ORIGINAL ARTICLE

CONTENTS

Histological and oncological determinants of postpancreatectomy acute pancreatitis following pancreatoduodenectomy

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ABSTRACT

Aim: This study aimed to evaluate the incidence of postpancreatoduodenectomy acute pancreatitis (PPAP) and analyze its association with histological and oncological features of the resected tumors.

Materials and Methods: Data from 296 patients who underwent PD between 2014 and 2023 were analyzed. The intergroup analysis compared patients in the PPAP (n=126) and no-PPAP (n=170) groups regarding tumor histology, stage, differentiation, resection margin status, and type of PD.

Results: PPAP occurred in 42,6% of cases, and clinically relevant PPAP in 30,1%. PPAP was more common in patients with cystic pancreas neoplasms (22,4% in the PPAP group vs. 9,0% in the no-PPAP group, p=0,001) and duodenal adenocarcinoma (4,0% vs. 0,6%, p=0,04) and tended to occur more often in distal bile duct adenocarcinoma (10.4% vs. 4.8%, p=0.07). In contrast, patients with pancreatic ductal adenocarcinoma had a lower PPAP rate (22,4% vs. 49,1%, p<0,0001). The tumor size (T1-T4) and differentiation (G1-G4) did not affect PPAP incidence. A higher incidence of PPAP was observed in the N0 group (46,7% vs. 30,8%, p=0,03), as well as in patients with R0 resections (91,0% vs. 70,3%, p=0,0006). Standard PD was also associated with a higher frequency of this complication (the difference at borderline significance: p=0,05).

Conclusions: The incidence of PPAP is associated with certain histological tumor types and the extent of surgery. Tumor size and grade of differentiation had no significant impact, while N0 lymph node status and R0 resection margins were associated with higher PPAP incidence.

KEY WORDS: pancreatoduodenectomy, postpancreatectomy acute pancreatitis, pancreatic tumors

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INTRODUCTION

Pancreatoduodenectomy (PD) remains the main treatment method for tumors of the pancreas and periampullary structures. This surgical intervention is technically complex and is associated with a high incidence of significant postoperative complications (Clavien-Dindo ≥ IIIa) [1]. One of the important aspects of the postoperative period is the development of postpancreatectomy acute pancreatitis (PPAP), which can influence the incidence and nature of other postoperative complications following PD. According to various authors, the incidence of clinically relevant forms of PPAP after PD ranges from 14,7% to 28% [2, 3].

Postoperative complications, particularly PPAP, significantly affect the duration of hospitalization. The overall complication rate after PD is 70,3%, increasing the average postoperative hospital stay from 22 to 30 days [4]. It has been proven that the incidence of other serious postoperative complications of PD is significantly higher in patients with PPAP. However, the impact of PPAP on long-term outcomes after PD remains uncertain. Intergroup analysis did not reveal a significant difference in five-year overall survival or disease-free survival after PD [5].

According to the literature, benign diseases are identified in only 5–13% of patients who have undergone PD [6]. In the vast majority of patients, the final diagnosis is established postoperatively. Histologic analysis plays a key role in verifying the diagnosis, allowing not only the determination of the tumor's morphological type but also the assessment of prognosis and treatment effectiveness. Despite considerable attention to the impact of PPAP on disease progression, there is currently no convincing evidence of its association with the histologic type of tumor, its oncologic characteristics, or the extent of surgery.

AIM

The study aimed to evaluate the incidence of PPAP in patients after PD, considering the histological and oncological characteristics of the pancreatic tumor.

MATERIALS AND METHODS

The study was based on a retrospective analysis of data from patients who underwent PD over a 10-year period (2014–2023) at the Department of Surgery, University Hospital Schleswig-Holstein, Lübeck, Germany. A total of 296 patients were included in the analysis. The surgeries were performed for both malignant and benign diseases of the pancreas and periampullary structures.

The study was conducted in accordance with the ethical standards of the Helsinki Declaration (2004 revision, Tokyo). The study design was approved by the local Ethics Committee. All patients provided informed consent for the use of their personal data, examination results, and treatment outcomes. Data were collected and stored in an anonymized form.

