

Prevention strategies for reducing the incidence of postoperative pancreatic fistulas in patients following pancreatoduodenectomy

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OBJECTIVE — to design and implement a preventive approach aimed at reducing the incidence of postoperative pancreatic fistulas and other complications following pancreatoduodenectomy in patients diagnosed with cancer of the pancreatic head and periampullary region.

MATERIALS AND METHODS. The present study involved the analysis of treatment outcomes for a cohort of 370 patients diagnosed with cancer of the pancreatic head and periampullary region who underwent pancreatoduodenectomy during the years 2015—2021. Between November 2018 and December 2021, a total of 141 patients were operated on using our modified pancreatic fistula risk score, an evaluation of preoperative sarcopenia status, and our risk mitigation strategies aimed at minimising postoperative complications. These patients made up the main group. The comparison group included a total of 229 patients. The surgical procedures were conducted between January 2015 and October 2018, employing generally accepted methods. However, the risk evaluation of potential pancreatic fistulas, the presence of sarcopenia, and the implementation of suggested prevention strategies were not taken into account.

RESULTS. The incidence of postoperative complications was significantly higher in the comparison group, with complications occurring in 94 (41.0%) patients, while in the main group, complications occurred in 43 (30.5%) patients ($\chi^2=4.1$; $p=0.04$). In the main group, a total of 16 (11.3%) patients experienced a clinically relevant grade B postoperative pancreatic fistula, which was significantly lower than in the comparison group, where the grade B or grade C fistula occurred in 64 (27.9%) patients ($\chi^2=14.2$; $p=0.0002$). In the main group, 2 patients died; the mortality rate was 1.4%. In the comparison group, 5 patients died, and the mortality rate was 2.2%. This rate was shown to be higher ($\chi^2=0.27$; $p=0.6$) when compared to the main group.

CONCLUSIONS. The implemented approach demonstrated a substantial reduction in the incidence of postoperative pancreatic fistulas from 27.9% to 11.3%, the number of postoperative complications from 41.0% to 30.5%, and mortality from 2.2% to 1.4%.

KEYWORDS

sarcopenia, pancreatoduodenectomy, pancreatic fistula risk score.

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The number of patients with pancreatic cancer, both throughout the world and in our country, is growing over time [4, 5, 24]. The only chance for recovery or prolonging life in this difficult category of patients is combined treatment with radical surgical

resection of the tumour and the administration of chemotherapy.

Pancreatoduodenectomy is the only radical method of treatment for patients diagnosed with cancer of the pancreatic head and periampullary region.

Despite global advances in pancreatic surgery, the 5-year survival rate has remained rather low, reaching a maximum of 15 % until recent times. It is widely acknowledged that malignant pancreatic tumours are a systemic disease. A crucial aspect of enhancing long-term outcomes involves implementing a multimodal approach that incorporates adjuvant chemotherapy, which is a mandatory step in the comprehensive management of this category of patients [24, 28].

Despite the achievements in pancreatobiliary surgery, the frequency of complications after pancreatoduodenectomy, even in high – volume world centres, remains high and reaches 20–60 %, with a postoperative mortality of up to 5 % [7, 28].

An important factor in pancreatic cancer is that postoperative complications have an impact on patient survival, given the fact that the general patient's condition in the postoperative period affects the timely administration of adjuvant chemotherapy.

Therefore, prevention of postoperative complications and timely administration of chemotherapy can improve oncological outcomes [15].

The most dangerous complication after pancreatoduodenectomy is postoperative pancreatic fistula (POPF), which, according to the literature, occurs in 5–40 % of patients after pancreatoduodenectomy. The development of POPF can lead to the occurrence of other life-threatening complications, such as postoperative bleeding, delayed gastric emptying, the failure of gastroenteroanastomosis, and severe infectious complications, which can have fatal consequences. Mortality after post-pancreatectomy haemorrhage reaches 30 to 50 %; this complication occurs most often during the development of a postoperative pancreatic fistula and septic complications due to the fistula [8, 11, 17].

