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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Observational Study

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

Marko Murruste, Ülle Kirsimägi, Karri Kase, Tatjana Veršinina, Peep Talving, Urmas Lepner

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Abstract

BACKGROUND

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

AIM

The aims of this study were to: Propose a pathophysiological classification of the complications of CP; evaluate their prevalence in a surgical cohort prior to, and following surgical management; and 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 of 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 institutional review board approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients (≥ 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 CP complications evaluated, according to the proposed classification, in a surgical cohort of 166 patients. Development of the pathophysiological classification was based on a literature review on the clinical presentation, course, and complications of CP, as well a review of previous classification systems of CP.

RESULTS

We distinguished four groups of complications: Pancreatic duct complications,

peripancreatic complications, pancreatic hemorrhages, and 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, at 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 complications of CP and the risk of development of new ones should be among the 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 no classification. This study proposes a pathophysiological classification of the complications of chronic pancreatitis (CP) and reports their prevalence in a surgical cohort. We distinguished 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[1]. 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[2,3]. Behind the myriad of symptoms, there can be distinct morphological changes of the pancreatic gland and surrounding structures[4]. 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[5]. 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[6,7]. 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[8], there are yet no pathophysiological classifications of complications available.

In this study, we proposed this classification comprising the major clinical problems seen in patients with CP. We reported 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 institutional review board approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients (≥ 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[9]. All patients gave their informed consent.

Aims and outcome

The aims of this study were to: Propose a classification of complications of CP based on the predominant pathophysiological mechanism and clinical presentation, evaluate the prevalence of complications of CP in a surgical cohort; and 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 computed tomography (CT) scan descriptions. CT scan was routinely used in all cases. CP-associated data comprised duration and etiology of CP, data on 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., Redmond, WA, United States). The main characteristics are presented as the mean \pm SD or the median with interquartile range 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, Palo Alto, CA, United States) was utilized for statistical calculations.

Classification of complications of CP

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

Histological features of CP-microscopic changes: The main microscopic features, or so-called 'triad of CP', were defined by Klöppel[10] and Kleeff *et al*[11] as progressive irreversible loss of acinar tissue (atrophy), its replacement by fibrotic tissue, and changes of the pancreatic duct (PD, atrophic epithelium, protein plugs, distortions)[10,11]. However, clinical decision making usually has to be done without histological confirmation of CP. Given the potential for complications, pancreatic biopsy is not indicated for proving the diagnosis of CP. Thus, diagnosis is usually based on a typical history of CP and radiological finding. The only indication for pancreatic biopsy is in suspected malignancy or autoimmune pancreatitis[11].

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: Pancreatic calcifications[12], pancreatic ductal changes (dilatations and strictures of PD; dilated PD was defined as PD with a diameter ≥ 3.5 mm); pancreatic head enlargement (chronic inflammatory mass or pancreatic pseudotumor, defined as antero-posterior diameter of the pancreatic head > 35 mm)[13], and pancreatic atrophy (defined as a thickness of the pancreas ≤ 20 mm in the left vertebral margin)[14]. 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 of screening for and treating complications.

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 four groups of complications: PD complications, peripancreatic complications, pancreatic hemorrhages, and pancreatic insufficiency (Figure 1). Figure 2 shows a schematic illustration of the main complications of CP.

Group I: PD 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[15,16]. PD disruption results in the development of pancreatic pseudocysts (PPC) or leakage of pancreatic secretions, and hence to the development of various types of pancreatic fistulas (PF)[17]. The source of PF can be leakage directly from a rupture of the 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[18].

Prevalence and main clinical problems: PPC are common complications of CP, with a reported prevalence as high as 10%-40%[19,20]. Most of the small PPC are 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[21]. Additionally, large PPC can alone, through compression or in conjunction with underlying CP, lead to obstruction of the lumen of adjacent organs (biliary tract, gastric outlet, and peripacreatic veins)[22]. 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[23].

