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*Observational Study*

**Complications of chronic pancreatitis prior to and following surgical treatment. A proposal for classification.**

Complications of chronic pancreatitis.

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## **Abstract**

### **BACKGROUND**

Chronic pancreatitis (CP) is a long-lasting disease frequently associated with complications for which there exists so far no comprehensive pathophysiological classification.

### **AIM**

Aims of the present study: 1) to propose a pathophysiological classification of the complications of CP, 2) evaluation their prevalence in a surgical cohort prior to, and following surgical management, 3) to assess the impact of the surgical treatment on the occurrence of new complications of CP during follow-up.

We hypothesized that optimal surgical treatment can resolve existing complications and reduce the risk for new complications, with the exclusion of pancreatic insufficiency.

The primary outcomes were prevalence of complications of CP at baseline (prior to surgical treatment) and occurrence of new complications during follow-up.

### **METHODS**

After IRB approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients ( $\geq 18$  years of age) with CP according to the criteria of the American Pancreas Association subjected to surgical management between 1997 and 2021, were included.

The prevalence of the complications of CP was evaluated, according to the proposed classification, in a surgical cohort of 166 patients.

The development of the pathophysiological classification was based on a literature review on the clinical presentation, course and complications of CP, as well review of previous classification systems of CP.

### **RESULTS**

We distinguished between four groups of complications: 1) 'Pancreatic duct complications'; 2) 'Peripancreatic complications'; 3) 'Pancreatic hemorrhages', and 4) 'Pancreatic insufficiency' (exocrine and endocrine). Their baseline prevalence was 20.5%, 23.5%, 10.2%, 31.3% and 27.1%, respectively. Surgical treatment was highly effective in avoiding new complications in the first and third groups. In the group of 'Peripancreatic complications' the 15-year Kaplan-Meier prevalence of new complications was 12.1%. The prevalence of pancreatic exocrine and endocrine insufficiency increased during follow-up, being 66.4% and 47.1%, respectively, 15 years following surgery.

Pancreatoduodenal resection resulted optimal results in avoiding new 'Peripancreatic complications', but was associated with the highest rate of pancreatic exocrine insufficiency.

## CONCLUSION

The proposed complication classification improves the understanding of CP. It could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient's needs on the one hand, and on the pros and cons of the treatment under consideration, on the other. The presence of the complications of CP and the risk of development of new ones should be among main determinants of surgical choice.

**Key Words:** Chronic pancreatitis; Complications; Classification; Pathophysiology; Surgical treatment

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**Core Tip:** Chronic pancreatitis is frequently associated with complications for which there exists so far no classification. The present study proposes a pathophysiological classification of the complications of CP and reports their prevalence in a surgical cohort. We distinguished between four groups of complications: 'Pancreatic duct complications'; 'Peripancreatic complications'; 'Pancreatic hemorrhages', and 'Pancreatic insufficiency'. We believe the proposed classification improves the understanding of CP and could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient's needs on the one hand, and on the pros and cons of the treatment under consideration, on the other.

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## INTRODUCTION

Chronic pancreatitis (CP) is a benign chronic inflammatory damage of the pancreatic gland, with common morphologic features including the triad of fibrosis, loss of the acinar tissue and ductal changes with highly heterogeneous clinical presentations [i]. The disease may present either with a single, most frequent symptom of CP, i.e. chronic abdominal pain, or as a combination of symptoms encompassing pain, symptoms of loss of pancreatic function and symptoms of local complications of peripancreatic organs [ii,iii]. Behind the myriad of symptoms, there can be distinct morphological changes of the pancreatic gland and surrounding structures [iv]. During the course of the disease, most of the patients suffer from some, or even many, of the complications of CP. Although surgical treatment is usually indicated in the case of intractable abdominal pain, in up to one third of cases, surgery is indicated mainly due to local complications of CP [v]. Previous systematic reviews have noted that surgery is the best option for the treatment of chronic pancreatic pain, and is effective in the treatment of most complications of CP [vi,vii]. However, the impact of surgical treatment on occurrence of new complications of CP is not sufficiently evaluated. Furthermore, it would be important to assess which pathophysiological pathways of the complications of CP are most effectively treated surgically and which surgical methods are most effective. A prerequisite for this kind analysis is a pathophysiological classification of

the complications of CP. Although the surgical literature offers high-quality descriptions of all known complications of CP and lists of them [lviii], there are yet no pathophysiological classifications of complications available.

In the present study, we propose this classification comprising the major clinical problems seen in patients with CP. We report data about the prevalence of the complications in a surgically treated cohort of 166 patients as well as data about the occurrence of new complications of CP during the postoperative period.

