

# Risk factors as criteria for drain use in gastrectomy: A prospective study

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**Abstract.** Total gastrectomy with D2 lymph node dissection remains the standard treatment option for resectable esophago-gastric junctional and gastric cancer; however, high rates of morbidity lead to challenges in perioperative care. The Enhanced Recovery after Surgery (ERAS) guidelines advise against the use of routine drains; yet, conflicting evidence leads to inconsistent use in clinical practice. The Drains After Gastrectomy (DRaG) trial was a prospective, non-randomized study conducted from February 2020 to March 2023 at the Hippocraton General Hospital, University of Athens. Patients undergoing open D2 total gastrectomy were treated with perianastomotic drainage based on evidence-based criteria, offering a tailored approach to treatment. Immediate and

short-term post-operative outcomes, including complications and key milestones in recovery, were assessed.

In total, 60 patients were included in the prospective study, with 40 receiving a drain based on evidence-supported, case-based criteria. The non-drain group exhibited lower pain scores, earlier rates of mobilization, lower levels of post-operative nausea and vomiting, and shorter hospital stays. By contrast, patients presenting with complications experienced a delayed post-operative recovery, which may have been associated with the use of the drain. Although adverse effects are common, the application of specific criteria may aid clinical decision making. In conclusion, the present study aimed to provide a criteria-based approach for individualising drain placement in gastrectomy. Notably, the findings of the present study are comparable with those of existing studies; thus, the suggested criteria offer a structured and reliable approach to the use of drain placement following gastrectomy in surgical practice.

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*Abbreviations:* AJCC, American Joint Committee on Cancer, CA 125, Cancer antigen 125; CA 153, cancer antigen 153; CA 19-9, cancer antigen 19-9; CEA, cancer embryonic antigen; CONSORT, Consolidated Standards of Reporting Trials; DRAG, drains after gastrectomy; ECOG, eastern cooperative oncology group; EGJ, esophago-gastric junction; ERAS, enhanced recovery after surgery; FBC, full blood count; FFP, fresh frozen plasma; IRB, institutional review board; LOS, length of stay; POD, post-operative day; PONV, post-operative nausea and vomiting; RBC, red blood cells; SSI, surgical site infection; TNM, tumour-nodes-metastasis; VAS, visual analogue score

*Key words:* prophylactic drain, total gastrectomy, gastric cancer, esophagogastric anastomotic leak, drain criteria

## Introduction

Gastric cancer is the fifth most common cancer globally, with the fifth highest rates of mortality (1). Notably, most patients with gastric cancer present with stages IB to IIIC of the disease, according to the American Joint Committee on Cancer (AJCC). At present, the gold standard of surgical treatment involves total gastrectomy combined with D2 lymph node dissection, followed by gastrointestinal tract reconstruction (2-5). The 5-year survival rates following R0 resection vary, ranging from 89.9% for stage IB disease to 20.2% for stage IIIC disease, as reported in the 8th edition of the TNM classification (6). Due to the high morbidity rates associated with gastrectomy, research has focused on improving perioperative care and the quality of life of patients (7,8). Moreover, despite its curative intent, total gastrectomy often leads to persistent post-gastrectomy syndromes that can significantly impair

short and long-term quality of life (9-11). Importantly, quality of life (HRQoL) has also been identified as an independent prognostic factor for survival, underscoring its importance in postoperative care (12,13).

Results of previous studies demonstrated that minimizing surgical intervention may be associated with improved rates of recovery (7,8,14). The Enhanced Recovery after Surgery (ERAS) guidelines offer globally recognized perioperative recommendations for various surgeries. Notably, the guidance recommends against the use of drain placement to reduce complications, such as pain, delayed mobilization and infection (8). Historically, drain placement remained a routine intervention during gastrectomy (15), with literature reporting usage rates of 57.7-62.8% (16-18). In 2014, Mortensen *et al* (19) introduced the ERAS guidelines for gastrectomy in gastric cancer, based on two meta-analyses (including 400 cases) and two prospective trials. Results of these studies revealed no significant differences in hospital stay, morbidity rates, mortality rates or complications between patients with and without drains (20-23). However, due to heterogeneity in surgery type and data collection, the evidence was considered insufficient.

Although the ERAS guidelines provide clear recommendations for the use of drains in surgeries such as pancreaticoduodenectomies and colectomies (24,25), their usage in gastrectomy for gastric cancer remains the topic of debate. Japanese guidelines support the routine use of drains following total gastrectomy, with removal by the fifth post-operative day (26). Results of previous studies in Japan also highlighted the prognostic value of drain contents post-gastrectomy, reinforcing this practice (15,27-31). By contrast, Western guidelines, such as those from the American College of Surgeons, advise against routine drain use, suggesting placement only in exceptional cases (32). This conflicting evidence may lead to uncertainty regarding drain use in gastrectomy, resulting in limited adherence to ERAS recommendations in Western practices (33,34).

The present prospective, non-randomized, controlled clinical trial aimed to individualize drain use following gastrectomy for the treatment of gastric cancer. The tailored approach described in the present study is based on criteria developed using previous literature, including established risk factors for post-operative complications. Significantly, the objective of the study was not to assess the benefit of drains themselves, but rather to determine whether these predefined clinical criteria can effectively guide the decision to place a drain during open total gastrectomy. To the best of our knowledge, the present study is the first to propose specific criteria addressing routine prophylactic drain use in total gastrectomy, aiming to provide a structured framework for clinical decision making in high-volume centers.

## Materials and methods

**Study design.** The DRains After Gastrectomy (DRAG) trial (Clinical Trials.gov NCT 04288661) was a prospective, non-randomized, controlled clinical trial involving patients diagnosed with gastric or esophagogastric junctional neoplasm. All surgeries were performed by experienced Foregut Surgeons in The University Surgical Department at

Hippocraton General Hospital in Athens, Greece, a leading referral centre for upper gastrointestinal tract diseases. Patients underwent open total gastrectomy with D2 lymph node dissection, followed by Roux-en-Y gastrointestinal tract reconstruction. This was performed in accordance with a pre-defined, ERAS-compliant perioperative departmental protocol. The study design was conducted according to the following sequence: i) A literature review was carried out to identify commonly reported risk factors for major intra-abdominal complications following total gastrectomy; ii) The most consistently cited risk factors were selected to form the basis for the drain placement criteria; iii) Eligible patients were screened according to predefined preoperative and intraoperative criteria; iv) The final decision regarding drain placement was made intraoperatively-after completion of the resection and reconstruction, and immediately prior to abdominal wall closure-based on the selected criteria; v) All patients were followed for 30 days postoperatively, in line with the institutional monitoring protocol.

As aforementioned, the first step involved a comprehensive review of the literature, focused on the use of gastrectomy for the treatment of gastric cancer, and on the identification of risk factors associated with post-operative complications, such as esophagojejunal anastomotic leak or bleeding. The present review included 11 retrospective studies and two randomized controlled trials, and these highlighted numerous risk factors associated with the aforementioned complications. Of these, the most consistently reported factors were selected for subsequent analyses. The following criteria were suggested for the placement of a drain, as the presence of these risk factors signified an increased risk of post-operative complications (15,35-47): i) Chronic cardiopulmonary disease; ii) chronic oral steroid use ( $\geq 5$  mg/day prednisone equivalent for  $>1$  month); iii) intraoperative hemodynamic instability requiring vasopressors; iv) intraoperative blood loss exceeding 250 ml (mean amount of estimated blood loss in all included studies), referring to intra-operative non-traumatic, non-vascular blood loss; v) vessel injury involving the celiac axis or the associated branches; vi) injury to adjacent structures, such as the pancreas, spleen or duodenum; vii) tension at the anastomosis, or the requirement for anastomosis reconstruction; and viii) concerns regarding the integrity of the duodenal stump, particularly due to potential staple misfiring or compromised tissue quality.

