Trials

STUDY PROTOCOL

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Influence of pancreas transection with cavitron ultrasonic surgical aspirator (CUSA) on incidence of postoperative pancreatic fistula after pancreatoduodenectomy (PANCUT): study protocol for a randomised controlled trial

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Abstract

Background Complications after pancreatoduodenectomy occur in up to 40% of patients. Postoperative pancreatic fistula (POPF) remains the most common complication after pancreatoduodenectomy and is associated with increased postoperative mortality. The cavitron ultrasonic surgical aspirator (CUSA) is a surgical instrument commonly used in liver and neurosurgery. The CUSA selectively dissects tissue parenchyma, leaving blood vessels and bile ducts undamaged, which are then selectively ligated or clipped. Only a few studies have investigated the relationship between the transection of pancreatic tissue with CUSA and the formation of POPF. The results were inconsistent and were published before the updated ISGPS consensus on the definition of POPF.

Methods The PANCUT study is a randomised controlled trial initiated at the Department of Abdominal Surgery, University Medical Centre Ljubljana. The aim of the study is to determine whether precise dissection of the pancreatic tissue with CUSA reduces the incidence of POPF. Patients scheduled for pancreatoduodenectomy will be randomly assigned to either the experimental group, in which the pancreatic tissue will be dissected with CUSA, or the control group, in which pancreas will be conventionally transected with scalpel. A total of 180 patients will be included in the study. The primary endpoint is the formation of POPF. Secondary endpoints include operation time, amount of intraoperative blood loss, postoperative infectious complications, postoperative bleeding, length of hospital stay and mortality.

Discussion To our knowledge, the PANCUT study is the first randomized controlled trial to investigate the role of CUSA in the transection of pancreatic tissue during pancreatoduodenectomy.

Trial registration ClinicalTrials.gov NCT06135012. Registered on 18 November 2023.

Keywords Pancreatic fistula, Postoperative complications, Pancreas resection, CUSA, Pancreatoduodenectomy, Pancreatic ducts

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Background

Pancreatic surgery is one of the most demanding fields of abdominal surgery due to the location of the organ, its complex anatomy and its proximity to major blood vessels [1]. Among the more common surgically treated diseases of the pancreas are mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, neuroendocrine tumours and pancreatic cancer [2–4]. The preferred treatment to achieve the best outcome is surgical removal of the tumour with healthy tissue. Depending on the indication and location of the pancreatic disease, various resections are possible. Pancreaticoduodenectomy (PD) is indicated for tumours of the pancreatic head and periampullary tumours. It involves the removal of the pancreatic head, the duodenum, the distal bile duct and the proximal part of the small intestine. This is followed by a complex reconstruction with the formation of a pancreaticoenterostomy, a hepaticojejunostomy and a duodenoenterostomy or a gastroenterostomy with an enteroenterostomy [5].

Complications after pancreatic resection are common and occur in 30 to 40% of patients [6]. These include bleeding, delayed gastric emptying, bile leakage, surgical site infections and postoperative pancreatic fistula (POPF) [7]. In the short term, they are associated with prolonged hospitalisation and increased postoperative mortality, but in the long-term they are associated with reduced overall survival as patients either miss the window of opportunity or become unsuitable for adjuvant chemotherapy [8]. The most troublesome and well-studied complication is POPF, which is defined as a pathologic connection between the epithelium of the pancreatic duct and the peritoneal cavity, leading to leakage of pancreatic juices into the peritoneal cavity. As pancreatic juices are rich in digestive enzymes, they can cause further complications such as bleeding due to erosion of vessels and formation of intra-abdominal abscesses or sepsis due to inflammation of other structures [9]. The updated consensus of the International Study Group on Pancreatic Surgery (ISGPS) from 2016 distinguishes asymptomatically elevated pancreatic enzyme levels in abdominal drains from clinically relevant POPF, which requires a change in postoperative management [10].

Important risk factors for the development of POPF include soft pancreatic tissue, tumour originating from the duodenum, the major duodenal papilla or the distal common bile duct, a small diameter of the main pancreatic duct and a major intraoperative blood loss. In addition, other non-specific factors such as increased body mass index (BMI), male gender, poor preoperative nutritional status and excessive perioperative fluid administration have also been associated with a higher incidence of POPF [11]. As POPF is essentially an anastomotic leakage, many studies have therefore investigated correlations between various pancreaticoenterostomy techniques and other strategies (e.g. stenting of the main pancreatic duct, administration of somatostatin analogues) with POPF formation. However, no specific technique or strategy has been shown to be superior to others [12]. Therefore, the choice of surgical technique is still within the domain of the treating surgeon. In addition to the different anastomosis techniques, the transection of the pancreatic tissue itself could also influence the incidence of POPF.

