the time of the data extraction.

RESULTS

Search Results and Study Characteristics

A total of 334 potential articles were identified from the search of electronic databases. A total of 39 full-text articles were assessed for eligibility and 15 articles dated since 2019 were included in the study (11–25) (**Figure 1**). Three research studies were conducted in Italy, three in Turkey, two in Spain, one in the United Kingdom, one in New Zealand, one in the United States, one in Egypt, one in Austria, one in Switzerland, and one in Ireland. In terms of the study design, cohort studies and one survey reporting data regarding the three different approaches for acute cholecystitis were included (**Table 1**).

Primary Outcomes

During COVID-19

In 6 studies, there were 475 patients in total that were diagnosed with acute cholecystitis. Among which, five of these assessed patients in a specific timeframe during the pandemic period, whereas one study differentiated patient management based on

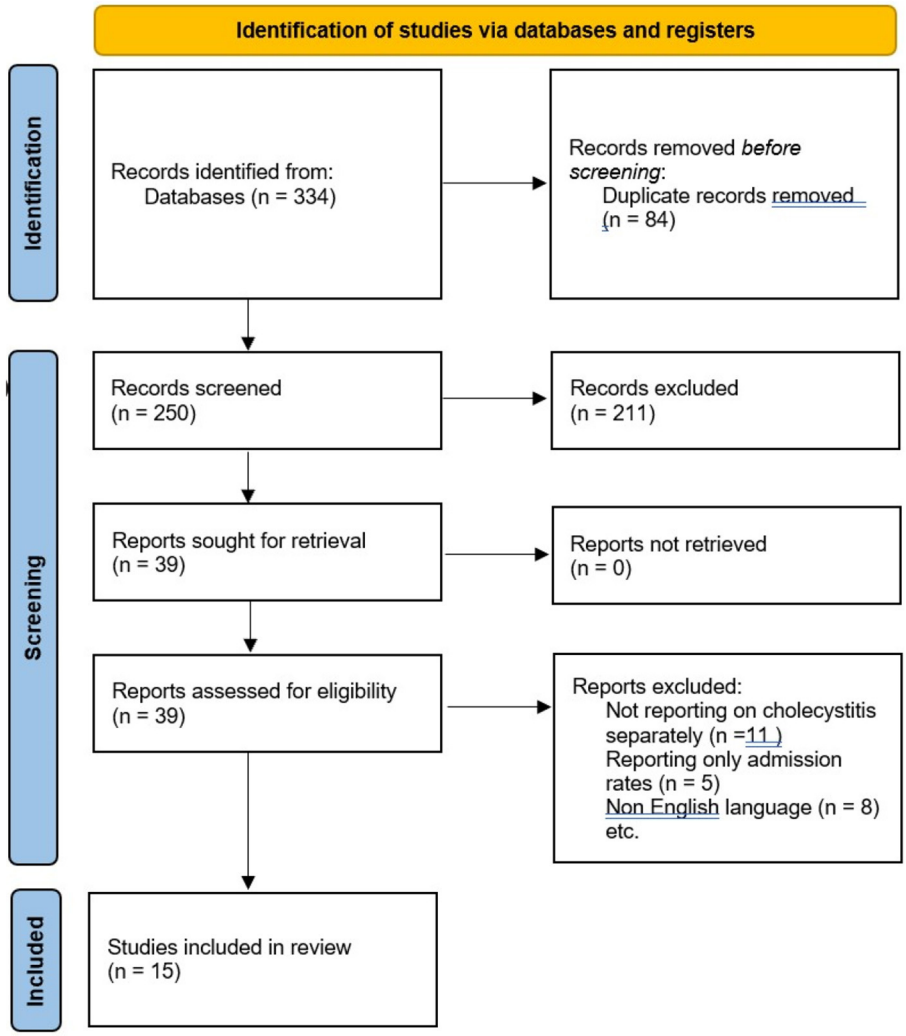

FIGURE 1 | Preferred reporting items for systematic review and meta-analyses (PRISMA) 2020 flow diagram for study selection.

the lockdown and pre-lockdown period. Data reported from all three categories in between the studies indicated that the most commonly selected approach was the non-surgical one with a total of 160/218 patients (73%). This approach consisted of either conservative management and sole use of antibiotics for 127 (58%) patients or PC for 33 (15%) patients. Martínez Caballero et al. (18) did not report exact numbers on all three categories, but it clearly indicates a shift toward conservative management. On the other hand, surgery was the selected approach for 139/475 patients (29.2%). This arguably low percentage could be attributed to the result of the growing concern of clinicians on the risks of laparoscopic operations (**Table 2**).

Before vs. During COVID-19

The different decisions concerning the management of patients with acute cholecystitis during the COVID-19 era in comparison with the pre-COVID-19 period were a matter of discussion in 9 studies. A total of 1,333 patients were studied before and 1,235 after the onset of the pandemic. Four studies reported numbers in all three different approaches regarding acute cholecystitis management and are therefore examined together (13, 15, 16, 23). Combining the results of these studies, 344 patients were examined before and 497 during the COVID-19 period. In total, conservative management was the preferred option in 125 patients (36.3%) before and 215 (43.2%) during the COVID-19 era. Surgical management was reported in 215 patients (62.5%) before and 275 (55.3%) during the pandemic. One study showed a relative increase in the number of PCs performed during the COVID-19 period (23). These results indicate that throughout the pandemic, there has been a slide tendency toward conservative management, whereas the surgical approach is less considered compared to the pre-COVID-19 period. Three studies, which only presented surgical data concerning acute cholecystitis management, reported, in total, 107 patients previously managed operatively vs. 68 patients during the pandemic (14, 15, 25). Another study showed that there was a

TABLE 1 | Characteristics of different studies.

References	Country	Duration	Multicenter	Type	N	Males	Age	Level of evidence (Oxford)
Barabino et al. (12)	Italy	27 Feb-30 April 2020	No	Retrospective Cohort	37	21	64	2b
Martínez Caballero et al. (18)	Spain	01 March to 30th May 2020	Yes	Combined (Retrospective–Prospective) Cohort	257	146	69	2b
Shakir et al. (19)	UK	30 March 2020-26 April 2020	No	Retrospective Cohort	16	NA	56	2b
Hugo et al. (14)	Turkey	March 11 and May 31, 2020	No	Retrospective Cohort	72	32	57.3	2b
Perrone et al. (15)	Turkey	March 10 and June 10, 2020	No	Retrospective Cohort	36	17	68	2b
McGuinness et al. (22)	New Zealand	22 February to 25 2020 and 26 March to 27 April 2020	No	Retrospective Cohort	57	NA	NA	2b
Farber et al. (23)	USA	March and June, 2019- March and June 2020	No	Retrospective Cohort	53–80	55–68	46.7–48.8	2b
Fouad et al. (11)	Egypt	June 15, 2019 to March 15, 2020- March 16, 2020 to March 16, 2021	Yes	Prospective Cohort	458–311	118–103	40.2–41.1	2b
Kurihara et al. (24)	Italy	21 February to 3 April 2019, same 2020	Yes	Survey	468–376	NA	NA	N/A
Presl et al. (25)	Austria	01 March−15 April 2019, same 2020	Yes	Retrospective Cohort	33–20	NA	NA	2b
Surek et al. (13)	Turkey	14 March−15 May 2019, same 2020	No	Retrospective Cohort	55–29	NA	NA	2b
Hugo et al. (14)	Switzerland	15 March to 20 April 2019, same 2020	Yes	Retrospective Cohort	30–31	10–15	51–54	2b
Perrone et al. (15)	Italy	March and April 2019, same 2020	No	Retrospective Cohort	34–17	NA	NA	2b
Guadalajara et al. (16)	Spain	March 14th to May 2nd 2019, same 2020 and 2021	Yes	Retrospective Cohort	169–130–219	102–76–115	66–70–64	2b
Kamil et al. (17)	Ireland	1 March to 31 May, same 2020	No	Retrospective Cohort	33 22	NA	NA	2b

NA, not applied; N, number of patients with acute cholecystitis.

shift toward the initial surgical approach of the patients (11). During the pre-COVID-19 era, a total of 458 patients admitted with confirmed cholecystitis were managed surgically following an average of 2.21 days from clinical presentation, whereas during the COVID-19-era, a total of 389 admitted patients were initially managed conservatively with intravenous antibiotics followed by oral antibiotics and PC when required. Out of the 389 non-surgically managed patients, 311 (79.94%) failed to comply with these treatments and were on average operated within 16.74 days from clinical presentation. The results revealed that after the initial conservative management, the inflammatory status progressed and equally the severity score significantly worsened, thus increasing the difficulties and complications during the intraoperative and postoperative periods (11). Finally, another study indicated a shift toward conservative treatment. In detail, during the pandemic, there was an increase of 200% in the use of PC ($n = 6$ vs. $n = 2$) and a 30.7% decrease in cholecystectomies performed ($n = 61$ vs. $n = 88$) (24) (**Table 3**).

TABLE 2 | Management of acute cholecystitis during COVID-19.

References	A.C number	Antibiotics	P.C	Surgery
Barabino et al. (12)	37	11	8	18
Martínez Caballero et al. (18)	257	NA	NA	81
Shakir et al. (19)	16	16	0	0
Hugo et al. (14)	72	61	11	0
Somuncu et al. (21)	36	14	14	8
McGuinness et al. (22)	57	25	0	32
Total	475	NA	NA	139

A.C, acute cholecystitis; P.C, percutaneous cholecystostomy; NA, not applied.

Secondary Outcomes

During COVID-19

A total of six studies that presented data during the pandemic period were evaluated taking into account the mean LOS as an outcome of their strategy (**Table 2**). In one study, results regarding LOS were not clearly stated (19). McGuinness and Hsee (22) retrospectively performed a comparison of the mean LOS before and during the lockdown period and found no statistically different results between the two periods. Moreover, two studies compared the mean LOS between PC and either conservative or laparoscopic approaches. Ciyiltepe et al. (20) reported an increase in the mean LOS in patients who underwent PC (9.2

TABLE 3 | Management of acute cholecystitis before vs. during COVID-19.

References	A.C number Before vs. During	Antibiotics Before vs. During	P.C Before vs. During	Surgical Before vs. During
Farber et al. (23)	53 vs. 80	4 vs. 12	4 vs. 7	45 vs. 61
Fouad et al. (11)	458 vs. 389	0 vs. NA	0 vs. NA	458 vs. 311
Kurihara et al. (24)	468 vs. 376	NA	2 vs. 6	88 vs. 61
Presl et al. (25)	33 vs. 20	0	0	33 vs. 20
Surek et al. (13)	55 vs. 29	38 vs. 24	0	17 vs. 5
Hugo et al. (14)	30 vs. 31	0	0	30 vs. 31
Perrone et al. (15)	34 vs. 17	0	0	34 vs. 17
Guadalajara et al. (16)	169 (2019) vs. 130 (2020) vs. 219 (2021)	54 (2019) vs. 89 (2020) vs. 69 (2021)	0	115 (2019) vs. 41 (2020) vs. 150 (2021)
Kamil et al. (17)	33 vs. 22	29 vs. 21	0	4 vs. 1

A.C, acute cholecystitis; P.C, percutaneous cholecystostomy; NA, not applied.

TABLE 4 | Complications before vs. during COVID-19.

References	Before COVID-19	During COVID-19
Perrone et al. (15)	0	1 death
Hugo et al. (14)	1 CDI (1%), 4 CDI (5%), 0 CDIII	1CDI (3%), 5CDII (7%), 2CDIII (3%)
Kurihara et al. (24)	NA	NA
Presl et al. (25)	NA	NA
Kamil et al. (17)	Inpatient 10 (16%), transaminitis 1 (2%)	Inpatient 11 (13%), 4 Sepsis (5%), 1 intra-abdominal abscess (1%), transaminitis 1 (1%), 1 death (1%)
Fouad et al. (11)	CDI (1.3%), CDII (6.3%), CDIIIa (0%), CDIIIb (0.21%), CDIVa (0.44%), CDIVb (0%)	CDI (11.6%), CDII (8.9%), CDIIIa (6.4%), CDIIIb (7.1%), CDIVa (2.6%), CDIVb (0%)
Guadalajara et al. (16)	Any CD grade: 28 (16.5%)	Any CD grade: 2020: 33 (25.2%) 2021: 33 (15%)
Kamil et al. (17)	1 CDII	1CDI, 3CDII
Surek et al. (13)	NA	NA

CD, clavien-dindo classification; NA, not applied.

days) compared to patients who were managed conservatively (3.9 days). Somuncu et al. (21) compared the mean LOS between PC and laparoscopic approach and subsequently reported an increase of LOS in the PC group. In a third study, the researchers found a similar post-procedural mean LOS of 9 days in patients who underwent PC (12). Finally, Martínez Caballero et al. (18) after comparing the mean LOS between surgical and non-surgical approaches revealed a statistically significant increase in the mean LOS, when non-surgical management was applied (9.74 vs. 4.48, $p = 0.001$).

As far as complications are concerned, mainly based upon the Clavien-Dindo classification (26), there were no surprising data to report. In two of the studies, only one complication was observed in each of them. More specifically, in the study by Somuncu et al. (21) there was one (7.1%) mortality due to cardiac arrest in the group of patients who underwent PC. Moreover, in the study by Barabino et al. (12) one out of the 8 patients who underwent a cholecystostomy experienced an immediate complication (transient parietal bleeding) requiring conservative treatment (blood transfusion and intravenous infusion of tranexamic acid). The study by Martínez Caballero et al. (18) reported an overall postoperative complications rate of 26%, with the most frequent ones classified as Clavien–Dindo grade I (70.1%, $p < 0.01$), while severe complications (grades IV–V) were noticed in 14.9% of patients. Mortality rate was 1.3 and 3.2% ($p = 0.075$) in surgical and non-surgical treatment groups, respectively. Mortality after PD was significantly higher (15.1%, $p = 0.001$) compared to cholecystectomy (1.2%) and antibiotic therapy (2.4%).

Before vs. During COVID-19

A total of nine studies evaluating patients with acute cholecystitis before and during the pandemic period compared the results between the aforementioned periods. Out of all studies, six of them measured the mean LOS as a secondary outcome of their research, while in the rest, results regarding the mean LOS were not applied. In general, all studies reported an increase in the mean LOS during the COVID-19 period, which suggests an unsuccessful approach for the management of acute cholecystitis during the pandemic. Two studies found a statistically significant increase in the average LOS during the pandemic period compared to the pre-COVID-19 era (11, 15). Fouad et al. (11) reported the most significant difference in the average LOS between the two periods (13.5 days in 2020 vs. 2.6 days in 2019). It is of high importance to mention that the low average LOS of the pre-COVID-19 period is a result of a complete surgical strategy, whereas, in 2020, conservative management was also applied. Farber et al. (23) reported similar results regarding median hospital LOS in surgically managed patients between the two periods. Finally, Guadalajara et al. (16) found a prolonged LOS in 2020 (6 days) compared to 2019 and 2021 (4 days both). This observation can be explained by the selection of conservative treatment and the fewer laparoscopy rates during the first wave of the pandemic, which can be attributed to concerns about the transmission of the virus with aerosolization.

As far as the complications are concerned, the majority of studies presented the complication rates based on the Clavien-Dindo classification (**Table 4**). Three of the articles comparing

COVID-19 and the pre-COVID-19 era did not clearly mention the complications of their management strategies (13, 24, 25). Perrone et al. (15) did not report any significant difference between the two periods, as only one death occurred in the COVID-19 era. Farber et al. (23) stated a slightly higher rate of complications during the COVID-19 period, which includes four cases of sepsis and one death, compared to the pre-COVID-19 period. Although not statistically significant, the researchers highlighted the existence of a longer duration of symptoms prior to presentation in the COVID-19 period, as a possible factor linked to this higher rate of complications. Other than that, Hugo et al. (14) reported more CDII complications in the pandemic period (7%) compared to 2019 (5%), as well as three complications of CDIII grade, whereas no CDIII complications are reported in the pre-COVID-19 era. Similarly, Kamil et al. (17) reported a higher rate of CDII complications in the pandemic period compared to the period before the viral spread. However, these differences are not statistically significant. Fouad et al. highlighted that the pandemic period was associated with the highest rate of postoperative complications, with 8.03% developing bile leakage, 5.14% having missed duct stones that needed further intervention with endoscopic retrograde cholangiopancreatography (ERCP), and 0.96% developed duodenal injury. Pulmonary complication rates were 6.11 and 19.6% before and during COVID-19, respectively ($p < 0.05$). These differences are also reflected in the Clavien-Dindo grading system, with 16.1% of patients presenting a CDIIIa or higher in the pandemic period. On the other hand, severe complications (CDIIIa or higher) were observed in only 0.6% of the population in the pre-COVID-19 era. The mild complication rate (CDI or CDII) was similarly higher in the pandemic period (11). Finally, Guadalajara et al. (16) reported increased complication rates of any Clavien-Dindo grade during 2020 compared both to 2019 and 2021. The difference between 2020 and 2021 is statistically significant ($p = 0.026$). However, no difference in the rate of severe complications (CDIII-IV) was observed between the 3 years.

DISCUSSION

During the COVID-19 era, there have been numerous modifications in the approach of emergent cases in every medical specialty and especially in situations with potential surgical intervention. Before the outbreak of this viral pandemic, laparoscopic cholecystectomy was the gold standard treatment in most patients diagnosed with acute cholecystitis. There are several studies in the current literature that suggest emergent surgery in acute cholecystitis, and the WSES further emphasizes that early laparoscopic cholecystectomy should be performed as soon as possible but can be safely performed up to 10 days after the onset of symptoms (2). However, early laparoscopic intervention is significantly associated with a shorter hospital stay, fewer complications, and operational costs (2, 27). Following the virus's global spread, guidelines regarding acute abdominal incidents were modified. Indeed, the BIGSG on COVID-19 stated that during the COVID-19 pandemic, whenever non-operative management is possible (such as for early appendicitis and acute cholecystitis), this should be performed. BIGSG recommended either non-surgical management or the utilization of a PC tube for the management of acute biliary disease (5). Similarly, other surgical societies, such as the SAGES and EAES, have also advocated for a more patient- and hospital-centered approach, which suggests conservative treatment whenever appropriate (6, 7).

With regard to the above, numerous hospitals considered altering their initial approach. This shift was mainly attributed to the fact that laparoscopy is an aerosol-forming procedure and carries a potential risk for transmission of SARS-CoV-2 to healthcare professionals (28). As a result, several hospitals began their treatment with antibiotics and "watchful waiting" while others performed PC. As a matter of fact, this potential risk was investigated and the results revealed a greater benefit in favor of laparoscopy with no reason of replacing it with laparotomy due to COVID-19 infection (28).

Additional safety precautions were recommended to avoid the possibility of virus transmission. Those measures concern mainly the prevention of pneumoperitoneum dispersion and potential viral spreading (29, 30), the safer operative technique with the proper evacuation of smoke developed from electrosurgery and ultrasonic surgery (29, 31), the disinfection of potentially contaminated devices and materials, and the usage of more protective equipment under each hospitals protocol. Finally, recommendations were proposed for the establishment of specific operating rooms for patients with COVID-19 regarding the risk of transmission between patients (29, 31, 32).

The various types of management of acute cholecystitis along with their outcomes were the topic of our systematic review. The studies were divided into two main categories with the first one focusing on different approaches exclusively during the COVID-19 outbreak, whereas in the second one, studies compared alternative managements before and after the start of the pandemic. In the first group, within a total of 218 patients with acute cholecystitis, there was a significantly high number of non-surgical treatments [160], of which 127 were only given antibiotics and 33 were treated with PC. In contrast, only a small number of patients [58] directly underwent surgery. The outcomes from most of the studies of the second category were similar. There was a notable change in the percentage of conservative management before (36.3%) and after (43.2%) the start of the pandemic. As a matter of fact, PC was frequently preferred on many occasions as a combination of potentially life-saving and less invasive treatment options, taking into consideration that it can serve as a bridge therapy allowing patients to survive severe disease and stabilize until they undergo a cholecystectomy (21). Moreover, in some cases, PC was chosen over surgery, taking into consideration the severity of pulmonary complications related to the disease (12, 33).