All patients that met the eligibility criteria underwent pre-operative evaluations, including clinical examinations, blood tests, imaging studies and consultations with specialist clinicians. The eligibility criteria included the following: Histologically confirmed gastric adenocarcinoma; planned open total gastrectomy with D2 lymphadenectomy; no evidence of distant metastasis (M1); absence of massive ascites or severe cachexia; no unplanned organ resections; no severe cardiovascular, respiratory, renal, hepatic, or psychiatric conditions; not currently enrolled in another clinical trial; and no contraindications such as pregnancy or poor compliance with clinical protocols. Intraoperative criteria that ruled out eligibility included findings of unresectable or metastatic disease and cases requiring conversion to subtotal gastrectomy.

Intra-operatively, all dissections were carried out with an ultrasonic vibration scalpel to minimise blood loss. Saline was

used for irrigating the surgical field, and volume was monitored and excluded from the total calculated blood loss. Notably, the protocol followed by the University Surgical Department at Hippocraton General Hospital does not routinely incorporate exploratory laparoscopy or peritoneal cytology. In some cases, high procedural complexity may necessitate lymphadenectomy beyond a standard D2 dissection (48). However, to maintain uniformity, only patients undergoing D2 gastrectomy were included in the present study.

Final allocation to the drain or non-drain group was made at the end of the procedure and prior to abdominal wall closure. The decision for drain was based on the aforementioned criteria. The patients for whom drain placement was decided, received a standard 10-mm (~30 Fr) silicone tube drain near the esophagojejunal anastomosis (Shanghai International Holding Corp GmbH). By contrast, no drain was placed in the patients who did not meet the criteria. A CONSORT flowchart illustrating patient enrolment, exclusion, and group allocation is provided in Fig. 1.

According to the departmental protocol, patients were gradually mobilized directly following surgery, when feasible. At 48 and 72 h post-surgery, an oral gastrografin fluoroscopy study was performed for each patient, for the detection of early anastomotic leaks. Following a routine radiological study, patients were initiated on a liquid diet, which was subsequently advanced to pureed food on the fourth post-operative day, and a soft diet on the fifth post-operative day. In the drain group, drains were monitored daily for 24-h output volume and fluid characteristics, including amylase and bilirubin concentrations. They were removed from patients in the drain group on the fifth post-operative day, when drainage volume was <50 ml within the preceding 48 h. Drain output was considered excessive if the volume exceeded 100 ml on postoperative day five (18,26) or if the drain fluid amylase level was greater than three times the upper limit of normal serum amylase on or after postoperative day three, consistent with the definition of a postoperative pancreatic fistula (49). Patients were discharged on the fifth post-operative day when no complications were observed.

Drain and non-drain groups were compared within the following cohorts: i) The overall study population; ii) patients with complications; and iii) patients without complications.

Primary outcomes were as follows: i) Pain level assessment during the first 5 post-operative days, using the Visual Analog Scale (VAS). Notably, the VAS is a 10-point scale, with 0 representing no pain and 10 indicating the highest level of pain. A score of >7 is considered high (50); ii) post-operative nausea and vomiting (PONV) within the first 5 post-operative days; iii) initiation of feeding, carried out between 48 and 72 h post-surgery. According to the ERAS-compliant institutional protocol, initiation of feeding beyond the third post-operative day is considered delayed; iv) post-operative bowel mobilization, primarily measured by the time to the first passage of flatus; v) patient mobilization, following a specific post-operative mobilization schedule for each day. Failure to meet the specific criteria was indicative of a delay in mobilization; and vi) length of hospital stay, referring to the time from the day of the operation to the day of discharge.

Secondary outcomes included: i) mortality, referring to death occurring within 30 days post-surgery; ii) readmissions

due to surgical complications, occurring within 30 days post-surgery, and iii) reoperations due to surgical complications, occurring within 30 days post-surgery.

The present study was conducted in accordance with the principles outlined in the Declaration of Helsinki (51) and the Guidelines of Good Clinical Practice (52). The final study protocol and the informed consent form for participant inclusion were approved by the Institutional Review Board of Hippocraton General Hospital (approval no. 1678/31-01-2020; Athens, Greece). The IRB also conducted regular assessments as required, to ensure ongoing compliance with lawful medical practice throughout the trial.

*Statistical analysis.* Statistical analysis was performed using R software (version, 4.3.0; R foundation for Statistical Computing). Descriptive statistics for quantitative data included descriptive characteristics, and these were expressed as the median and minimum/maximum values and quartile 1 (Q1) to quartile 3 (Q3) range, and/or for completeness reasons the mean  $\pm$  standard deviation (SD). Descriptive statistics for qualitative data were expressed as the frequency of occurrence and the relevant percentage. Comparisons were performed between patients with drainage and those without drainage, and additional analyses were performed between patients with and without complications. Qualitative data were analysed using Chi-squared and Fisher's exact tests when required and quantitative data were analysed using the Mann Whitney U test, as data normality was not always confirmed (via the Shapiro Wilk test).  $P < 0.05$  was considered to indicate a statistically significant difference. For time to event analysis, that is to visualize and report time to gut mobilization and days of hospitalization, the Kaplan-Meier estimator was applied.

To address potential confounding and strengthen causal inference between study groups, a propensity score matching (PSM) approach was applied using R version 4.4.0 (53). The binary clinical covariates were blood loss, vessel damage, anastomosis, stump and respiratory issues, the criterion of adjacent structures was not involved since none of the patients had such issues in addition drainage volume was also not possible to account as only two patients had abnormal drainage volume. Eventually, the application of a drain was modelled using logistic regression to estimate the propensity scores and matching was performed using 1:1 nearest neighbour matching without replacement through the MatchIt package (54) especially developed for the R environment. Covariate balance was evaluated using standardized mean differences. Moreover, to explore potential impact of possible confounders, a Rosenbaum sensitivity analysis was conducted using the rbounds package (55). Finally, subgroup analysis was performed between patients with and without a drain, separately for the patients that had complications and those who did not experience such complications.

## Results

*Comparison of the overall study population.* The present study was conducted from February 2020 to March 2023. Of the 60 eligible participants, 40 were assigned to the drain group, while 20 were included in the non-drain group, as per the aforementioned criteria. The mean age of patients was