## **MATERIALS AND METHODS**

### **Patients**

After IRB approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients ( $\geq 18$  years of age) with CP according to the criteria of the American Pancreas Association subjected to surgical management between 1997 and 2021, were included [li]. All patients gave their informed consent.

### **Aims and outcome**

Aims of the present study: 1) to propose a classification of complications of CP based on the predominant pathophysiological mechanism and clinical presentation, 2) to evaluate the prevalence of complications of CP in a surgical cohort, 3) to assess the impact of surgical treatment on the occurrence of new complications of CP during follow-up.

We hypothesized that optimal surgical treatment can resolve existing complications and reduce the risk for new complications, with the exclusion of pancreatic insufficiency.

The primary outcomes were prevalence of complications of CP at baseline (prior to surgical treatment) and occurrence of new complications during follow-up.

### **Baseline and follow-up data**

Data about the patients' demographics, indications for surgical treatment, and operative characteristics, as well as about local changes in the pancreatic gland were recorded

prospectively after surgical treatment; additional data were retrieved from surgical case files and CT scan descriptions. CT scan was routinely used in all cases.

CP associated data comprised duration and etiology of CP, data of pancreatic function, and local changes in the pancreatic gland. All data about complications of CP occurring before surgical treatment and during follow-up were collected. The patients were followed up from surgical treatment until the end of the study (August 31, 2021) or until death. No patients were lost during follow-up.

Additional health- related data were obtained from hospital case files, from the National Electronic Health Database (E-health), and from general practitioners' reports. E-health contains full information about in- and outpatient visits.

### Statistics

Collected data were entered in a computerized database (Microsoft Access 2016, Microsoft Inc., WA, USA). The main characteristics are presented as means with standard deviation (SD), or as medians with the interquartile range (IQR) as appropriate.

The prevalence of the complications of CP was assessed according to the proposed pathophysiological classification. Complication free survival was characterized using the Kaplan-Meier method. The impact of surgical treatment on the occurrence of new complications during the postoperative period was assessed using the Kaplan-Meier method. The log-rank test was deployed to assess differences between the Kaplan-Meier curves. The software package Statistica version 13.3 (TIBCO Software, CA, USA) was utilized for statistical calculations.

### **Classification of complications of CP**

All pathological changes of CP were divided into three groups: 1) cardinal histological features of CP ('microscopic changes'), 2) common anatomical changes seen in pancreatic imaging ('macroscopic changes'), and 3) complications of CP.

#### 1) Histological features of CP – 'microscopic changes'

The main microscopic features, or the so called 'triad of CP', were defined by Klöppel *et al* and Esposito *et al* as progressive irreversible loss of the acinar tissue (atrophy), its replacement by the fibrotic tissue and changes of the pancreatic duct (PD, atrophic epithelium, protein plugs, distortions) [lii,liii]. However, clinical decision making has to be done usually without histological confirmation of CP: given the potential for complications, pancreatic biopsy is not indicated for proving the diagnosis of CP. Thus, the diagnosis is usually based on typical history of CP and radiological finding. The only indication for pancreatic biopsy is in suspected malignancy or autoimmune pancreatitis [11].

### 2) Common anatomical changes in pancreatic imaging – 'macroscopic changes'

The second group of pathological changes was defined as macroscopic abnormalities of the pancreatic gland and ducts that are commonly seen in pancreatic imaging. Four distinguished findings of CP were noted: a) pancreatic calcifications [liv], b) pancreatic ductal changes (dilatations and strictures of PD; dilated PD was defined as PD with a diameter of  $\geq 3.5$  mm), c) pancreatic head enlargement ('chronic inflammatory mass' or 'pancreatic pseudotumor'; defined as antero-posterior diameter of the pancreatic head of  $> 35$  mm) [lv], and d) pancreatic atrophy (defined as a thickness of the pancreas of  $\leq 20$  mm in the left vertebral margin) [lvii]. Although the magnitude of these changes may significantly vary, none of them (if asymptomatic) is an indication for any type of treatment, as there is currently no known therapy to reverse or stop the progression of chronic inflammation in the pancreatic gland. Clinical management primarily consists in screening for and treating complications.

### 3) Complications of CP – 'changes with clinical relevance'

The third group of pathological changes of CP was titled 'Complications of CP' due to association with more or less severe clinical signs and symptoms. According to predominant pathophysiology and associated clinical presentation, we distinguished between four groups of complications: 1) 'Pancreatic duct complications'; 2) 'Peripancreatic complications'; 3) 'Pancreatic hemorrhages', and 4) 'Pancreatic



insufficiency' (Figure 1). Schematic illustration of the main complications of CP (Figure 2).