Despite the fact that PF are relatively rare, the gross prevalence of various types of PF is reportedly as high as 3.5%[24,25]. 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[26,27]. 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[28,29].

Group II: Peripancreatic complications

Main pathophysiology: The second group of complications comprises obstructive complications of organs adjacent to the 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[30,31]. An additional contributing factor to obstruction can be PPC, especially in the region of the pancreatic head[32]. Duodenal obstruction usually occurs in the second or third part of the duodenum[33]. 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[34]. 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[35]. The pathophysiology of this particular condition remains unclear, despite many suggested theories[36]. 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[37]. Groove pancreatitis is more common in middle-aged men and is strongly associated with history of alcohol consumption and tobacco smoking[38].

Prevalence and main clinical problems: Biliary strictures in patients with CP are relatively common with a prevalence of 3% to 23% and a mean of 6%[39]. Some patients with biliary obstruction may be asymptomatic and have only modestly deranged liver function tests[40]. However, common bile duct obstruction may lead to jaundice, persistent cholestasis, acute cholangitis, and secondary biliary cirrhosis[41]. Timely treatment of symptomatic strictures is required to prevent these secondary complications[40].

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

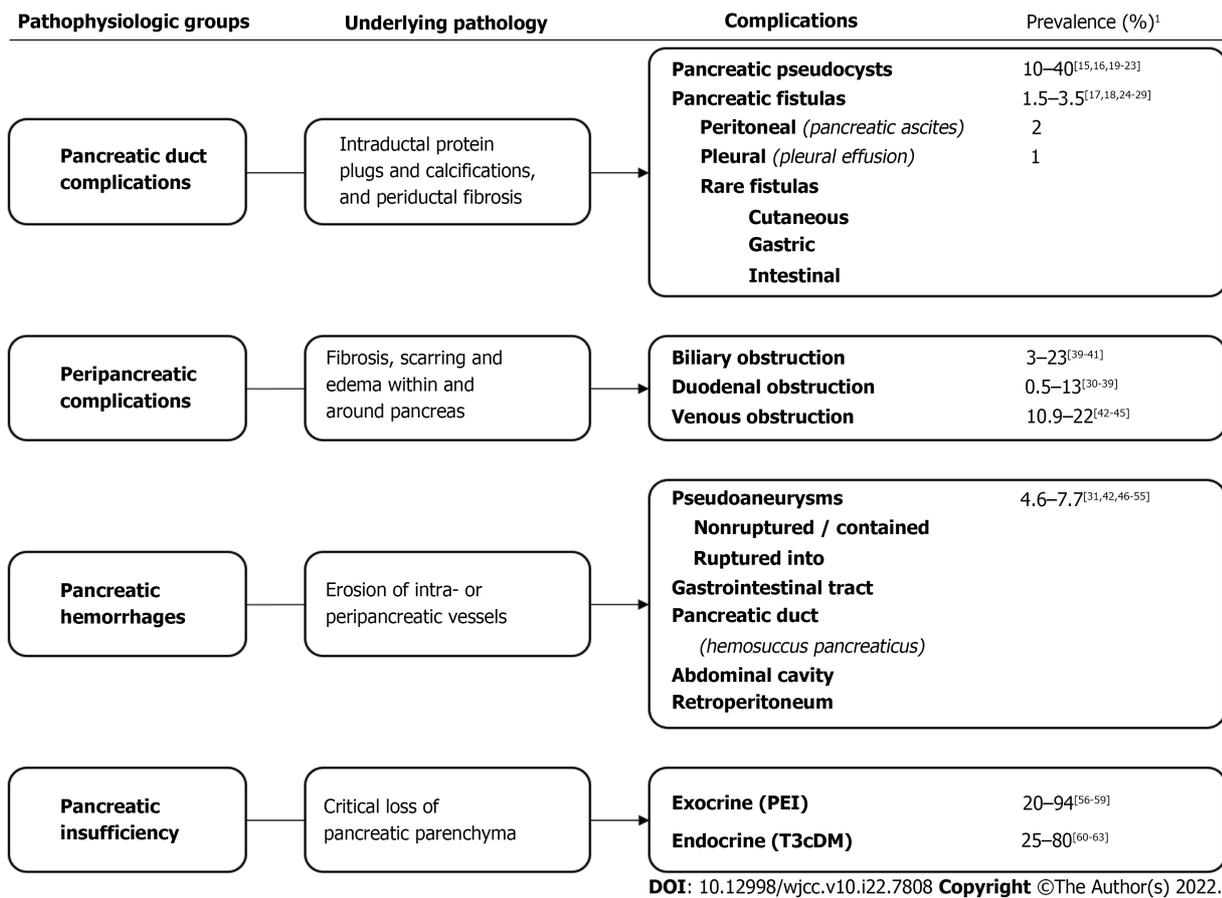


Figure 1 Pathophysiological classification of complications of chronic pancreatitis. ¹References to the rates of prevalence. PEI: Pancreatic exocrine insufficiency; T3cDM: Type 3c diabetes mellitus.

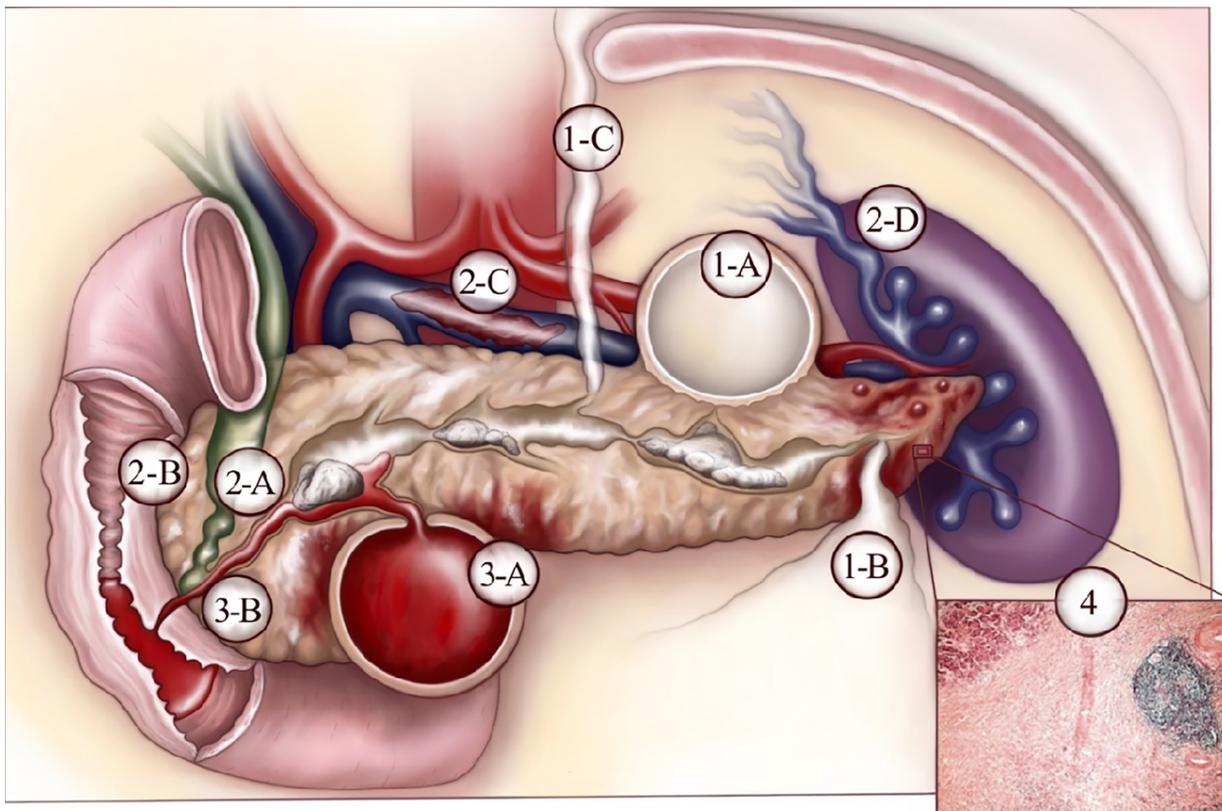
The prevalence of major peripancreatic vein thrombosis varies from 10.9% to 22.0% with a pooled prevalence of 11.6%^[42,43]. Splenic vein is mainly involved (up to 80.6%), followed by portal vein. Splenic vein thrombosis leads to left-side portal hypertension; these patients are at risk of development of gastric varices, splenomegaly, and severe variceal bleeding, which reportedly occurs in 4%-17% of all cases^[44]. Several other splenic complications such as spontaneous splenic rupture, intrasplenic PPC, and splenic infraction have also been reported, but their prevalence remains well below 1%^[45].