Thus, it is very important not only to recognize and treat complications but also to predict their occurrence and work out methods aimed at preventing the development of postoperative complications before and during surgery [1].

To date, there are no effective general methods for preventing the development of postoperative pancreatic fistulas.

Currently, the world knows several scoring systems for predicting the risk of postoperative pancreatic fistula occurrence (pancreatic fistula risk score), which take into account both preoperative and intraoperative risk factors. A risk score that takes into account intraoperative assessment of pancreatic density, type of pathology, pancreatic duct diameter, and intraoperative blood loss was proposed by Mark Callery and presented in 2011 [9]. These indicators are significant risk factors for the occurrence of postoperative pancreatic fistulas.

We believe that determining the density of the pancreatic remnant through intraoperative palpation, followed by a final assessment of its hardness or softness, is subjective. Based on our surgical observations, it is evident that the pancreas frequently exhibits increased density upon palpation. However, this finding should not be attributed to long-term structural cellular changes in the pancreatic parenchyma. In fact, it is primarily caused by inflammation and swelling of the pancreas following the placement of endobiliary stents in patients with bile duct tumour obstruction. In order to objectify the indicators, we have suggested the assessment of pancreatic fibrosis in a section of the pancreatic gland tissue during surgery. This routine practice allows us to determine the resection status and inspect the resection margin for the presence of malignant cells.

We also identified statistically significant metabolic risk factors for the occurrence of postoperative pancreatic fistulas and postoperative complications.

Since 1989, the world has become aware of such an indicator of a patient's nutritional status as sarcopenia. According to the World Sarcopenia and Cachexia Association, sarcopenia is a condition associated with the loss of muscle tissue, muscle mass, and function. Sarcopenia is a degenerative loss of skeletal muscle mass that can be quantified using axial slices on computed tomography (CT) by measuring the area of the psoas major muscle at the level of the third lumbar vertebra and muscle tissue density [10]. A number of studies have shown that sarcopenia has an effect on the occurrence of postoperative complications and postoperative pancreatic fistula in patients after pancreatic resections and may be associated with a poor prognosis in patients with pancreatic adenocarcinoma [12–14, 27].

Therefore, the ability to predict the occurrence of pancreatic fistulas and other postoperative complications in patients with cancer of the pancreatic head and periampullary region after pancreatoduodenectomy, along with the development of risk mitigation strategies aimed at preventing such complications, can potentially improve treatment outcomes and oncological results.

OBJECTIVE – to design and implement a preventive approach aimed at reducing the incidence of postoperative pancreatic fistulas and other complications following pancreatoduodenectomy in patients diagnosed with cancer of the pancreatic head and periampullary region.

Materials and methods

The present study includes an analysis of treatment outcomes in a cohort of 370 patients diagnosed with

cancer of the pancreatic head and periampullary region. The patients underwent pancreatoduodenectomy during the period 2015–2021. The average age of the participants was 56.9 ± 9.4 years, ranging from 27 to 82.

The findings from our earlier investigations indicate a notable association between sarcopenia and an increased incidence of postoperative pancreatic fistulas (grades B and C), as well as a higher frequency of postoperative complications. Based on the available data, it can be shown that the occurrence of sarcopenia exhibited a notable impact on the incidence of postoperative pancreatic fistula (POPF) and other complications following pancreatoduodenectomy [2, 3]. The presence of sarcopenia in patients was found to be associated with a statistically significant increase in the incidence of clinically relevant postoperative pancreatic fistulas. Consequently, a series of measures were taken for patients with sarcopenia with the aim of improving their sarcopenic profile before surgery.

We implemented our modification of the pancreatic fistula risk score in clinical practice. Prior to the surgical procedure, we conducted examinations to determine the presence of sarcopenia. Based on the identified risk of a postoperative pancreatic fistula, we adjusted our surgical tactics accordingly.

Patients were divided into two groups. Since November 2018, we have used our risk mitigation strategies to decrease the occurrence of postoperative pancreatic fistulas and other postoperative complications in patients following pancreatoduodenectomy.