#### *Group I 'Pancreatic duct complications'*

*Main pathophysiology.* This particular group consists of complications caused by obstruction of PD by calcifications, protein plugs and/or periductal fibrosis, followed by intraductal hypertension and disruption of the main PD or its branches [lvii], [lviii]. PD disruption results in development of pancreatic pseudocysts (PPC) or leakage of pancreatic secretions, and hence to development of various types of pancreatic fistulas (PF) [lix]. The source of PF can be leakage directly from a rupture of PD or, more frequently, leakage from a ruptured PPC. In the case of pancreatic ascites, pancreatic secretions leak into the abdominal cavity. In the case of pancreaticopleural fistula, pancreatic secretion flows through the retroperitoneum *via* the area of least resistance into the pleural cavity, usually through the esophageal hiatus. The tract of fistula directly through the diaphragm has also been described [xl].

*Prevalence and main clinical problems.* PPC are common complications of CP, with reported prevalence as high as 10%-40% [xii], [xiii]. Most of the small PPC are typically asymptomatic and do not need any treatment. Clinical presentation tends to occur if some of the secondary complications of PPC, such as bleeding, rupture or infection, evolve [xiiii]. Additionally, large PPC can alone, through compression, or in conjunction with underlying CP, lead to the obstruction of the lumen of adjacent organs (biliary tract, gastric outlet and peripacreatic veins) [xiv]. All secondary complications of PPC can occur throughout the clinical course and, if present, usually do need active treatment [20]. Although the complications of PPC and related clinical presentation can be diverse and dependent on the localization and size of PPC, patients most frequently present with abdominal pain [xv].

Despite the fact that PF are relatively rare, the gross prevalence of various types of PF has been reported as high as 3.5% [xvi], [xvii]. Pancreaticoperitoneal fistulas with a prevalence of 2% (leading to pancreatic ascites) and pancreaticopleural fistulas with a

prevalence of 1% (leading to pancreatic pleural effusions) are more common [xviii], [xix]. Both of them need PD decompression, in most cases endoscopic stenting of PD is sufficient [19]. Pancreaticogastric or -intestinal fistulas, which may appear as symptomless findings in endoscopic evaluation, are rarer. Pancreaticocutaneous fistulas are usually the consequence of previous percutaneous drainages of PPC or pancreatic fluid collections, and may lead to significant loss of pancreatic juice and local skin problems. Pancreaticopericardial fistulas (leading to pancreatic pericardial effusion) and pancreaticoportals fistulas (leading usually to portal thrombosis with following consequences), are casuistic [xx], [xxi].

#### *Group II 'Peripancreatic complications'*

*Main pathophysiology.* The second group of complications comprises obstructive complications of organs adjacent to pancreas (biliary tract, duodenum and major peripancreatic veins). Although the particulars of the process of the development of these obstructions are slightly different, it is hypothesized that obstructive complications occur mainly as a consequence of recurrent episodes of acute pancreatitis, which may ultimately result in fibrosis and scarring within and around the pancreatic gland [xxii], [xxiii]. An additional contributing factor to obstruction can be PPC, especially in the region of the pancreatic head [xxiv]. Duodenal obstruction is usually reported to occur in the second or third part of the duodenum [xxv]. It has been suggested that an underlying mechanism in its evolution is duodenal ischemia caused by arterial narrowing and thrombosis in the region of inflammatory mass in the pancreatic head [xxvi]. An uncommon form of CP is groove pancreatitis or paraduodenal pancreatitis characterized by inflammation in the 'groove' between the duodenal wall and the pancreatic head [xxvii]. The pathophysiology of this particular condition remains unclear, despite of many suggested theories [xxviii]. Among the various pathological findings of groove pancreatitis, fibroinflammatory process in the pancreatoduodenal groove has been described as the only consistent finding in this disease [xxix]. Groove

pancreatitis is more common in middle-aged men and is strongly associated with history of alcohol consumption and tobacco smoking [xxx].

*Prevalence and main clinical problems.* Biliary strictures in patients with CP are relatively common with a prevalence of 3% to 23% with a mean of 6% [xxxii]. Some patients with biliary obstruction may be asymptomatic and have only modestly deranged liver function tests [xxxiii]. However, common bile duct obstruction may lead to jaundice, persistent cholestasis, acute cholangitis and secondary biliary cirrhosis [xxxiii]. Timely treatment of symptomatic strictures is required to prevent these secondary complications [40].