The cavitron ultrasonic surgical aspirator (CUSA) device is a surgical instrument that uses ultrasound to dissect the parenchymal tissue and aspirate it from the surgical site. During its routine and well-established use in liver surgery, blood vessels and bile ducts are not damaged in the process but are isolated from the parenchyma. Consequently, the surgeon ensures these structures with ligatures or clips [13]. Utilisation of CUSA in pancreatic surgery has not been well established yet. Only a few studies have investigated the relationship between the transection of the pancreatic tissue with CUSA and the formation of POPF. Specifically, three studies have examined the role of CUSA in patients undergoing distal pancreatectomy and another three studies have examined the role of CUSA in patients undergoing PD. The authors demonstrated safety and feasibility of this method. However, the results of these studies were inconsistent, but none of the studies showed differences in patient mortality. Importantly, these studies were published prior to the publication of the updated ISGPS consensus on the definition of POPF [10, 14–16].

In our randomised controlled trial, we therefore aim to determine whether precise dissection of pancreatic tissue with CUSA and continuous clipping of all branch pancreatic ducts and blood vessels reduce the incidence of POPF in patients undergoing PD for benign and malignant pancreatic disease.

Materials and methods

The aim of the study

This study aims to evaluate the role of transection of the pancreatic parenchyma with CUSA on the incidence of POPF after PD.

Study design and setting

The PANCUT study is a prospective, randomised controlled trial developed and initiated at the Department of Abdominal Surgery, University Medical Centre Ljubljana. From December 1, 2023, to December 31, 2025, we intend to enrol patients undergoing PD in the study. Patients eligible for the study will be enrolled and randomised into Arm A (experimental group—transection

with CUSA) and Arm B (control group—conventional transection with scalpel). Clinically relevant data will be collected. During surgery, some patients will be found to have locally inoperable or metastatic disease and will thus be consequently excluded from the study. Patients to successfully undergo PD will be routinely monitored and cared for in the intensive care unit (ICU) according to hospital policy and transferred to a regular ward if deemed appropriate by the attending physicians. A 90-day follow-up interval is planned after surgery. The study has been approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 0120–137/2023/3), and the study is conducted in accordance with the Declaration of Helsinki. This study protocol was designed in accordance with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guidelines for clinical trials [17]. The schedule for enrolment, intervention and assessments is shown in Fig. 1.

Inclusion criteria

The inclusion criteria are as follows:

- Patients of all genders aged 18 years or older
- Patients capable of understanding the provided information about the study
- Patients with signed informed consent
- Planned elective open pancreaticoduodenectomy for any indication

Exclusion criteria

The exclusion criteria are as follows:

- Patients younger than 18 years
- Patient incapable of understanding the provided information about the study
- Pregnant women
- Previous surgical procedures on the pancreas
- Immunosuppressive therapy
- Preoperative radiotherapy
- Minimally invasive (robotic) approach

Informed consent

All patients eligible for participation in the study will be identified by the study medical team. Patients will be admitted to the hospital ward 1 day before the scheduled surgery and will receive an information sheet about our study upon admission. Thorough discussion and explanation of the study protocol and aims will be done by a member of our research team. If willing, a written informed consent will be obtained from the patients.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			
TIMEPOINT	*Before surgery*	Operative day	*POD 1*	*POD 3-5*	*POD 14*	*POD 90*
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Intervention group		X				
Control group		X				
ASSESSMENTS:						
Baseline variables	X	X	X	X	X	X
Outcome variables			X	X	X	X

Fig. 1 The SPIRIT schedule of enrolment, interventions and assessments. POD, postoperative day

Randomisation and blinding

Randomisation is performed preoperatively after eligibility is confirmed, and written informed consent is obtained by trial personnel. Patients are randomly assigned in a 1:1 ratio either to Arm A (transection with CUSA) or Arm B (conventional transection with a scalpel) using a block randomisation.