The diagnosis of PPAP was made based on the ISGPS classification (2022), which defines it as inflammation of the pancreatic stump occurring within the first three days after surgery. Modified ISGPS criteria were used for diagnosis, in particular serum lipase levels, which have higher specificity in detecting acute pancreatitis [7]. An increase in serum lipase concentration (>60 U/L) on postoperative days 2 and 3 was considered diagnostically significant. PPAP was classified into three degrees: biochemical (only changes in laboratory analyses), grade B (moderate complications), and grade C (severe, life-threatening conditions) [8]. The main characteristics of the study group are shown in Table 1.

The median age of patients who underwent PD was 69 years. Males predominated over females (61,15% vs. 38,85%). The majority of patients underwent pylorus-preserving PD (77%), compared to those who underwent the classic Whipple procedure (23%). The most common histological diagnosis was pancreatic ductal adenocarcinoma (37,5%). In total, 42,6% (n=126) of patients developed PPAP, of whom 30,1% had clinically significant forms (grades B and C). In-hospital mortality rate was 7,8% (23/296 cases).

Before surgery, all patients underwent a comprehensive clinical and laboratory examination, which included blood tests, biochemical markers, tumor markers (CA 19-9, CEA), and the determination of alkaline phosphatase and gamma-glutamyltransferase levels. Serum lipase levels were assessed before surgery and in the early postoperative period (1-3 days), and in the case of hyperlipasemia, the levels were monitored until normalization. Drainage fluid was routinely analyzed for bilirubin and amylase levels during the first three days of the postoperative period, with further analyses performed as needed. Instrumental diagnostic methods included gastroduodenoscopy, abdominal ultrasound, contrast-enhanced computed tomography, and magnetic resonance imaging. Macroscopic specimens obtained during surgery were subjected to pathomorphological examination.

All patients were divided into two groups: PPAP (126 patients) and no-PPAP (170 patients). An intergroup analysis was conducted in both groups depending on the histological type of the tumor, the stage of cancer according to the TNM classification, tumor grade (G1-G4), resection margin status (R0/R1), and the type of PD (standard or extended) [9, 10].

The data were processed using SPSS software (version 20, IBM). Qualitative variables (absolute and relative frequency [%]) were evaluated using the χ^2 test. For specific parameters, intergroup analyses were conducted in subgroups of patients for whom the corresponding data were available. The actual sample size used in each analysis is indicated below the respective figures. Differences were considered statistically significant at $p < 0,05$.

ETHICS

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

RESULTS

In most cases, the final diagnosis was not established before PD. Histological verification of pancreatic pathology was usually performed intraoperatively as a frozen section, as well as postoperatively. Histological variants of pancreatic pathology identified in the operated patients, depending on the presence or absence of PPAP, are shown in Fig. 1.

Among the histological findings obtained from postoperative macroscopic specimens, malignant variants of pancreatic pathology predominated. However, benign pathology was confirmed in some patients: CP was identified in 15,6% of patients in the no-PPAP group and in 11,2% of patients in the PPAP group (p=0.28). Regarding histological variants of pancreatic tumors, the most common tumor types were PDAC (22,4% - 49,1%), CNP (9,0% - 22,4%), and AMPAC (9,0% - 12,0%). Other histological variants of pancreatic tumors were much less common.

The results of the intergroup analysis showed that in the PPAP group, compared to the no-PPAP group, CNP were more common (22,4% vs. 9,0%, p=0,001), as well

Table 1. Baseline characteristics of the study group of patients undergoing pancreatoduodenectomy (n=296)

Characteristics	Number (%)
Age, years (median; percentiles)	69.0 (59.0; 77.0)
Gender:	
• male	181 (61.15 %)
• female	115 (38.85 %)
Type of PD:	
• pylorus-preserving PD	228 (77.0 %)
• Whipple procedure	68 (23.0 %)
Histological conclusion:	
• chronic pancreatitis	40 (13.5%)
• cystic neoplasms of the pancreas	43 (14.5 %)
• neuroendocrine tumors of the pancreas	13 (4.4 %)
• pancreatic ductal adenocarcinoma	111 (37.5 %)
• ampullary adenocarcinoma	30 (10.1 %)
• distal bile duct adenocarcinoma	21 (7.1 %)
• duodenal adenocarcinoma	6 (2.0 %)
• other	32 (10.8 %)