According to the suggested preventive approach, a total of 141 patients were operated on in the period from November 2018 to December 2021, which made up the main group. The comparison group consisted of 229 patients who were operated on from January 2015 to October 2018. In patients in the comparison group, we did not assess the risk of postoperative pancreatic fistulas or the presence of sarcopenia; pancreatojejunostomies were performed depending on the preferences of the operating surgeon. These groups were compared by gender, tumour location, stage of the disease, presence of concomitant pathology, and number of extended resections of the pancreas.

The study was conducted according to guidelines implemented in consideration of GCP-ICH and the Declaration of Helsinki. All participants gave written informed consent.

All patients underwent a standard examination before surgery, which included a computed tomography scan with intravenous contrast no later than 4 weeks before surgery.

In the main group, we additionally determined

the presence of sarcopenia by computer tomography before surgery. In our work, we used the definition of Hounsfield Units Average Calculation (HUAC) to calculate the level of sarcopenia: the average calculation of Hounsfield units using the OsiriX 9 program. For men, the presence of sarcopenia was considered when the HUAC value was less than 18.8, and for women, when the HUAC was less than 20.3.

We defined pancreatic fistula according to the International Study Group on Pancreatic Fistula (ISGPF), which was published in 2005 and revised in 2016 [8].

In our opinion, the existing pancreatic fistula risk score incorporates a subjective evaluation of the pancreatic density as it takes into account only its softness and hardness. In this study, we suggest a technique to determine the density of pancreatic tissue intraoperatively by using pathomorphological investigation. It allows for the establishment of the extent of fibrosis.

During pancreatoduodenectomy, a section of the tissue of the pancreatic stump was excised along the resection margin after pancreatic transection. Subsequently, an intraoperative pathomorphological investigation was conducted. The studied material was analysed to evaluate the «purity of the section» by detecting the presence of tumour cells, and the extent of pancreatic fibrosis was measured.

The resection margin was subjected to intraoperative evaluation using the standard method of obtaining a frozen section on a cryotome. At this stage, it was important to get the entire cross-sectional area of the pancreas for a more accurate assessment. The specimen, which was exposed to hematoxylin-eosin staining, was examined using the Olympus BX-43 light microscope. During microscopic examination, the extent of fibrosis in the specimen was evaluated using the Avtandilov ocular grid. In most cases, the pancreas consisted of about 5% of fibrous tissue. In patients with chronic pancreatitis, the percentage of fibrous tissue increased to 90%.

The density of the gland was determined based on the extent of fibrosis [21]. If the level of fibrosis was less than 15%, this gland was considered soft (Fig. 1).

If the level of fibrosis was 15–30%, this pancreas was considered a gland of moderate density (Fig. 2).

If the level of pancreatic fibrosis was more than 30%, this gland was considered firm (Fig. 3).

Thus, taking into account the aforementioned factors, we developed our modification of the pancreatic fistula risk score, which is presented in the Table.

The range of points varies from 0 to 10. 7 points or more indicate a high risk of pancreatic fistula.

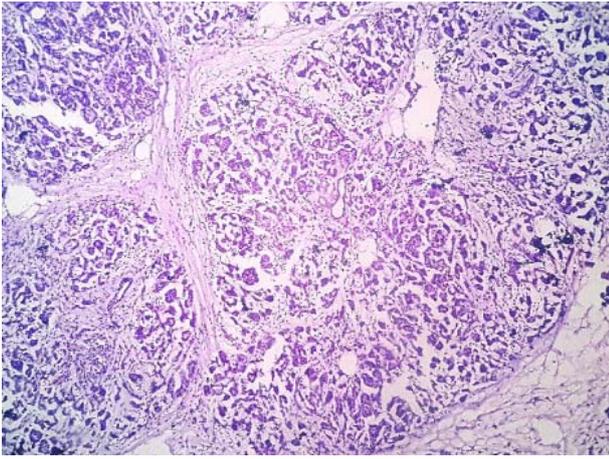


Figure 1. **Frozen section of pancreatic tissue. Fibrosis 5%. Hematoxylin-eosin staining, × 100**