Duodenal obstruction is much rarer, with prevalence of 0.5% to 13% with a mean of 1.2% [39]. Patients usually present with symptoms of gastric outlet obstruction such as vomiting, fluid and electrolytes imbalance, and weight loss.

The prevalence of major peripancreatic vein thrombosis varies from 10.9% to 22.0% with a pooled prevalence of 11.6% [xxxiv,xxxv]. Splenic vein is mainly involved (up to 80.6%), followed by portal vein. Splenic vein thrombosis leads to left-side portal hypertension; these patients are at risk of development of gastric varices, splenomegaly and severe variceal bleeding, which is reported to occur in 4%-17% of all cases [xxxvi]. Several other splenic complications such as spontaneous splenic rupture, intrasplenic PPC, and splenic infarction have also been reported, but their prevalence remains well below 1% [xxxvii].

### *Group III 'Pancreatic hemorrhages'*

*Main pathophysiology.* The third group of complications comprises all pancreatic hemorrhages due to the erosion of major intra and peripancreatic vessels, mainly arteries. Local inflammation, possibly combined with local release of pancreatic enzymes, pressure necrosis from ductal calcifications, and PPC may result in either pseudoaneurysm (PA) formation or bleeding into pre-existing PPC, which transforms PPC into PA [xxxviii,xxxix].

*Prevalence and main clinical problems.* Although pancreatic bleeding in patients with CP is considered uncommon, the prevalence among in-patient cohorts is reported to be 4.6% to 7.7% [xli,xlii]. Splenic artery is the commonest involved vessel, followed by gastroduodenal and pancreaticoduodenal arteries [31,xliii]. As severity of blood loss and patients' hemodynamical status depend on the rupture of PA, it is important from the clinical point of view distinguish between non-ruptured ('contained PA') and ruptured PA. Patients with non-ruptured PA have the best prognosis, as blood loss is relatively small and the effect of self-tamponade can provide spontaneous hemostasis [xliiii]. Usually, these patients present with abdominal pain combined with symptoms of moderate blood loss, or sometimes even without the latter. Radiological imaging is essential to establish the diagnosis. Diagnosis of PA is usually made on the basis of abdominal contrast-enhanced computer-tomography (CECT) scan done for evaluation of the etiology of abdominal pain [42].

Almost two thirds of the patients with PA have ruptured PA that is associated with much more severe hemorrhage and often with shock [48]. The most common site of rupture is the gastrointestinal tract (GIT), presenting as an acute upper GIT bleeding with hematemesis and/or melena [xliiv]. Rarely, PA can rupture into the pancreatic duct and further into GIT through the papilla of Vater, leading to *hemosuccus pancreaticus* [xlv]. This condition is in most cases associated with diagnostic difficulties because of the concealed source of bleeding. Correct diagnosis is commonly made only after many episodes of bleedings and numerous endoscopic evaluations and CECT scans. High index of suspicion should arise if the triad of symptoms i.e. GIT bleeding, abdominal pain and hyperamylasemia, is present [47].

The two other possible sites of PA rupture are the abdominal cavity, presenting as massive intrabdominal hemorrhage, and the retroperitoneum, presenting as retroperitoneal hematoma [xlvi,xlvii].

Acute gastrointestinal tract hemorrhages in patients with CP, which are directly not associated with CP (e.g. variceal bleedings, peptic ulcers bleedings, Mallory-Weiss syndrome), are not included in this group of complications.



#### Group IV 'Pancreatic insufficiency'

*Main pathophysiology.* The fourth group represents complications due to extensive loss of the functioning pancreatic parenchyma leading, to pancreatic exocrine and endocrine insufficiency.

*Prevalence and main clinical problems.* As damage to the pancreatic tissue is continuous process throughout the course of the disease, the prevalence of pancreatic exocrine insufficiency (PEI) in patients with CP increases steadily with times, being from 20% in early CP to 94% in the late phase of the disease [[xlvi](#)], [[xlvii](#)]. Long duration of CP (>30years) is associated with higher than 80% prevalence of PEI [[lviii](#)]. Patients' main complaints are steatorrhea, weight loss, flatulence and abdominal discomfort. If untreated, the deficit of fat-soluble vitamins may lead to secondary complications (osteoporosis, fractures, immunodeficiency and infections) [[lix](#)].