Source: compiled by the authors of this study

as DUOAC (4,0% vs. 0,6%, p=0,04), and DBDAC (10,4% vs. 4,8%, p=0,07). The latter showed only a trend toward significance in the analyzed groups. In addition, a significant decrease in cases with histologically confirmed PDAC was recorded in the PPAP group compared to no-PPAP group (22,4% vs. 49,1%, p<0,0001). As previously mentioned, PDAC was the most common histological variant of pancreatic tumors in the operated category of patients.

Regarding the characteristics of the primary tumor according to the TNM classification system, the analysis of tumor size and location (T1–T4) in the groups (Fig. 2) showed that T3 (45,3% and 42,5% of cases in the no-PPAP and PPAP group, respectively) and T2 stages (35,9% and 35,6%, respectively) were the most common, while T1 and T4 were significantly less common (9,4% and 11,0% of cases, respectively). There was no statistically significant intergroup difference among the T stages in the analyzed patient groups.

The analysis of tumor spread to regional lymph nodes (N0-N2) according to the TNM staging system in the groups showed (Fig. 3) that N0 and N1 stages prevailed in both studied groups. Moreover, in the PPAP group compared to the no-PPAP group, the N0 stage was significantly more often recorded (46,7% vs. 30,8%, p=0,03). In other groups, no significant intergroup differences were observed.

Regarding the assessment of tumor grade, the results of tumor cell differentiation (G1–G4) in the PPAP and no-PPAP groups of patients are presented in Fig. 4. The most common differentiation grade was G2, identified in 54,3% and 59,5% of cases, respectively. The G3 grade was less frequent, occurring in 28,6% and 28,8% of cases, respectively. The G1 grade was found in 17,1% and 9,9% of cases, while G4 was identified in only 2 patients (1,8%) in the no-PPAP group. Analysis of tumor cell differentiation did not reveal significant statistical differences between the studied groups in the incidence of PPAP.

The assessment of the radicality of PD was based on the resection margin status (R). The results of the analysis of the resection margin status of the pancreas in the PPAP and no-PPAP groups are presented in Fig. 5. It was found that in 70,3% of cases in the no-PPAP group and in 91,0% of cases in the PPAP group, cancer cells were absent at the resection margins. Conversely, their presence was detected in 29,7% and 9,0% of cases, respectively (p = 0,0006), indicating that cancer cells were significantly less frequently found at the resection margins in the PPAP group compared to the no-PPAP group.

The analysis of the type of PD in the PPAP and no-PPAP groups (Fig. 6) showed that in the no-PPAP patients, extended PD was performed more often (48,2% vs. 36,8%) and standard PD was performed less frequently (51,8% vs. 63,2%) (the difference at borderline significance: p=0,05).

DISCUSSION

The obtained results indicate a different incidence of PPAP after PD depending on the histological variants of pancreatic pathology. In this study, PPAP developed after both benign and malignant pancreatic pathologies. However, the incidence of PPAP varied significantly depending on the histological type of neoplasm, which aligns with findings from other studies.

In patients with chronic pancreatitis and PDAC, the frequency of PPAP was lower compared to other histologically verified pathologies. Postoperative PPAP was