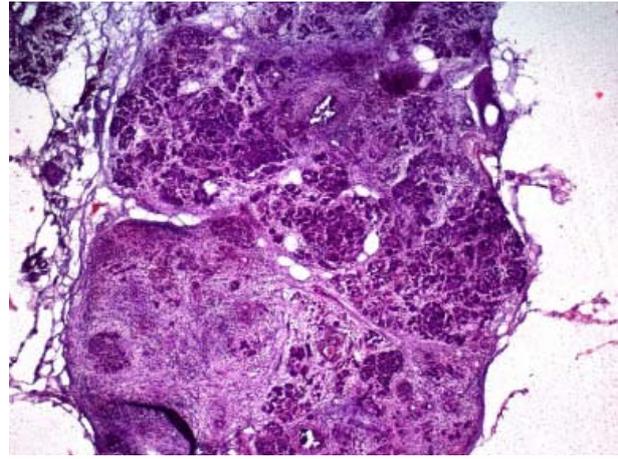


Figure 2. **Frozen section of pancreatic tissue. Fibrosis 30%. Heme-eosin staining, × 100**

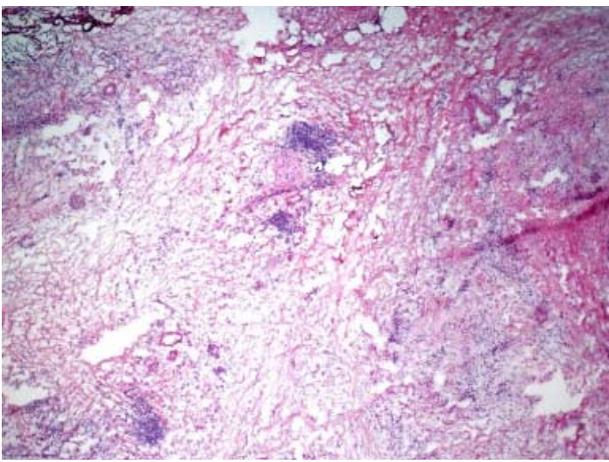


Figure 3. **Frozen section of pancreatic tissue. Fibrosis 95%. Heme-eosin staining, × 100**

Table. **Our modification of the pancreatic fistula risk score**

Risk factor	Points
Pathology	
Pancreatic adenocarcinoma or pancreatitis	0
Adenocarcinoma of the major duodenal papilla, distal part of the common bile duct, duodenum, cystic tumours, neuroendocrine tumours	1
Pancreatic duct diameter, mm	
≥ 5	0
4	1
3	2
2	3
≤ 1	4
Intraoperative blood loss, ml	
≤ 400	0
401–700	1
701–1000	2
> 1000	3
Pancreatic fibrosis, %	
< 15	2
15–30	1
> 30	0

We developed surgical tactics aimed at preventing the occurrence of postoperative pancreatic fistulas. In patients with a high risk of postoperative pancreatic fistula, we consider it expedient to perform pancreatojejunostomy with external drainage of the main pancreatic duct (MPD) during the reconstruction after pancreatoduodenectomy.

Patients with a scoring range of 4 to 6 were classified as having an intermediate risk and requiring duct-to-mucosa pancreatojejunostomy or pancreatojejunostomy with the invagination technique. According to our previous studies, this type of pancreatojejunal anastomosis resulted in the lowest number of postoperative pancreatic fistulas.

For cases with a low risk level (defined as a number of points less than 4), the decision about the type of pancreatic anastomosis to be done was left to the discretion of the operating surgeon.

If sarcopenia was found in the patient during the preoperative CT scan, appropriate nutritional

support and a series of procedures were administered during the preoperative phase to address the sarcopenic condition.

Statistical analysis. The obtained data were computerized and compiled into a common database.

Mathematical data processing methods were used to specify potential risk factors for postoperative complications. The existence of a relationship between the specified factors and the frequency of complications was studied using the analysis of tables of proportions and proportions using the chi-square test. The Student's test was used to assess the reliability of the difference in indicators. The difference was considered significant at $p < 0.05$.