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^[46,47].

Prevalence and main clinical problems: Although pancreatic bleeding in patients with CP is considered uncommon, the prevalence among in-patient cohorts is reportedly 4.6% to 7.7%^[48,49]. Splenic artery is the most commonly involved vessel, followed by gastroduodenal and pancreaticoduodenal arteries^[31,50]. 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^[51]. 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 CT (CECT) scan done for evaluation of the etiology of abdominal pain^[42].

Almost two-thirds of 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 acute upper GIT bleeding with hematemesis and/or melena^[52]. Rarely, PA can rupture into the PD and further into GIT through the papilla of Vater, leading to *hemosuccus pancreaticus* ^[53]. In most cases, this condition is associated with diagnostic difficulties because of the concealed source of bleeding. Correct diagnosis is commonly made only after many episodes of bleedings and



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Figure 2 Main complications of chronic pancreatitis. (1) Pancreatic duct complications: 1-A: Pancreatic pseudocyst; 1-B: Pancreatic ascites; 1-C: Pancreatic pleural effusion; (2) Peripancreatic complications: 2-A: Common bile duct stenosis; 2-B: Duodenal stenosis; 2-C: Venous thrombosis (splenic vein); 2-D: Left-side portal hypertension due to splenic vein thrombosis; (3) Pancreatic hemorrhages: 3-A: Peripancreatic pseudoaneurysm; 3-B: Ruptured pseudoaneurysm (into pancreatic duct–*hemosuccus pancreaticus*); and (4) Pancreatic exocrine and endocrine insufficiency due to extensive loss of functional pancreatic parenchyma (acinar atrophy, fibrosis, inflammatory infiltrates).

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[54,55]. Acute GIT hemorrhages in patients with CP, which are not directly associated with CP (*e.g.*, variceal bleeding, peptic ulcer bleeding, 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 a 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[56,57]. Long duration of CP (> 30 years) is associated with > 80% prevalence of PEI[58]. 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)[59].

Diabetes mellitus (DM) secondary to pancreatic diseases or pancreatic surgery is classified as pancreatogenic diabetes or type 3c DM (T3cDM) according to the current classification of DM[60]. The prevalence of DM in CP is between 25% and 80%[61,62]. Similar to PEI, T3cDM shows a 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[63].

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; diabetes to possible decompensation of *etc*), they

remain beyond the scope of this classification.

RESULTS

Patients and surgical treatment

All surgically treated CP patients, operated on 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 males (84.3%) and 26 females (Table 1). In 148 patients (89.2%), CP was alcohol-induced; in the remaining cases, the etiology was idiopathic or rare causes. The median duration of symptomatic CP before surgical treatment was 18 mo.

Similar to a previous study[64], 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 variable (from asymptomatic PPC to ruptured PA). Ten patients (6.0%) 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 PD 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 'PD complications' during follow-up (only one new PPC developed).