Treating patients conservatively as outpatients or inpatients does spare surgical capacity; however it renders the overall hospital stay much longer, and, in some cases, it reflects in more complicated cholecystitis. Our systematic review depicts that this is the result of both antibiotic therapy and PC. In the case of PC, the LOS was noted even longer which can be

attributed to delay in PC insertion (20). In this setting, the WSES underlines that the extravagant use of PC jeopardizes the standard level of care and that this method should be reserved for only a small, selected subset of patients (8). The shift toward more conservative treatments was thought to minimize the risk of aerosol transmission of COVID-19 through laparoscopic procedures and, therefore, protect from the viral spread. However, this type of management is associated with extended hospitalizations and, therefore, longer viral exposure for the patients and the professionals. When comparing the two periods, several studies reported a higher rate of complications since the outbreak of COVID-19. More specifically, Fouad et al. (11) highlighted a statistically significant difference in intra-operative, post-operative, and non-surgical complications (predominantly pulmonary) during the pandemic compared to the pre-COVID-19 period. However, the longer LOS and complication rates during the COVID-19 period may be attributed to a prolonged duration of symptoms prior to admission, due to the patients' concern of possible virus transmission (11, 23).

The majority of studies were conducted during the onset of the pandemic, a period without straight facts about COVID-19. Nowadays, due to the contribution of many studies, knowledge has been acquired concerning both the transmission of the virus and the strategies that are necessary for the protection and risk minimization of healthcare providers. Therefore, it is a thought-provoking question whether the modifications in acute cholecystitis management analyzed in this review are still existent or whether treatment strategies have returned back to their prior state.

This systematic review has a number of limitations. First, our research was mainly based on retrospective studies with no available randomized trials, due to the ongoing status of the COVID-19 pandemic. Moreover, each study reports in different lockdown periods based on the country and the existing circumstances at the time of conduction, thus leading to a discrepancy in terms of quality and completeness of data between the studies. The fact that the observation period of the studies is not equally long should also be noted. In addition, this systematic review presents only the short-term outcomes of conservative treatment with no reference to the long-term recurrence rates of this approach. Finally, stratification of the results according to Tokyo grade could not be done as only a few studies used this classification.

In summary, the ongoing pandemic has had a tremendous impact on surgical emergencies, and thus, the management of acute cholecystitis could not pose an exception and has been dramatically affected. Most studies reported a tendency toward more conservative approaches, namely, the use of antibiotics or PC, for the treatment of acute cholecystitis, in comparison to the widely used early laparoscopic cholecystectomy in the pre-pandemic era. This review highlights that this approach is associated with a longer LOS and, in certain circumstances, higher complication rates. Due to the unknown course of the pandemic, future studies, especially randomized controlled trials, are compulsory to investigate the safety profile of non-surgical management for acute cholecystitis patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

KS and IL: conceptualization. MK: methodology. GK, KS, IL, and MK: literature review, writing—original draft preparation, and project administration. AI: validation, writing, reviewing, editing, and supervision. KS and MK: formal analysis. IL and GK: investigation. KS: resources. IL: data curation. GK: visualization. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.871685/full#supplementary-material

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Identification of Main Influencers of Surgical Efficiency and Variability Using Task-Level Objective Metrics: A Five-Year Robotic Sleeve Gastrectomy Case Series

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Objective: Surgical efficiency and variability are critical contributors to optimal outcomes, patient experience, care team experience, and total cost to treat per disease episode. Opportunities remain to develop scalable, objective methods to quantify surgical behaviors that maximize efficiency and reduce variability. Such objective measures can then be used to provide surgeons with timely and user-specific feedbacks to monitor performances and facilitate training and learning. In this study, we used objective task-level analysis to identify dominant contributors toward surgical efficiency and variability across the procedural steps of robotic-assisted sleeve gastrectomy (RSG) over a five-year period for a single surgeon. These results enable actionable insights that can both complement those from population level analyses and be tailored to an individual surgeon's practice and experience.

Methods: Intraoperative video recordings of 77 RSG procedures performed by a single surgeon from 2015 to 2019 were reviewed and segmented into surgical tasks. Surgeon-initiated events when controlling the robotic-assisted surgical system were used to compute objective metrics. A series of multi-staged regression analysis were used to determine: if any specific tasks or patient body mass index (BMI) statistically impacted procedure duration; which objective metrics impacted critical task efficiency; and which task(s) statistically contributed to procedure variability.

Results: Stomach dissection was found to be the most significant contributor to procedure duration ($\beta = 0.344$, $p < 0.001$; $R = 0.81$, $p < 0.001$) followed by surgical inactivity and stomach stapling. Patient BMI was not found to be statistically significantly correlated with procedure duration ($R = -0.01$, $p = 0.90$). Energy activation rate, a robotic system event-based metric, was identified as a dominant feature in predicting stomach dissection duration and differentiating earlier and later case groups. Reduction of procedure variability was observed between earlier (2015-2016) and later (2017-2019) groups (IQR = 14.20 min vs. 6.79 min). Stomach dissection was found to contribute most to procedure variability ($\beta = 0.74$, $p < 0.001$).

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Conclusions: A surgical task-based objective analysis was used to identify major contributors to surgical efficiency and variability. We believe this data-driven method will enable clinical teams to quantify surgeon-specific performance and identify actionable opportunities focused on the dominant surgical tasks impacting overall procedure efficiency and consistency.

Keywords: robotic-assisted surgery, sleeve gastrectomy, objective performance indicators, surgical task, workflow analysis, video analytics

INTRODUCTION

Surgical efficiency and variability are critical contributors to optimal outcomes, patient and care team experience, and total cost to treat per disease episode (1–3). However, it is often unclear to clinical teams how to objectively quantify their own surgical efficiency and variability. Further, population-level analyses alone are not always able to deliver actionable insights to an individual surgeon due to unique aspects during practice. Therefore, objective methods to characterize surgical workflow and identify actionable areas for improvement with tailored feedback for each surgeon still need to be developed and made widely available.

Although multiple factors influence outcomes and efficiencies, many studies focus on how surgery is performed by describing subjectively initial case series or critical aspects within the procedure. Few studies use objective methods to identify which surgical activities and how surgeon performance affect overall procedure efficiency or surgical outcomes throughout a surgeon's learning curve (4–8). These studies are largely agnostic to the underlying surgical activities by using global subjective rating scales like Global Evaluative Assessment of Robotic Skills (GEARS) (9) or Objective Structured Assessment of Technical Skills (OSATS) (10). Further, although some studies describe the tasks within a surgery (11–13), there is room for improvement through the establishment of quantitative methods to provide actionable objective measures. Finally, task-based objective performance indicators (OPIs) other than total operative time are often neglected despite offering the potential for improved and focused feedback (14–17). There exists an opportunity to develop more objective methods that can scale for broad use (18–20) given a limited number of studies use subjective methods to estimate the impact of a surgeon's technical skills on patient outcomes (21–25). Additionally, these objective methods need to be able to be applied to an individual surgeon, within institutions, or across institutions.

The purpose of this study was to demonstrate a novel, data-driven method that retrospectively identifies dominant factors that influenced a surgeon's performance efficiency and variability over five years when performing robotic-assisted sleeve gastrectomy (RSG) procedures. Specifically, we (1) identified the dominant factors of surgical efficiency and variability within RSG by focusing on surgical tasks, (2) examined the influence of body mass index (BMI), an important patient factor within bariatric surgery (26), on efficiency, and (3) identified OPIs with greatest impact on efficiency of the identified critical step. The data-driven methods developed in this study might also be further generalized for clinical teams, residents during training and educators to quantify performance and identify actionable and scalable changes.

MATERIALS AND METHODS

Study Design

Seventy-seven RSG procedures performed by a single surgeon from April 21st, 2015 to June 3rd, 2019 were retrospectively reviewed. All procedures were performed using the da Vinci Xi surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA). Nine surgical tasks were defined that constitute the major steps needed to complete a sleeve gastrectomy (**Figure 1**). The tasks included stomach dissection, hiatal hernia dissection (optional), lay stomach back, place bougie, stomach stapling, hiatal hernia repair (optional), oversew staple line, leak test and stomach extraction. Any additional surgical activities were defined as "other" and idle time between tasks were defined as "surgical inactivity."

Detailed criteria for task start and stop times was also defined to minimize annotation variability. For example, the start time of stomach dissection was defined as the time when a dissection tool engages with tissue to initiate dissection along the greater curve of the stomach. The start and stop times for each task in each video were then annotated by three professionally trained annotation technicians. An expert surgeon reviewed samples of these annotations to ensure quality. Note that hiatal hernia dissection and repair were optional tasks in RSG procedures and thus excluded from procedure time and subsequent analysis.

To observe and compare the changes in task completion time, we grouped the surgical videos into earlier and later case groups. Specifically, earlier cases included 39 videos from the years 2015 through 2016, and the later cases included 38 videos from the years 2017 through 2019. Note that the earlier cases were a subset from the first 50 cases of the surgeon and the later cases were a subset from the latest 80 cases of the same surgeon.

Procedure Efficiency and Variability

Overall procedure duration was considered as a measure of efficiency, and interquartile range (IQR) of consecutive case durations was used as a measure of variability. To further study the efficiency of the identified task(s), surgeon behavior was characterized by OPIs derived from three major surgical robotic system events: camera movement, energy activation and arm swap. The start and stop timestamps for each event were used

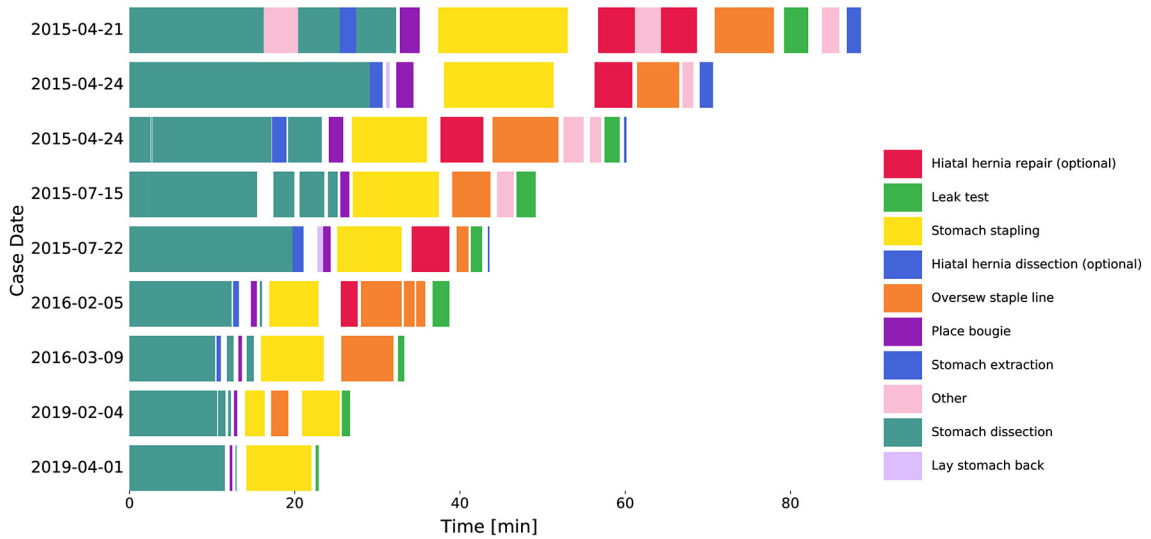

FIGURE 1 | Procedure workflow changes over years. Segmented tasks from 9 example cases. Hiatal hernia dissection and repair were excluded from further analysis. Surgical inactivity time was denoted as the gaps between tasks.

to calculate event-based OPIs, including rates of occurrences, and median durations of all occurrences. Identifying the OPIs that contribute to overall improvement of the task assists with identifying the skills that need to be focused on during training to improve efficiency.

Statistical Analysis

We used a three-staged regression analysis to identify main contributor(s) to procedure efficiency: (1) Spearman rank-order correlation test between each independent variable and procedure duration; (2) multivariable regression analysis; (3) recursive feature elimination (RFE) (27). The variables considered in efficiency analysis were task durations and patient BMI. Specifically, the correlation matrix of all independent variables was first checked to ensure no multicollinearity in the data. Task duration, procedure duration, and BMI were then normalized by corresponding median values from the first 5 cases to capture a baseline of surgeon behavior and patient factors. Next, β coefficients from a multivariable linear regression analysis were compared to identify variable(s) with the highest impact on procedure efficiency. Finally, RFE was used to rank the independent variables. This analysis leads to identifying the critical task that can be focused on for further analysis. Confounding effect of BMI on the critical task in association with procedure efficiency was also examined.

To characterize the impact of surgeon behavior on efficiency, we computed event-based OPIs for the identified critical task and investigated the association between OPIs and task duration using the three-staged regression analysis. We also evaluated the ability of these OPIs in differentiating between earlier and later case groups using logistic regression. RFE and LASSO (28, 29) feature selection methods were again used to rank the OPIs.

Finally, we examined association between procedure and task duration variability across all procedures. IQRs of procedure and task durations were computed by applying a sliding window for every five consecutive procedures with a stride of one procedure in earlier and later groups, respectively. Task(s) that contributed most to overall procedure variability was then identified using the same three-staged analysis. Furthermore, logistic regression with RFE was used to identify tasks with most variability between earlier and later groups. $p < 0.05$ was considered statistically significant in all of our statistical analysis. Statistical analysis was performed using Python's statistical functions (Python 3.7.9; SciPy v1.5.2; scikit-learn 0.23.2).

RESULTS

Procedure Characteristics

Surgical task annotation results of nine example cases ordered chronologically were shown in **Figure 1**. Each row corresponded to one case and each color bar corresponded to an annotated task in the case. Reductions in procedure duration and task duration and variability can also be observed as the surgeon progressed over years (**Figures 1**, **2**).

Detailed characteristics of the case series, including the number of occurrences, median value and IQR of different case groups were provided in **Table 1**. Among the seven surgical tasks, five tasks were identified as frequent tasks across the case series: stomach dissection, place bougie, stomach stapling, oversew staple line and leak test, with occurrences of oversew staple line decreased [earlier 36 (92.3%) vs. later 8 (21.1%)]. When comparing earlier and later case groups at procedure level, median procedure duration and IQR decreased (earlier 41.89 min, IQR = 14.2 min vs. later 27.73 min, IQR = 6.79 min). Similarly, median duration of all frequent tasks decreased except for stomach stapling, and IQRs of all five frequent tasks decreased. The decreases in both median durations and IQRs indicates procedure efficiency improvement and variability

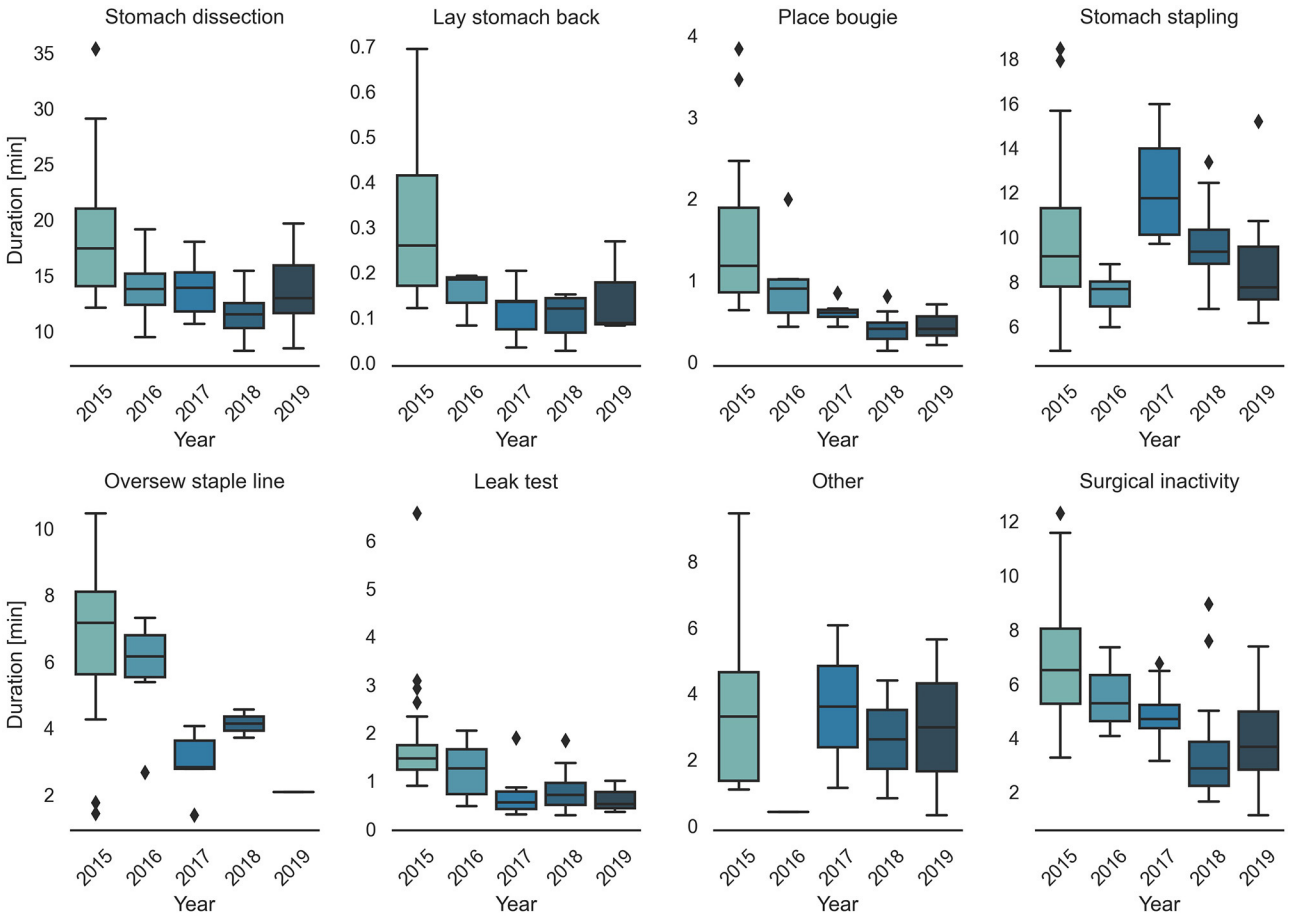

FIGURE 2 | Trend in task duration change of all 77 cases over five years.

reduction between the earlier and later groups. There is no obvious change in patient BMI characteristics (earlier 44.14, IQR = 8.85 vs. later 44.25, IQR = 9.62). Distribution of BMI and procedure time can be found in **Figure 3**.

Efficiency Analysis

Critical Task Identification

In the first-stage analysis, none of the independent variables were found to be highly correlated with each other (Spearman rank-order correlation coefficients R ranging from −0.24 to 0.66) (detailed correlation matrix is visualized in **Supplementary Figure 1**). Correlation coefficients between each variable and procedure duration were summarized in **Table 2** and visualized in **Figure 3**. Among all variables, stomach dissection was found to be most significantly correlated with procedure duration ($R = 0.81$, $p < 0.001$). BMI was not found to be statistically significantly correlated with procedure duration ($R = -0.01$, $p = 0.90$).

In the subsequent multivariable regression analysis, all independent variables were normalized by corresponding median durations of the first 5 cases from the surgeon (**Table 1**) to ensure fair comparison. The β coefficients of each variable were compared among earlier, later and all cases (**Table 2**). In the earlier group, a unit increase in stomach dissection duration relative to the median duration from the first 5 cases (i.e., increases by 21.18 min) was associated with a 34.3% increase (β = 0.343, 95% CI 0.324 to 0.362, $p < 0.001$) in baseline procedure duration (i.e., a 34.3% increase from 62.54 min). Compared with all other variables, stomach dissection was found to be associated with the largest β coefficient. Similarly, when considering later cases and all cases, stomach dissection was again associated with the largest β coefficients (**Table 2**). Surgical inactivity also contributed to procedure duration increase in both earlier and later groups (earlier $\beta = 0.158$, 95% CI 0.135 to 0.182, $p < 0.001$ vs. later $\beta = 0.140$, 95% CI 0.138 to 0.143, $p < 0.001$). In contrast, BMI was not found to be statistically significant in association with procedure duration in all cases ($\beta = 0.001$, 95% CI −0.012 to 0.014, $p = 0.88$; $R = -0.01$, $p = 0.90$) and neither in earlier or later groups.