Patients are blinded to which arm they are assigned to. In addition to patients, outcome assessors are also blinded to the study. Surgeons, however, cannot be blinded to the study, as different techniques are used for pancreas transection. The way of pancreas transection is introduced to the surgeons performing the operation just before the onset of surgery and cannot be switched during the procedure; the latter would result in patient exclusion postoperatively. Patients excluded from the study postoperatively, whether due to inoperable disease, a total pancreatectomy performed, or on the patient's demand, will be removed from the registry.

If any contraindications or technical difficulties with CUSA are encountered during surgery in Arm A, patients will be excluded from the study and pancreas transection will be performed in a standard manner with a scalpel.

During the postoperative course, the patients and the outcome assessors will remain blinded to the study. In addition, intensive care doctors, ward doctors and nurses will also be blinded to the allocation of the patients. The operating surgeon, who cannot be blinded, will participate in the postoperative care of his patients. Thus, the operating surgeon could potentially influence the assessment of the endpoints. However, according to their ethics, the National Medical Ethics Committee of the Republic of Slovenia and the Declaration of Helsinki, they are obliged to do the best for each individual patient. Nonetheless, this is a possible limitation of our study, which will be discussed in the final manuscript.

Data collection

Prior to surgery, the patient's basic demographic and clinical data is collected, including gender, age, BMI, history of smoking and alcohol consumption, other comorbidities, history of pancreatitis or chemotherapy and American Society for Anaesthesiology (ASA) score. Furthermore, the main pancreatic duct diameter and the diameter (in the anterior–posterior axis) of the pancreas at the level of the portal vein will be measured on the latest radiologic modality (computed tomography (CT), magnetic resonance (MR), or magnetic resonance cholangiopancreatography (MRCP)).

The intraoperative protocol collects data on the type of surgery and pancreatic tissue texture, thickness and the main pancreatic duct diameter. In the Arm A, the time for pancreatic transection with CUSA is recorded as well as the number of structures isolated and clipped. In all patients, the type of reconstruction of the pancreaticoenterostomy, the use of the stenting tube, the number of intra-abdominal drains placed, the intraoperative blood loss and the operative time and perioperative application of somatostatin (or analogues) are also recorded.

After the surgery, a routine determination of amylase and lipase from the abdominal drains is done on postoperative day (POD) 1, 3 and 5. The administration of somatostatin or analogues is recorded as well as the time of removal of the abdominal drain, the initiation of oral fluids and food intake and possible delayed gastric emptying. Information is collected on various postoperative complications, blood transfusions, possible radiologic imaging, the use of antibiotics or other interventions (percutaneous drain placement, endoscopic intervention, reoperation or transfer to the ICU) and the length of hospital stay. Pathohistological report of the resected pancreas is taken into notice, and at the end of clinical follow-up (up to 90 days postoperatively), potential pancreatic fistula grade is determined. The flow chart of the study design is shown in Fig. 2.

Interventions

Arm A: transection with CUSA

In the patients in the experimental group, the pancreas is transected with a CUSA 36 kHz tip. The pancreatic parenchyma is aspirated from the surgical site by the machine and the small branch pancreatic ducts and blood vessels are isolated and clipped with metal microclips before transection. Tissue around the main pancreatic duct is dissected with CUSA and the duct is then sharply cut with scissors. The time of transection with CUSA is measured, and the number of microclips left at the pancreatic remnant (number of structures treated) is counted. The thickness of the pancreatic resection surface is measured in the anterior–posterior axis as well as the diameter of the main pancreatic duct.

The pancreaticoenterostomy is then created according to surgeon's preference, and two abdominal drains (Ch. 21) are placed near the anastomosis.

Arm B: conventional transection with scalpel

In the patients in the control group, the pancreas is transected conventionally with a scalpel. Haemostasis of the transection surface is then performed with haemostatic sutures or with transient application of absorbable haemostats. Electrocautery is only used for the surrounding fatty tissue. Small branch ducts are not treated in any way (i.e. sutured, ligated or clipped). The thickness of the pancreatic resection surface is measured in the anterior–posterior axis, as is the diameter of the main pancreatic duct.