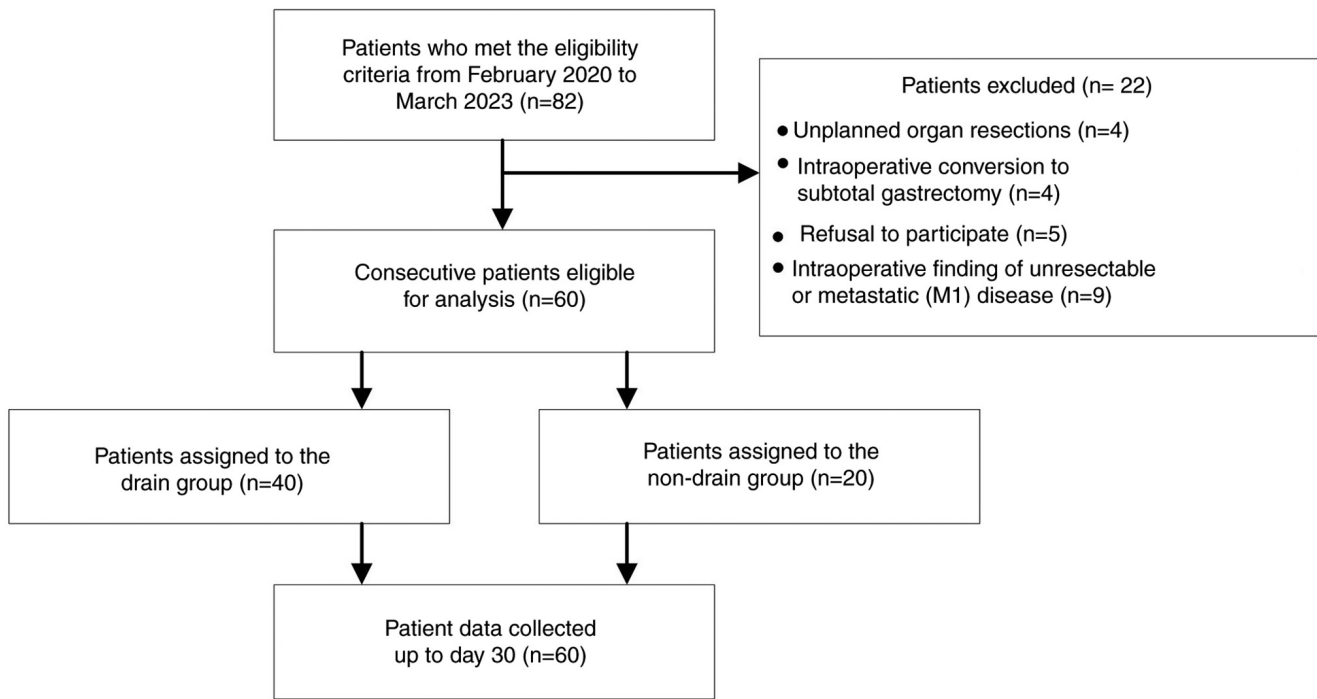


Figure 1. Consolidated Standards of Reporting Trials flowchart of patient selection and allocation for inclusion in the study.

71±9.6 years. Pre-operative histological diagnosis primarily identified intestinal-type gastric cancer in 46.6% of cases, with the body of the stomach being the most common location of observed lesions (43.3%). In addition, 25% (n=15) of patients had undergone pre-operative chemotherapy due to nodal positivity (N≥1) at diagnosis, or due to unresectability observed during exploratory laparotomy (Table I). As there were no patients on chronic steroids or patients that developed intra-operative hemodynamic instability, these factors were not included in the results. Results of the present study revealed no statistically significant differences in pre-operative characteristics between the drain and non-drain groups (Table II).

The mean duration of gastrectomy was 197±37 min. Blood transfusion was required in 13.3% of patients, and 8.3% received fresh frozen plasma (FFP) only. The most common intra-operative indications for drain placement were significant blood loss (33.3%; n=20) and tension at the anastomosis site (18.3%; n=11). Further details on intra-operative characteristics are provided in Table I. Regarding age distribution, Table II shows no statistically significant difference between the two groups: the median age was 73.5 years (IQR: 63-78) in the drain group and 73 years (IQR: 66.5-77.5) in the non-drain group (P=0.8138). No other statistically significant differences were observed when comparing intra-operative characteristics between the two groups (Table II).

Post-operatively, ~56% (n=34) of patients reported severe pain during the first 5 days post-surgery. Results of the present study also revealed that high VAS scores (>7) were significantly less frequent in the non-drain group (15%; n=3) when compared with the drain group (77.5%; n=31; P<0.0001; Fig. 2).

PONV was common in the overall study population, affecting 48.3% (n=29) of patients. Significant differences were observed between groups, with a lower incidence of

PONV in the non-drain group (25%; n=5) compared with the drain group (60%; n=24; P=0.0142). Thus, there was a ~5X higher risk of PONV in the drain group [odds ratio (OR), 0.22].

Surgical site infections (SSI) were observed in 12 patients (20%), with no statistically significant difference between the drain and non-drain groups.

Timely mobilization was impeded in 37% (n=22) of patients in the overall study population. Delays in mobilization were notably less frequent in the non-drain group, occurring in only 10% (n=2) of patients, compared with 50% (n=20) in the drain group (P=0.0038). Notably, these results were statistically significant.

In 28.3% of patients (n=17), feeding initiation was delayed, despite the recommendation that feeding should be initiated 48-72 h post-surgery. Notably, the delay in feeding initiation was less common in the non-drain group, occurring in 10% (n=2) of patients, compared with 37.5% (n=15) in the drain group (P=0.0340). These results were statistically significant.

Gut motility resumed at a mean of 3.58±1 days, as illustrated by the Kaplan-Meier plot (Fig. 3). The initiation of bowel movement occurred significantly earlier in the non-drain group, with a median time of 3 days, compared with 4 days in the drain group (P=0.0142).

Intra-abdominal complications, Clavien-Dindo ≥II (56/57) occurred in 15% (n=9) of patients, accounting for 10% (n=2) of the non-drain group and 17.5% (n=7) of the drain group. Notably, there was no statistically significant difference between the two groups.

Among the intra-abdominal complications observed, the most common was esophagojejunal anastomotic leak, affecting four patients in the drain group. In total, two patients required reoperation with hybrid intra-operative stent suturing (58), one patient received endoscopic stenting, and one patient succumbed during the study period. The

Table I. Descriptive statistics of perioperative characteristics.

Characteristics	Value
Age, years	71±9.6, median (Q1-Q3): 73 (65-77.5), min: 48, max: 87
Sex, male	32 (53.33%)
Charlson score	2.45±0.85, median (Q1-Q3): 2 (2-2.5), min: 2, max: 5
ECOG	
1	8 (13.33%)
0	52 (86.66%)
Histology	
Diffuse	22 (36.67%)
Intestinal	28 (46.67%)
Other	7 (11.67%)
Location	
Esophago-gastric junction	12 (20.00%)
Fundus	5 (8.33%)
Body	26 (43.33%)
Prepyloric antrum	16 (26.67%)
Pylorus	1 (1.67%)
Positive preoperative chemotherapy	15 (25.42%)
CA positivity <sup>a</sup>	
CA 19.9	8 (13.33%)
CA 15.3	6 (10.00%)
CA 125	3 (5.00%)
CEA	7 (11.60%)
Intraoperative characteristics	
Duration of operation, min	197.5±37.2, median (Q1-Q3): 200 (180-227.5), min 120, max 180
Blood transfusion	8 (13.33%)
FFP transfusion	5 (8.33%)
Allergic reaction to drugs	0 (0.00%)
Intraoperative incidents	7 (11.67%)
Criteria for drain placement	
Blood loss of >250 ml	20 (33.33%)
Vessel injury	3 (5.00%)
Anastomosis concerns	11 (18.33%)
Adjacent structures injury	0 (0.00%)
Stump integrity concerns	3 (5.00%)
Chronic cardiopulmonary comorbidity	3 (5.00%)
Postoperative characteristics	
Swallow test (negative)	58 (96.67%)
Visual analogue score (high)	34 (56.67%)
Postoperative nausea and vomiting	29 (48.33%)
Surgical site infection	12 (20.00%)
Mobilization delay	22 (36.67%)
Oral feeding delay	17 (28.33%)
Gut motility start (postoperative day)	3.58±1.04, median (Q1-Q3): 3 (3-4), min: 2, max 6
Intra-abdominal complication	9 (15.00%)
Extra-abdominal complication	5 (8.33%)
Length of stay (post-op to exit)	9.5±9.01, median (Q1-Q3): 6.5 (5-8), min: 5, max: 59

Table I. Continued.