Peripancreatic complications showed a baseline prevalence of 23.5% (39 patients); 3 patients had concurrent biliary tract and duodenal or venous obstruction. The most common complication was biliary tract obstruction with 29 cases (17.5%), 8 patients had duodenal obstruction (4.8%) and venous occlusion was seen in 5 patients (3.0%). Endoscopic common bile stenting precedes to surgical therapy in 18 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 (8 patients), followed by venous thrombosis (4 patients) and duodenal obstruction in 1 case. Five patients with biliary stenosis were managed *via* endoscopic stenting, and the remaining 3 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: Pancreatic drainage operations, pancreatic resections (excluding Whipple's procedure), and 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. No new complications appeared in the group of Whipple's procedure (11 patients); among the other types of pancreatic resections (49 patients), five complications occurred and in the group of pancreatic drainage operations (93 patients), there were 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 2 cases and as an acute recurrent gastrointestinal hemorrhage in 8 cases: Fistulation into GIT occurred in 6 cases and into PD, in 2 cases (*hemorrhagic pancreatitis*). All patients with ruptured PA were treated *via* pancreatic resection. All but 1 patient with contained PA underwent intra-aneurysmal hemostasis and a pancreatic drainage procedure. In 1 case, the affected part of pancreas was resected. Surgical treatment of pancreatic hemorrhages was highly

Table 1 Characteristics of the surgically treated patients with chronic pancreatitis

Characteristic	Patients, <i>n</i> = 166
Age in yr	49.8 ± 9.9
Duration of CP before surgery, median (IQR)	1.5 (0.5–3.0)
Male sex, <i>n</i> (%)	140 (84.3)
Etiology of CP, <i>n</i> (%)	
Alcoholic	148 (89.2)
Other	18 (10.8)
Predominant indication for surgery, <i>n</i> (%)	
Chronic pain	112 (67.5)
Complications of CP ¹	54 (32.5)
Follow-up (yr), median (IQR)	7.2 (3.8–10.8)
Long-term survival (Kaplan-Meier), (95%CI)	
1 yr	100
5 yr	88.2 (83.0–93.5)
10 yr	70.4 (61.7–79.1)
15 yr	41.2 (27.4–55.1)
Median survival in yr	13.9

¹In many cases, patients had also more or less intense abdominal pain.

Data are presented as mean ± SD, unless otherwise specified. CI: Confidence interval; CP: Chronic pancreatitis; IQR: Interquartile range; SD: Standard deviation.

Table 2 Surgical treatment of 166 patients with chronic pancreatitis

Type of surgery	<i>n</i> (%)
Pancreatic resection	60 (36.2)
Pancreatoduodenal resection (Whipple procedure)	11
DPPHR (Beger or Berne or Frey procedure)	34
Pancreatic distal resection	15
Pancreatic drainage operation	93 (56.0)
Pancreaticojejunostomy (Partington-Rochelle)	93
Palliative procedures	13 (7.8)
Biliodigestive anastomosis	11
Gastrointestinal anastomosis	2

DPPHR: Duodenum-preserving pancreatic head resection.

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 exocrine 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

Table 3 Baseline and 15-yr Kaplan-Meier prevalence of complications of chronic pancreatitis in a surgically treated cohort of 166 patients

Complications	Baseline, n (%)	15-yr, Kaplan-Meier, %
Pancreatic duct complications	34	20.5
<i>Pancreatic pseudocysts</i>	18	10.8
<i>Pancreatic fistulas</i>	16	9.6
<i>Pancreaticoperitoneal (pancreatic ascites)</i>	4	2.4
<i>Pancreaticopleural (pancreatic pleural effusion)</i>	5	3.0
<i>Other (mostly pancreaticocutaneous)</i>	6	4.2
Peripancreatic complications	39 ¹	23.5
<i>Bile duct obstruction</i>	29	17.5
<i>Duodenal obstruction</i>	8	4.8
<i>Venous thrombosis (splenic or portal vein)</i>	5	3.0
Pancreatic hemorrhages	17	10.2
<i>Contained pseudoaneurysms</i>	7	4.2
<i>Ruptured pseudoaneurysms into</i>	10	6.0
<i>Abdominal cavity</i>	2	1.2
<i>Gastrointestinal tract</i>	6	3.6
<i>Pancreatic duct</i>	2	1.2
Pancreatic exocrine insufficiency-PEI	52	31.3
Pancreatic endocrine insufficiency-T3cDM	45	27.1