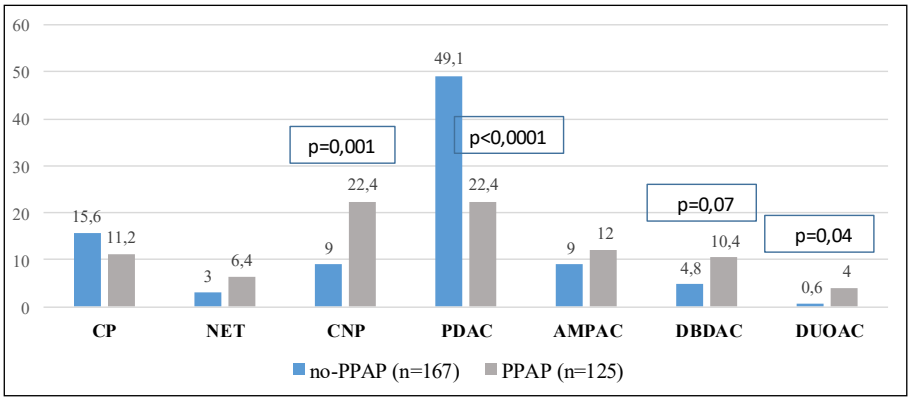

Fig. 1. Histologic variants of pancreatic pathology (malignant and benign) verified in the PPAP and no-PPAP groups (in %)
Notes: CP – chronic pancreatitis, NET – neuroendocrine tumors of the pancreas, CNP – cystic neoplasms of the pancreas, PDAC – pancreatic ductal adenocarcinoma, AMPAC – ampullary adenocarcinoma, DBDAC – distal bile duct adenocarcinoma, DUOAC – duodenal adenocarcinoma, PPAP – postpancreatectomy acute pancreatitis
Picture taken by the authors

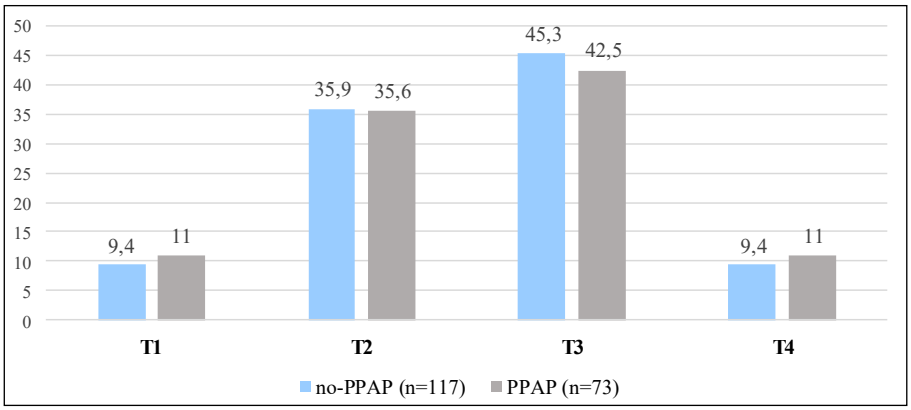

Fig. 2. The size of the primary tumor (T1-T4) according to the TNM staging system in the PPAP and no-PPAP groups (%)
Picture taken by the authors

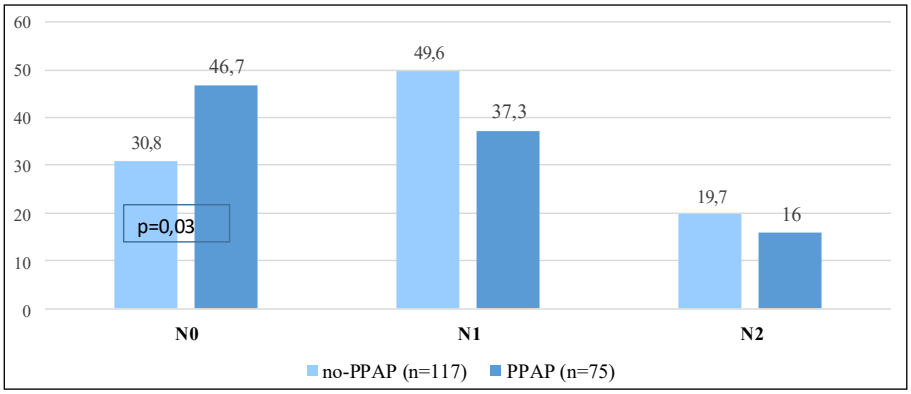

Fig. 3. Spread of the tumor process to regional lymph nodes (N0-N2) according to the TNM staging system in the PPAP and no-PPAP groups (in %)
Picture taken by the authors

significantly less frequent among patients with PDAC. Among patients with chronic pancreatitis, the frequency of PPAP was also lower, although this difference did not reach statistical significance. In all other histological variants of pancreatic pathology, the proportion of PPAP patients was higher than that of no-PPAP patients, with a significant difference observed in the CNP and DUOAC groups, while in the DBDAC group there was only a tendency toward a higher proportion of PPAP patients.