Characteristics	Value
AJCC stage	
1A	9 (15.00%)
1B	10 (16.66%)
2A	16 (26.66%)
2B	12 (20.00%)
3A	5 (8.33%)
3B	6 (10.0%)
3C	2 (3.33%)
Outcomes	
Mortality	3 (5.00%)
Re-admission	5 (8.33%)
Re-operation	6 (10.00%)

<sup>a</sup>CA test normal values: CA 125 (0-31 U/ml), CA 153 (0-36 U/ml), CA 19-9 (0-37 U/ml) and CEA (0-5 ng/ml). For the qualitative characteristics, outcomes are presented as frequency and the relevant percentage and for quantitative characteristics is presented as the mean value  $\pm$  the standard deviation, as well as median quartile 1(Q1) to quartile (Q3) range and minimum and maximum values. CA, cancer antigen; CEA, cancer embryonic antigen; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer.

second most common complication was post-operative bleeding, occurring in two patients. Notably, one patient experienced bleeding on Day 0, and bleeding was evident in the drain. This patient required reoperation. In addition, one patient experienced delayed bleeding on Day 9, and this was managed non-surgically. A duodenal stump leak was identified in one patient via computed tomography on Day 7, and this patient was managed conservatively. Necrotizing pancreatitis developed in one patient from the non-drain group due to a pancreatic leak detected on Day 3, and this led to reoperation. Notably, this patient died during the study period. Post-operative ileus requiring nasogastric tube placement occurred in one patient. A detailed summary of the aforementioned findings is provided in Table I.

Extra-abdominal complications occurred in 8.3% (n=5) of patients, comprising 5% (n=2) of the non-drain group and 10% (n=3) of the drain group. All extra-abdominal complications involved the respiratory system, including three cases of atelectasis, one pleural effusion and one case of respiratory failure in a patient who also experienced the pancreatic leak. However, there was no statistically significant difference between the drain and non-drain groups.

The mean length of hospital stay was  $9.5 \pm 9$  days (Fig. 3). Patients in the non-drain group experienced a significantly shorter length of stay with a median of 5 days, compared with 7 days in the drain group (P=0.0001).

The majority of cases were classified as stages 1B (16.7%), 2A (26.7%) and 2B (20.0%) according to the AJCC. Comparisons between the drain and non-drain groups revealed no statistically significant differences in the distribution of AJCC stages.

In the overall study population, the 30-day post-operative outcomes included a 5% mortality rate, an 8.33% readmission rate and a 10% reoperation rate we reviewed the ages of the patients who died compared with those who

survived. The mean age of deceased patients was 69.7 years (76, 66 and 67 years, one female and two males), while the mean age of survivors was 71.1 years. This indicates that there was no statistically significant association (P>0.05) between age and mortality within our cohort. No other statistically significant differences were observed between the drain and non-drain groups.

Of the 40 patients who received a drain, 4 (10%) exhibited excessive drain output by postoperative day five, and 5 (12.5%) met the criteria for postoperative pancreatic fistula. Among those with excessive output, 2 patients-who also had a pancreatic fistula-developed intra-abdominal complications. All comparisons made between the two groups, including demographic, histological and intra-operative characteristics are summarized in Fig. 2.

Propensity score matching was feasible for 20 cases from each group, the covariate balance as measured via standardized mean differences had values as follows: blood loss: 1.4, vessel damage: 0.38, anastomosis: 0.12, stump: 0.57, respiratory issues: 0.57 indicative for not perfect balance between the two categories, however we applied additional sensitivity analysis.

The Rosenbaum sensitivity test evaluated how sensitive the outcomes of the matched data were to a potential presence of unmeasured confounding. Under the assumption of no hidden bias, Gamma=1 the test yielded a P-value of 0.0899 (marginally non-significant) suggesting that, in the absence of unmeasured confounding, there is weak evidence that the treatment effect differs from zero. At increased Gamma=2, the bounds of the P-value were in the range 0.0134 to 0.2635, meaning that if there is an unmeasured factor that doubles the odds of being assigned to non-drain group, the true P-value could vary from being statistically significant (0.0134) to clearly non-significant (0.2635). In summary, the sensitivity analysis indicated that there results moderately sensitive to hidden bias.

Table II. Comparison of demographics, and preoperative and intraoperative characteristics between the two groups.

Characteristic	Without drain (n=20)	With drain (n=40)	P-value
Age, years	73 (66.5-77.5)	73.5 (63-78)	0.8138
Sex (male)	9/45.00%	23/57.50%	0.4180
Charlson score	2 (2-2)	2 (2-3)	0.1567
ECOG	0 (0-0)	0 (0-0)	0.5943
Histology			
Diffuse	7/35.00%	15/37.50%	1.0000
Intestinal	11/55.00%	17/42.50%	0.4180
Mixed	1/5.00%	6/15.00%	0.4065
Location			
Esophago-gastric junction	6/30.00%	6/15.00%	0.1893
Fundus	3/15.00%	2/5.00%	0.3216
Body	7/35.00%	19/47.50%	0.4162
Prepyloric antrum	4/20.00%	12/30.00%	0.5408
Pylorus	1/5.00%	0/0.00%	0.3333
Positive preoperative chemotherapy	5/25.00%	10/25.64%	1.0000
CA positivity <sup>a</sup>			
CA 19.9	2/10.00%	6/15.00%	0.7068
CA 15.3	1/5.00%	5/12.50%	0.6532
CA 125	0/0.00%	3/7.50%	0.5441
CEA	3/15.00%	4/10.00%	0.6760
Intraoperative characteristics			
Duration of operation, min	195 (160-205)	200 (180-230)	0.2095
Packed red blood cells transfusion	4/20.00%	4/10.00%	0.4218
Fresh frozen plasma transfusion	2/10.00%	3/7.50%	1.0000
Any allergic reaction to drugs	-	-	-
Intraoperative incidents	2/10.00%	5/12.50%	1.0000

<sup>a</sup>CA test normal values: CA 125 (0-31 U/ml), CA 153 (0-36 U/ml), CA 19-9 (0-37 U/ml) and CEA (0-5 ng/ml). For the qualitative characteristics, outcomes are presented as frequency and the relevant percentage and for quantitative characteristics is presented the median and the minimum and maximum values. P-values were obtained from the  $\chi^2$  test for qualitative data and the Mann-Whitney U test for quantitative data. CA, cancer antigen; CEA, cancer embryonic antigen; ECOG, Eastern Cooperative Oncology Group. P-values are obtained from for chi-square test for the qualitative data, and from Mann-Whitney U test for the quantitative data.

*Comparison of patients with intra-abdominal complications.* Of the 60 eligible patients, nine (15%) experienced intra-abdominal complications, classified as Clavien-Dindo  $\geq$ II. In the drain group, complications included one grade IIIa, three grade IIIb, two grade II and one grade IV. In the non-drain group, complications included one grade V and one grade II.

Patients with complications were compared with those without complications to identify perioperative factors that may influence or be influenced by complications. Fisher's exact test was used for the analysis of categorical data. Results of the present study revealed no significant differences in pre-operative characteristics between the two groups (Table III and Fig. 4).

Intra-operatively, although FFP transfusion was not initially considered a potential risk factor for developing intra-abdominal complications, we later observed that patients who developed such complications had received FFP transfusion more frequently than those without complications

( $P=0.0208$ ; OR, 12.3). In addition, vessel injury was the most common indication for drain placement ( $P=0.05$ ; OR, 14.3; Table III).

The analysis of post-operative characteristics revealed differences between patients with and without intra-abdominal complications. Notably, differences were observed in oral contrast, SSIs, patient mobilization delays, extra-abdominal complications, length of hospital stay (LOS), readmissions and reoperations (Fig. 4).