¹Three patients had two concurrent complications at baseline.

PEI: Pancreatic exocrine insufficiency; T3cDM: Type 3c diabetes mellitus.

in patients undergoing Whipple's pancreatoduodenal resection (Figure 4B). According to Cox regression analysis, hazard ratio for the development of new cases of PEI was 9.3 [95% confidence interval (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

This study proposed a new pathophysiological classification of complications of CP, reported their prevalence in a surgically treated cohort, and assessed 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 of screening for and treating of complications[3]. The most effective treatment of complications is pathophysiological treatment. The proposed classification allows the easy determination of the predominant pathophysiological 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 (*e.g.*, pain relief, quality of life), as 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 (PD 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 1 PPC developed during follow-up *vs* 34 preoperative complications. Unfortunately, we failed to find previous data about

Table 4 Distribution of complications of chronic pancreatitis according to the used type of surgical procedure prior to surgical treatment, and appearance of new complications during follow-up, in 166 surgically treated patients

Classification	Type of surgical procedure, n (%)					Total, n = 166
	PD resection, n = 11	DPPHR, n = 34	Distal resection, n = 15	Drainage procedure, n = 93	Palliative procedures, n = 13	
Complications, n (%)						
Pancreatic duct complications	1 (9.1)	1 (2.9)	4 (26.7)	29 (31.2)	-	35 (21.1)
Preoperative cases	1	1	4	28	-	34
New cases, FU	-	-	-	1	-	1
Peripancreatic complications	6 (54.5)	9 (26.5)	-	25 (26.9)	13 (100) ¹	55 (33.1)
Preoperative cases	6	4	-	17	13	42
New cases, FU	-	5	-	8	-	13
Pancreatic hemorrhages	1 (9.1)	1 (2.9)	9 (60.0)	6 (6.5)	-	17 (10.2)
Preoperative cases	1	1	9	6	-	17
New cases, FU	-	-	-	-	-	-
PEI	8 (72.7)	15 (44.1)	5 (33.3)	46 (49.5)	9 (69.2)	83 (50.0)
Preoperative cases	1	6	3	33	9	52
New cases, FU	7	9	2	13	-	31
T3cDM	3 (27.3)	12 (35.3)	8 (53.3)	39 (41.9)	11 (84.6)	73 (44.0)
Preoperative cases	1	7	2	25	10	45
New cases, FU	2	5	6	14	1	28

¹Three patients had simultaneously two peripancreatic complications. DPPHR: Duodenum-preserving pancreatic head resection; FU: Follow up; PD: Pancreatoduodenal resection; P: Pancreatic; PEI: Pancreatic exocrine insufficiency; T3cDM: Type 3c diabetes mellitus.

the recurrence rate of PPC or PF after PD 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*[65], the recurrence rate of PPC was 11.2% after pseudocystojejunostomy and 7.5% after pseudocystogastrostomy, with an average follow-up of 42.7 mo[65]. However, the authors did not provide data about the etiology of the PPC (acute or chronic pancreatitis). Endoscopic treatment seems to be associated with a higher recurrence rate: Rückert *et al*[66] 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[66]. Farias *et al*[67] compared endoscopic and surgical drainage (mainly *via* pseudocystogastrostomy) of PPC in a meta-analysis and found no significant difference in their recurrence rates [67]. 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 Whipple's procedure group, 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 Beger or Berne modifications of pancreatic head resection, and pancreatic tail resection, new peripancreatic complications developed, which necessitated readmissions and reoperations. In most cases, there were biliary strictures (8 patients) and venous thrombosis of SV or PV (4 patients); 1 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[68,69]. 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