Finally, RFE with linear regression was used to recursively eliminate and rank these eight features in predicting procedure duration change. Stomach dissection, stomach stapling and surgical inactivity were consistently ranked the top three most

TABLE 1 | Statistics of surgical tasks, procedure duration and BMI.

	No. (%)		Median Value[a] (IQR)			
	Earlier ($n = 39$)	Later ($n = 38$)	First 5 cases[b]	Earlier	Later	All cases
Stomach dissection	39 (100%)	38 (100%)	21.18 (5.75)	16.45 (6.57)	12.23 (4.13)	14.19 (5.29)
Lay stomach back	18 (46.2%)	14 (36.8%)	0.42 (0.00)	0.21 (0.22)	0.12 (0.07)	0.16 (0.14)
Place bougie	38 (97.4%)	38 (100%)	1.75 (1.35)	1.09 (0.98)	0.43 (0.24)	0.68 (0.66)
Stomach stapling	39 (100%)	38 (100%)	15.15 (2.39)	8.79 (3.16)	9.52 (2.79)	9.15 (3.05)
Oversew staple line	36 (92.3%)	8 (21.1%)	7.96 (1.79)	6.90 (2.61)	3.23 (1.19)	6.25 (3.41)
Leak test	38 (97.4%)	36 (94.7%)	2.24 (1.03)	1.42 (0.56)	0.60 (0.43)	1.07 (0.92)
Stomach extraction	10 (25.6%)	0 (0%)	0.55 (1.11)	0.42 (0.70)	0.00 (0.00)	0.42 (0.70)
Other	12 (30.8%)	6 (15.8%)	4.84 (3.61)	2.66 (3.09)	2.77 (4.42)	2.66 (3.79)
Surgical inactivity	39 (100%)	38 (100%)	8.81 (3.28)	6.45 (2.23)	3.52 (2.29)	5.03 (3.29)
Total procedure	39	38	62.54 (7.81)	41.89 (14.20)	27.73 (6.79)	34.37 (14.57)
BMI	39	38	42.17 (6.65)	44.14 (8.85)	44.25 (9.62)	44.14 (9.71)

[a]*For task and procedure, median durations (IQR) in minutes from all non-zero occurrences were reported. For BMI (calculated as weight in kilograms divided by height in meters squared), median value (IQR) was reported.* [b]*The values from the first 5 cases were used as baseline for normalization during the analysis.*

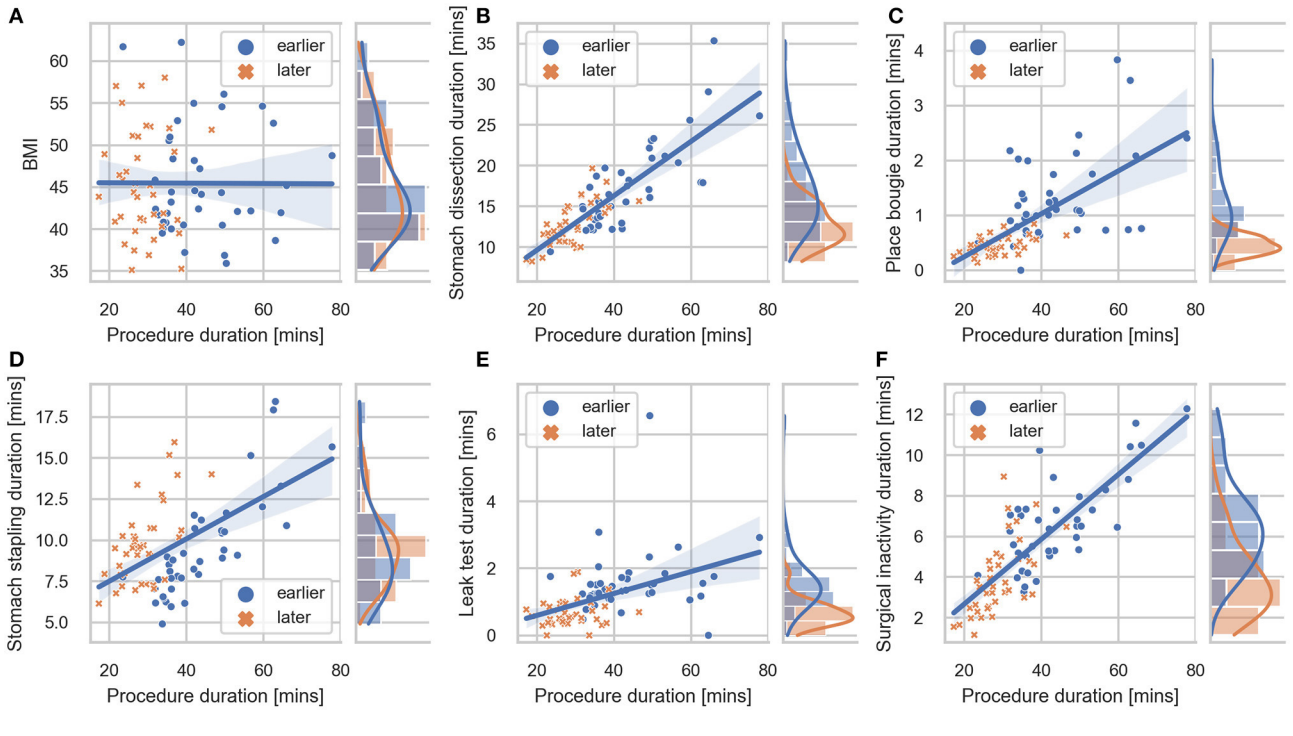

FIGURE 3 | Correlation plot between BMI, task durations and procedure duration. Regression lines are included for each sub-comparison. The 95% confidence intervals were shown as the translucent bands around the regression line. Distributions of **(A)** BMI, **(B)** stomach dissection, **(C)** place bougie, **(D)** stomach stapling, **(E)** leak test, **(F)** surgical inactivity with regard to procedure durations are included for earlier and later case groups, respectively.

important features (**Table 2**). Patient BMI was consistently ranked the lowest across all groups.

Overall, stomach dissection was found to be the major critical task and main contributor to procedure efficiency considering all three stages of analysis. To further examine confounding effect of BMI on stomach dissection, β coefficient of dissection from a univariate linear regression ($\beta = 0.703$, 95% CI 0.595 to 0.810, $p < 0.001$) was compared to the coefficient from a multivariable regression model after adding BMI ($\beta = 0.711$, 95% CI 0.604 to 0.819, $p < 0.001$). The results indicate a 1.14% increase in the coefficient thus showing no confounding effect of BMI on stomach dissection task.

Event-Based Objective Performance Indicator

Five event-based OPIs were computed from surgical system events that occurred during stomach dissection. To investigate

TABLE 2 | Regression models examining procedure duration change by surgical task duration and BMI change.

	Spearman correlation		Multivariable linear regression							
	All cases		Earlier			Later			All cases	
	R	*p* value	β Coefficient (95% CI)	*p* value	RFE rank	β Coefficient (95% CI)	*p* value	RFE rank	β Coefficient (95% CI)	*p* value	RFE rank
Stomach dissection	0.81	**<0.001**	0.343 (0.324 to 0.362)	**<0.001**	2	0.337 (0.334 to 0.340)	**<0.001**	1	0.344 (0.333 to 0.355)	**<0.001**	1
Place bougie	0.74	**<0.001**	0.031 (0.022 to 0.041)	**<0.001**	6	0.027 (0.023 to 0.032)	**<0.001**	7	0.031 (0.025 to 0.037)	**<0.001**	6
Stomach stapling	0.39	**<0.001**	0.244 (0.216 to 0.272)	**<0.001**	1	0.246 (0.244 to 0.248)	**<0.001**	2	0.246 (0.235 to 0.258)	**<0.001**	3
Oversew staple line	0.78	**<0.001**	0.129 (0.117 to 0.141)	**<0.001**	4	0.128 (0.126 to 0.131)	**<0.001**	4	0.129 (0.123 to 0.135)	**<0.001**	4
Leak test	0.55	**<0.001**	0.028 (0.021 to 0.035)	**<0.001**	7	0.030 (0.028 to 0.032)	**0.035**	6	0.029 (0.024 to 0.033)	**<0.001**	7
Other	0.45	**<0.001**	0.059 (0.050 to 0.069)	**<0.001**	5	0.061 (0.060 to 0.062)	**<0.001**	5	0.061 (0.056 to 0.065)	**<0.001**	5
Surgical inactivity	0.74	**<0.001**	0.158 (0.135 to 0.182)	**<0.001**	3	0.140 (0.138 to 0.143)	**<0.001**	3	0.149 (0.138 to 0.159)	**<0.001**	2
BMI	−0.01	0.90	0.004 (−0.025 to 0.033)	0.79	8	0.002 (−0.001 to 0.005)	0.17	8	0.001 (−0.012 to 0.014)	0.88	8

Bold values are corresponding to statistically significant p-values.

the association between OPIs and the critical task (i.e. stomach dissection) efficiency, the same three-staged regression analysis was performed. The absolute values of the correlation coefficients R between each pair of OPIs were in the range of (0.01, 0.44) ensuring no multicollinearity (**Supplementary Figure 2**). Energy activation rate, median duration of camera movement and camera movement rate were found to be statistically correlated with stomach dissection duration (**Table 3**). In the subsequent multivariable regression analysis, all variables were normalized to the median of the first 5 cases. Among all variables, energy activation rate was found to be statistically significantly associated with task duration (β =-2.40, 95% CI −3.90 to −0.91, $p = 0.002$). Finally, RFE was performed along with the linear regression to rank OPIs in association with stomach dissection duration. The rankings indicate that median duration of camera movement and energy activation rate were the two most influential OPIs on task efficiency. Overall, energy activation rate was found to be a consistent indicator of task efficiency considering all three-staged analyses.

To further investigate surgeon's behavior change throughout the longitudinal dataset, we identified the OPIs that can best differentiate surgeon's performance in the critical task between earlier and later case groups. Two feature selection methods (LASSO and RFE) with logistic regression were used. Energy activation rate was again selected as the top feature by both methods. All features along with their ranks from RFE feature selection and coefficients from LASSO feature selection were summarized in **Table 3**. The comparisons of all OPIs for the earlier and later case groups were shown in **Figure 4**.

Variability Analysis

We observed decreases in IQRs of procedure and task durations between earlier and later groups (**Table 1**). To further investigate the association between task and procedure duration variability, IQRs of task and procedure durations were computed for every five consecutive cases in earlier and later groups. The IQRs were then combined to analyze variability among all cases. Five tasks were selected as independent variables to ensure equal occurrences between earlier and later groups. To compare different tasks, all IQRs were normalized by the values from the first five cases (**Table 1**). None of the independent variables were found to be highly correlated (coefficients ranging from −0.18 to 0.33) (see **Supplementary Figure 3**).

When considering all cases, stomach dissection variability was found to contribute most to procedure variability with high consistency according to our three-staged analysis (**Table 4**). Specifically, a unit increase in stomach dissection IQR from 5 consecutive cases compared to the baseline IQR (**Table 1**) was associated with a 74% increase ($\beta = 0.74$, 95% CI 0.31 to 1.17, $p = 0.001$) in procedure duration IQR (i.e. a 74% increase from the baseline IQR = 7.81 min). Finally, stomach dissection and surgical inactivity were among the top three features in predicting procedure variability ranked by RFE.

To identify tasks with most variability between earlier and later groups, we used RFE with logistic regression. These results showed that place bougie, leak test and surgical inactivity

TABLE 3 | Regression models examining stomach dissection duration change by event OPIs.

OPIs	Spearman correlation		Multivariable linear regression			Logistic regression	
	R	*p* value	β Coefficient (95% CI)	*p* value	RFE rank	RFE rank	LASSO coefficient
Energy activation rate, counts per minute	−0.65	**<0.001**	−2.40 (−3.90 to −0.91)	**0.002**	2	1	4.21
Median of energy duration, seconds	0.15	0.26	0.58 (−0.36 to 1.53)	0.221	5	4	0
Camera movement rate, counts per minute	−0.29	**0.02**	−1.1 (−2.83 to 0.64)	0.211	4	3	0.32
Median duration of camera movement, seconds	0.50	**<0.001**	2.08 (−2.28 to 6.45)	0.341	1	2	0
Arm swap rate, counts per minute	−0.15	0.27	1.36 (−2.30 to 5.02)	0.459	3	5	0

Bold values are corresponding to statistically significant p-values.

contributed most to variability differences between the two groups (**Table 4**).

DISCUSSION

We believe this study outlines a novel method to identify the dominant influencers to overall procedure efficiency and variability within RSG through surgical task decomposition and task-based OPIs. The multi-staged regression analysis can help to identify dominant factors that influence surgery through quantitative measures, which is critically important to delivering actionable and focused surgeon-specific feedback but may also be generalized to enable objective and scalable insights across institutions. These objective and scalable feedbacks could also be especially helpful for surgeons during training.

In order to gain a deeper insight into RSG, the procedures were segmented into nine distinct surgical tasks based upon clinical relevance, consistency across the case series, and the ability to establish clear definition of start and stop times. Moreover, the nine surgical steps were defined in such a way to accommodate for minor technique changes over the case series (i.e., hiatal hernia dissection and repair and oversew the staple line were not present in all procedures). Stomach dissection and gastric sleeve stapling were two critical tasks within RSG. Additional surgical activities beyond the nine distinct tasks were classified as other or surgical inactivity. The surgical task segmentation is a foundational component that enables the ability to perform focused and granular analysis than conventional learning curve analysis (8, 30, 31) for this RSG case series.

The multi-staged regression analysis was first used to analyze the case series to determine the critical surgical task impacting overall efficiency and variability. As one might expect, overall variability decreased as overall efficiency increased. The critical task the correlates highest with the total procedure efficiency and variability for this single surgeon RSG case series was identified as stomach dissection (**Tables 2**, **4**). Stomach dissection requires a combination of clinical judgment, such as identification of the gastromesenteric ligament, pylorus, and short gastric vessels, as well as technical skill, such as energy use, retraction, dissection, and camera control. Education around clinical knowledge and technique and associated technical skills for this step offer an opportunity for focused gains on efficiency.

Surgical inactivity was another important factor impacting overall efficiency. Efforts to reduce periods of inactivity can be pursued by both the surgeon and OR team by reducing interruptions and training around the equipment and technique required to complete the procedure. Development of repeatable techniques, surgical approach, proficiency, and coordination by both the operating surgeon and OR team are essential to ensure consistency and predictability.

Notably, patient BMI consistently ranked the least dominant feature to impact total operative time. One possible explanation may be due to the fact that these cases were performed robotically, which may eliminate the ergonomic challenges of operating on high-BMI patients seen in conventional

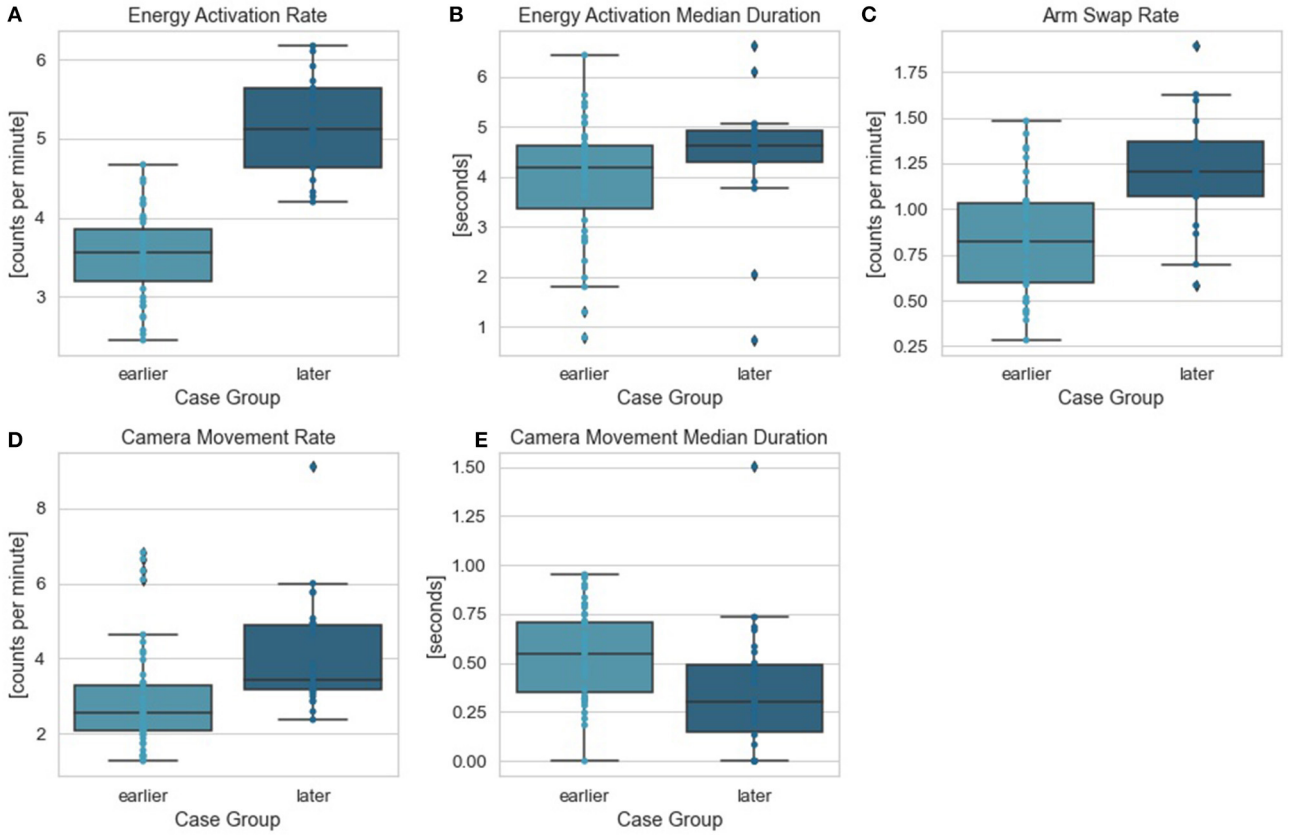

FIGURE 4 | Stomach dissection OPIs between earlier and later case groups. Comparisons between earlier and later cases groups were provided for OPIs: **(A)** energy activation rate, **(B)** energy activation median duration, **(C)** arm swap rate, **(D)** camera movement rate, **(E)** camera movement median duration.

TABLE 4 | Regression models examining procedure variability by surgical task variability.

	Spearman correlation		Multivariable linear regression			Logistic regression
	R	*p* value	β Coefficient (95% CI)	*p* value	RFE rank	RFE rank
Stomach dissection	0.45	**<0.001**	0.74 (0.31 to 1.17)	**0.001**	1	4
Place bougie	0.26	**0.03**	0.07 (0.43 to 0.58)	0.78	5	1
Stomach stapling	0.30	**0.01**	0.25 (0.04 to 0.46)	**0.02**	4	5
Leak test	−0.16	0.20	−0.59 (−1.38 to 0.19)	0.14	2	2
Surgical inactivity	0.26	**0.03**	0.52 (0.09 to 0.96)	**0.02**	3	3

Bold values are corresponding to statistically significant p-values.

laparoscopy, a compelling result within robotic-assisted bariatric surgery. This finding is consistent with those reported in other robotic-assisted bariatric procedures (26, 32, 33). In addition to which steps (or patient factors) influenced efficiency and variability, this study also identified objective metrics that quantify what surgeon behaviors within the most influential step—stomach dissection—differed most over the surgeon learning curve. Specifically, we used OPIs as objective measures, which were derived from three major surgical robotic system events: camera movement, energy activation, and arm swap. In addition to performing the multi-stage regression analysis across the entire case series, a second analysis was performed comparing earlier vs. later cases in the series to determine if there was any change over time. Counts of energy activation per minute was the top ranked OPI, which might be linked to dissection technique and surgeon technical skill using the energy pedals. By focusing training on related surgeon behaviors, one might allow for improved efficiency and reduced variability. Furthermore, the OPIs reported here removed the subjectivity inherent to rating scales (e.g., GEARS) and enabled scalability by eliminating the reliance on experts or crowds of lay people to complete the ratings.