As aforementioned, nine patients experienced intra-abdominal complications, with seven patients included in the drain group and two patients included in the non-drain group. The most common complications included anastomotic leak and bleeding, and these significantly affected the LOS and rates of reoperation. The median day of complication detection was 5.8 (range, 1-11; Table SI). Although the number of cases in this subgroup is relatively small, the statistical analysis was performed to ensure completeness and the outcomes revealed no statistically significant differences in the detection of

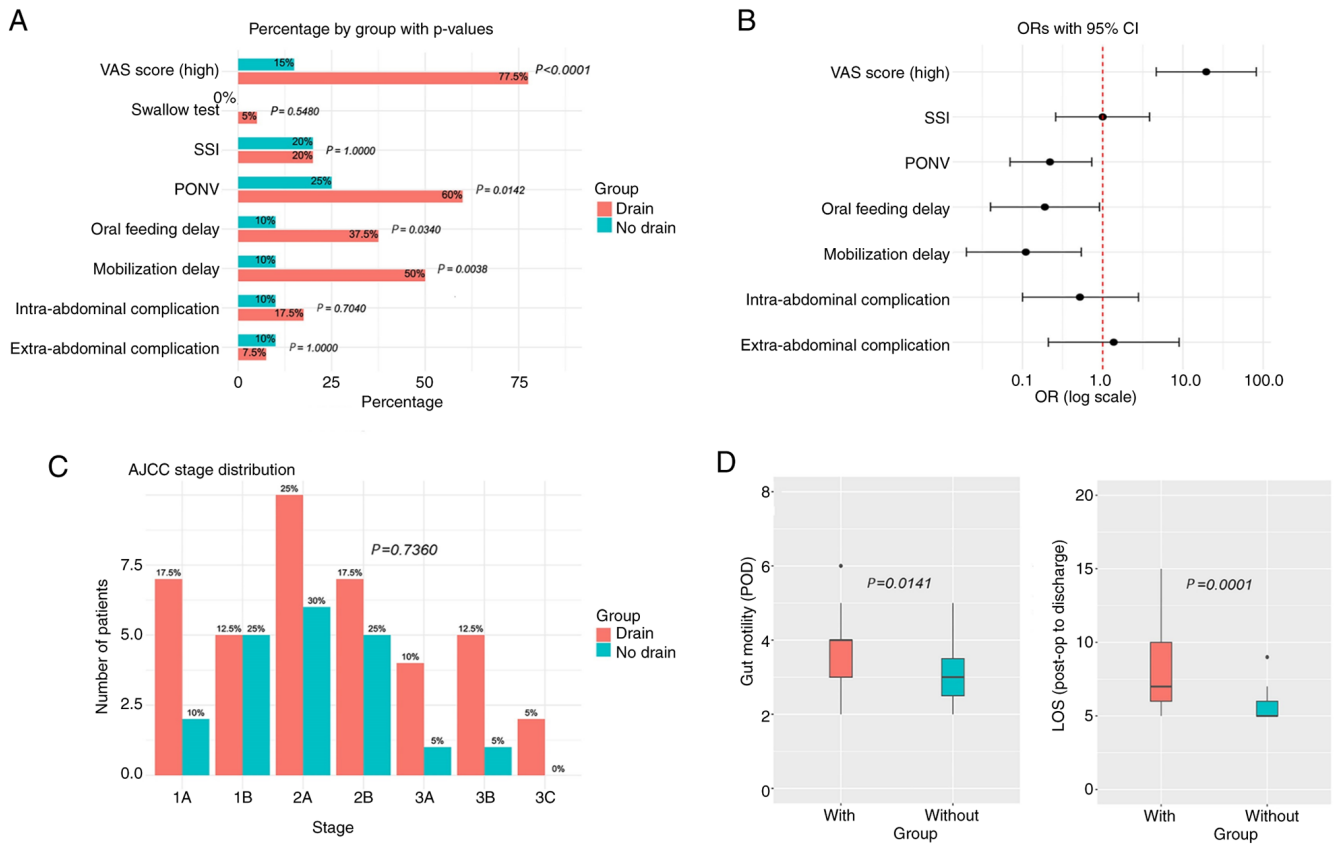


Figure 2. Comparison between postoperative characteristics and short-term outcomes between the two groups. (A) Proportions of several study outcomes with corresponding P-values ( $\chi^2$  test or Fisher's exact test). (B) OR and 95% CIs for the characteristics. A valid OR could not be calculated for the swallow test. Characteristics for which the 95% CI does not cross the vertical red line are considered statistically significant. (C) Bar charts showing the number and percentage of patients at each AJCC stage for both study groups (P-value based on Fisher's exact test). (D) Box-and-whisker plots for time to gut mobilization (in days) and LOS. In each plot, boxes represent the interquartile range (Q1-Q3), horizontal lines within boxes indicate the median, whiskers show the range excluding outliers, and circles represent outliers. P-values are derived from Kruskal-Wallis tests. AJCC, American Joint Committee on Cancer; OR, odds ratio; CI, confidence interval; LOS, length of hospital stay; PONV, post-operative nausea; SSI, surgical site infections; VAS, visual analog scale; POD, post-operative day.

anastomotic leaks, post-operative day of complication detection, diagnosis based on drain content, hospitalization duration, reoperation rates or mortality between the two groups.

Drains were closely monitored for signs suggestive of intra-abdominal complications. Notably, four patients with complications were identified through drain content analysis, while three were detected based on clinical presentation and blood tests. A comparison between patients diagnosed via drain analysis and those diagnosed through other methods revealed no significant differences in terms of detection method, post-operative day of diagnosis, LOS or rates of mortality (Table SII).

*Comparison of patients without intra-abdominal complications.* A total of 51 patients did not exhibit any intra-abdominal complications. A comparative analysis was performed within this subgroup to determine whether non-abdominal adverse effects were more prevalent in the drain or non-drain group. When comparing the pre- and intra-operative characteristics of each group, no statistical significance was observed (Table SIII). Results of the present study revealed that a blood loss of >250 ml was the most common indication for drain placement in this group ( $P < 0.001$ ).

Moreover, statistically significant differences in pain score, delay of patient mobilization, oral feeding delay,

initiation of gut motility and LOS were observed between groups post-surgery (Table IV).

### Discussion

The use of drains following elective total D2 gastrectomy remains a topic of debate in surgical practice. The ERAS guidelines recommend against the use of drains, with reduced recovery periods and hospital stays, and an earlier return to daily activities when their use is avoided (7,8,19,24,25,59). Yet, compliance with the aforementioned guidelines varies globally, with the use of smaller drainage tubes being supported in some practices. However, reductions in drain size exerted minimal impact on psychological outcomes or the rates of SSIs (16,60,61). Notably, the present study aimed to provide specific criteria to support clinical decision making on drain placement following total gastrectomy for the treatment of gastric cancer.

Expertise is a critical factor in the present study, as it influences the quality of care provided. In this context, an experienced surgeon in a high-volume centre plays a key role in assessing post-operative risk and tailoring drain placement (60,62).