Diabetes mellitus (DM) secondary to pancreatic diseases or pancreatic surgery is classified as pancreatogenic diabetes or type 3c diabetes (T3cDM) according to the current classification of DM [[lxi](#)]. The prevalence of DM in CP has been reported to be between 25% and 80% [[lxii](#)], [[lxiii](#)]. Like PEI, T3cDM shows clear correlation with duration of CP. In CP patients with associated T3cDM, blood glucose control may be complicated due to the loss of glucagon response to hypoglycemia, food malabsorption, and irregular eating patterns because of debilitating pain and/or continuous alcohol abuse [[lxiv](#)].

The proposed classification does not include infectious complications of CP. The authors of the classification believe that infectious complications are mainly caused by exacerbations of pancreatitis: 'acute' or 'acute on chronic' pancreatitis. Secondary complications are also excluded. Although it is well known that all complications of CP can lead to secondary complications (e.g. biliary obstruction, to cholangitis or biliary cirrhosis; duodenal obstruction, to fluid and electrolytes imbalance; portal hypertension, to bleeding from esophageal varices; PEI, to osteopathy; possible decompensation of *etc.*), they remain beyond the scope of this classification.

## **RESULTS**

### **Patients and surgical treatment**

All surgically treated CP patients were operated at a single referral hospital between 1997 and 2021 were prospectively enrolled. A total of 166 patients were subjected to surgical management due to chronic pain or local complications of CP. The average rate of surgical treatment of CP was 18.1% from all patients admitted due to CP. The mean age of the patients was 49.8±9.9 years, there were 140 male (84.3%) and 26 female (Table 1). In 148 patients (89.2%) CP was alcohol-induced, in the rest of the cases the etiology was idiopathic or rare causes. The median duration of symptomatic CP before surgical treatment was 18 mo.

Similar to previous studies [11], the most common indication for surgical treatment was chronic abdominal pain, being the predominant indication in 112 cases (67.5%). Local complications of CP were the predominant indication for surgical treatment in 54 cases (32.5%). However, almost half of the patients (81 patients, 48.8%) had had at least one local complication of CP before surgical treatment. The clinical relevance of these was highly varying (from asymptomatic PPC to ruptured PA). Ten patients (6.0%) had had more than one local complication.

Besides local anatomical complications, 52 patients (31.3%) had PEI and 45 patients (27.1%) had T3cDM prior to surgical treatment. Surgical treatment was pancreatic resection in 60 cases (36.2%), pancreatic drainage operation in 93 cases (56.0%), and extrapancreatic palliative procedure in 13 cases (7.8%, Table 2). There was no perioperative mortality. Cumulative Kaplan-Meier 10-year survival and median survival were 70.4% and 13.9 years, respectively. Median follow-up was 7.2 years. During follow-up 12 patients required secondary surgery, mostly due to emerged new local complications of CP (predominantly biliary stenosis).

### **Prevalence of complications of CP prior to, and following surgical treatment**

The impact of surgical treatment on the occurrence of the de novo complications of CP during postoperative years was assessed according to the above proposed pathophysiological classification of complications of CP (Figure 1).

The prevalence of 'Pancreatic duct complications' was at baseline (before surgical treatment of CP) 20.5% (Figure 3). 10.8% of the patients had PPC, and 9.6% had various types of PF (Table 3). Endoscopic PD stenting precedes to surgical therapy in two out of 16 patients (12.5%) with PF. Further surgical treatment was undertaken due to continuous PD leakage.

Surgical treatment demonstrated high effectiveness in decompressing PD, with very low risk of new 'Pancreatic duct complications' during follow-up (only one new PPC developed).

'Peripancreatic complications' showed a baseline prevalence of 23.5% (39 patients); three patients had concurrent biliary tract and duodenal or venous obstruction. The most common complication was biliary tract obstruction with 29 cases (17.5%), eight patients had duodenal obstruction (4.8%) and venous occlusion was seen in five patients (3.0%). Endoscopic common bile stenting precedes to surgical therapy in 18 out of 29 cases (62.1%) of patients with common bile duct stenosis. Further surgical treatment was indicated because of unsuccessful endoscopic treatment (defined as inconsistent effect of endoscopic stenting). During follow-up 13 new complications were documented in 11 patients, which resulted in a 15-year Kaplan-Meier prevalence of 12.1% of new 'Peripancreatic complications'. The total 15-year prevalence of 'Peripancreatic complications' was 35.6%. The most common among them was biliary tract obstruction (eight patients), followed by venous thrombosis (four patients) and duodenal obstruction in one case. Five patients with biliary stenosis were managed *via* endoscopic stenting, remaining three patients needed secondary surgery.