To evaluate the immediate results of surgical treatment, we used indicators of hospital mortality as well as the percentage of patients with a complicated course. To assess the long-term results of treatment, 1-, 3-, and 5-year survival rates were used, which were calculated using the Kaplan-Meier procedure. Survival curves were compared using the Logrank LR test. All calculations were performed using MS Excel, Osirix 9, and GraphPad Prism 7.

Results

Out of 370 operated patients, adenocarcinoma of the pancreatic head was diagnosed in 226 (61.1%) patients, adenocarcinoma of the ampulla of Vater – in 108 (29.2%) patients, and adenocarcinoma of the distal part of the common bile duct – in 36 (9.7%) patients. The main group consisted of 141 patients.

In the main group, according to our pancreatic fistula risk score, 61 (43.3%) patients had a high risk of pancreatic fistula, 46 (32.6%) had an intermediate risk, and 34 (24.1%) had a low risk. The groups were comparable in terms of the age of the patients, stage of the disease, and concomitant pathology. Operation time, overall blood loss, and length of hospital stay were comparable in both groups. The number of patients with sarcopenia was not significantly different in both groups.

In the main group, postoperative complications were observed in 43 (30.5%) patients. A postoperative pancreatic fistula of grade B or grade C was detected in 16 (11.3%) patients. Acute postoperative pancreatitis occurred in 8 (5.7%) patients. 2 (1.4%) patients had gastrointestinal bleeding, which was treated conservatively. Delayed gastric emptying was reported in 7 (5.7%) patients, and lymphorrhea was noted in 3 (2.1%) patients. 3 (2.1%) patients had postoperative wound infections. In the main group, 2 patients died, resulting in a mortality rate of 1.4%.

In the comparison group, postoperative complications occurred in 94 (41.0%) patients. A postoperative pancreatic fistula of grade B or grade C was observed in 64 (27.9%) patients. Delayed gastric emptying was reported in 6 (2.6%) patients. 43 (18.8%) patients had infectious complications, and postpancreatectomy haemorrhage was noted

in 14 (6.1%) patients. In the comparison group, 5 (2.2%) patients died from septic complications due to a postoperative pancreatic fistula of grade C.

The level of postoperative complications was significantly higher in the comparison group ($\chi^2 = 4.1$; $p = 0.04$). Clinically relevant gr. B or gr. C pancreatic fistulas occurred in 64 patients in the comparison group, which is significantly higher than in the main group, where gr. B or gr. C fistulas occurred in 11 patients ($\chi^2 = 14.2$; $p = 0.0002$).

In the comparison group, 5 patients died, resulting in a mortality rate of 2.2%. The implemented preventive approach demonstrated a substantial reduction in the mortality rate from 2.2% to 1.4% ($\chi^2 = 0.27$; $p = 0.6$) in patients with cancer of the pancreatic head and periaampullary region after pancreatoduodenectomy.

Discussion

One of the most important factors in the occurrence of postoperative complications and mortality after pancreatoduodenectomy is the formation of the postoperative pancreatic fistula, which remains the «Achilles heel» of pancreatic surgery. Despite the improvement of surgical techniques, the rate of postoperative pancreatic fistula, even in high-volume world centres of pancreatic surgery, remains high at 5–40% [18].

There are many studies that confirm the influence of such factors as a body mass index above 25 kg/m², pancreatojejunostomy technique, the use of pancreatic stents, intra-abdominal drains, and somatostatin analogues on the occurrence of POPF. However, to date, no standard methods aimed at minimizing the risk of postoperative pancreatic fistulas have been developed [18].