Results of the present study revealed no significant pre-operative or demographic differences between patients

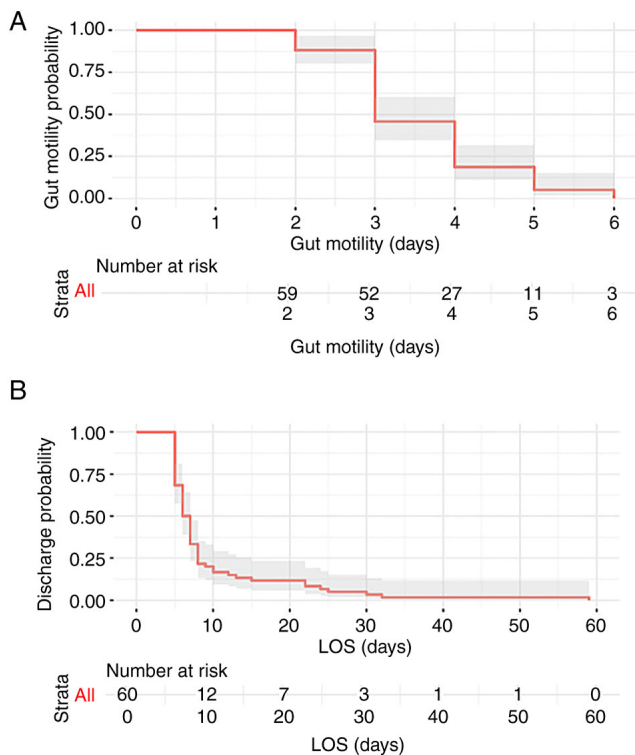


Figure 3. Kaplan-Meier plots showing (A) time to gut mobilization and (B) length of hospital stay. Shaded areas represent 95% confidence intervals; numbers below the x-axis indicate at-risk patients per postoperative day. LOS, length of stay.

with and without drains across all three groups. The absence of statistically significant differences between the drain and non-drain groups indicated that the cohorts were comparable, enhancing the reliability and robustness of the present statistical analyses. While the results of the present study may further the current understanding of the use of drains, larger, multi-centre studies with more diverse populations are required, to provide more definitive conclusions and validate the applicability of these criteria in different clinical settings.

Results of the present study revealed that patients who required FFP transfusion during surgery exhibited a higher incidence of complications, including anastomotic leaks. As it has been previously reported, packed red blood cell transfusions may adversely affect post-operative outcomes (63-65). Previous studies suggest that FFP transfusion may exert immunosuppressive effects through several mechanisms. These include downregulation of proinflammatory cytokines such as TNF- $\alpha$  and upregulation of anti-inflammatory mediators such as IL-10, resulting in attenuated systemic inflammatory responses-reflected by lower C-reactive protein levels and altered leukocyte counts. Additionally, soluble HLA class I molecules and fibroblast-derived ligands present in stored plasma can impair natural killer cell cytotoxicity and suppress T-cell proliferation, further contributing to immune modulation (63,66). Thus, FFP transfusion should be considered as an intra-operative risk factor. Future studies could include measurement of systemic inflammatory markers, such as IL-6 and CRP, to improve elucidation of the relationship between drain use and immunomodulatory effects.

In the present study, vessel injury was identified as a significant risk factor for post-operative complications. Thus, vessel injury should be considered when deciding on drain placement during gastrectomy.

By contrast, blood loss exceeding 250 ml was the primary factor for selecting drain placement in patients who exhibited no intra-abdominal complications. Notably, 250 ml was selected as the minimum mean value based on the results of previous studies (15,42-46,67-71). Results of previous studies demonstrated an association between post-operative intra-abdominal complications and non-vascular blood loss that does not require transfusion. Fibrinolytic and inflammatory pathway activation may play a role in non-vascular blood loss (67-71). However, there were no detailed methods for estimating blood loss in each study, which may have led to discrepancies between the reported and actual values associated with intra-abdominal complications.

Moreover, results of previous studies highlighted multiple risk factors associated with post-operative complications, such as advanced age (>65 years), male sex, diffuse tumor histology, extensive lymphadenectomy, extended surgery duration and impaired blood supply (35-40). However, the literature is often based on retrospective studies with variation in the type of gastric surgery, indication and patient cohort. In the present study, the aforementioned factors were not statistically significant; thus, further investigations are required.

In the present study, the gastrografin swallow test was performed 48-72 h post-surgery, and the results demonstrated a sensitivity of 50%. This oral contrast study is routinely performed on or after the fifth following total gastrectomy. However, results of previous studies revealed that 46.6-63.6% (72-75) of esophagojejunal anastomotic leaks occur prior to the scheduled contrast study. Thus, the oral contrast study was conducted 48-72 h following surgery in the present study, to determine the potential for improved sensitivity in anastomotic leak detection. However, the results of the present study were comparable with those previously obtained, highlighting the low levels of sensitivity (20-60%) of this technique in confirming esophagojejunal anastomotic integrity (72-75).

In the present study, pain was determined using VAS score. The results revealed marginal levels of statistical significance between the drain and non-drain groups when complications were present. However, a significant difference was observed in patients without complications, suggesting that drain placement may be avoidable in these cases. Results of the present study were comparable with those previously obtained, further highlighting that drains may negatively impact the levels of post-operative pain (21,22,59).

Moreover, results of the present study revealed a significant difference in PONV between the drain and non-drain groups in the overall study population. These findings supported the rationale for the selective use of drains, limiting them to high-risk patients, as per the suggested criteria. Previous studies focused on drain-related PONV in bariatric surgery (76,77); however, studies focused on the use of drains in gastrectomy for the treatment of gastric cancer are limited. The use of drains should be carefully considered, as PONV may contribute to prolonged hospital stays.

Table III. Pre- and intra-operative characteristics among patients with and without intra-operative complications.

Characteristic	With intra-abdominal complications (n=9)	Without intra-abdominal complications (n=51)	P-value	OR and 95% CI
Age, years	73 (67-76)	73 (64-78)	0.9257	N/A
Sex (male)	6/66.67%	26/50.98%	0.4820	1.92 (0.43-8.54)
Charlson score	2 (2-2)	2 (2-3)	0.3258	N/A
ECOG	0 (0-0)	0 (0-0)	0.8329	N/A
Histology				
Diffuse	3/33.33%	19/37.26%	1.0000	0.84 (0.19-3.77)
Intestinal	3/33.33%	25/49.02%	0.4820	0.52 (0.12-2.31)
Other	1/11.11%	6/11.76%	1.0000	0.94 (0.1-8.86)
Location				
Esophago-gastric junction	1/11.11%	11/21.57%	0.6713	0.45 (0.05-4.03)
Fundus	0/0.00%	5/9.80%	1.0000	N/A
Body	6/66.67%	20/39.22%	0.1574	3.1 (0.69-13.83)
Antrum	2/22.22%	14/27.45%	1.0000	0.76 (0.14-4.08)
Pylorus	1/11.11%	0/0.00%	0.1500	N/A
Positive preoperative chemotherapy	2/22.22%	13/26.00%	1.0000	0.81 (0.15-4.42)
CA positivity <sup>a</sup>				
CA 19.9	0/0.00%	8/15.69%	0.3394	N/A
CA 15.3	0/0.00%	6/11.76%	0.5777	N/A
CA 125	0/0.00%	3/5.88%	1.0000	N/A
CEA	1/11.11%	6/12.00%	1.0000	0.94 (0.10-8.87)
Intraoperative characteristics				
Duration of operation, min	200 (190-225)	200 (170-230)	0.4164	N/A
Blood transfusion	1/11.11%	7/13.72%	1.0000	0.79 (0.08-7.28)
Fresh frozen plasma transfusion	3/33.33%	2/3.92%	0.0208	12.25 (1.69-88.71)
Allergic reaction to drugs	-	-	N/A	N/A
Intraoperative incidents	2/22.22%	5/9.8%	0.2805	2.63 (0.42-16.26)
Criteria for drain placement				
Blood loss >250 ml	4/44.44%	16/31.37%	0.4644	1.75 (0.41-7.4)
Vessel injury	2/22.22%	1/1.96%	0.0561	14.29 (1.14-178.87)
Anastomosis concerns	2/22.22%	9/17.65%	0.6644	1.33 (0.24-7.51)
Adjacent structures injury	-	-	N/A	0 (0-0)
Stump integrity concerns	1/11.11%	2/3.92%	0.3914	3.06 (0.25-37.84)
Chronic cardiopulmonary comorbidity	0/0%	3/5.88%	1.0000	N/A

<sup>a</sup>CA test normal values: CA 125 (0-31 U/ml), CA 153 (0-36 U/ml), CA 19-9 (0-37 U/ml) and CEA (0-5 ng/ml). For the qualitative characteristics, outcomes are presented as frequency and the relevant percentage and for quantitative characteristics is presented the median along with the minimum and maximum values. Fisher's exact test was used to compare qualitative data and Mann-Whitney U test to compare quantitative data. CA, cancer antigen; CEA, cancer embryonic antigen; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; CI, confidence interval.