As the occurrence of new complications requiring retreatment, is a major drawback, we re-evaluated the distribution of these complications by the surgical subgroups depending on the type of surgical procedure applied. Analysis was performed for three subgroups: 1) pancreatic drainage operations, 2) pancreatic resections (excluding

Whipple's procedure), and 3) Whipple's pancreatoduodenal resection as the only procedure incorporating new biliary and gastric bypasses (Table 4).

The analysis revealed differences in the occurrence of new 'Peripancreatic complications'. There appeared no new complications in the group of Whipple's procedure (11 patients); among the other types of pancreatic resections (49 patients), there occurred five complications and in the group of pancreatic drainage operations (93 patients), there occurred eight complications. The 15-year Kaplan-Meier prevalence of 'Peripancreatic complications' following surgical treatment of CP was 0%, 11.4% and 16.5%, respectively (Figure 4A).

The baseline prevalence of 'Pancreatic hemorrhages' was 10.2% (17 patients). There were 10 cases (58.8%) of ruptured pancreatic PA and 7 cases of contained PA. Ruptured PA presented as an acute life-threatening intraabdominal hemorrhage in two cases and as an acute recurrent gastrointestinal hemorrhage in eight cases: fistulation into GIT occurred in six cases and into PD, in two cases (*hemosuccus pancreaticus*). All patients with ruptured PA were treated *via* pancreatic resection. All but one patient with contained PA underwent intra-aneurysmatic hemostasis and a pancreatic drainage procedure. In one case, the affected part of pancreas was resected. Surgical treatment of pancreatic hemorrhages was highly effective: there were no recurring hemorrhages among patients with PA, nor were there new hemorrhages among the entire surgically treated cohort, regardless of the indication for surgical treatment of CP.

'Pancreatic insufficiency' was evaluated for two subgroups: PEI and T3cDM. Prior to surgical treatment 73 patients (44.0%) had one of these or both. The prevalence of PEI was 31.3% (52 patients) and the prevalence of T3cDM was 27.1% (45 patients). During follow-up, a steady and almost synchronous increase in both complications was evident, resulting in a 15-year Kaplan-Meier prevalence of 66.4% and 47.1%, respectively. The 15-year Kaplan-Meier prevalence of either exo- or endocrine insufficiency was 74.5%.

Re-evaluation of the development of pancreatic insufficiency was performed for the surgical subgroups depending on the type of surgical procedure. The highest rate of



new cases of PEI was seen in patients undergoing Whipple's pancreatoduodenal resection (Figure 4B). According to Cox regression analysis, HR for development of new cases of PEI was 9.3 (95%CI 3.6-24.2) in the group of Whipple's procedure and 1.9 (95%CI 0.8-4.2) in the group of other resections, compared to pancreatic drainage operations. Development of endocrine insufficiency did not show any significant dependency on the type of surgery. However, the rate of T3cDM was slightly higher for patients undergoing distal pancreatectomy (Figure 4C).

## **DISCUSSION**

The present study proposes a new pathophysiological classification of complications of CP, reports their prevalence in a surgically treated cohort, and assesses the impact of surgical treatment on occurrence of new complications during the further course of the disease.

As there is currently no treatment to reverse or delay disease progression in CP, clinical management consists primarily in screening for and treating of complications [3]. The most effective treatment of complications is pathophysiological treatment. The proposed classification allows to easily determine the predominant pathophysiologic mechanism. This could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient's needs on the one hand, and on the pros and cons of the treatment under consideration, on the other. Moreover, this classification could be used as an instrument for quality improvement in the treatment of CP. We strongly believe that the potential of any treatment to avoid further complications of CP would serve, besides known indicators of quality of treatment (pain relief, quality of life *etc.*), an additional relevant indicator.

The goal of the surgical treatment of CP is usually to decompress PD or to resect the nidus of chronic inflammation, and to eliminate local complications of CP. In our study, the clinical impact of surgical treatment on different complications of CP was highly variable and clearly dependent on the underlying predominant pathophysiological mechanism.