These findings highlight the varying impact of histological forms of pancreatic pathology on the prognosis of PPAP after PD.

A connection has been established between the inflammatory process in the pancreas and the development of malignant formations, which is associated with changes in the microenvironment in PDAC [11]. Patients with chronic pancreatitis have a significantly higher risk of developing PDAC [12]. The period between the diagnosis of CP and PDAC usually lasts from one to two decades [13]. Currently, research is ongoing to investigate the relationship between stromal and cancerous cells. It is known that PDAC is characterized by a pronounced desmoplastic stromal reaction surrounding cancer cells [14]. Stellate cells create a microenvironment that is favorable for tumor growth, immunosuppression, and metastasis [15]. It appears that the increased density of pancreatic tissue that develops in CP and PDAC contributes to a reduced risk of PPAP, which explains the lower incidence of PPAP in this study among patients with PDAC.

Currently, there are no studies on the incidence of PPAP at different stages of the oncological process. Although the size of pancreatic tumors is known to affect

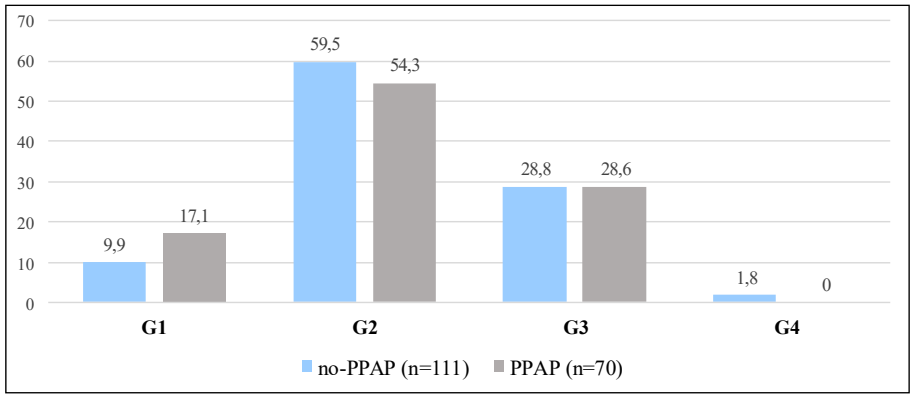

Fig. 4. Tumor differentiation (G1-G4) in the PPAP and no-PPAP groups (in %)
Picture taken by the authors

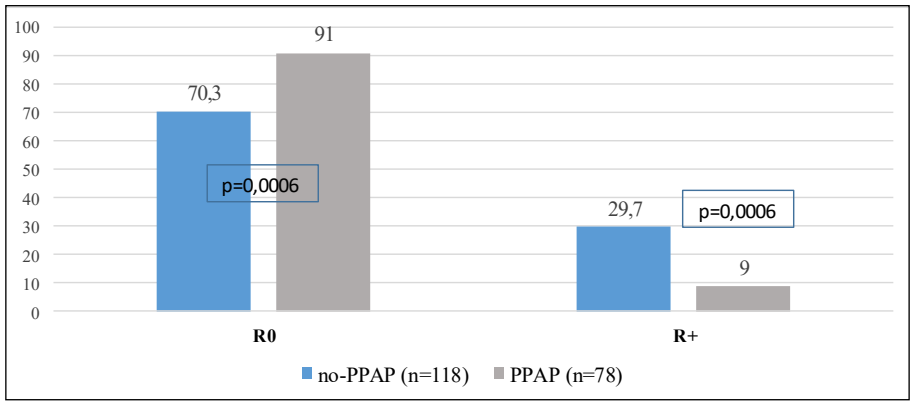

Fig. 5. Resection margin status (R) of the pancreas in the PPAP and no-PPAP groups (in %)
Picture taken by the authors