This study has several limitations. First, this was a case series by a single surgeon across two institutions, and thus the identified

dominant factors associated with efficiency and variability need to be reproduced by other surgeons and institutions to evaluate generalizability. Additionally, different surgical tasks and additional OPIs could be explored to see if they are more impactful to efficiency or variability. Community consensus across procedures will allow for more robust analysis and broad adoption (34). Finally, this work did not explore correlations between performance and additional, discrete outcomes, such as re-admission, re-operation, and blood transfusion. It will be important to focus future outcomes research in areas that could be significantly impacted by task-based surgeon performance vs. others that might be influenced by surgeon decisions (e.g., length of stay).

In future research, we plan to explore how these methods can be extended to account for variations in how surgery is delivered across institutions and geographies, and to examine other procedures and specialties and their main contributors to efficiency and variability. Additionally, we plan to incorporate more patient factors and outcomes to extend this work beyond efficiency. Related work has shown promising results that link OPIs from critical steps of robotic-assisted prostatectomy to outcomes (13, 14). Finally, we plan to develop machine learning techniques that overcome manual video annotation (11, 13, 35, 36).

CONCLUSIONS

This study demonstrated the feasibility of using objective task analysis to identify main factors around surgeon and OR team behavior that influence overall procedure efficiency and variability. In particular, stomach dissection was identified as the most critical step, and energy activation rate within stomach dissection was the most critical behavior. Importantly, BMI did not influence overall efficiency of the surgeon, suggesting robotic-assisted surgery might decouple patient BMI and surgical efficiency. This is particularly important to deliver minimally invasive surgery to bariatric patients. We believe this data-driven objective task analysis approach could be used to provide actionable, surgeon-specific feedback that may also be generalized to be used by clinical teams to quantify and influence best practices for those aspects of surgery contributing most to overall efficiency and consistency.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MT performed the surgical procedures, collected data, contributed to study design, manuscript drafting, and revision. XL and ME performed statistical analysis, contributed to manuscript drafting, and revision. AJ contributed to study design, manuscript drafting, and revision. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Efficacy and Safety of Totally Laparoscopic Gastrectomy Compared with Laparoscopic-Assisted Gastrectomy in Gastric Cancer: A Propensity Score-Weighting Analysis

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Objectives: To compare the short- and long-term outcomes of totally laparoscopic gastrectomy (TLG) with laparoscopic-assisted gastrectomy (LAG) in gastric cancer (GC) patients and evaluate the efficacy and safety of TLG.

Methods: This retrospective study was based on GC patients who underwent laparoscopic radical gastrectomy in the Qilu Hospital from January 2017 to December 2020. The groups' variables were balanced by using the propensity score-based inverse probability of treatment weighting (PS-IPTW). The primary outcomes were 3-year relapse-free survival (RFS) and 3-year overall survival (OS). Postoperative recovery and complications were the secondary outcomes.

Results: A total of 250 GC patients were included in the study. There were no significant differences in baseline and pathological features between the TLG and the LAG groups after the PS-IPTW. TLG took around 30 min longer than LAG, while there were more lymph nodes obtained and less blood loss throughout the procedure. TLG patients had less wound discomfort than LAG patients in terms of short-term prognosis. There were no significant differences between groups in the 3-year RFS rate [LAG vs. TLG: 78.86% vs. 78.00%; hazard ratio (HR) = 1.14, 95% confidence interval (CI), 0.55–2.35; $p = 0.721$] and the 3-year OS rate (LAG vs. TLG: 78.17% vs. 81.48%; HR = 0.98, 95% CI, 0.42–2.27; $p = 0.955$). The lymph node staging was found to be an independent risk factor for tumor recurrence and mortality in GC patients with laparoscopic surgery. The subgroup analysis revealed similar results of longer operation time, less blood loss, and wound discomfort in totally laparoscopic distal gastrectomy, while the totally laparoscopic total gastrectomy showed benefit only in terms of blood loss.

Conclusion: TLG is effective and safe in terms of short- and long-term outcomes, with well-obtained lymph nodes, decreased intraoperative blood loss, and postoperative wound discomfort, which may be utilized as an alternative to LAG.

Keywords: totally laparoscopic gastrectomy, laparoscopic-assisted gastrectomy, laparoscopic surgery, gastric cancer, surgery prognosis

INTRODUCTION

Gastric cancer is one of the most common and deadly cancers in the world, particularly in East Asia (1). Radical gastrectomy is indispensable for resectable gastric cancer (2, 3). Since Kitano et al. (4) reported the first case of laparoscopic-assisted distal gastrectomy (LADG) in 1994, laparoscopic gastrectomy has developed rapidly and been widely used.

Laparoscopic gastrectomy has two main surgical types: laparoscopic-assisted gastrectomy (LAG) and totally laparoscopic gastrectomy (TLG). The most typical procedure is LAG, which means the stomach and lymph node dissection is performed under laparoscopy, while the stomach resection and anastomosis are performed externally assisted by a 5- to 8-cm abdominal incision. Many studies have shown that there is no significant difference between LAG and open gastrectomy in the long-term prognosis for early or advanced gastric cancer (5–7). Because of the benefits of a smaller incision, less discomfort, and a speedy recovery, laparoscopic gastrectomy has increasingly become a mainstream treatment for gastric cancer (8, 9). In TLG, gastrectomy, lymph node dissection, and gastrointestinal reconstruction are performed under the laparoscopic vision, finally through an approximately 3-cm abdominal incision to take out the resection specimen. TLG eliminates the need for a large abdominal incision and provides apparent benefits in terms of exposure and anatomy (10). However, due to the lack of tactile input and the surgeon's greater technical requirements, TLG finds it difficult to precisely define the tumor's border and intracorporeal anastomosis.

Improvements in laparoscopic equipment, gastrointestinal reconstruction methods, and lymph node tracking technologies such as carbon nanoparticle (11) or indocyanine green (ICG) tracer-guided technologies (12, 13) are ushering in a new age of minimally invasive surgery. TLG and new intracorporeal anastomosis have attracted increased attention from scholars (14–16). However, there is currently a paucity of large-scale clinical trials to demonstrate TLG's safety and efficacy, and the short- and long-term effects require additional medical proof to be proven.

In this study, we retrospectively analyzed TLG and LAG in gastric cancer patients by using the method of the propensity score-based inverse probability of treatment weighting (PS-IPTW) to eliminate the groups' differences and then evaluating the short- and long-term prognoses to access the safety and effectiveness of TLG.

METHODS

Patients

This study was based on gastric cancer patients who received laparoscopic radical gastrectomy in the department of gastrointestinal surgery of the Qilu Hospital from January 2017 to December 2020. The follow-up procedures mainly depended on the hospital's record system and the telephone. The inclusion criteria were as follows: pathological diagnosis as gastric cancer, no history of other malignancies, and surgical methods of distal or total gastrectomy. The exclusion criteria were as follows: neoadjuvant chemotherapy, palliative surgery, distant metastasis, operation converted to laparotomy, and incomplete clinical data. The data of all patients were approved by the Ethical Review Committee of Qilu Hospital.

Surgical Quality Control

To determine the boundary of the tumor, all TLG patients were endoscopically injected carbon nanoparticles or ICG suspension into the submucosal layer around the tumor 1 day before surgery by the same team of endoscopists. The carbon nanoparticle suspension was 0.5 mm per injection. ICG was prepared with 1.25 mg/ml sterile water and 0.5 milliliters per injection (17). All surgeries were performed by the same surgical team that had previously conducted more than 200 laparotomy and laparoscopic gastric cancer surgeries. According to the Japanese Gastric Cancer Treatment Guidelines (18), all surgeries were performed by radical gastrectomy with D2 lymph node dissection.

The patient was placed in the supine position and given general anesthesia. A subumbilical port was created and used to produce pneumoperitoneum (12–15 mmHg) (1 mmHg = 0.133 KPa). A five-port approach was used for the Trocar position. By utilizing laparoscopic exploration, the gastric resection range and digestive tract rebuilding could be determined. The upper margin should be kept at least 3–5 cm away from the cancer's edge, while the esophageal junction cancer should be kept as far away from the cancer as feasible when enough room is conserved for esophagojejunal anastomosis, and fast-frozen pathology should be conducted when necessary.

For totally laparoscopic distal gastrectomy (TLDG), the reconstruct method was Billroth-II with Braun anastomosis. After the dissection of gastric lymph nodes, the duodenum and the distal stomach were separated with a linear closure device. A small hole was formed on the greater curvature side of the remnant stomach and on the antimesenteric border of the jejunum, 15–20 cm from the Treitz ligament. Then, a

TABLE 1 | Patient demographic data and tumor characteristics.

Characteristics	Overall	Relapse	Cox analysis		Death	Cox analysis	
	N = 250	*N* = 48	HR (95% CI)	*p*	*N* = 39	HR (95% CI)	*p*
Operation method							
LAG	156 (62.4)	29	Ref		24	Ref	
TLG	94 (37.6)	19	0.92 (0.51–1.65)	0.392	15	0.75 (0.39–1.44)	0.770
Age (years)	59 [51, 66]	48	1.01 (0.98–1.03)	0.661	39	1.05 (0.98–1.05)	0.378
Sex							
Female	60 (24.0)	12	Ref		12	Ref	
Male	190 (76.0)	36	0.95 (0.49–1.82)	0.871	27	0.68 (0.34–1.34)	0.267
BMI (kg/m^2)	24.51 ± 3.44	48	0.97 (0.89–1.05)		39	0.99 (0.91–1.08)	0.798
Complications							
0	154 (61.6)	28	Ref		21	Ref	
1	72 (28.8)	17	1.31 (0.72–2.39)	0.382	16	1.68 (0.88–3.22)	0.119
2	18 (7.2)	3	0.89 (0.27–2.92)	0.842	2	0.86 (0.20–3.65)	0.833
3	5 (2.0)	0	NA	0.996	0	NA	0.996
4	1 (0.4)	0	NA	0.998	0	NA	0.999
ASA score							
I	27 (10.8)	5	Ref		4	Ref	
II	206 (82.4)	39	1.00 (0.39–2.55)	0.996	32	0.99 (0.35–2.81)	0.989
III	17 (6.8)	4	1.44 (0.38–5.42)	0.586	3	1.53 (0.34–6.89)	0.581
Tumor site							
Lower	148 (59.2)	20	Ref		9	Ref	
Middle	67 (26.8)	18	2.08 (1.10–3.94)	0.024	12	1.44 (0.69–3.00)	0.325
Upper	35 (14.0)	10	2.00 (0.94–4.28)	0.073	18	1.90 (0.85–4.24)	0.117
Gastrectomy							
Distal	155 (62.0)	18	Ref		15	Ref	
Total	95 (38.0)	30	1.06 (1.61–5.18)	<0.001	24	2.58 (1.36–4.93)	0.004
Tumor size							
≤3 cm	105 (42.0)	7	Ref		6	Ref	
>3 cm	145 (58.0)	41	4.74 (2.13–10.58)	<0.001	33	4.34 (1.82–10.36)	<0.001
Grade							
Differentiated	219 (87.6)	45	Ref		36	Ref	
Undifferentiated	31 (12.4)	3	0.45 (0.14–1.45)	0.183	3	0.56 (1.17–1.82)	0.335
pT stage							
T1a	40 (16.0)	0	Ref		0	Ref	
T1b	36 (14.4)	2	NA	0.997	2	NA	1
T2	48 (19.2)	3	NA	0.997	0	NA	0.997
T3	91 (36.4)	23	NA	0.997	19	NA	0.997
T4a	35 (14.0)	20	NA	0.996	18	NA	0.997
pN stage							
N0	120 (48.0)	4	Ref		2	Ref	
N1	32 (12.8)	3	2.97 (0.67–13.27)	0.154	2	4.21 (0.59–29.90)	0.151
N2	42 (16.8)	11	8.62 (2.74–27.08)	<0.001	9	13.54 (2.92–62.67)	<0.001
N3A	29 (11.6)	16	26.02 (8.66–78.2)	<0.001	13	41.83 (9.42–185.8)	<0.001
N3B	27 (10.8)	14	27.85 (9.10–85.3)	<0.001	13	tH5 (11.89–236.6)	<0.001

(*continued*)

TABLE 1 | Continued

Characteristics	Overall	Relapse	Cox analysis		Death	Cox analysis	
	N = 250	*N* = 48	HR (95% CI)	*p*	*N* = 39	HR (95% CI)	*p*
pTNM stage							
I	96 (38.4)	3	Ref		2	Ref	
II	65 (26.0)	5	2.55 (0.61–10.65)	0.201	2	1.455 (0.20–10.33)	0.708
III	89 (35.6)	40	20.48 (6.32–66.38)	<0.001	35	26.68 (6.40–111.17)	<0.001

TLG, totally laparoscopic gastrectomy; LAG, laparoscopic-assisted gastrectomy; BMI, body mass index; Complications, the number of preoperative complications such as hypertension, heart disease, diabetes, or chronic obstructive pulmonary diseases; ASA score, assessment method by the American Society of Anesthesiologists; Gastrectomy, selection of gastrectomy included distal and total gastrectomy; TNM stage, the pathological classification under the Gastric Cancer Staging AJCC 8th edition; HR, hazard ratio; NA, not applicable; CI, confidence interval.

side-to-side gastrojejunostomy was performed by using a linear stapler. The entry hole for the stapler was also closed by stapling, and the anastomosis was continuously reinforced with absorbable sutures. The Braun anastomosis was performed between the input and the output loops of jejunum at 10–15 cm from the gastrojejunum anastomosis with a linear stapler. The resection specimen was put in the endobag and extracted through a small periumbilical incision.

For totally laparoscopic total gastrectomy (TLTG), the reconstruct method was the reverse puncture device reconstruction (19, 20). Following lymph node dissection, duodenum separation, and abdominal esophagus dissociation, a small hole was made on the anterior wall of the esophagus and then a small incision was made in the upper abdomen to enter the abdominal cavity. The anvil of the esophageal stump was inserted into the residual end of the esophagus, tightened, and ligated with a purse string. The linear stapler was used to close the esophagus under the anvil. The main body of the tubular stapler was placed in the distal end of the jejunum. The pneumoperitoneum was then re-established, the tubular stapler was inserted into the distal jejunum, and the central rod was connected with the anvil after penetrating the intestinal wall to complete the esophagojejunal anastomosis. The process for removing the specimen was the same as above.

For the LAG group, the Billroth-II with Braun anastomosis was performed for LADG, and the Roux-en-Y reconstruction was performed for laparoscopic-assisted total gastrectomy (LATG). The surgical methods are detailed in reference (21, 22).

Outcome Measurements

Short-term outcomes were determined as the postoperative recovery during hospitalization. The postoperative complications were defined as the Clavien–Dindo classification ≥II (23). Long-term outcomes were measured using the time from surgery to tumor recurrence (RFS) and the time from surgery to death (OS).

Statistical Analysis

All statistical analyses of the data were performed by using the R software 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and the SPSS software 25.0 (IBM Corporation, Armonk, NY, USA). The continuous variables were represented by a median or average depending on the normal distribution and were analyzed by using the independent *t*-test or the Mann–Whitney *U*-test. The categorical variables were represented by the frequency and its percentage of the total and were analyzed by using the Chi-square test. To make this study closely resemble a randomized clinical trial setting, the method of the PS-IPTW was employed. Multivariable logistic regression was applied to all the baseline and pathological features between the TLG and LAG groups to generate a propensity score. And using the stabilized weights to reduce variability in IPTW models. With the goal of balancing observable characteristics, each patient was weighted by the inverse probability of being in TLG vs. LAG. The univariate and multivariate Cox proportional hazards regression model was used to analyze the independent risk factors of recurrence and mortality. The Kaplan–Meier technique and the log-rank test were used to create survival curves. Statistical significance was set at $p < 0.05$.

RESULT

The demographic data and tumor characteristics are shown in **Table 1**. This research comprised 250 of 314 gastric cancer patients who underwent laparoscopic radical gastrectomy. A total of 156 patients were divided into the LAG group, and 90 patients were divided into the TLG group. In this study, 38 of 250 patients (15.2%) obtained a fast-frozen pathology, with only 3 cases of LAG having a positive margin, and received a second resection. All surgeries completed the R0 resection. The patients' median age of the total group was 59 (IQR 51–66) years; 190 patients (76.0%) were men, and the average BMI was 24.51 (SD 3.44) kg/m^2. For preoperative complications such as hypertension, heart disease, diabetes, or chronic obstructive pulmonary disease, most patients were mostly combined with 0 or 1 chronic disease (90.4%) and graded as the ASA score I/II (93.2%). Advanced gastric cancer (pT1b or above) accounted for 84% of them, and half of the tumors had lymph node metastasis (52.0%).

The results of univariate Cox analysis revealed that the tumor site, gastrectomy, tumor size, pN stage, and pTNM stage were all closely related to tumor recurrence ($p < 0.05$). While with the exception of the tumor site, similar results were shown in the

TABLE 2 | Baseline characteristics between operation method groups.