Results of the present study also highlighted that there was no statistically significant difference in SSIs between the drain and non-drain groups. However, in patients with post-operative complications, the drain group exhibited a significantly higher rate of SSI, which is comparable with the results obtained in previous studies. No statistically significant differences were observed between drain and non-drain groups in patients without complications. Notably, the potential association between drains and SSIs remains to be fully elucidated, with several studies reporting no association (18,22,23,78), and

others suggesting that retro-grade bacterial contamination or leakage of protein-rich ascitic fluid may play a role in SSI development (79). Thus, the use of drains in patients with complications should be carefully considered to minimize the risk of SSIs.

Results of the present study revealed that extra-abdominal complications, limited to respiratory tract infections in the present study, were more prevalent in patients with drains when intra-abdominal complications occurred. However, no statistically significant difference was observed when comparing

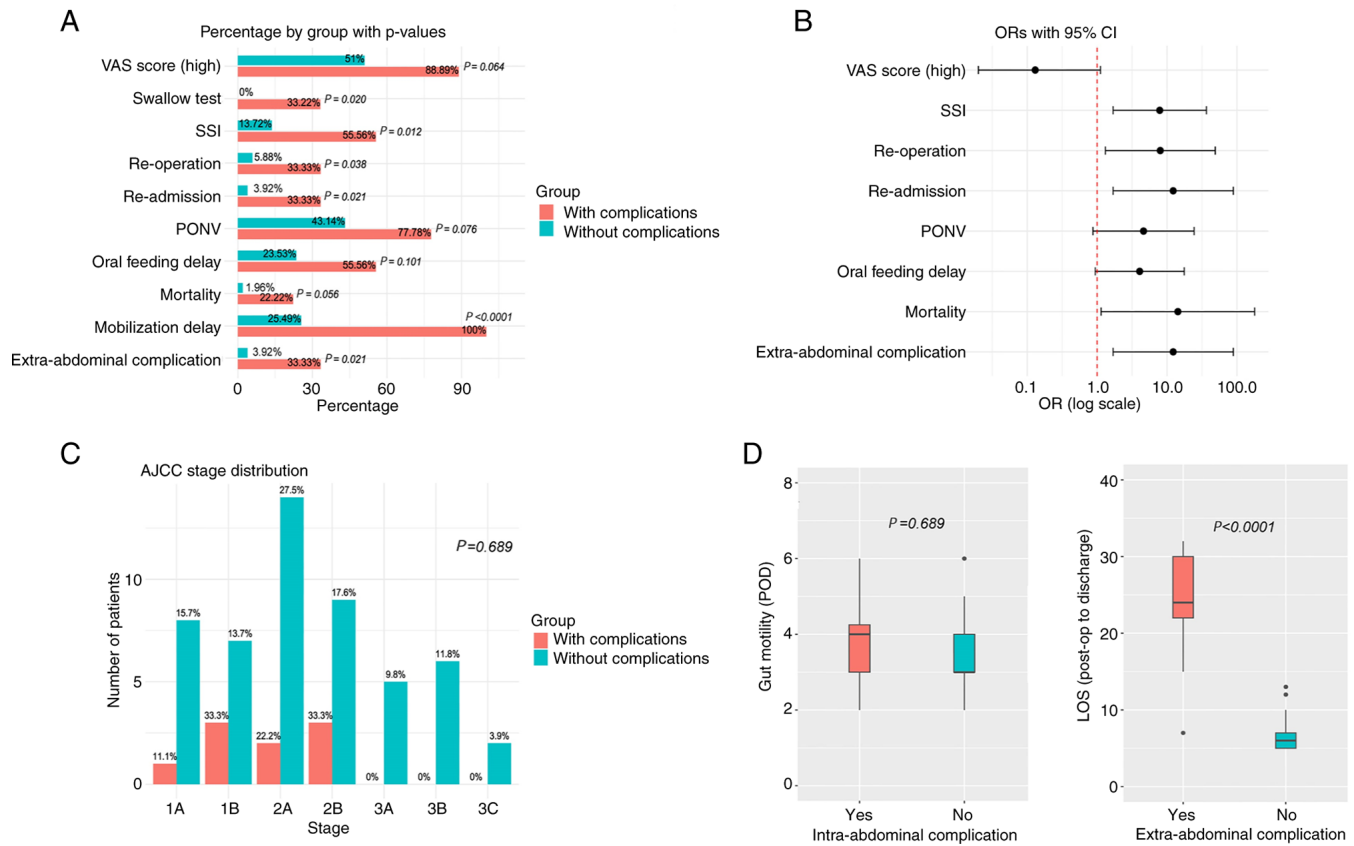


Figure 4. Comparison of postoperative characteristics and short-term outcomes between patients with and without intra-abdominal complications. (A) Proportions of various study outcomes with corresponding P-values (Fisher's exact test). (B) ORs and 95% CIs for the characteristics shown in panel A. Valid ORs could not be calculated for the swallow test and mobilization delay. Characteristics for which the 95% CI does not cross the vertical red line were considered statistically significant. (C) Bar charts displaying the number and percentage of patients at each AJCC stage in both groups (P-value based on Fisher's exact test). (D) Box-and-whisker plots for time to gut mobilization (in days) and LOS. In each plot, boxes represent the interquartile range (Q1-Q3), horizontal lines within boxes indicate the median, whiskers denote the range excluding outliers, and circles represent outliers. P-values are based on Kruskal-Wallis tests. AJCC, American Joint Committee on Cancer; OR, odds ratio; CI, confidence interval; LOS, length of hospital stay; PONV, post-operative nausea; SSI, surgical site infections; VAS, visual analog scale; POD, post-operative day.

patients without complications. Results of a previous study demonstrated that drain-induced pain may be associated with micro-atelectases and subsequent respiratory tract infections (60), and a further study revealed that drain placement may facilitate the dissemination of pathogens (16,79). By contrast, numerous retrospective studies focused on total and subtotal gastrectomy revealed no statistically significant differences in the incidence of pulmonary-related complications between groups that received post-operative drains and those that did not (18,22). Conflicting results highlight the requirement for further investigations that focus on the role of post-operative drains in pulmonary events.

Results of the present study also revealed that drain placement in patients with no intra-abdominal complications was associated with delays in mobilization, oral feeding and gastrointestinal tract motility. However, statistical significance was marginal when compared with patients with intra-abdominal complications. Thus, delays in mobilization, oral feeding and gastrointestinal tract motility may be associated with the specific complication, rather than with the presence of a drain. By contrast, the drain was considered the primary contributing factor in the absence of complications. Previous studies focused on the impact of drains on mobilization and gastrointestinal function demonstrate conflicting results, with

some studies reporting no significant differences between drain and non-drain groups, and further studies demonstrating that drains may hinder recovery (15,16,18,20,59).