The first group of complications ('Pancreatic duct complications') were effectively treated by pancreatic drainage operations, as well as by pancreaticojejunostomies created during pancreatic resection. The achieved effect was long-lasting over time: only one PPC developed during follow-up *vs* 34 preoperative complications. Unfortunately, we failed to find previous data about the recurrence rate of PPC or PF after pancreatic duct drainage for comparison. Less radical treatment modalities, *e.g.* anastomoses with PPC and endoscopic drainage, have shown relatively high rate of recurrence. According to Ye *et al*, the recurrence rate of PPC was 11.2% after pseudocystojejunostomy and 7.5% after pseudocystogastrostomy, with an average follow-up of 42.7 mo [ii]. However, these authors did not provide data about the etiology of the PPC (acute or chronic pancreatitis). Endoscopic treatment seems to be associated with higher recurrence rate: Rückert *et al* reported a recurrence rate of 23.3% after endoscopic drainage during 42.2 mo of follow-up and underlined the high recurrence risk of CP-associated PPC [iii]. Farias *et al* compared endoscopic and surgical drainage (mainly *via* pseudocystogastrostomy) of PPC in a meta-analysis and found no significant difference in their recurrence rates [iiii]. Our data support surgical decompression of PD in the case of CP-provoked PPC and PF. High effectiveness of surgical decompression is attributable to the most radical relief of main pathology (PD obstruction and intraductal hypertension).

The impact of surgical treatment on 'Peripancreatic complications' revealed significant dependency on the surgical method used. During follow-up, there were no new complications in the group of Whipple's procedure, which can be explained by the nature of this procedure (creation of new bilioenteric and gastroenteric anastomoses). After the other surgical procedures (pancreatic drainage operations and non-Whipple's pancreatic resections: mostly the Beger or the Berne modifications of pancreatic head resection, and pancreatic tail resection) there developed new 'Peripancreatic complications', which necessitated readmissions and reoperations. In most cases there were biliary strictures (eight patients) and venous thrombosis of SV or PV (four patients); one patient developed duodenal obstruction. The causes of new

'Peripancreatic complications' in the postoperative period can be variable. It seems that among the predominant causes are further development of the fibrotic tissue and the process of scarring within and around the pancreas. This theory is indirectly supported by the results of endoscopic stenting of CP-associated biliary strictures. Several studies have found that long-lasting stenting (10-12 mo) is more effective than short-term therapy (3-6 mo), indicating persistent fibrosis and scarring [liv],lv]. The present study showed that biliary strictures can occur even many years after surgical treatment of CP. In these cases, exacerbations of CP, whether clinical or subclinical, might be responsible, as they are associated with additional extrinsic compression due to edema or development of PPC in the region of the pancreatic head [lvil]. The ability to avoid new 'Peripancreatic complications' is one of the obvious advantages of Whipple's procedure in the treatment of CP, as reported earlier by Diener *et al* in the ChroPac trial and by Müller *et al* [lvii],lviii]. Whether this advantage of the Whipple's procedure is sufficient to prefer this operation to other surgical options remains a subject of discussion. In fact, Whipple's operation has also disadvantages, such as longer operating time and, according to most studies, higher perioperative morbidity and mortality, and higher rate of postoperative PEI.

The third group of complications ('Pancreatic hemorrhages') are associated with the poorest prognosis. Even with prompt diagnosis and immediate therapy, the mortality rate reported in earlier studies is 15% to 50% [lix]. In the past two decades, owing to the enormous improvement in radiological techniques and instrumentation, angiographic treatment as the first-line therapy has been widely employed to stop bleeding from visceral PA in hemodynamically stable patients. In a recent meta-analysis Sagar *et al* reported a technical success rate of 88%, a clinical success rate of 86%, a rebleeding rate of 16.3%, and a morality rate of 8% for endovascular therapy [lx]. Surgical treatment is reserved for patients for whom vascular interventional therapy has failed or is not accessible, as well as for those with unstable vital signs; during the study period we had 17 such patients. Our surgical approach was relatively radical: in cases of recurrent GIT bleeding from the fistulation of PA and ineffective endovascular therapy, or in cases of

ongoing bleeding in an unstable patient, surgical treatment always consisted in resection of the affected area of the pancreas.

In most such cases pancreatic tail resection was performed (eight cases), as hemorrhages emerged from the splenic artery, but in two cases pancreatic head resection was necessary. In cases of contained PA, the treatment of choice was intra-aneurysmatic hemostasis followed by pancreatic drainage operation. This approach resulted in a highly effective treatment result: there were no recurrent pancreatic hemorrhages in our cohort during follow-up (median 7.2 years). As there occurred no re-bleedings after surgery in our cohort and we managed to achieve zero perioperative mortality, we are convinced that surgical therapy remains an important highly effective treatment modality for patients with pancreatic hemorrhage. In unstable patients, surgery should be the first-line therapy; in hemodynamically stable patients, surgery should be indicated in cases of unsuccessful endovascular therapy, as the next step of treatment.