Characteristics	Before PS-IPTW			Logistic analysis		After PS-IPTW[a]			IPTW-Logistic analysis	
	LAG (*N* = 156)	TLG (*N* = 94)	*p*	OR (95% CI)	*p*	LAG (*N* = 161)	TLG (*N* = 90)	*p*	OR (95% CI)	*p*
Age (years)	59.5 [51.8, 67.0]	57.0 [49.0, 64.0]	0.091	0.98 (0.95–1.00)	0.091	57.0 [50.0, 66.0]	58.0 [49.0, 65.0]	0.999	1.00 (0.98–1.02)	0.952
Sex										
Female	32 (20.5)	28 (29.8)	0.131	Ref		43 (26.7)	23 (25.6)	0.887	Ref	
Male	124 (79.5)	66 (70.2)		0.61 (0.34–1.10)	0.097	118 (73.3)	67 (74.4)		1.06 (0.60–1.92)	0.849
BMI (kg/m^2)	24.50 ± 3.39	24.52 ± 3.53	0.971	1.00 (0.93–1.08)	0.971	24.33 ± 3.30	24.48 ± 3.43	0.759	1.01 (0.94–1.10)	0.729
0	96 (61.5)	58 (61.7)	0.683	Ref		103 (64.0)	57 (63.3)	0.954	Ref	
1	47 (30.1)	25 (26.6)		0.88 (0.49–1.57)	0.669	45 (28.0)	26 (28.9)		1.03 (0.57–1.83)	0.932
2	10 (6.4)	8 (8.51)		1.32 (0.49–3.55)	0.576	11 (6.8)	7 (7.8)		1.17 (0.40–3.18)	0.765
3	2 (1.3)	3 (3.19)		2.48 (0.40–19.27)	0.327	2 (1.2)	1 (1.1)		1.49 (0.11–17.07)	0.735
4	1 (0.6)	0 (0.00)		NA	0.987	1 (0.6)	0 (0.0)		NA	0.984
ASA score										
I	24 (15.4)	3 (3.19)	0.001	Ref		17 (10.6)	9 (10.0)	0.984	Ref	
II	118 (75.6)	88 (93.6)		5.97 (2.00–25.66)	0.004	133 (82.6)	76 (84.4)		1.11 (0.48–2.76)	0.806
III	14 (9.0)	3 (3.19)		1.71 (0.28–10.41)	0.542	11 (6.8)	6 (6.7)		1.09 (0.29–4.02)	0.886
Tumor site										
Lower	89 (57.1)	59 (62.8)	0.463	Ref		99 (61.5)	54 (60.0)	0.964	Ref	
Middle	42 (26.9)	25 (26.6)		0.90 (0.49–1.62)	0.723	40 (24.8)	24 (26.7)		1.10 (0.59–2.00)	0.765
Upper	25 (16.0)	10 (10.6)		0.60 (0.26–1.32)	0.218	22 (13.7)	13 (14.4)		1.06 (0.48–2.26)	0.874
Gastrectomy										
Distal	93 (59.6)	62 (66.0)	0.386	Ref		103 (64.0)	58 (64.4)	0.979	Ref	
Total	63 (40.4)	32 (34.0)		0.76 (0.44–1.29)	0.318	58 (36.0)	32 (35.6)		0.99 (0.58–1.69)	0.976
Tumor size										
≤3 cm	58 (37.2)	47 (50.0)	0.063	Ref		72 (44.7)	37 (41.1)	0.603	Ref	
>3 cm	98 (62.8)	47 (50.0)		0.59 (0.35–0.99)	0.047	89 (55.3)	54 (60.0)		1.18 (0.70–2.00)	0.536
Grade										
Differentiated	138 (88.5)	81 (86.2)	0.738	Ref		143 (88.8)	80 (88.9)	0.998	Ref	
Undifferentiated	18 (11.5)	13 (13.8)		1.23 (0.56–2.63)	0.595	18 (11.2)	10 (11.1)		1.00 (0.42–2.24)	0.998
pT stage										
T1a	24 (15.4)	16 (17.0)	0.192	Ref		23 (14.3)	13 (14.4)	0.994	Ref	
T1b	21 (13.5)	15 (16.0)		1.07 (0.43–2.69)	0.883	23 (14.3)	14 (15.6)		1.05 (0.40–2.74)	0.918
T2	24 (15.4)	24 (25.5)		1.50 (0.64–3.54)	0.349	37 (23.0)	19 (21.1)		0.92 (0.39–2.25)	0.861
T3	64 (41.0)	27 (28.7)		0.63 (0.29–1.39)	0.248	55 (34.2)	33 (36.7)		1.09 (0.48–2.45)	0.857
T4a	23 (14.7)	12 (12.8)		0.78 (0.30–2.00)	0.610	23 (14.3)	12 (13.3)		0.93 (0.34–2.47)	0.877

(*continued*)

TABLE 2 | Continued

Characteristics	Before PS-IPTW			Logistic analysis		After PS-IPTW[a]			IPTW-Logistic analysis	
	LAG (*N* = 156)	TLG (*N* = 94)	*p*	OR (95% CI)	*p*	LAG (*N* = 161)	TLG (*N* = 90)	*p*	OR (95% CI)	*p*
pN stage										
N0	70 (44.9)	50 (53.2)	0.476	Ref		80 (49.7)	41 (45.6)	0.984	Ref	
N1	22 (14.1)	10 (10.6)		0.64 (0.27–1.43)	0.286	20 (12.4)	12 (13.3)		1.12 (0.48–2.52)	0.781
N2	30 (19.2)	12 (12.8)		0.56 (0.25–1.18)	0.136	27 (16.8)	15 (16.7)		1.10 (0.52–2.27)	0.807
N3A	19 (12.2)	10 (10.6)		0.74 (0.31–1.69)	0.480	17 (10.6)	11 (12.2)		1.27 (0.54–2.90)	0.580
N3B	15 (9.6)	12 (12.8)		1.12 (0.48–2.59)	0.792	17 (10.6)	11 (12.2)		1.28 (0.54–2.94)	0.570
pTNM stage										
I	52 (33.3)	44 (46.8)	0.098	Ref		66 (41.0)	36 (40.0)	0.875	Ref	
II	45 (28.8)	20 (21.3)		0.53 (0.27–1.01)	0.057	39 (24.2)	20 (22.2)		0.95 (48–1.86)	0.880
III	59 (37.8)	30 (31.9)		0.60 (0.33–1.09)	0.094	56 (34.8)	34 (37.8)		1.15 (0.64–2.07)	0.645

TLG, totally laparoscopic gastrectomy; LAG, laparoscopic-assisted gastrectomy; PS-IPTW, propensity score-based inverse probability of treatment weighting; ASA score, assessment method by the American Society of Anesthesiologists; TNM stage, the pathological classification under the Gastric Cancer Staging AJCC 8th edition; OR, odds ratio; CI, confidence interval.

[a]*Counts in the weighted cohort may not sum up to the expected totals owing to rounding. Because of rounding, percentages may not total 100, and discrepancies between numbers and percentages in the weighted cohort are the consequence of the rounding of noninteger number values.*

**The p-value was calculated by using the Chi-square test, independent t-test or Mann–Whitney U-test.*

TABLE 3 | Multivariate Cox analysis after PS-IPTW.

Characteristics	PS-IPTW	RFS-Cox analysis		Multi-Cox analysis		OS-Cox analysis		Multi-Cox analysis	
	N = 251	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Tumor site									
Lower	s	Ref				Ref			
Middle	64 (25.5)	1.65 (0.78–3.49)	0.194			1.09 (0.47–2.56)	0.838		
Upper	35 (13.9)	1.74 (0.75–4.02)	0.196			1.58 (0.64–3.94)	0.322		
Gastrectomy									
Distal	161 (64.1)	Ref		Ref		Ref		Ref	
Total	91 (36.3)	2.70 (1.33–5.50)	0.006	1.00 (0.46–2.16)	0.999	2.35 (1.08–5.15)	0.032	0.66 (0.26–1.69)	0.387
Tumor size									
≤3 cm	108 (43.0)	Ref		Ref		Ref		Ref	
>3 cm	143 (57.0)	4.74 (2.13–10.58)	<0.001	1.21 (0.42–3.50)	0.729	4.08 (1.55–10.75)	0.004	0.99 (0.32–3.06)	0.984
pN stage									
N0	121 (48.2)	Ref		Ref		Ref		Ref	
N1	31 (12.4)	2.77 (0.59–13.13)	0.199	1.46 (0.21–10.11)	0.702	3.2 (0.43–24.06)	0.258	3.29 (0.71–15.20)	0.127
N2	42 (16.7)	9.08 (2.72–30.27)	<0.001	2.57 (0.44–15.00)	0.294	12.15 (2.48–59.6)	0.002	5.08 (1.48–17.45)	0.010
N3A	29 (11.6)	40.29 (12.32–131.7)	<0.001	8.91 (1.36–58.33)	0.022	59.2 (12.4–283.2)	<0.001	20.36 (4.70–88.2)	<0.001
N3B	28 (11.2)	29.84 (8.42–105.75)	<0.001	6.60 (0.97–45.03)	0.054	49.5 (9.6–254.6)	<0.001	18.30 (3.84–87.1)	<0.001
pTNM stage									
I	102 (40.6)	Ref		Ref		Ref		Ref	
II	59 (23.5)	2.73 (0.61–12.2)	0.190	1.67 (0.22–12.81)	0.620	1.29 (0.17–9.63)	0.801	0.52 (0.10–2.64)	0.434
III	90 (35.9)	26.23 (7.32–93.97)	<0.001	4.66 (0.48–45.10)	0.184	29.71 (6.5–135.73)	<0.001	3.25 (0.78–13.61)	0.106

RFS, relapse-free survival; OS, overall survival; PS-IPTW, propensity score-based inverse probability of treatment weighting; TNM stage, the pathological classification under the Gastric Cancer Staging AJCC 8th edition; HR, hazard ratio; CI, confidence interval.

patients' overall survival ($p < 0.05$). The pN3b stage had the highest risk factors related to recurrence [OR = 27.85 (9.10–85.30), $p < 0.001$] and death [OR = 53.05 (11.89–236.60), $p < 0.001$] in GC patients. However, the operation methods did not show significant differences in patients' long-term prognosis ($p > 0.05$).

The PS-IPTW was applied to eliminate group bias, and the results are presented in **Table 2**. Before the PS-IPTW, the results of the logistic analysis of operation methods revealed that there was a significant difference between LAG and TLG in terms of ASA score and tumor size ($p < 0.05$), while age, sex, and pTNM stage showed a possible trend toward significance ($p < 0.1$). After the PS-IPTW, both the Chi-square test and the logistic analysis revealed that all the baseline and pathological variables were well-matched between the two groups ($p > 0.1$). After rounding, a total of 251 GC patients were selected for this study, of which 161 patients were of LAG and 90 patients were of TLG. In the TLG group, the median age was 58 (IQR 49–65) years, 67 (74.4%) were men, and the average BMI was 24.48 (SD 3.43) kg/m^2. Most TLG patients were combined with 0 or 1 chronic disease (92.2%) and ASA I/II (94.4%). In terms of tumor characteristics, the majority of tumors were differentiated adenocarcinoma (88.9%) and located in the lower stomach (60.0%). A total of 77 tumors (85.6%) had invaded the submucosa or deeper regions, and 49 tumors (54.4%) had metastasized to lymph nodes. Stage II and III of pTNM constituted a majority of the TLG group (60.0%).

To demonstrate the high-risk factors after the PS-IPTW, the same Cox analysis procedures were used. Those significant high-risk variables before the PS-IPTW that included the tumor site, gastrectomy, tumor size, pN stage, and pTNM stage ($p < 0.05$) were reanalyzed by using univariate Cox analysis (**Table 3**). Following the PS-IPTW, those significant variables ($p < 0.05$) in the univariate Cox analysis were selected and included in the multivariate Cox analysis. The results showed that the pN stage was the only independent risk factor of RFS and OS in laparoscopic surgery ($p < 0.05$).

Operative and Prognosis Outcomes

The characteristics of operative and prognosis outcomes are presented in **Table 4**. Similar outcomes could be found during the PS-IPTW procedures. Following the operative outcomes, both LAG and TLG groups showed a significant difference in operation time, blood loss, and the number of lymph nodes dissected ($p < 0.05$). TLG took 30 min more than LAG (LAG vs. TLG: 240 min vs. 270 min, $p < 0.001$) but resulted in 20 ml less blood loss (LAG vs. TLG: 50 ml vs. 30 ml, $p < 0.001$). In lymph node dissection, both surgeries obtained a good number of lymph nodes (more than 16 lymph nodes), but TLG performed better (LAG vs. TLG: 28 vs. 30, $p = 0.018$).

In terms of short-term outcomes, the gastrointestinal function recovery of TLG, which included the median time of the first flatus, and first defecation were about 3 and 4 days,

TABLE 4 | Characteristics of operative and prognosis outcomes.

Characteristics	Before PS-IPTW (*N* = 250)			After PS-IPTW (*N* = 251)		
	LAG (*N* = 156)	TLG (*N* = 94)	*p*	LAG (*N* = 161)	TLG (*N* = 90)	*p*
Operative Outcomes						
Operation time (minutes)	240.0 [210.0, 285.0]	270.0 [240.0, 300.0]	<0.001	240.0 [210.0, 282.5]	270.0 [240.0, 300.0]	<0.001
Blood loss (ml)	50.0 [40.0, 80.0]	30.00 [25.00, 40.00]	<0.001	50.0 [40.0, 90.3]	30.0 [30.0, 45.9]	<0.001
Positive LN	1.0 [0.0, 6.0]	0.0 [0.0, 6.0]	0.532	0.48 [0.00, 5.89]	1.00 [0.00, 7.00]	0.400
Dissected LN	27.0 [21.0, 35.0]	29.0 [23.0, 40.0]	0.040	28.0 [21.0, 34.0]	30.0 [24.0, 40.6]	0.018
Transfusion						
No	137 (87.82)	85 (90.43)	0.67	141 (87.6)	80 (88.9)	0.844
Yes	19 (12.18)	9 (9.57)		20 (12.4)	10 (11.1)	
Short-Term Outcomes						
First flatus (days)	3.0 [3.0, 3.0]	3.0 [2.0, 3.0]	0.486	3.0 [3.0, 3.0]	3.0 [2.0, 3.0]	0.350
First defecation (days)	4.0 [3.5, 6.0]	4.0 [3.62, 5.0]	0.831	5.0 [3.5, 5.0]	4.0 [3.50, 5.0]	0.723
First drinking water (days)	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	0.834	5.0 [4.0, 6.0]	5.0 [4.0, 7.0]	0.558
First liquid food (days)	7.0 [6.0, 8.0]	7.0 [7.0, 9.0]	0.338	7.0 [6.0, 8.0]	8.0 [7.0, 9.0]	0.177
Nasogastric tube (days)	4.0 [3.0, 6.0]	5.0 [4.0, 6.0]	0.264	4.0 [3.0, 6.0]	5.0 [4.0, 6.0]	0.168
Pain scores (points)	2.6 [2.2, 2.8]	2.2 [2.0, 2.6]	<0.001	2.6 [2.2, 2.8]	2.2 [1.8, 2.6]	<0.001
Postcomplications	20 (12.82)	8 (8.51)	0.289	20 (12.4)	9 (10.0)	0.558
PPCs	19 (12.18)	7 (7.45)	0.330	19 (11.8)	8 (8.9)	0.509
Gastroparesis	5 (3.21)	0 (0.00)	0.380	5 (3.1)	0 (0.0)	0.399
Anastomotic fistula	2 (1.28)	2 (2.13)	0.693	2 (1.2)	1 (1.1)	0.628
Bleeding	2 (1.28)	0 (0.00)	0.320	4 (2.5)	3 (3.3)	0.294
Hospitalization cost (CNY)	89,614 [76,778, 97,986]	83,963 [72,476, 94,814]	0.065	87,869 [74,123, 97,931]	85,361 [72,487, 94,936]	0.624
Length of stays (days)	10.00 [9.00, 12.00]	11.00 [9.00, 12.00]	0.675	10.0 [9.0, 12.0]	11.0 [9.0, 12.0]	0.243
Long-Term Outcomes						
3-year RFS	75.20%	79.12%		78.86%	78.00%	
Cox analysis	HR = 0.92, 95% CI (0.51–1.65)		0.392	HR = 1.14, 95% CI (0.55–2.35)		0.721
3-year OS	74.16%	82.19%		78.17%	81.48%	
Cox analysis	HR = 0.75, 95% CI (0.39–1.44)		0.770	HR = 0.98, 95% CI (0.42–2.27)		0.955

LN, lymph node; Pain scores, the average scores of the 11-point (0–10) numerical rating scales 5 days after surgery; PPCs, postoperative pulmonary complications; TLG, totally laparoscopic gastrectomy; LAG, laparoscopic-assisted gastrectomy; PS-IPTW, propensity score-based inverse probability of treatment weighting; RFS, relapse-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

respectively. The median times of first drinking water, first liquid food, and removal of the nasogastric tube were 5, 8, and 5 days, respectively. According to Clavien–Dindo classification, the most common postoperative complications were postoperative pulmonary complications (PPCs) (8.9%). The median hospitalization cost was 85,361 (IQR 72,487, 94,936) CNY, and the median length of stay was 11 (9, 12) days. Among them, TLG showed that its short-term outcomes were not significantly different from those of LAG ($p > 0.05$). Although TLG showed a benefit in reducing wound discomfort, which the median pain score was 0.4 points lower than LAG (LAG vs. TLG: 2.6 vs. 2.2, $p < 0.001$).

In terms of long-term outcomes, all 250 patients had completed follow-up by September 2021, and the median follow-up time was 25.1 (IQR 21.3–29.0) months. During the follow-up period, 48 patients relapsed after surgery, and 39 died. After the PS-IPTW, there were no significant differences between groups in the 3-year RFS rate (LAG vs. TLG: 78.86% vs. 78.00%; HR = 1.14, 95% CI, 0.55–2.35; $p = 0.721$) and the 3-year OS rate (LAG vs. TLG: 78.17% vs. 81.48%; HR = 0.98, 95% CI, 0.42–2.27; $p = 0.955$). **Figure 1** depicts the Kaplan–Meier survival curves and log-rank tests, showing that TLG has similar survival outcomes to LAG.

Subgroup Analysis

By using the same PS-IPTW procedures to balance the between-group disparities, except for the dissected numbers of lymph nodes, similar prognosis outcomes could be found in the subgroup analysis of LADG and TLDG (**Table 5**). However, as compared to LATG, TLTG did not increase the operation time ($p = 0.216$), and the wound pain scores did not indicate a significant advantage ($p = 0.126$). The 3-year RFS rate (LADG vs. TLDG: 87.32% vs. 78.26%; HR = 2.19, 95% CI, 0.69–6.92; $p = 0.182$) and the 3-year OS rate (LADG vs. TLDG: 88.23%

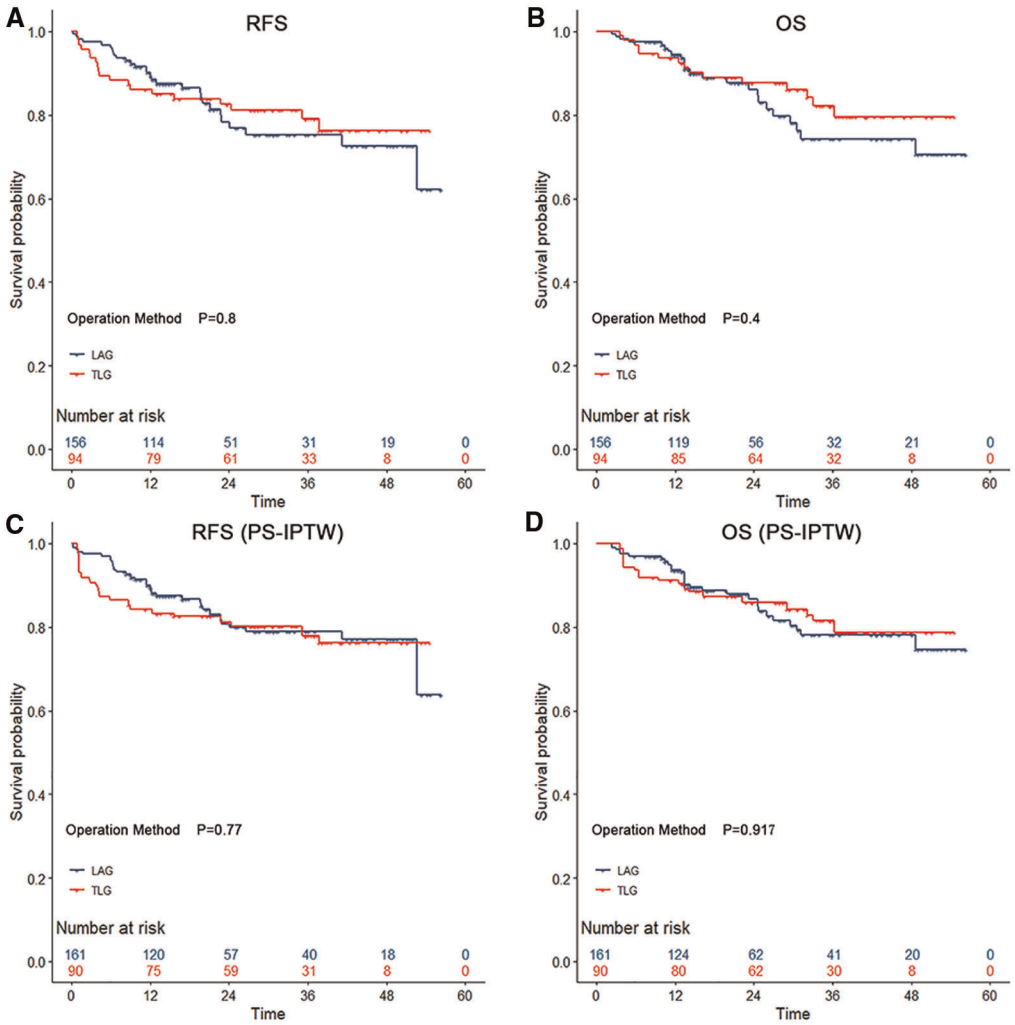

FIGURE 1 | The survival curves among gastric cancer with operation methods during the propensity score-based inverse probability of treatment weighting. According to the type of surgery, both totally laparoscopic gastrectomy and laparoscopic-assisted gastrectomy showed no significant differencess in relapse-free survival and overall survival ($p > 0.05$ by the log-rank test). The risk tables show the actual number of patients with operation methods.

vs. 76.25%; HR = 2.21, 95% CI, 0.64–7.57; $p = 0.209$) showed no significant difference in distal gastrectomy. The 3-year RFS rate (LATG vs. TLDG: 68.96% vs. 67.20%; HR = 1.19, 95% CI, 0.46–3.08; $p = 0.716$) and the 3-year OS rate (LATG vs. TLTG: 67.63% vs. 74.30%; HR = 1.03, 95% CI, 0.34–3.12; $p = 0.959$) also showed no significant difference in total gastrectomy. **Figure 2** demonstrates that TLG has comparable survival outcomes to LAG in both distal and total gastrectomy.