In the present study, the use of drains significantly impacted the LOS. As expected, patients who experienced delays in mobilization, dietary resumption and restoration of gastrointestinal motility were less likely to be discharged in a timely manner. These results are comparable with those obtained previously (20-23,59,80). Drains may delay mobilization due to a fear of dislodgement or pain, leading to prolonged bowel motility recovery and feeding initiation. Thus, individualized drain use is suggested.

Results of the present study also indicated that the number of readmissions and reoperations was highest in patients in the drain group who developed intraabdominal complications. Notably, results of a previous study also revealed that the number of reoperations may be associated with complications (15); however, evidence for the potential association between readmissions and complications is conflicting (80,81). The results of two meta-analyses demonstrated higher readmission rates in non-drain groups, primarily due to undetected complications during the initial hospital stay and a poor ERAS compliance. Thus, low rates of readmission may be attributed to the implementation of the selected criteria, which were

Table IV. Postoperative characteristics among patients without intra-operative complications.

Characteristics	Without drain (n=19)	With drain (n=32)	P-value	OR and 95% CI
Swallow test (positive)	-	-	N/A	N/A
Visual analog scale score (high)	3 (15.79%)	23 (71.88%)	<0.0001	0.07 (0.02-0.31)
Post-operative nausea and vomiting	5 (26.30%)	17 (53.13%)	0.1150	0.32 (0.09-1.08)
Surgical site infections	4 (21.05%)	3 (9.38%)	0.4021 <sup>a</sup>	2.58 (0.51-13.05)
Mobilization delay	1 (5.26%)	12 (37.50%)	0.0178 <sup>a</sup>	0.09 (0.01-0.78)
Oral feeding delay	1 (5.26%)	11 (34.38%)	0.0201 <sup>a</sup>	0.11 (0.01-0.90)
Gut motility start	3 (2, 5)	4 (2, 6)	0.0179	N/A
Intra-abdominal complication	-	-	N/A	N/A
Extra-abdominal complication	1 (5.26%)	1 (3.13%)	1.000 <sup>a</sup>	1.72 (0.10-29.24)
AJCC stage				
1A	2 (10.53%)	6 (18.75%)	0.3710 <sup>a</sup>	N/A
1B	5 (26.31%)	2 (6.25%)		
2A	6 (31.57%)	8 (25.00%)		
2B	4 (21.05%)	5 (15.63%)		
3A	1 (5.26%)	4 (12.50%)		
3B	1 (5.26%)	5 (15.63%)		
3C	0 (0.00%)	2 (6.25%)		
Length of hospital stay (post-op to exit)	5 (5, 9)	7 (5, 13)	<0.0001	N/A
Short-term outcomes				
Mortality	1 (5.26%)	0 (0.00%)	0.3732 <sup>a</sup>	5.27 (0.20-136.1)
Re-admission	0 (0.00%)	2 (6.25%)	0.5234 <sup>a</sup>	0.31 (0.01-6.87)
Re-operation	1 (5.26%)	2 (6.25%)	1.0000 <sup>a</sup>	0.83 (0.07-9.86)

<sup>a</sup>P-values for categorical data were obtained using the Fisher's exact test, otherwise they were obtained using the  $\chi^2$  test. Data are presented as frequency and percentage or median and within parentheses minimum and maximum values. OR, odds ratio; CI, confidence interval.

systematically applied to identify patients in whom omitting the perianastomotic drain was considered both appropriate and safe.

In the present study, the rates of mortality differed between patients with and without intra-abdominal complications; however, the levels of statistical significance were marginal. Moreover, no statistically significant difference in mortality rates was observed between the drain and non-drain groups. Studies focused on the rates of mortality in these groups are limited, with two previous studies reporting that there were no statistically significant differences in mortality between the drain and non-drain groups (22,23).

In summary, the present study demonstrated that a criteria-based approach may aid in standardizing drain placement in gastrectomy. The use of pre-defined criteria ensures a more consistent decision-making process; thus, reducing variability in surgical practice. While the study was not designed to evaluate the benefit of drain use itself, the presence of statistically significant differences between certain subgroups supports the clinical relevance of a selective approach. These criteria could be considered for application in routine clinical settings.

The present study exhibits numerous limitations. For example, the sample size included in the present study was small, and this was largely due to constraints imposed by the coronavirus-19 pandemic when conducted. The small sample size may have introduced selection bias, reduced statistical

power and limiting the generalizability of the findings, which could have affected the observed statistical significance levels. Moreover, the present study was not designed to assess the clinical benefit of drain placement itself, but rather to evaluate the feasibility and relevance of predefined criteria guiding their use in open total gastrectomy. The small sample size further limits any conclusions regarding efficacy of the drains and reinforces the need for cautious interpretation, as for example the role of the drain in the intra-abdominal complication. Thus, further investigations with increased sample sizes are required. Additionally, the present study focused on patients undergoing open D2 gastrectomy, which may have led to selection bias. Notably, a focus on these patients may have led to the exclusion of more complex cases requiring extended lymphadenectomy, subtotal gastrectomy, or laparoscopic approach restricting the applicability of the results to broader populations. In addition, an absence of randomization and blinding in the present study introduces possible selection bias, especially in subjective outcomes (for example, pain, PONV). However, due to the specific design and objectives of the study, randomization was not feasible. As previously outlined, the literature presents conflicting evidence on the use of prophylactic drains, with opposing perspectives supported by multiple randomized trials and studies (15-23). However, none of the trials incorporated predefined criteria for drain placement. Future studies that will include criteria on drain insertion should adopt RCTs

with strict baseline matching. Finally, our study analysed some patients' parameters collectively, potentially obscuring differences among subgroups. Future larger studies could consider patients' tumor stage, surgical complexity, and preoperative chemotherapy status.

In conclusion, debate is ongoing regarding the use of drains in total gastrectomy. While national guidelines provide recommendations for their use in clinical practice, decision-making is the responsibility of the clinician. The present study proposed evidence-based criteria that may lead to standardization of drain usage, providing a practical decision-making tool that may be applied in cases with and without complications.

To the best of our knowledge, the present study is the first prospective study to implement literature-based criteria for drain use in gastrectomy for the treatment of gastric cancer. Results of the present study provide a novel theoretical basis for drain use, and further investigations should focus on refining and expanding the outlined criteria.

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### Availability of data and materials

The data generated in the present study may be found in the Clinical Trial.gov under accession number NCT04288661 or at the following URL: <https://clinicaltrials.gov/study/NCT04288661?term=drag&rank=1>.

### Authors' contributions

ME served as the principal investigator of the study, contributing to its conception and design, data acquisition, interpretation, and manuscript drafting. MD provided data interpretation and analysis, as well as critical revisions to the manuscript draft. AP and DK conducted data statistical analysis and had substantial contribution to the design of the manuscript. DA contributed to data interpretation and critical manuscript revisions. DT was the study sponsor and surgical lead for all procedures; alongside ME, he contributed to the study's conception and design. TT was responsible for data acquisition and analysis. GZ and KT contributed to data analysis and interpretation along with critical revisions, ensuring the intellectual rigor of the manuscript. All authors read and approved the final version of the manuscript. Additionally, ME, DT and TT have agreed to be accountable for all aspects of the work, so that any questions relating to research integrity or scientific accuracy in any part of the study are appropriately investigated and resolved. ME, DT and TT confirm the authenticity of all the raw data.

### Ethics approval and consent to participate

The present study was conducted in accordance with the principles outlined in the Helsinki Declaration of Human Rights and with the Guidelines of Good Clinical Practice. The final

study protocol received approval from the Institutional Review Board (IRB) of Hippocraton General Hospital (approval no. 1678/31-01-2020; Athens Greece). Informed consent was obtained from all patients involved in the study, both for the study participation and the results' publication.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests

### Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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