Besides effective treatment of pancreatic hemorrhages, surgical therapy demonstrated also the potential to avoid pancreatic hemorrhages: there were no episodes of pancreatic hemorrhage during follow-up in the entire surgically treated cohort. One explanation of this might be the beneficial effect of PD decompression: previous studies have revealed PPC as the most important risk factor for development of PA and pancreatic hemorrhage [42]. Regarding occurrence of chronic PPC, which usually precedes PD obstruction and intraductal hypertension [xii], surgical PD decompression has a preventive effect on development of PPC, as well as on its transformation into PA.

The fourth group of complications ('Pancreatic insufficiency') showed continuous steady deterioration of pancreatic function. A similar result, i.e. impairment of pancreatic function over time, has been repeatedly demonstrated earlier, most recently by Kempeneers *et al*, on the basis of data from the Dutch Chronic Pancreatitis Registry [xiii]. Comparison of the surgical options revealed higher rate of PEI after Whipple's pancreatoduodenal resection (compared to the other types of surgery) and slightly higher rate of T3cDM in the group of pancreatic tail resection.

Several studies have found that early surgery could be beneficial in terms of slowing impairment of pancreatic function [xiii],xiv]. The data of the present study are insufficient to provide any additional information regarding this effect, as our patients were clearly not 'early cases' of CP.

An important contribution to the understanding of complications of CP was made by a study of Olesen's *et al* [xv]. The cluster analysis used by these authors distinguished between inflammatory, fibrotic and functional complications and they assessed association between clusters and etiological risks. The present pathophysiological classification is aimed at facilitating clinical decision-making: *e.g.* should one eliminate pancreatic duct problems *vs* peripancreatic problems *vs* pancreatic hemorrhage *vs* treat pancreatic insufficiency?

Based on pathophysiological grouping, our analysis shows that there exist no ideal surgical options suitable for all cases of CP. Nevertheless, despite the lack of evidence supporting the universal superiority of any available surgical procedure, it is obvious that each of them has its own specific advantages. Thus, the choice of the surgical procedure should proceed from at least four aspects: predominant indication for surgery; anatomical changes of the pancreatic gland; presence and entity of local complications of CP; and procedure-specific risks of surgery (immediate and long-term). This is consistent with the conclusion by Frola *et al* according to which a tailored approach to CP patients is mandatory [xvi].

### **Limitations**

Our center is a tertiary care referral center and hence the prevalence of complications of CP may be an overestimation.

### **CONCLUSION**

The proposed complication classification improves the understanding of CP. It could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient's needs on the one hand, and on the pros and cons of the treatment under consideration, on the other.



Existing complications of CP and the risk for development of new complications should be among the main determinants of surgical choice.

## **ARTICLE HIGHLIGHTS**

### ***Research perspectives***

It would be interesting to compare the effectiveness of the surgical and endoscopic treatment of complications of chronic pancreatitis using our proposed classification.

### ***Research conclusions***

The proposed complication classification improves the understanding of CP. It could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient's needs on the one hand, and on the pros and cons of the treatment under consideration, on the other. The presence of the complications of CP and the risk of development of new ones should be among main determinants of surgical choice.

### ***Research results***

We distinguished between four groups of complications: 1) 'Pancreatic duct complications'; 2) 'Peripancreatic complications'; 3) 'Pancreatic hemorrhages', and 4) 'Pancreatic insufficiency' (exocrine and endocrine). Their baseline prevalence was 20.5%, 23.5%, 10.2%, 31.3% and 27.1%, respectively. Surgical treatment was highly effective in avoiding new complications in the first and third groups. In the group of 'Peripancreatic complications' the 15-year Kaplan-Meier prevalence of new complications was 12.1%. The prevalence of pancreatic exocrine and endocrine insufficiency increased during follow-up, being 66.4% and 47.1%, respectively, 15 years following surgery.

### ***Research methods***

After IRB approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients ( $\geq 18$  years of age) with CP according to the criteria of the American Pancreas Association subjected to surgical management between 1997 and 2021, were included. The prevalence of the complications of CP was evaluated, according to the proposed classification, in a surgical cohort of 166 patients.

### ***Research objectives***

To describe the full diversity of severe complications of CP seen in our cohort during 20 years of study using proposed classification of complications of chronic pancreatitis. To assess the impact of surgical treatment on the development of new complications during follow-up.

### ***Research motivation***

The motivation of present study was: 1) to propose a pathophysiological classification of the complications of CP, 2) evaluation their prevalence in a surgical cohort prior to, and following surgical management, 3) to assess the impact of the surgical treatment on the occurrence of new complications of CP during follow-up.

### ***Research background***

Chronic pancreatitis (CP) is a long-lasting disease frequently associated with complications for which there exists so far no comprehensive pathophysiological classification.

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