DISCUSSION

The usefulness and effectiveness of intracorporeal vs. extracorporeal approaches in a variety of surgical disciplines are currently a matter of dispute. Many studies have shown that in early or locally advanced gastric cancer, the long-term result of laparoscopic gastrectomy is comparable to that of open gastrectomy (24, 25). A majority of laparoscopic procedures are LADG, and large-scale prospective studies of TLG are still lacking.

This study compared the short- and long-term prognoses of gastric cancer patients who had LAG and TLG. A total of 250 GC patients were included in the study. After using the PS-IPTW to balance the baseline and pathological features of the TLG and LAG groups, we found that TLG took a longer operation time than LAG ($p < 0.05$) but resulted in more lymph nodes retrieved, less blood loss, and less wound discomfort ($p < 0.05$). Furthermore, there was no significant difference in long-term prognosis between the two groups ($p > 0.05$).

For TLDG, Jin et al. (26) reported that a meta-analysis of 25 studies involving 4,562 gastric cancer patients revealed that postoperative complications were comparable for TLDG and

TABLE 5 | Subgroup analysis of operation methods after PS-IPTW.

Characteristics	Distal Gastrectomy (*N* = 156)			Total Gastrectomy (*N* = 92)		
	LADG (*N* = 97)	TLDG (*n* = 59)	*p*	LATG (*n* = 65)	TLTG (*n* = 27)	*p*
Operative Outcomes						
Operation time (minutes)	240.0 [195.0, 278.3]	270.0 [240.0, 300.0]	0.001	265.0 [240.0, 289.1]	270.0 [240.0, 316.4]	0.216
Blood loss (ml)	50.0 [40.0, 74.2]	30.0 [25.0, 40.0]	<0.001	60.0 [50.0, 100.0]	30.0 [30.0, 50.0]	<0.001
Positive LN	0.0 [0.0, 3.0]	1.0 [0.0, 4.2]	0.338	2.0 [0.0, 10.3]	3.6 [0.0, 16.0]	0.435
Dissected LN	28.0 [21.0, 32.0]	28.9 [24.0, 39.9]	0.089	25.0 [21.1, 38.2]	34.6 [23.6, 43.6]	0.195
Transfusion						
No	93 (95.9)	50 (84.7)	0.100	51 (78.5)	26 (96.3)	0.084
Yes	5 (5.2)	9 (15.3)		14 (21.5)	2 (7.4)	
Short-Term Outcomes						
First flatus (days)	3.0 [3.0, 3.0]	3.0 [2.0, 3.0]	0.226	3.0 [3.0, 4.0]	3.0 [2.0, 4.0]	0.362
First defecation (days)	4.0 [3.0, 5.0]	4.0 [3.3, 5.0]	0.739	5.0 [4.0, 6.0]	5.0 [3.5, 6.0]	0.908
First drinking water (days)	5.0 [4.0, 6.0]	5.0 [4.0, 5.5]	0.147	6.0 [5.0, 6.0]	6.0 [5.0, 7.0]	0.052
First liquid food (days)	7.0 [6.0, 8.0]	7.0 [6.0, 8.0]	0.824	8.0 [7.0, 9.0]	8.9 [7.0, 9.0]	0.102
Nasogastric tube (days)	4.0 [3.0, 6.0]	4.0 [3.0, 6.0]	0.935	6.0 [4.0, 8.0]	5.0 [5.0, 7.0]	0.911
Pain scores (points)	2.6 [2.0, 2.8]	2.2 [1.8, 2.6]	0.012	2.8 [2.6, 2.8]	2.44 [2.2, 2.8]	0.126
Postcomplications	8 (8.2)	3 (5.1)	0.344	10 (15.4)	2 (7.4)	0.368
PPCs	7 (7.2)	2 (3.4)	0.234	10 (15.4)	2 (7.4)	0.368
Gastroparesis	4 (4.1)	0 (0.0)	0.300	1 (1.5)	0 (0.0)	0.528
Anastomotic fistula	1 (1.0)	1 (1.7)	0.385	1 (1.5)	0 (0.0)	0.527
Bleeding	3 (3.0)	1 (1.7)	0.447	1 (1.5)	3 (11.1)	0.129
Hospitalization cost (CNY)	85,118 [68,384, 97,922]	84,167 [69,566, 92,822]	0.800	92,435 [79,281, 97,840]	85,141 [76,809, 91,180]	0.152
Length of stays (days)	10.0 [9.0, 11.0]	10.0 [9.0, 11.0]	0.628	11.4 [10.0, 13.00]	12.0 [11.1, 14.0]	0.079
Long-Term Outcomes						
3-year RFS	87.32%	78.26%		68.96%	67.20%	
Cox analysis	HR = 2.19, 95% CI (0.69–6.92)		0.182	HR = 1.19, 95% CI (0.46–3.08)		0.716
3-year OS	88.23%	76.25%		67.63%	74.30%	
Cox analysis	HR = 2.21, 95% CI (0.64–7.57)		0.209	HR = 1.03, 95% CI (0.34–3.12)		0.959

RFS, relapse-free survival; OS, overall survival; PS-IPTW, propensity score-based inverse probability of treatment weighting; LADG, laparoscopic-assisted distal gastrectomy; TLDG, totally laparoscopic distal gastrectomy; LATG, laparoscopic-assisted total gastrectomy; TLTG, totally laparoscopic total gastrectomy; LN, lymph node; PPCs, postoperative pulmonary complications; HR, hazard ratio; CI, confidence interval.

LADG. However, TLDG had favorable short-term results such as blood loss, time of liquid feed, and hospital stay ($p < 0.05$). Besides, Milone et al. (27) reported that a meta-analysis of 3,818 gastric cancer patients under distal gastrectomy showed that the less intraoperative blood loss, the more the harvested lymph nodes and the shorter the length of hospital stay in TLDG than in LADG ($p < 0.05$). Our study also showed similar results in TLDG. We found that this similarity may be due to the fact that intracorporeal reconstruction proved difficult, and TLDG took 30 min longer operation time than LADG, but there did not seem to be an increased risk of postoperative complications. Despite the longer operation duration, TLG showed benefits in terms of decreased intraoperative blood loss and wound pain, as well as a greater number of lymph node dissections ($p < 0.05$), without increasing hospital stay or costs ($p > 0.05$). The possible reasons for these might be that the intracorporeal approaches minimize inadequate surgical field exposure, severe anastomotic tugging, and bleeding produced by laparoscopically assisted small incisions. Besides, the lymph node tracking technologies may result in a more dissected number of lymph nodes. While possibly due to the conservative treatment strategies, the small length of the abdominal incision and pain response of TLG patients did not result in a significant advantage in gastrointestinal function recovery.

Umemura et al. (28) completed a review paper that covered 25 articles on TLTG and demonstrated that it tended to consume more surgical time while having advantages in terms of intraoperative blood loss and postoperative recovery. However, Milone et al. (27) revealed that TLTG was not statistically different from LATG for the above-mentioned outcomes. Our study also showed similar results for TLTG. TLTG revealed no significant difference in prognosis outcomes compared with LATG ($p > 0.05$), except for blood loss (LATG vs. TLTG: 50 ml vs. 30 ml, $p < 0.001$). A clearer vision of

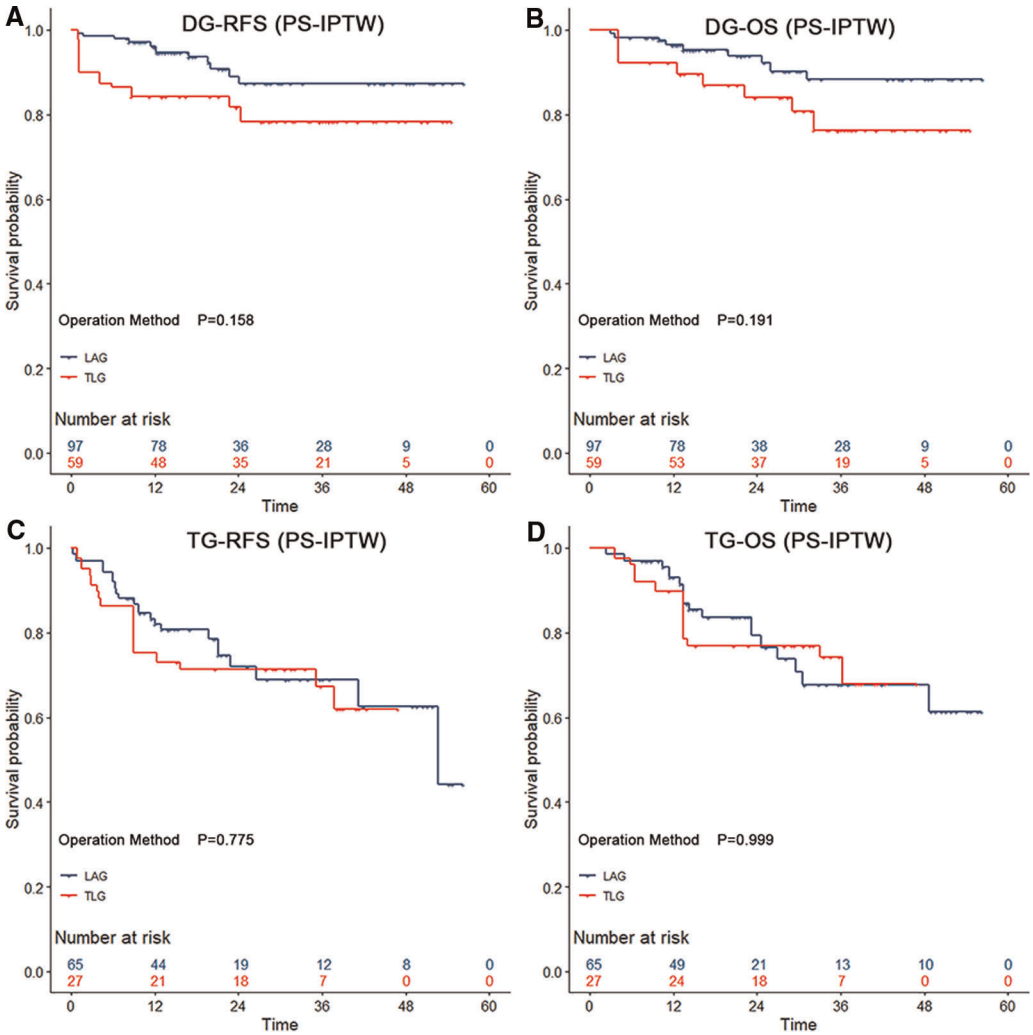

FIGURE 2 | The survival curves among distal and total gastrectomy after the propensity score-based inverse probability of treatment weighting. Both distal gastrectomy and total gastrectomy showed no significant difference in relapse-free survival and overall survival ($p > 0.05$ by the log-rank test). The risk tables show the actual number of patients with operation methods.

intracorporeal approaches, particularly in esophageal exposure and esophagojejunal anastomosis, could explain why the operation time of TLTG is not longer than that of TLAG. Furthermore, our research found that TLG had advantages in the sense that less intraoperative traction can prevent subsequent injury caused by excessive traction of the residual stomach, esophagus, and other tissues. This was also more consistent with the principle of a tumor-free operation in which the excision specimens were intracorporeally put into the bag, which could prevent their appearance in the tumor tissue of extrusion.

Studies (29, 30) showed that the occurrence of complications was not determined by the totally laparoscopic approach. Our study also confirmed this, as the Chi-square test revealed no significant difference between the two groups. All 94 TLG patients completed the R0 resection, including 62 TLDG patients (66.0%) and 32 TLTG patients (34.0%), of which only 8 patients (8.51%) suffered from postoperative complications, including 7 cases of PPCs (7.45%) and 2 cases of anastomotic fistula (2.13%) (One patient developed both complications). No gastroparesis and postoperative bleeding occurred in the TLG group. Once the postoperative complications occurred, the same treatments were given in both surgery groups, including conservative and special treatments. Conservative treatments included atomizing, expectorant drugs, antibiotic therapy, dietary abstinence, gastric tube drainage, abdominal drainage, or abdominal double-cannula lavage. Special treatments included chest drainage, trachea cannula, a second surgery, or intensive care. The aforementioned two of seven PPC patients who had respiratory failure were admitted to the Intensive Care Unit (ICU) and treated with a trachea cannula, anti-infection, and other Advanced Cardiac Life Support measures. The two

patients with anastomotic fistula were diagnosed with small fistula and were treated with dietary abstinence, anti-infection, continuous gastric tube, and abdominal drainage.

Following the PS-IPTW in our study, the multivariate Cox regression analysis revealed that the pN stage was an independent risk factor for the recurrence and mortality of laparoscopic surgery, regardless of the operation method. Favorable long-term outcomes have been reported in the limited number of studies comparing LAG with TLG. Moisan Fabrizio et al. (31) reported in a matched cohort study of 31 patients of both open and TLG groups that the 3-year RFS rate and the 3-year OS rate were 79.4% and 82.3%, respectively. Besides, the survival outcomes also showed similar survival rates of LAG and TLG after the PS-IPTW, in which RFS and OS were 78.86% vs. 78.00% and 78.17% vs. 81.48%, respectively. Similar results could be found in the subgroup analysis. TLG did not increase the survival risks in long-term outcomes.

The limitation in our research was that it was a retrospective study, which meant that the treatment strategies were not determined by random assignments, and, therefore, selection bias may have occurred even when using the groups' balanced method of the PS-IPTW. Secondly, except for the reverse puncture device reconstruction, our surgical team also attempted to perform other intracorporeal endoscopic anastomoses such as overlap (32), isoperistaltic jejunum-later-cut overlap (33), or π-shaped esophagojejunal anastomoses (34) during the study period. Although no serious postoperative complications occurred in these operations, the small number of these surgeries may have resulted in confounding bias, and, therefore, they were not included in this analysis. Besides, because the survival rates in both groups were comparable, the other survival outcomes that were lacking in this study might more substantially guide decisions on the manner of operation.

In conclusion, minimally invasive treatment is a major trend in surgical development (35). However, TLG should be based on the surgeon's technical skills, the patient's physical condition, objective economic status, and the features of the equipment used. The following are some of our study's recommendations: (1) We could endoscopically inject carbon nanoparticles or ICG suspension around the tumor 1 day before TLG to identify the tumor boundaries. (2) For Billroth-II with Braun anastomosis in TLDG, the input loop should not be too long, and the mesenterium should not be twisted. (3) For the reverse puncture device reconstruction in TLTG, place the anvil of the esophageal stump first and then cut the esophagus. It is easy to place the anvil under esophageal traction; (4) Choose a smooth needle thread with high tension resistance, with an appropriate length of around 10 cm, and continuously reinforce the anastomosis under laparoscopy. (5) All should follow the same fundamental principles as an open radical gastrectomy. In case of severe complications that are difficult to manage under laparoscopy, we should switch over to laparotomy. Elaborate considerations should be made to maximize the benefits accrued to patients.

This study showed that TLG for stomach cancer is safe and feasible in both short- and long-term prognoses. Although the surgical procedure is tough to perform, it necessitates greater expertise and coordination on the part of the surgeon. The current long-term efficacy of totally laparoscopic radical gastrectomy still needs evidence-based medical confirmation in the form of large randomized controlled trials.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Review Committee of the Qilu Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The study concept, statistical analysis, and drafting of the manuscript were developed by XZ. The critical revision of the manuscript and the review and approval of the final manuscript were done by MW and WY. The acquisition and interpretation of the data were done by JO, WC, ZC, YL, YH, and RZ. All authors have read and approved the final manuscript.

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REVIEW
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The Use of Indocyanine Green (ICG) and Near-Infrared (NIR) Fluorescence-Guided Imaging in Gastric Cancer Surgery: A Narrative Review

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Near-infrared fluorescence imaging with indocyanine green is an emerging technology gaining clinical relevance in the field of oncosurgery. In recent decades, it has also been applied in gastric cancer surgery, spreading among surgeons thanks to the diffusion of minimally invasive approaches and the related development of new optic tools. Its most relevant uses in gastric cancer surgery are sentinel node navigation surgery, lymph node mapping during lymphadenectomy, assessment of vascular anatomy, and assessment of anastomotic perfusion. There is still debate regarding the most effective application, but with relatively no collateral effects and without compromising the operative time, indocyanine green fluorescence imaging carved out a role for itself in gastric resections. This review aims to summarize the current indications and evidence for the use of this tool, including the relevant practical details such as dosages and times of administration.

Keywords: indocyanine Green, ICG, near-infrared fluorescence imaging, near-infrared, nir, gastric cancer

INTRODUCTION

Gastric cancer is the fourth malignancy worldwide and the fourth cause of cancer-related deaths, with an incidence of 5.6% among new cancer diagnoses (1).

Surgery remains the cornerstone of curative-aim treatment, and the implementation of surgical quality represents one of the main branches of research on this topic. During the last two decades, intraoperative navigation tools have been introduced in various aspects of oncosurgery to improve the quality of care. One of the emerging technologies with the widest diffusion is near-infrared (NIR) fluorescence imaging with indocyanine green (ICG). ICG was approved for the first time in clinical practice by the FDA more than 50 years ago; however, its use has significantly expanded with the development of minimally invasive surgery. In fact, thanks to specific

visualization tools such as NIR cameras, new possibilities for augmented visualization have been opened, which allow for real-time, high-definition visualization by switching between different modalities to visualize the indocyanine green fluorescence with the same laparoscope. Recently, laparoscopic surgery has been validated as a safe option for the treatment of gastric cancer in both Eastern and Western countries (2–14). Results of trials that investigate the non-inferiority of this technique in treating advanced gastric cancer are ongoing, but it is foreseen that mini-invasive approaches to gastrectomy will be pursued. The aim of this study was to summarize the current indications and evidence on the use, dosage, and timing of ICG administration in gastric cancer surgery, summarize the current evidence on the topic to familiarize gastric surgeons with this technology, and identify the gaps in knowledge to guide future research.

ICG - PHARMACOKINETICS AND PHARMACODYNAMICS

ICG is a water-soluble compound with a molecular weight of 774.96g/mol. It is a tracer that emits fluorescence when stimulated by near-infrared light or a laser beam, and it possesses a maximum absorption wavelength of 800–820nm in water. Once injected into the human body, it immediately binds to plasma proteins, is processed in the liver by hepatocytes, and is then excreted into the bile juice. Its half-life is less than 3min. Because of the high protein content in the lymph, the bound ICG accumulates in the lymphatic system and highlights node stations prior to being metabolized by the liver. ICG reaches its maximum fluorescence when it binds to plasma proteins at a wavelength of 840nm in the blood. It has been recently shown that ICG preferentially binds to alpha-1 lipoprotein more than albumin, as traditionally reported; additionally, high-density lipoproteins are the most involved in ICG fluorescence (15). The scope adopted to capture the fluorescence uses both infrared light at wavelengths greater than 800nm and light-emitting diode (LED) light at a wavelength of 760nm; a filter is then used to switch to fluorescence mode, excluding lights below 820nm, thus allowing the tracer in the tissue to be visible (16). Fluorescence intensity does not relate to ICG concentration in a linear fashion; instead, it increases in the low concentration range of ICG, peaks, and then decreases with higher concentrations. This phenomenon has been described as the "quenching effect" (15). With regard to the dosages of the injections, there were no fixed rules: ICG powder in vials is diluted in sterile water at different concentrations and then administered directly to the four cardinal points around a tumor or directly in the serosa. When used intravenously, the dose of an ICG powder solution diluted in sterile water is usually 0.2–0.5mg/kg. The dosage can also be affected by the timing and site of injection. There is no standard rule for the time of injection, which varies from the day before to 20min before dissection (**Table 1**). The safety dose has been established between 0.025 and 0.5mg/kg; adverse reactions, including nausea, fever, and shock have been reported with a dose over 0.5mg/kg (17). Intraoperative injection may be preferable in terms of visualization of the lymphatics and the related guide functions during laparoscopic procedures, without spillage. This could also be a safer solution in cases of anaphylaxis (18).