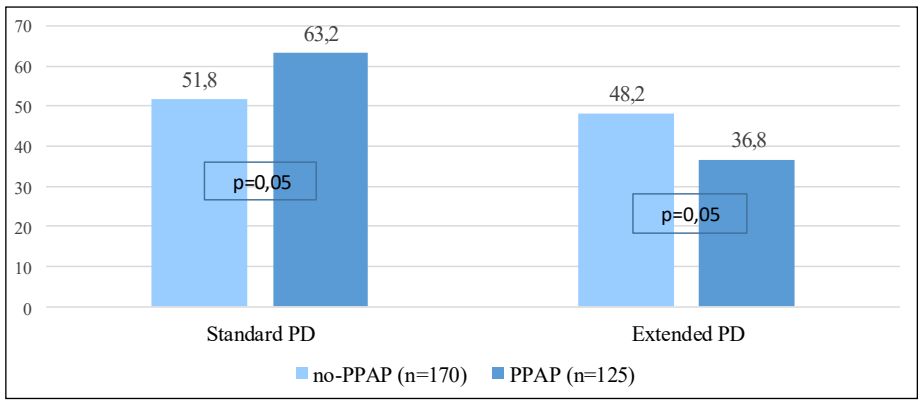

Fig. 6. Variant of pancreatoduodenectomy (standard or extended) in the PPAP and no-PPAP groups (in %)
Picture taken by the authors

postoperative outcomes, its prognostic role remains controversial [16]. T-stage determination depends on the method [17], and tumors larger than 2 cm worsen the survival of patients with PDAC [18, 19].

The incidence of postoperative complications after PD at different TNM stages requires further investigation. Low tumor differentiation and lymph node metastases are recognized as independent predictors of poor survival in PDAC patients after PD [20]. Our analysis did not reveal a statistically significant difference in PPAP incidence among tumors sizes (T1–T4). However, patients with N0 were significantly more likely to develop PPAP, whereas different tumor grades (G) did not significantly affect the incidence of PPAP.

Resection margin status (R) is of great importance. Achieving R0 status should be the primary goal in the surgical treatment of PDAC [21]. However, for a long time, the significance of R0 remained unclear, and its impact on prognosis varied depending on the analyzed datasets and different definitions of R0 [22, 23]. Some authors reported that both recurrence-free and overall survival were significantly higher in pancreatic cancer patients with R0-resected tumors [24]. At the same time, numerous studies have shown that positive resection margins (R1) reduce survival rates for all types of pancreatic cancer, including adenocarcinoma [25]. Recent studies have shown that in patients receiving neoadjuvant therapy, the prognostic significance of a positive margin is less important [26, 27]. In contrast, a recent population-based study by German authors showed that R0 status remained an independent predictor of overall and disease-free survival after PDAC resection [28].

In the available literature, data on the incidence of postoperative complications depending on different resection margin statuses (R) are limited. In our study, PPAP was significantly more common in patients with R0 resection. We suggest that this is related to a more radical surgical approach and, consequently, greater postoperative tissue injury.

Regarding the type of surgery, according to our data, standard PD was associated with a higher incidence of PPAP, while extended PD was associated with a lower incidence, and these differences were of borderline statistical significance. Similar results were obtained by De Reuver and colleagues (2015) [20]. In contrast, Hartwig W. et al. (2016) demonstrated that extended resections in patients with pancreatic cancer are associated with a higher complication rate [29]. On the other hand, according to Mitra A. et al. (2018), the incidence of severe postoperative complications (Clavien grades III, IV, and V) in patients after extended and standard pancreatectomies did not differ significantly [30].

Thus, the results of this study indicate the importance of an individualized approach to PD, taking into account the histological type of the tumor, TNM stage, R status, and extent of resection. Further research is necessary to gain a deeper understanding of the mechanisms underlying PPAP development and to improve surgical strategies.

CONCLUSIONS

The incidence of PPAP varies significantly depending on the histologic type of pancreatic tumor. PPAP was more common in CNP and DUOAC, less common in patients with PDAC. Tumor size and grade of differentiation did not influence the incidence of PPAP. N0 status of regional lymph nodes and R0 resection margin status were associated with a higher incidence of PPAP. Standard pancreatoduodenectomy was associated with a higher incidence of PPAP compared with extended procedures.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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