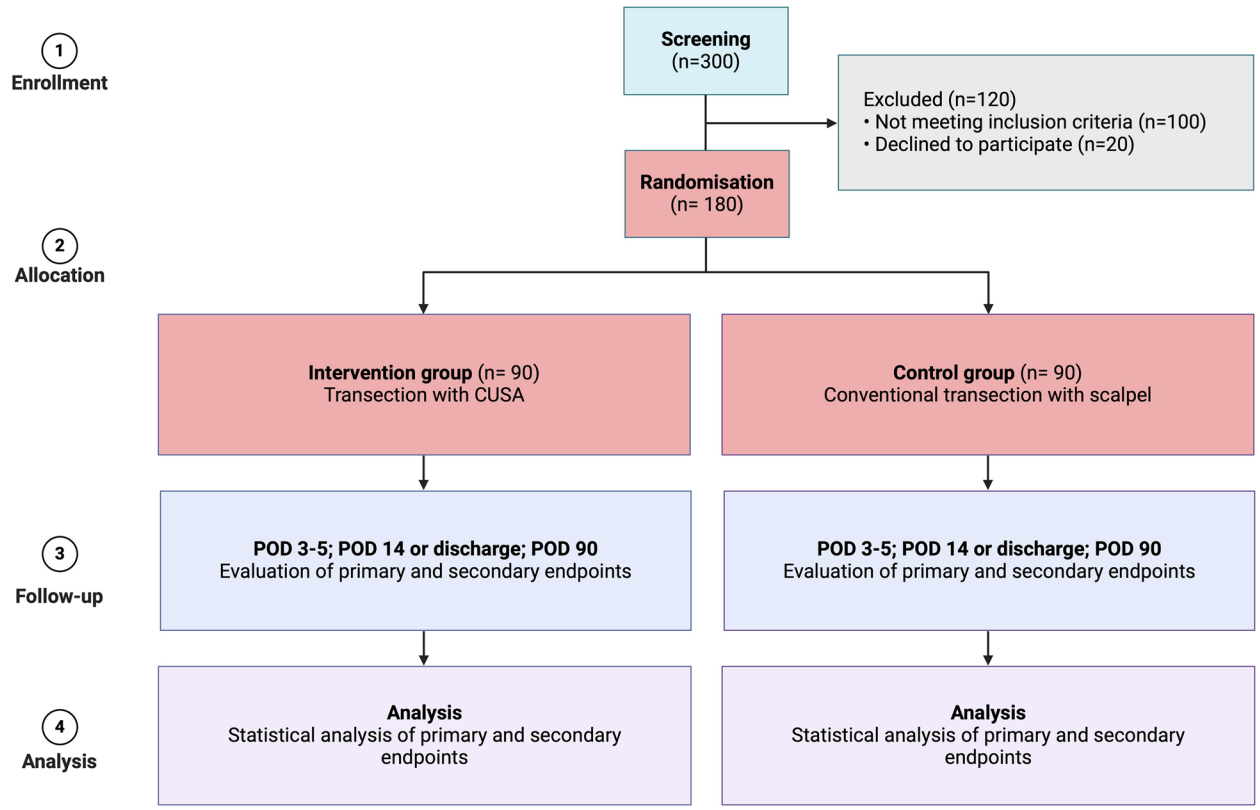

Fig. 2 Flow chart of the PANCUT study. CUSA, cavitron ultrasonic surgical aspirator; POD, postoperative day

Pancreaticoenterostomy is then created according to surgeon's preference and two abdominal drains (Ch. 21) are placed in near the anastomosis.

Clinical follow-up

All patients are postoperatively transferred to the intermediate care unit where they receive standardised therapy and are cared for according to the department's protocol. Routine blood tests are performed according to the attending physician's judgement as well as potential radiologic imaging. Amylase and lipase levels from both abdominal drains are determined on POD 1, 3 and 5. Possible interventions, whether antibiotic, interventional-radiologic, endoscopic, or surgical, are indicated by the surgeon or other attending physicians. Patients are referred to the outpatient clinic for routine follow-up regarding the histopathological report of the resected pancreas. Study data is collected until the end of hospital stay and up to 90 days after surgery. If no follow-up is needed, relevant data on possible complications is collected from a telemedicine database.

Study endpoints

The primary endpoint is POPF incidence. The secondary endpoints are operative time, amount of intraoperative blood loss, postoperative septic complications (intra-abdominal fluid collections, antibiotic treatment), postoperative bleeding, number of postoperative interventions (endoscopic, percutaneous or surgical), hospital stay and mortality. All outcomes are assessed until the end of primary hospitalisation or up to 90 days postoperatively.