In contemporary medical practice, several scoring systems have been developed to determine the risk of postoperative pancreatic fistulas. They take into account both preoperative and intraoperative assessments of several parameters. It is essential to implement all available methods and strategies in order to minimize the likelihood of POPF in patients with a high risk of this complication. The density of the pancreatic parenchyma, namely its soft texture, is widely recognized as a prominent risk factor in the pathogenesis of pancreatic fistulas. The findings of many studies conducted by M. Timothy, T. Pawlik, and other authors have demonstrated a notable correlation between the soft structure of the gland and a substantial increase in the risk of postoperative pancreatic fistula [6, 22, 29]. Mark P. Callery included the criterion of the pancreatic structure, which is assessed intraoperatively

by the surgeon during palpation of the pancreas, in his pancreatic fistula risk score. However, in our opinion, the evaluation of this indicator is subjective, and in cases of pancreatitis, tissue density may change, which prompts the search for an objective assessment of pancreatic density.

P. Pessaux et al. proposed the use of external drainage of the MPD during the reconstructive stage of pancreatoduodenectomy in order to reduce the risk of pancreatic fistulas. His prospective multicenter randomized trials showed a significant reduction in the incidence of pancreatic fistulas from 42 to 26% ($p = 0.034$). Similar results were confirmed by Yoh K. et al. [29].

Clinical randomized trials have been conducted and published and have shown the benefits of using pancreatic stents in reducing the number of cases of postoperative pancreatic fistula compared to pancreatojejunostomy without stenting of the MPD. Recent data suggest that an external stent placed through the pancreatojejunoanastomosis does not reduce the frequency of postoperative pancreatic fistula in patients of all risk categories, instead providing a real benefit only to those patients who are considered a high-risk group [6]. We also consider it necessary to perform pancreatojejunostomy with an external pancreatic stent only in high-risk patients.

There is no clear position regarding the use of an external stent in the category of patients with intermediate risk [17].

In our research, we obtained comparable results, which allowed us to recommend pancreatojejunoanastomosis with external MPD drainage in patients with a high risk of pancreatic fistula occurrence.

Data from many studies report that drainage of pancreatic juice from the area of pancreatojejunal anastomosis (with a stent placed in the MPD) is an effective method that promotes healing of the anastomotic site and prevents trypsin irritation of the pancreatic stump and the anastomotic site in the early postoperative period, thereby reducing the incidence of postoperative pancreatic fistulas [17]. There are also randomized studies on the use of internal stents. But compared to the internal stent, the external stent has advantages in that it allows for more complete drainage of the pancreatic juice from the area of the pancreatojejunoanastomosis and prevents the activation of pancreatic enzymes by bile and pancreatic trypsin from corroding the anastomotic site during the early stages of pancreatic surgery. According to the literature, there are also negative aspects of the use of external drainage for pancreatojejunal anastomosis. The authors also reported the development of complications related to the stent: bending of the stent, its dislocation, or

obstruction [17]. In our study, we observed only stent obstruction in 2 patients; the patency of the stents was restored, and this did not affect the general condition of the patients in the postoperative period or the outcome of treatment. As for the internal stent, according to the literature, it is impossible to control the position of the stent, and its migration occurs very often. Randomized studies have shown no advantages of internal stents in reducing the number of postoperative pancreatic fistulas [18]. In our practice, we perform pancreatojejunostomy with external drainage of the MPD.

There are many global studies that have shown a reliable influence of the presence of sarcopenia on the occurrence of postoperative complications, on the level of infectious complications, and on the occurrence of postoperative pancreatic fistulas in patients with pancreatic cancer after pancreatic resections [22]. According to Tosei Takagi et al., sarcopenia is an objective and reliable preoperative predictor of postoperative infectious complications after pancreatic resections [25]. According to their study, sarcopenia, preoperative biliary drainage, blood loss, and the soft pancreas are reliable risk factors for postoperative infectious complications.

N. Yasunori and K. Tanaka showed a significant increase in the number of pancreatic fistulas after pancreatoduodenectomy in patients with sarcopenia [19, 26]. Youngju Ryu showed in his study that sarcopenia is the only independent risk factor for clinically relevant POPF after pancreatoduodenectomy in patients with cancer of the pancreatic head on multivariable analysis [23]. Jang M. and co-authors, in their study, proved the impact of sarcopenia and visceral obesity on postoperative pancreatic fistulas after pancreaticoduodenectomy [16].