SEARCH STRATEGY

The electronic databases PubMed, Scopus, Web of Science, Cochrane Library, and clinicaltrials.gov were searched from May 2021 to January 2022 for papers inherent to the topic of this review. The search terms were "gastric cancer," "near-infrared," "near-infrared imaging," "near-infrared fluorescence imaging," "indocyanine green," and "ICG." Abstracts were selected, and the full text was evaluated. Articles were considered according to their level of evidence, timeliness, and ability to influence the current treatment for gastric cancer.

SUMMARY OF THE APPLICATIONS IN GASTRIC SURGERY

In gastric cancer surgery, NIR with ICG has been employed according to the surgical procedure and technique required and the clinical stage of the disease. Initially, it was used for the detection of sentinel lymph nodes in early gastric cancer (19, 20). Its use has then been extended to preoperative endoscopic marking to assess tumor location, with the aim of achieving negative resection margins (21) and node mapping during D2 gastrectomy (22–22). The technique has also proven to be relevant in detecting anatomical structures, considering the complex anatomy of the perigastric vessels; it is also used in esophagogastric junction (EGJ) and esophageal tumors for the assessment of good perfusion of the anastomosis. Although the use of NIR with ICG has been increasingly popularized for laparoscopic gastrectomy, it allows for the performance of multiple real-time intraoperative evaluations in open procedures (26).

LYMPH NODES

Sentinel Node Navigation

The sentinel lymph node (SLN) is the first draining node from a primary neoplasm, and if the first draining node is considered negative for metastasis, all others are assumed to be negative as well. Different types of tracers have been proposed over the last decade, including radioisotopes and dyes (99mTc, sulfan blue, and isosulfan blue), for the effective detection of sentinel nodes in gastric cancer. In a 2013 prospective multicenter trial, a group from the Japan Society of Sentinel Node Navigation Surgery (SNNS) suggested a dual tracer submucosal injection with a radioisotope (technetium 99 m–labeled tin colloid) and 1% isosulfan blue dye. The technique was shown to be safe and effective in detecting sentinel lymph nodes in cT1 and cT2 tumors smaller than 4cm. A total of

TABLE 1 | Summary of included studies.

	Aim	Time of injection	Injection point	Dosage
Yano K. et al. (2012) (19)	Identify the sentinel lymph node	After the surgical incision	Tumor marking at 4 sites Endoscopical submucosal injection	0.5 mL of a 0.5 mg/mL solution
Ushimaru Y. et al. (2019) (21)	Determining the tumor location	1 day before	Tumor marking at 4 sites Endoscopical submucosal injection	1 mL of a 0.05 mg/mL solution
Romanzi A. et al. (2021) (22)	Visualization of draining nodes	18h before surgery	Tumor marking at 4 sites Endoscopical submucosal injection	0.6 mL of a 1.25 mg/mL solution
Chen Q. et al. (2020) (23)	Visualization of draining nodes	1 day before	Tumor marking at 4 sites Endoscopical submucosal injection	0.5 mL of a 1.25 mg/mL solution
Kwon IG. et al. (2019) (24)	Visualization of draining nodes	1 day before	Tumor marking at 4 sites Endoscopical submucosal injection	0.6 mL of a 1.25 mg/mL solution
Kim T. et al. (2018) (25)	Visualization of draining nodes	15min before dissection	Tumor marking at 4–5 sites Endoscopical submucosal injection	1 mL of a 0.05 mg/mL solution
Park J. et al. (2021) (26)	Visualization of draining nodes	After surgical incision	20–25 sites along the greater and lesser curvatures Intraoperative administration by the surgeon	0.5 mL of a 0.025 mg/mL solution
An JY. et al. (2020) (31)	Identify the sentinel lymph node	During surgery	Tumor marking at 4 sites Endoscopical submucosal injection	1 mL of a mixed solution (2 mL of 2.5 mg/mL ICG and 2 mL of 99mTc-radiolabelled human serum albumin)
Miyashiro I. et al. (2011) (33)	Identify the sentinel lymph node	During surgery	Tumor marking at 4–8 sites Endoscopical submucosal injection	2–4 mL of a 0.25–1.25 mg/0.5 mL solution
Miyashiro I. et al. (2014) (34)	Identify the sentinel lymph node	During surgery	Tumor marking at 4 sites Intraoperatively serosal injection	4–5 mL of a 5 mg/mL solution
Roh CK. et al. (2020) (36)	Assess the completeness of the lymphadenectomy	1 day before	Tumor marking at 4 sites Endoscopical submucosal injection	0.6mL of a 1.25 mg/mL solution (da Vinci® Si) 0.6mL of a 0.625 mg/mL solution (da Vinci® Xi)
Tajima Y. et al. (2010) (40)	Visualization of draining nodes	1 to 3 days before the operation or during surgery	Tumor marking at 4 sites Endoscopical submucosal injection and intraoperatively serosal injection	0.5 mL of a 0.5% solution
Lan Y. et al. (2017) (56)	Visualization of draining nodes	Intraoperative and then 1 day before surgery	Tumor marking at 4 sites Intraoperatively serosal injection then endoscopical submucosal injection	0.6 mL of a 2.5 mg/mL solution
Cianchi F. et al. (2020) (58)	Visualization of draining nodes	1 day before	Tumor marking at 4 sites Endoscopical submucosal injection	0.5 mL of a 1.25 mg/mL solution
Chen Q. et al (2021) (59)	Visualization of draining nodes	1 day before VS 20 min before dissection	Tumor marking at 4 sites with endoscopical submucosal injection vs. intraoperatively at six specific sites along the lesser and greater curvature of the stomach	0.5 mL of a 1.25 mg/mL solution vs. 1.5 mL of a 0.5 mg/mL solution
Hunag Z. et al (2021) (61)	Visualization of draining nodes	After preoperative exploration	Intraoperatively at six specific sites along the lesser and greater curvature of the stomach	1.5 mL of a 0.5 mg/mL solution
Lee S. et al (2021) (33)	Visualization of draining nodes	1 day before	Tumor marking at 4 sites Endoscopical submucosal injection	0.6 mL of a 1.25 mg/mL solution (da Vinci® Si) 0.6 mL of a 0.625 mg/mL solution (da Vinci® Xi)
Huh Y. et al (2019) (62)	Perfusion of anastomosis	Immediately after anastomosis	Intravenous administration	1–2 mL bolus of a 2.5 mg/mL solution
Mori M. et al (2020) (69)	Perfusion of anastomosis	Immediately after anastomosis	Intravenous administration	Bolus of a 0.5 mg/kg solution

397 patients underwent sentinel node biopsy, and the method showed high accuracy in detecting sentinel nodes and metastatic sentinel nodes, with a false negative rate of 1% (27).

Recently, near-infrared (NIR) ICG fluorescence has been proposed as a solution to overcome the factors associated with radioactive tracers or dyes, including its cost, iatrogenic effects,

and ease of use. Notably, the first use of ICG was for the detection of sentinel lymph nodes in early gastric cancer (28); since then, its use has expanded tremendously. Given its good tropism for lymphoadipose tissue and the low incidence of allergic reactions, it has been considered preferable to other traces such as sulfan blue. In a 2014 systematic review and meta-analysis, Xiong et al. described an improvement in the detection rate of sentinel nodes and in sensitivity with the use of ICG as an alternative to conventional tracers after 2012, despite the relative heterogeneity among the studies considered. This trend in ICG use was judged positively in terms of technological advancement, and the results of future studies are anticipated. In terms of ICG guided sentinel node biopsy results in the detection of gastric cancer, the detection rate was 100%, despite a sensitivity of 84% (29). The existing literature documents a positive trend in the data reported over the last decade, which may reflect improvements in the technique.

In 2020, a systematic review and meta-analysis by Huang et al. indicated that compared with blue dye or radiocolloid tracer, ICG exhibited increased identification rates over time, as well as increased sensitivity and negative predictive values (NPVs of 98%, 88%, 96% in 2001–2010 to 99%, 92%, 98% in 2011–2020). The review suggested some theoretical advantages related to the use of both NIR ICG fluorescence alone and in combination with a dual-tracer method (radiocolloid + ICG) that allows objective measures. The authors exposed concerns regarding the costs, risks, and logistics associated with the use of radioactive substances. Therefore, the ICG technique could be considered the preferred technique by experts (30).

In the SENORITA clinical trial from the Korean National Cancer Center, the SEntinel Node ORIented Tailored Approach study group randomized 580 patients with cT1 N0 tumors that were <3cm in size and compared the results of laparoscopic stomach-preserving surgery and sentinel lymph node basin dissection (LSNNS) versus laparoscopic standard gastrectomy (LSG) after the injection of 99mTc-radiolabelled human serum albumin and indocyanine green. The trial also performed an intraoperative pathological examination protocol, including immunohistochemistry and molecular biological techniques, which are crucial for the detection of metastatic lymph nodes. Results from the trial suggest that the dual-tracer method is superior to ICG alone for successful laparoscopic sentinel node navigation surgery. The 30-day complication rates were similar in the LSNNS and LSG groups. The authors recommend precise preoperative evaluation of both patient and tumor characteristics in order to improve the success rate of the procedure. Maximum attention must also be paid intraoperatively to guarantee adequate perfusion and innervation of the remnant stomach to ensure a safe organ-sparing procedure. In terms of 3-year disease-free survival, the primary endpoint of the trial, LSNNS did not show non-inferiority compared to LSG. However, the 3-year overall survival and 3-year disease-specific survival rates were comparable, leaving a place for sentinel node navigation surgery in clinical practice (31, 32). More studies are needed to demonstrate the efficacy and safety of this approach in terms of patient quality of life and the risk of recurrence. Currently, most authors tend to administer injections for sentinel lymph node navigation in locations that are proximal, distal, and lateral to the tumor. This type of cardinal pattern is sufficient for most neoplasms, particularly early gastric cancer; in addition, if needed, additional injections can be administered for larger tumors (33). Injections can be subserosal, performed by a surgeon, or submucosal, performed by an endoscopist. Once detected, the sentinel lymph node must be removed "en bloc" with the corresponding lymph node basin according to the Japanese classification of gastric node stations. This could be considered the standard sentinel node biopsy technique. In SNNS papers, the definition of a basin can vary: it can refer to stations along the five principal arteries supplying the stomach or to limited areas specifically described, typically comprising lymphatic routes flowing from the tumor.

To obtain high-quality data, the Gastric Cancer Surgical Study Group (GCSSG) published a multicentric prospective clinical trial (JCOG0302) that aimed to evaluate the feasibility and accuracy of sentinel node evaluation in T1 gastric tumors smaller than 4cm. The protocol called for the injection of indocyanine green into the subserosal layer in proximity to the neoplasm. The rate of green nodes detected was high (97.8%), but there was an unexpected incidence of false negative cases (46.4%) (i.e., negative for metastasis in the intraoperative frozen section but positive during the definitive pathological evaluation). Subsequently, the trial was terminated. One of the main concerns was attributed to the single plane intraoperative histological examination performed on the bioptic material, which determined to not be proficient. The study aim was to demonstrate the feasibility of the intraoperative examination, but a large number of green, negative nodes were intraoperatively found to be metastatic *via* finally paraffin sectioning, misleading the surgeon in whether to perform a gastrectomy or not. Another limitation of the study was related to the learning curve, which was too short and could not be evaluated due to the termination of the trial (34). Compared to the SNNS trial, the JCOG0302 trial included 30 hospitals that contributed 5 patients each, while the former included 12 hospitals with at least 30 cases of experience. According to the existing literature, the learning curve allowing a success rate of 95% for sentinel node dissection could be attested in 26 cases (35). ICG fluorescence lymphography has also been studied after endoscopic submucosal dissection (ESD) when the specimen revealed a neoplasm classified as Sm > 1 and was therefore treated with gastrectomy. ICG was proficient in identifying lymphatic drainage, despite the scars produced by the endoscopy, suggesting that SNNS is still possible after ESD. The study, while considering the concerns regarding SNNS after ESD, also evaluated the drainage patterns during gastrectomy: they noted 100% sensitivity and 100% NPV for the detection of lymph node (LN) metastasis in the fluorescent station. No metastatic nodes were outside the highlighted area, suggesting that more targeted lymphadenectomy should be considered in this particular setting (36).

Drawbacks to SNNS

The main concerns after performing SNNS are false-negative results and skip metastasis. False negatives are usually due to larger and more invasive tumors that have higher rates of lymph metastases, with approximate rates of 5%, 20%, and 50% respectively for T1a, T1b and T2 tumors. These proportions increase for early gastric cancers greater than 4cm (37). In fact, ICG fluorescence could indicate drainage of the tissue surrounding the tumor but not metastatic nodes, as well as the chance of "false-negatives." This phenomenon could be due to the obstruction of the lymphatics caused by cancer cells. Consequently, the tracer moves to the second-tier node. This is the reason why the sentinel lymph node technique is not considered by some authors to be appropriate for gastric tumors >T1. To date, false negative rates vary between 23.5% and 60% (38–42). Therefore, to reduce false negatives, some authors have suggested exploring stations 7, 8, and 9 if the sentinel node is not found in the perigastric stations (43). Attempts have been made to reduce false negative rates with the development of new technologies such as nucleic acid amplification, which directly amplifies the mRNA of the molecular marker used in the supernatant of homogenized lymph nodes, with the aim of improving the sensitivity offered by hematoxylin and eosin intraoperative analysis (44–46). Other attempts included reverse transcription polymerase chain reaction (RT-PCR) (47, 48) and immunohistochemistry (49). On the other hand, skip metastasis (i.e., the presence of second-level positive stations with negative perigastric stations) may be a major concern in sentinel node navigation for gastric cancer among both Eastern (when evaluating T1–2 cancers) and Western institutions (when evaluating more advanced tumor stages) (50–52). Skip metastases reflect the tumor's location. For gastric tumors located in the lesser curvature, particularly in the lower part or circumferentially, there is a higher risk of skip metastasis, with a reported incidence up to 11% (53). Given the relatively low incidence of lymph node metastasis from early gastric cancer, studies collecting thousands of cases may be required to obtain high-quality data.

Lymph Node Mapping

ICG has also been tested as an effective guide for LN dissection during standard gastrectomy. Harvesting a sufficient number of lymph nodes is essential for proper staging. Most guidelines recommend retrieval of a minimum of 16 regional nodes for pathological examination, and it remains desirable to collect 30 or more nodes (54, 55). In this setting, ICG lymph node mapping is intended to recognize lymph nodes and lymphatics and to help perform complete lymphadenectomy for the selected procedure. Small-sample retrospective studies were conducted to evaluate the effectiveness of ICG-guided lymphadenectomy. These studies reported non-unique results and highlighted some limitations, including difficulties in resecting fluorescent stations that are usually not included in standard D2 lymphadenectomy (i.e., stations 13, 14v, or 16a). In contrast, some studies have shown a greater number of retrieved nodes in the critical stations of laparoscopic procedures that use NIR ICG (22, 25, 39, 56).

A recent prospective study by Kwon et al. compared the results from performing robotic gastrectomy in stage I gastric cancer patients that underwent fluorescent lymphography using NIR imaging, with historical controls. An endoscopic injection of a 1.25mg/mL ICG solution in sterile water was injected into the submucosal layer the day before surgery. In the NIR-ICG group, a larger number of lymph nodes was retrieved: more than 30 lymph nodes were retrieved in 92.5% of patients. The number of lymph nodes dissected from the fluorescent stations was significantly higher, especially at stations 2, 6, 7, 8, and 9, and all metastatic lymph nodes were fluorescent. In this study, non-compliance per patient was defined as the absence of lymph nodes from two or more lymph node stations that were supposed to be harvested, and non-compliance per lymph node was defined as the absence of lymph nodes from the dissected station. The proportion of non-compliance per station was 5.2% for fluorescent stations compared to 27.3% for non-fluorescent stations and 18.5% for historical controls. The proportion of non-compliance per patient was 35% in the NIR group compared to 57.5% in the historical group ($p = 0.04$). The authors supported the hypothesis of a reduction in the non-compliance rate at each draining station. The contamination rate (more than two stations collected that should not have been removed) per patient was 7.5% in the NIR group compared to 2.5% in the sample ($p = 0.62$). Therefore, the authors hypothesized that fluorescence would facilitate node retrieval during pathological examination. This method guarantees an intraoperative assessment of the completeness of the dissection and allows for more accurate diagnosis and pathological staging, corroborating the hypothesis that NIR fluorescent lymphography plays a decisive role in diagnosis and staging. This could possibly lead to the detection of groups of patients in which stage migration (i.e., a change in the prognostic group after reclassification of the extent of the disease) has occurred, which could benefit from adjuvant treatment. With higher sensitivity and specificity for metastatic nodes, the authors suggested that it could be possible in the near future to perform personalized dissection according to individual drainage patterns. In addition, no differences in postoperative complications were observed (24).

A retrospective study was published by the same study group as above, which aimed to evaluate the diagnostic accuracy in lymph node metastasis detection during fluorescent guided lymphadenectomy for T1–4a N0–3 M0 tumors. This was done by assessing the congruency between NIR imaging and histopathological examination of "fluorescent" and "non-fluorescent" lymph nodes. In this study, robotic D1+ gastrectomy was performed for early gastric cancer, and robotic D2 gastrectomy was performed for advanced gastric cancer. Fluorescent nodes beyond the D2 stations were not resected, except at station 14v. The technique showed high accuracy and low false negative rates, with NPVs of 99.3% in non-fluorescent stations, suggesting that changes in lymphadenectomy strategies are possible in order to perform

personalized treatments. Therefore, this study suggests that this technique is valid for use in advanced gastric cancer, with the option to minimize the extent of lymphadenectomy, especially in high-risk patients. Notably, the authors expressed concerns regarding false negatives that resulted in acceptable but not satisfactory rates (4.7%) (57).

A Western prospective study analyzed a matched population of patients undergoing robotic gastrectomy with D2 lymphadenectomy (37:37), with and without NIR ICG administration. The number of examined lymph nodes in the control group was 40.1. However, ICG fluorescence failed to demonstrate diagnostic value for metastatic nodes, with sensitivity and specificity values far lower than 90%; in addition, the number of metastatic nodes retrieved was similar between the two groups (58). To obtain high-level evidence, a randomized clinical trial (FUGES-012) was recently conducted in 266 patients with resectable gastric cancer (cT1–4, N0/+, M0). A significantly greater mean number of dissected lymph nodes was registered in the ICG group based on the D2 criteria. A 1.25mg/mL ICG solution in sterile water was injected endoscopically the day before surgery into the submucosa. The authors concluded that ICG-guided equipment may be of great value to newly trained gastric surgeons and can be useful in the dissection of station 14v, considering that metastasis was observed in 33.3% of patients with fluorescent 14v and that 11.6% of the retrieved nodes were metastatic (higher data compared to previous studies). The authors suggested that ICG imaging could significantly reduce the lymph node non-compliance rate for distal and total gastrectomy by performing complete dissection of the stations. Finally, the authors emphasized that only 56.3% of metastatic lymph nodes displayed fluorescence in the study, suggesting that ICG fluorescence could not accurately indicate metastatic lymph nodes and that, from a future perspective of technique diffusion, technological advancements are needed (23).