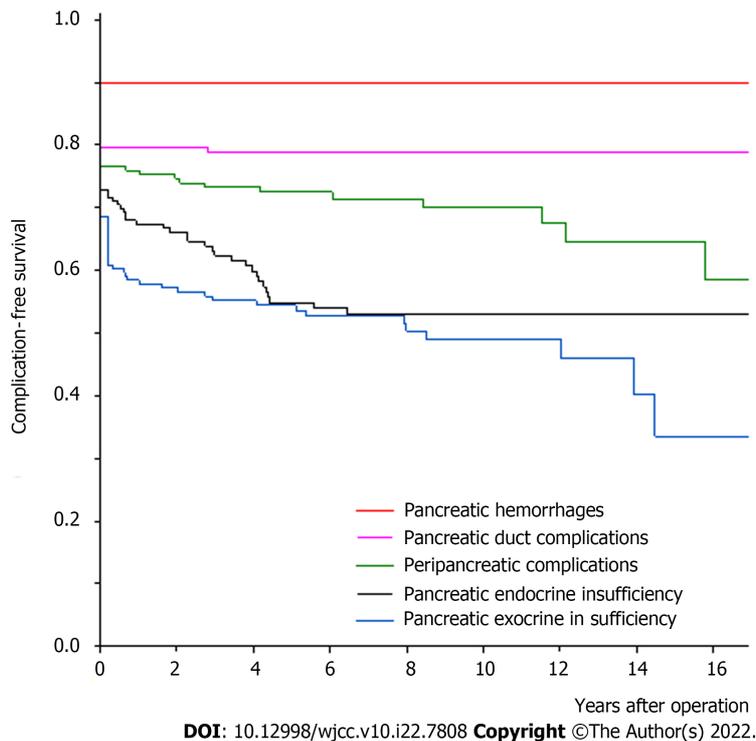


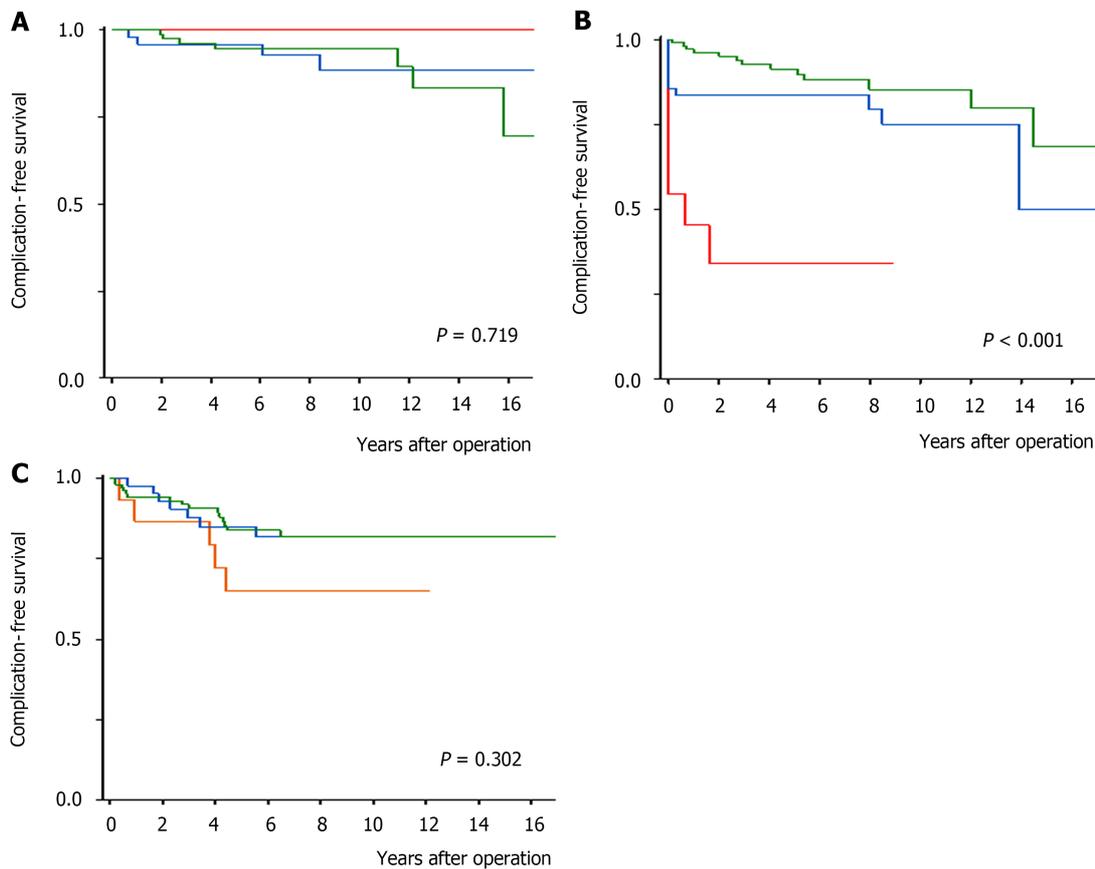
Figure 3 Kaplan-Meier curves of complication-free survival of pathophysiologically grouped complications prior to, and following surgical management of chronic pancreatitis in a cohort of 166 patients.