Evaluation and validation of POPF

Presence and severity of POPF will be evaluated according to the updated consensus of the ISGPS from 2016. Based on the levels of amylase and lipase from abdominal drain on POD 3 and 5, we distinguish "non-dangerous" biochemical leakage of pancreatic juice (previously called POPF grade A), POPF grade B and POPF grade C. Leakage of pancreatic juice into the abdominal cavity is defined by determining the concentration of amylase in the abdominal drain, which is at least three times the upper limit of its normal serum concentration. If clinical intervention is not required, it is not considered POPF but rather biochemical leakage. POPF grade B occurs when the abdominal drain remains in place for more than 3 weeks or when percutaneous/endoscopic drainage or antibiotic treatment is required due to fluid collection. POPF grade C is a complication that necessitates

reoperation due to fluid collection, organ failure or patient death [10].

Patient safety and protocol deviations

The safety of our patients is of our upmost concern. Therefore, postoperative complications are documented according to the Clavien-Dindo classification [18]. The complications are also assessed by our independent internal medical team at various time checkpoints (every 3 months). If a higher incidence of postoperative complications is observed in the intervention arm, the team will present interim results to the committee and discuss early discontinuation of the study. In addition, any patient experiencing a grade four or five Clavien-Dindo complication will be presented to the committee. Again, early discontinuation of the study will be discussed if high-grade complications are observed in the intervention arm.

Any protocol deviation will be considered. Major protocol deviations (e.g. non-compliance with inclusion/exclusion criteria, inadequate informed consent, unreported serious event) will lead to patient exclusion from the study. In addition, every major protocol deviation will be documented and discussed to prevent future reoccurrences and protect the safety of study participants. Minor protocol deviations (e.g. out-of-schedule analysis of pancreatic enzymes from abdominal drains, missing intraoperative data) do not immediately lead to exclusion from the study. Minor deviations will be discussed with the principal investigator and documented for further analysis.

Calculation of sample size

The required sample size was calculated to achieve 80% power at the 5% level of significance using a chi-square test for binary outcome. The calculation was performed in PASS 16 Sample Size Software version 16.0.12. To our knowledge, this is a first study investigating the relationship between CUSA and incidence of POPF after PD; therefore, the effect size could not be meaningfully determined from the literature. The assumed event proportion in the control group was determined from a pilot study to be 0.22, while for the intervention group we assumed the event proportion to be 0.08. The effect size w was 0.21, resulting in sample size of 180 patients, 90 in each group.

Statistical analysis

Statistical analysis of the primary endpoint, POPF, will be analysed on the intention to treat (ITT) and as treated (AT) principle. In the ITT, the outcomes will be assessed based on the groups to which the patients were randomised, while in AT the outcomes will be evaluated based on the actual intervention they have received. In the case of missing data, their effect on conclusions will be estimated by sensitivity analysis, where we will assume the most optimistic (all missing values will be imputed with 0 for POPF) and pessimistic (all the missing values will be imputed with 1 for POPF) scenario. The POPF distribution per group will be described by absolute and relative frequencies per group. The reported measures of effect will be risk ratio (RR) and the risk difference (RD) with corresponding 95% confidence intervals.

The distribution of categorical baseline characteristics will be presented as absolute and relative frequencies. Ordinal variables will be summarised using the median and interquartile range, while continuous variables will be described by the mean and standard deviation if their empirical distribution is approximately symmetric, or by the median and interquartile range if the distribution is asymmetric. To compare the two groups, chi-square or Fisher's exact test will be used for categorical variables, Mann–Whitney for ordinal and asymmetric variables and *t*-test for independent samples for continuous variables. *p*-values smaller than 0.05 will be considered statistically significant. Analysis will be carried out using R software for statistical analysis.

Discussion

During PD, pancreatic tissue is usually indiscriminately and completely divided using a scalpel, followed by formation of pancreaticoenterostomy. This study aims to evaluate the role of transection of the pancreatic parenchyma with CUSA on the incidence of POPF after PD.