The FUGES-019 trial, with a design similar to that of FUGES-012, compared subserosal and submucosal injections of ICG. Submucosal injection was performed endoscopically the day before the planned surgery in 133 patients, while the subserosal administration was initiated 20min prior to the beginning of the laparoscopic lymphadenectomy in the other 133 patients. ICG contamination due to mistakes in the administration of ICG during endoscopy or due to intraoperative leakage was very low in both the groups. Twenty minutes after the intraoperative subserosal injection, the luminescence of the D2 stations was comparable to that of the submucosal group. There was no difference in the number of nodes retrieved ($p = 0.713$), and no differences were observed in terms of the nodes collected station by station between the groups. In addition, the non-compliance rates were comparable: 32.3% for the submucosal injection group vs. 33.3% for the subserosal injection group ($p = 0.860$), regardless of the planned surgery (total or distal gastrectomy). The authors concluded that both methods allow for precise staging. Moreover, they analyzed the pattern of diffusion of ICG and found that the dye flowed from the submucosal layer to the serosa through the intermuscular lymphatic network, resulting in a lack of difference in the lymphatic mapping in relation to the site of injection. The authors suggest a specific method for subserosal injection denoted the Huang's subserosal hexa-point maneuver, which consists of the administration of ICG at six specific points along the lesser and greater curvature of the stomach. Ultimately, the cost-effectiveness analysis performed in this study demonstrated how a subserosal injection can be a valid, cheaper solution, particularly considering the workload reduction experienced by endoscopists for tumors other than cT1. In conclusion, the authors did not find any difference in the lymph node-related outcomes between the two methods, with better patient satisfaction and cost effectiveness in favor of subserosal injection; however, they underlined how similar studies should be conducted by analyzing data from neoadjuvated patients (59).

In a cohort study, Zhong et al. presented pooled data from the previously cited FUGES-012 trial (23) and FUGES-019 trial (59). The authors confirmed a higher number of retrieved lymph nodes and a reduction in the non-compliance rate of D2 lymphadenectomies performed using ICG. Moreover, for cT1 and cT2 tumors, the sensitivity for detecting metastatic nodes and the NPV of the non-fluorescent stations were both 100%; lower percentages were reported for advanced T stages, but with documented benefits in terms of the number of nodes retrieved and non-compliance rates. The authors concluded that D1 plus selective imaging-guided lymphadenectomy for cT1-cT2 and D2+ selective imaging-guided lymphadenectomy for cT3-cT4 tumors could be hypothetically included in the current clinical practice guidelines. Interestingly, the reported metastasis rate for stations 10 and 14v was higher than that previously reported, reinforcing the role of image-guided additional lymphadenectomy. However, the authors performed a systematic lymphadenectomy in all patients included in the study, and further studies are needed to assess the feasibility of non-fluorescent lymph node station omission. Furthermore, both the FUGES-012 and FUGES-019 trials collected data from patients who did not undergo neoadjuvant treatment, and different outcomes could be expected from procedures after neoadjuvant treatment due to different node drainage patterns. Therefore, long-term oncological outcomes are still anticipated (60).

To evaluate the safety, effectiveness, and feasibility of ICG in patients with advanced gastric cancer after neoadjuvant chemotherapy (NAC), Huang et al. retrospectively compared 313 propensity score-matched patients in ICG and non-ICG groups. The neoadjuvant treatment consisted of intravenous oxaliplatin and oral fluoropyrimidine S-1. The data showed that ICG was helpful for dissecting a higher number of lymph nodes (40.8 ± 13.7 vs. 31.8 ± 13.5 $p < 0.001$), reducing lymph node dissection non-compliance rates (35.1% vs. 51.1%, $p = 0.027$) even in non-responder patients (22.4% vs. 56.2%, $p < 0.001$), and reducing blood loss (45.6 ± 19.1 vs. 89.6 ± 89.3mL, $p < 0.001$). ICG was particularly useful for dissecting stations 5 and 12a. Moreover, its advantage in terms of node collection

was attested in patients with progressive or stable disease after neoadjuvant treatment; non-significant benefits were registered in good responders, even if ICG was merely useful for determining the burden of the nodes and vessels. This is particularly relevant for the accurate staging and determination of the appropriate subsequent treatment in NAC patients (61). Recently, a retrospective study compared the perioperative and long-term outcomes of patients treated with minimally invasive D2+ station 10 total gastrectomy with and without ICG administration. The authors concluded that, with a 54% prevalence of fluorescence at station 10, independent of the tumor epicenters, the lymph node drainage patterns were determined by the areas of tumor involvement, which are unique in every case. The NPV of the method in regard to station 10 dissection was 97%, and the non-compliance rate registered was lower when there was fluorescence at station 10. Interestingly, there was no difference in overall survival, and there was a positive trend in the relapse-free survival between the groups. For patients with negative lymph node metastasis, the relapse-free survival was higher in the ICG group, with marginal significance ($p = 0.054$) (62).

EVALUATION OF PARENCHYMAL PERFUSION TO AVOID ANASTOMOTIC LEAKAGE

ICG has also been tested in the assessment of anastomosis quality in both total and subtotal gastrectomy and esophagectomy. Despite recent advancements, anastomotic leakage is a major concern in gastric surgery. The incidence ranges between 2.1% and 14.6% in Eastern countries and up to 26% in Western countries. It is the leading cause of mortality related to the procedure (in a 0–50% range) and leads to poor long-term outcomes (63). To date, subjective evaluations have lacked predictive accuracy for anastomotic leakage. These evaluations include tension-free state, proper tissue apposition, minimal spillage of bowel contents, and adequate blood perfusion (64). Several studies have been conducted to evaluate esophagogastric anastomosis by attempting to quantify the blood supply of the gastric conduit and anastomotic region using ICG, suggesting that fluorescence angiography is useful for reducing anastomotic leakage after esophagectomy (65–68). However, few studies have evaluated esophagojejunal anastomosis using ICG.

Recently, Huh et al. conducted a prospective exploratory study on laparoscopic gastrectomy. Thirty ICG-guided procedures (distal gastrectomy with BI or BII reconstructions, total gastrectomy with Roux-en-Y, and pylorus-preserving gastrectomy) were evaluated with an NIR camera by injecting 2.5–5.0mg/mL of ICG solution immediately after the anastomosis was performed. Clinical and fluorescence assessments were performed with separate perfusion scores. The clinical score based on visual observations (dusky, patchy, pink appearance, pulsatility of the mesenteric vessels, and bleeding cut edges) was high for all procedures, and fluorescence was obtained in 100% of patients, with a gap of visualization of 4.1 ± 3.2 min (range, 2–15) after ICG injection. Although ICG visualization was considered unsuccessful in seven patients (23.3%), no changes in the surgical plan were advised; anastomotic leakage occurred in one patient with high clinical and fluorescence scores. The authors confirmed the feasibility of the technique but advocated further studies to prove its effectiveness and determine the appropriate dosage of injected ICG (69).

Another retrospective study analyzed 100 gastric cancer procedures performed by the same senior surgeon. A subjective evaluation was conducted, followed by NIR ICG fluorescence evaluation. All the patients received a solution dose of 0.5mg/kg. The videos of the procedures were revised, and the evaluation was performed 60 s after the ICG injection. This study demonstrated that the gap in visualization between the two time points of the anastomosis was a useful predictor of anastomotic leaks. Overall, 100% of patients with a defined faint pattern of perfusion developed anastomotic leaks, and one of the four anastomotic leaks had a homogeneous pattern. The authors speculated that the patients' nutritional status, blood pressure, arteriosclerosis, evaluation of ICG flow speed, or technical issues could explain the leaks, apart from reasons related to intraoperative perfusion. Moreover, they underlined that quantitative measurement of fluorescence is still difficult in clinical practice because of the need for designated software (70). Recently, it has been created the European registry on Fluorescence Image-Guided Surgery aiming to collect high-volume data on the use of NIR fluorescence imaging. To date, most cases in the database involved colorectal procedures. Results from the registry have been presented by Spota et al. (71). Procedures for esophageal and gastric cancer were 21/1240 (1.7%) and 45/1240 (3.6%) respectively. As regard gastric cancer, due to the small size of the sample (27 subtotal gastrectomies and 16 total gastrectomies) subgroup analysis has not been conducted yet. Therefore, the authors advocate for future inclusions among European centers, standardization in terms of equipment or procedural techniques and quantitative analysis to better understand the impact of fluorescence image-guided surgery. In conclusion, more studies are needed to confirm that NIR ICG fluorescence evaluation of anastomosis for gastric cancer surgery can reduce anastomotic leakage and to compare the relevant intraoperative and postoperative parameters (such as variations in blood pressure).

PERIGASTRIC VESSEL NAVIGATION

ICG can be useful in vessel navigation as it can identify the shape and origin of small vessels that may not be detected by preoperative imaging studies. Tissue thickness is not considered an issue for near-infrared light when the tissues are 2–4 cm-thick (72, 73). In a recent study, Kim et al. injected a 2.5mg/mL solution of ICG immediately after ligation of the right gastroepiploic vein during 20 consecutives, prospectively enrolled robotic and laparoscopic

TABLE 2 | Ongoing randomized clinical trials.

Ongoing RCTs	Brief description	Primary outcomes
Multicenter non-randomized phase III study of sentinel node navigation surgery for early gastric cancer (UMIN000014401)	Evaluate the long-term outcomes of sentinel node navigation surgery for early gastric cancer compared with conventional distal or total gastrectomy	Postoperative 5-year recurrence free survival (RFS) ratio
Fluorescence Image-Guided Lymphadenectomy Using Indocyanine Green and Near Infrared Technology in Robotic Gastrectomy (NCT03931044)	Evaluate the role of fluorescence imaging during robotic lymphadenectomy for gastric cancer	Mean difference of total number of LNs retrieved during surgery (mean ± DS) Fluorescent lymph nodes identification rate (No. %) Accuracy (%; 95% CI)
Prospective Randomized Controlled Trials on Clinical Outcomes of Indocyanine Green Tracer Using in Laparoscopic Gastrectomy With Lymph Node Dissection for Gastric Cancer (NCT03050879)	Predict the positive lymph nodes in gastric adenocarcinoma; guide the scopes in laparoscopic lymph node dissections for gastric adenocarcinoma	Total number of retrieved lymph nodes
Prospective Clinical Trials on Clinical Outcomes of Indocyanine Green Tracer Using in Laparoscopic Distal Gastrectomy With Lymph Node Dissection for Early Gastric Cancer (NCT04973475)	Explore the value of indocyanine green (ICG) in laparoscopic distal gastrectomy with lymph node dissection for early gastric cancer	False negative rate
Feasibility Study of Sentinel Navigation Surgery in Early Gastric Cancer Patients After Non-curative Endoscopic Resection (NCT03123042)	To prove the feasibility of sentinel node navigation surgery (SNNS) in early gastric cancer patients with the risk of lymph node metastasis after endoscopic resection; preparation of the phase 3, multicenter stomach-preserving surgery trial in these patients	Detection rate (%)
Indocyanine Green Lymphangiography as a Tool for Improving Lymphadenectomy in Gastric Cancer (NCT04591028)	Evaluate the safety and added benefit of using the indocyanine green dye (ICG) during surgery	Positive ICG fluorescence lymph nodes Disease positive lymph nodes Number of lymph nodes removed at each lymphatic station
[The iGreenGO Study]. Investigation About the Clinical Value of Indocyanine Green Imaging Fluorescence (NIR/ICG) Technology as a Modifier of Surgeon's Conduct During Curative Treatment of Advanced Gastric Cancer. Study Protocol for a Western, Observational, Prospective, Multicentric Study	Investigate whether the intraoperative application of NIR/ICG technology is associated with a change in the surgical conduct (CSC) during curative-intent gastrectomy with D2 lymphadenectomy in a cohort of Western patients affected by advanced gastric cancer	Incidence of "changes in surgical conduct" (CSC) at the moment of intraoperative NIR/ICG technology activation after a D2 lymphadenectomy performed "with the naked eye"

gastrectomies. The purpose of this study was to assess the presence of an infrapyloric artery, which is to be spared during pylorus-preserving gastrectomy, or an accessory splenic artery emerging from the left gastroepiploic artery in order to prevent inferior polar infarction of the spleen. An infra pyloric artery was identified in 80% of cases, with a procedural time of less than one minute, and the accessory splenic artery, when present, was always easily identified. The authors suggested that ICG could be useful for inexperienced surgeons during infrapyloric dissection and for reducing operative times, blood loss, and the number of unintended injuries (72).

In a retrospective study of 31 patients, Lee et al. described the advantages of ICG technology for detecting accessory left hepatic artery during surgery. The authors evaluated the grade of liver surface fluorescence after an endo-clamp was placed on the artery near the left lobe, assuming that fluorescence mainly depends on the arterial irroration. They then intravenously injected 5mg of ICG diluted in 2 mL of sterile water, and the entire fluorescence of the liver was evaluated. In case of a reduction in the fluorescence of the left lobe, the clamp was removed, and vascularization was reassessed with a new intravenous injection of ICG. According to the accessory artery territories highlighted by NIR ICG, the artery was ligated in 20 patients and preserved in 10 patients, and no differences were observed in terms of intraoperative or postoperative outcomes. The authors concluded that accessory left hepatic arteries could be safely ligated after NIR fluorescence evaluation, avoiding potentially difficult and longer dissections during gastrectomies (73).

ONGOING TRIALS

Ongoing trials investigating the role for ICG in lymph node navigation surgery and lymph node mapping include the "multicenter non-randomized phase III study of sentinel node navigation surgery for early gastric cancer" study, which is being conducted by Japanese institutions (UMIN000014401) and aims to evaluate the long-term outcomes of sentinel node navigation surgery for early gastric cancer compared to conventional distal or total gastrectomy. Another is the prospective "Fluorescence Image-Guided Lymphadenectomy in

Robotic Gastrectomy (IG-MIG) (NCT03931044)" trial, which compares ICG guided robotic gastrectomy vs. standard robotic gastrectomy, aiming to measure the mean difference in the total number of LNs retrieved during surgery and the percentage of fluorescent nodes detected. The phase II "Indocyanine Green Tracer Using in Laparoscopic Gastrectomy with Lymph Node Dissection (ICGTinLG) (NCT03050879)" RCT aims to evaluate the difference in the number of nodes retrieved between ICG laparoscopic gastrectomy and standard gastrectomy. The phase two "Prospective Clinical Trials on Clinical Outcomes of Indocyanine Green Tracer Using in Laparoscopic Distal Gastrectomy with Lymph Node Dissection for Early Gastric Cancer (NCT04973475)" study has the primary outcome of evaluating the false negative rates of ICG. The "SENORITA 2 Feasibility Study of Sentinel Navigation Surgery in Early Gastric Cancer Patients after Non-curative Endoscopic Resection (NCT03123042)" aims to evaluate the detection rate and false negative rate of sentinel node navigation surgery. The "Indocyanine Green Lymphangiography as a Tool for Improving Lymphadenectomy in Gastric Cancer (NCT04591028)" trial has the primary outcomes of establishing the total number of lymph nodes removed after surgery that are positive for ICG fluorescence, how many are positive for metastasis, and the number of nodes collected per station. Finally, the "iGreenGO Study (NCT04943484)" intends to investigate the "changes in surgical conduct" (CSC) at the moment of intraoperative NIR/ICG technology activation after a D2 lymphadenectomy performed "with the naked eye" (**Table 2**).

FUTURE PERSPECTIVES

The future is bright, and the technological implementation of surgical devices will be inevitable. Almost every producer has developed an integrated NIR ICG system for new optical tools. The use of these systems could prevent the need for upper abdominal incisions, achieve better oncological outcomes, shorten the learning curve, and pursue function-preserving curative gastrectomy. Moreover, integrated technologies capable of quantifying the fluorescence produced by ICG in real time are currently being investigated; presently, only case reports on real-time fluorescence quantification have been reported (74). Studies are in progress regarding the role of ICG in detecting peritoneal carcinomatosis (75). There is also great potential for the implementation of the dye in combination with other molecules, tracers, or monoclonal antibodies that are capable of detecting metastasis and that can be detected by multiple diagnostic tools (MRI, NIR, and multi-modality imaging (FMI) using multiple novel fluorophores) (76, 77); some of these methods have already been tested and are awaiting approval for clinical use. An increasing number of devices are in development with the aim of making the fluorescence quantifiable, overcoming the dual tracer method (78), or in order to assess the quality of perfusion (79). A fascinating angle on new technologies that could well integrate with ICG fluorescence imaging is offered by studies on hyperspectral imaging (HSI) and confocal laser endomicroscopy (CLE). HSI is a method able, through real time analysis of tissues' chemical properties, to potentially detect early mucosal lesions, to measure anastomotic perfusion, to assess resection margins and extent of node dissection in combination with deep learning models (80). CLE is, on the other hand, an optical imaging modality that provides an *in vivo* histopathological assessment of the mucosa, for example in terms of quality of perfusion. (81)

CONCLUSIONS

With relatively no collateral effects and without significantly compromising operative times, ICG fluorescence imaging applications are carving out a role in future studies on gastric resections. The most effective application of this tool has been debated. With regard to sentinel node mapping, ICG guidance is still in the preliminary phase. Steps are being taken to invest in the concept of basin dissection instead of node picking, collecting more nodes to reduce the risk of false negatives, and developing more precise techniques for intraoperative pathological examinations. Nevertheless, high-quality evidence with which to provide a strong statement on the topic is still lacking. As previously mentioned, especially for the Western population, due to the low incidence of metastasis for early gastric cancer, thousands of cases may be required to obtain high-quality data. Indocyanine green fluorescence appears to be helpful for the dissection of more lymph nodes, even during planned lymphadenectomies. Preliminary evidence suggests that NIR with ICG can help surgeons assess the completeness of D1, D1+, or D2 lymphadenectomy and define the boundaries of the dissection, all while highlighting the anatomical landmarks and fluorescent stations. This could be particularly useful for training young surgeons to perform minimally invasive procedures to retrieve enough nodes and perform adequate lymphadenectomies.

The impact of ICG on non-compliance and contamination rates must be investigated. Therefore, by systematically exploring beyond the secondary level stations under the guidance of ICG fluorescence, we could better define the real locations of stations such as station 14v or even 13, and consider, in particular contexts (such as in large tumors of the antrus or in the lower part of the great curvature, with serous invasion, or with station 6 confirmed nodal involvement), the search and removal of such stations. The use of ICG could also lead to less extended, tissue-sparing surgeries and perhaps more precise staging, especially in T1 or T2 tumors, by assessing their nodal state and detecting micrometastasis, thus allowing the evaluation of any adjuvant treatment. From this standpoint, apart from identifying the first draining node, which is the protocol in the sentinel node scenario, identifying the last draining node may have added value in achieving lymph nodal R0 resections.

Based on the suggestions offered by the authors of the papers presented in this review, it can be speculated that D1+ or D2 lymphadenectomy is not always perfect or even necessary. Moreover, according to the findings of this review, patients with advanced gastric cancer who underwent surgery after neoadjuvant chemotherapy could benefit from the use of NIR with ICG. In fact, it seems capable of defining lymphatic drainage in progressive or stable disease after neoadjuvant treatment. Standardization and objective measures are required for the development of real-time software. Once the technique is standardized, surgeons will speculate on the usefulness of the tool and analyze the direct and indirect costs of its use. Increasing evidence is still needed to support this trend due to the multiple benefits offered.

AUTHOR CONTRIBUTIONS

FB, AB, and AA designed the review; FB and PS collected and analyzed the data; FB, AB, AA and PS drafted the article; FB, AB, AA, PS, AL, LL, RP, FT, LF, DD and RP revised the paper and gave the final approval of the definitive version of the article. All authors contributed to the article and approved the submitted version.

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