pancreatic head[70]. 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*[71] in the ChroPac trial and by Müller *et al*[72]. 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 also has 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 hemorrhage) is associated with the poorest prognosis. Even with prompt diagnosis and immediate therapy, the mortality rate reported in earlier studies is 15% to 50%[73]. In the past two decades, due 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*[74] reported a technical success rate of 88%, a clinical success rate of 86%, a rebleeding rate of 16.3%, and a mortality rate of 8% for endovascular therapy[74]. Surgical treatment is reserved for patients in whom vascular interventional therapy has failed or is not accessible, as well as in 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 (8 cases), as hemorrhages emerged from the splenic artery, but in 2 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 re-bleedings occurred 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 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[75], surgical PD decompression has a preventive effect on development of PPC, as well as on its transformation into PA.



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Figure 4 Kaplan-Meier curves of complication-free survival characterizing the impact of the type of surgery on occurrence of the new complications of chronic pancreatitis. The log-rank test was used to assess differences between the curves. A: Peripancreatic complications (Whipple's pancreatoduodenal resection—red line, other pancreatic resections—blue line, pancreatic drainage operations—green line); **B:** Pancreatic exocrine insufficiency (Whipple's pancreatoduodenal resection—red line, other pancreatic resections—blue line, pancreatic drainage operations—green line); **C:** Pancreatic endocrine insufficiency (pancreatic distal resection—orange line, other pancreatic resections—blue line, pancreatic drainage operations—green line).

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*[76], on the basis of data from the Dutch Chronic Pancreatitis Registry[76]. 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[77,78]. 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 *et al*[79]'s. 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 PD 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*[80] according to which a tailored approach to CP patients is mandatory[80].

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 background

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

Research motivation

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

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 CP; and to assess the impact of surgical treatment on the development of new complications during follow-up.

Research methods

After institutional review board approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients (≥ 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 results

We distinguished four groups of complications: Pancreatic duct complications, peripancreatic complications, pancreatic hemorrhages, and 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 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 perspectives

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

FOOTNOTES

Author contributions: Murruste M, Kirsimägi Ü, Kase K, Veršinina T, Talving P, and Lepner U designed the study; Murruste M, Kirsimägi Ü, Kase K, and Veršinina T performed the study; Murruste M and Kirsimägi Ü produced the statistics and wrote the paper.

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