CUSA is a surgical device used for precise tissue dissection. The use of CUSA became popular in neurosurgery in the late 1970 s [19]. Since then, it has also become a valuable tool in liver surgery [20]. Essentially, CUSA combines tissue fragmentation, aspiration, and irrigation in a single instrument. The ultrasonic vibration of the tip of the handpiece selectively fragments the tissue. Simultaneous automatic irrigation via the tip enables effective aspiration of the fragmented tissue. In addition, selective fragmentation is a unique feature of the system. CUSA therefore only fragments water-rich parenchymal tissue, while highly elastic tissue with fibrillary elements (i.e. interstitium, blood vessels and duct structures) is spared [13]. In the healthy liver, hepatocytes contain fewer fibrillar elements than the surrounding tissue. In a cirrhotic liver, however, the amount of fibrillar component in the hepatocytes is increased, which makes dissection with CUSA more difficult [21]. This must be taken into the account when dissecting pancreatic tissue with CUSA, as the pancreatic parenchyma is more fibrotic compared to the liver parenchyma. In addition, chronic inflammation of the pancreas which is associated with increased

fibrosis of the tissue, is an independent risk factor for the development of pancreatic cancer [21, 22].

There are few studies investigating the relationship between the use of ultrasonic dissection and the incidence of POPF. In 1999, Suzuki et al. found a lower incidence of POPF in a group of patients in whom the pancreas was divided using ultrasonic dissection and the ducts were continuously ligated compared to a group of patients in whom the pancreas was divided with a scalpel and the stump was sutured over [23]. Similar results, albeit in a smaller sample, were also found in a study from 2001 [24]. In addition to a lower incidence of POPF in the group of patients in whom the pancreas was divided with ultrasonic dissection, Yui et al. also found a lower incidence of intra-abdominal abscesses and a shorter hospital stay [14]. All three studies included only patients who underwent distal pancreatectomy. Studies have also been published examining the relationship between the use of ultrasonic dissection and the incidence of POPF in patients undergoing more complex PD. Satoi et al. found no significant differences in the incidence of POPF or other postoperative complications between the groups of patients in whom the pancreas was dissected with or without ultrasonic dissection. However, they found a lower intraoperative blood loss in the group of patients where ultrasonic dissection was used [25]. Similar results were reported in a 2012 study in which patients in the control group had their pancreas dissected with a harmonic scalpel [26]. On the other hand, in 2016, Takahashi et al. found a higher incidence of POPF in the group of patients with ultrasonic dissection compared to the group of patients where the pancreas was dissected with a scalpel. In the aforementioned study, the pancreatic stump was treated with electrocauterization, and ducts were not ligated [15]. No differences in patient mortality between the different groups were observed in the studies. However, a limitation of all these studies is the relatively small number of patients included, the different methods and surgical techniques, which are inadequately described in some studies, and lastly, the changed classification of POPF from 2016 compared to 2005 [10, 16].

Trial status

Registration number of this trial is NCT06135012 (http://clinicaltrials.gov). It was registered 18 November 2023.

Study protocol version 1: October 1, 2023.

Start date of recruitment: December 1, 2023.

Estimated date for end of recruitment: December 31, 2025.

Estimated date for study completion: March 31, 2026.

Abbreviations

ASA	American Society for Anaesthesiology
AT	As treated
BMI	Body mass index
CUSA	Cavitron ultrasonic surgical aspirator
CT	Computed tomography
ISGPS	International Study Group on Pancreatic Surgery
ICU	Intensive care unit
ITT	Intention to treat
MR	Magnetic resonance
MRCP	Magnetic resonance cholangiopancreatography
PD	Pancreaticoduodenectomy
POD	Postoperative day
POPF	Postoperative pancreatic fistula
RD	Risk difference
RR	Risk ratio

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

BH (conceptualisation, investigation, methodology, writing—original draft, writing—review and editing), HZ (conceptualisation, writing—original draft), MP (writing—review and editing), MD (writing—review and editing), BT (writing—review and editing), AT (writing—review and editing, supervision) and DB (conceptualisation, investigation, methodology, writing—original draft, writing—review and editing, supervision). All authors critically reviewed and revised the manuscript and approved the final manuscript.

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Data availability

All study data is collected and monitored exclusively by the research personnel. Data is maintained in paper form as well as with the electronic data capture application, REDCap. REDCap is a secure web platform for building and managing online databases and surveys. Data will not be accessible to unauthorised personnel.

Declarations

Ethics approval and consent to participate

Ethical approval has been obtained by the National Medical Ethics Committee of the Republic of Slovenia (No. 0120–137/2023/3), and the study is be conducted in accordance with the Declaration of Helsinki. A written informed consent is obtained from the patients.

Competing interests

The authors declare that they have no competing interests.

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