According to a multicenter study published by Pecorelli, sarcopenic obesity is associated with a failure to prevent major complications in patients who undergo pancreaticoduodenectomy for pancreatic cancer [20]. We obtained similar results and included the determination of sarcopenia in the compulsory preoperative examination of patients, with the mandatory therapy for patients with sarcopenia aimed at improving the patient's sarcopenic profile and preparing the patient for surgery.

As a result, the detection of sarcopenia in patients before surgery, assessment of pancreatic parenchymal fibrosis, and incorporation of this parameter into our modified pancreatic fistula risk score, along with the implementation of our mitigation strategies, including changes in preoperative and intraoperative tactics, contributed to the improvement of treatment outcomes for patients diagnosed with cancer of the pancreatic head and periampullary region.

Conclusions

The implemented preventive approach demonstrated a substantial reduction in the incidence of postoperative pancreatic fistulas from 27.9% to 11.3%, the number of postoperative complications from 41.0% to 30.5%, and mortality from 2.2% to 1.4% in patients with cancer of the pancreatic head and periampullary region after pancreatoduodenectomy.

The use of our modified pancreatic fistula risk score and the adoption of appropriate surgical tactics have the potential to improve the results of surgical treatment for patients diagnosed with cancer of the pancreatic head and periampullary region after pancreatoduodenectomy.

DECLARATION OF INTERESTS

The authors declare that they have no conflicts of interest.

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AUTHORS CONTRIBUTIONS

Concept and design of the study: V.M. Kopchak, L.O. Pererva; material collection, material processing, statistical data processing, and writing the manuscript: L.O. Pererva, V.O. Kropelnyskyi, V.V. Khanenko, P.A. Azadov, Z.Y. Holobor.

All authors have read and approved the final manuscript.

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Стратегії профілактики виникнення післяопераційної панкреатичної нориці у пацієнтів після панкреатодуоденектомії

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Мета — розробити систему заходів, яка дає змогу знизити частоту виникнення післяопераційної панкреатичної нориці та кількість післяопераційних ускладнень після виконання панкреатодуоденектомії.

Матеріали та методи. Проаналізовано результати лікування у відділі хірургії підшлункової залози та жовчних проток Національного інституту хірургії та трансплантології імені О. О. Шалімова в 2015—2021 рр. 370 хворих після панкреатодуоденектомії. За період із листопада 2018 р. до грудня 2021 р. прооперовано 141 хворого з використанням розробленої нами шкали ризику виникнення післяопераційної панкреатичної нориці, оцінкою наявності саркопенії та застосуванням профілактичних заходів для зменшення кількості післяопераційних ускладнень. Ці хворі утворили основну групу. У групу порівняння залучено 229 хворих, прооперованих у період із січня 2015 р. до жовтня 2018 р. за загальноприйнятими методиками без оцінювання ризику виникнення панкреатичної нориці, наявності саркопенії та застосування відповідних профілактичних заходів.

Результати. Рівень післяопераційних ускладнень був статистично значущо вищим у групі порівняння (у 94 (41,0%) та 43 (30,5%) хворих, $\chi^2=4,1$; $p=0,04$). Клінічно значуща післяопераційна панкреатична нориця ступеня В виникла у 16 (11,3%) пацієнтів основної групи, що було статистично значущо менше, ніж у групі порівняння, в якій нориця ступеня В або С виникла у 64 (27,9%) хворих ($\chi^2=14,2$; $p=0,0002$). В основній групі померло 2 хворих (летальність — 1,4%), у групі порівняння — 5 (летальність — 2,2%, $\chi^2=0,27$; $p=0,6$).

Висновки. Розроблена система заходів дала змогу статистично значущо зменшити кількість випадків післяопераційної панкреатичної нориці (з 27,9 до 11,3%), кількість післяопераційних ускладнень (з 41,0 до 30,5%) і знизити летальність (з 2,2 до 1,4%).

Ключові слова: саркопенія, панкреатодуоденектомія, шкала ризику виникнення панкреатичної нориці.

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