Pancreatology 17 (2017) 572–579

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

The Belgian national registry on chronic pancreatitis: A prospective multi-centre study covering more than 800 patients in one year

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ARTICLE INFO

Article history:
Received 30 November 2016
Received in revised form
12 May 2017
Accepted 24 May 2017
Available online 26 May 2017

Keywords:
Chronic pancreatitis
Observational study
Belgian registry

ABSTRACT

Background/Objectives: The epidemiology, natural history, complications, and therapeutic management of chronic pancreatitis (CP) are not well described at the national level. This multi-centre prospective observational study involving eight Belgian hospitals aimed to improve the understanding of these aspects of CP in Belgium.
Methods: All patients with a diagnosis of CP based on imaging were eligible for this study. Data were gathered regarding epidemiology, etiology, CP complications, and treatment modalities.
Results: A total of 809 patients were included between 1/9/2014 and 31/8/2015. Most patients (794) were adults ≥16-years old, 74% were male, the median age at symptom onset was 47 (38–57) years, the median disease duration was 7 (3–13) years, and the median Izbicki pain score (IPS) was 96 (0–195). The main etiological risk factors according to the TIGAR-O classification were alcohol and tobacco (67%). Current drinkers had lower body mass index (BMI) (21.4 kg/m^2 vs 24.1 kg/m^2), higher IPS (110 vs 56), and longer inability to work than non-drinkers. Current smokers had lower BMI (21.5 kg/m^2 vs 25 kg/m^2) and higher IPS (120 vs 30) than non-smokers. Endocrine insufficiency and/or clinical steatorrhea was recorded in 41% and 36% of patients, respectively. The highest IPS was reported in patients with ongoing endotherapy (166 vs 50 for patients who completed endoscopy).
Conclusion: This multicentric study on CP patients showed that current alcohol drinking and smoking are associated with pain and malnutrition. Pain scores were higher in patients with ongoing endotherapy, independently of surgery.

Introduction

Chronic pancreatitis (CP) is an irreversible, progressive, inflammatory, and fibrotic process leading to the destruction of pancreatic tissue [1]. The incidence of CP is estimated to be between 4 and 13 per 100,000 inhabitants annually and the prevalence ranges from 26 to 42 per 100,000 inhabitants in Western countries [2–4]. Some studies suggest that the frequency is increasing over time due to increases in alcohol consumption and an improved ability to diagnose CP at earlier stages [5,6]. Currently, there are no epidemiological data about CP at the national level in Belgium.

Previously, alcohol was considered to be the main etiological

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http://dx.doi.org/10.1016/j.pan.2017.05.387
1424-3903/

Abbreviations

BMI	Body Mass Index
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CP	Chronic Pancreatitis
CRF	Case Report Form
CT	Computed Tomography
ESWL	Extracorporeal Shock Wave Lithotripsy
ET	Endoscopic Treatment
EUS	Endoscopic Ultrasonography
ID	Insulin-dependent
IPS	Izbicki Pain Score
IQR	Interquartile range
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
NA	Not Available
NID	Non-Insulin-dependent
P50	Percentile 50
PRSS1	Cationic Trypsinogen-Serine Protease 1
SPINK1	Serine Protease Inhibitor, Kazal type 1
'T', 'I', 'G', 'A', 'R', 'O' groups	Toxic, Idiopathic, Genetic, Auto-immune, Recurrent acute and severe pancreatitis, and Obstructive group
VAS	Visual Analog Scale
VS	Versus

factor for CP [6,7] but other risk factors, including genetic and immunological factors, have been identified [7]. The TIGAR-O classification system allows the categorization of patients with CP into one of six etiological categories: toxic (T), idiopathic (I), genetic (G), autoimmune (A), recurrent acute and severe pancreatitis (R), and obstructive cause (O) [7]. The evolution of CP and its complications are highly related to its etiology and may be specific to each patient [8]. Complications, such as diabetes and clinical steatorrhea, pain as well as the calcifying nature vary from one patient to another [9–12]. There is no specific medical therapy for CP except for treatment of pain, diabetes, clinical steatorrhea, and malnutrition. Currently, there is no definitive consensus regarding the choice between endoscopy and surgery in the treatment of CP [10,13]. Both approaches have proven effective and the decision to perform endoscopy or surgery varies mainly depending on clinical criteria [14–16]. As CP is quite a rare disorder, with limited population-based data, the aims of this national multi-centre prospective observational study were to improve our knowledge of its epidemiology, complications, natural course, and treatment modalities in Belgium.

Patients and methods

- Patients

  This was a prospective multi-centre observational study involving eight hospitals carried out in the three Belgian regions. This included:

  - ***Brussels region***: Erasme Hospital and Cliniques universitaires Saint-Luc, both university medical centres.
  - ***Walloon region***: CHU Sart-Tilman, a university medical centre; CHR la Citadelle and CHC Liège, both community hospitals.
  - ***Flanders region***: Universitair Ziekenhuis Leuven, Universitair Ziekenhuis Antwerpen, Universitair Ziekenhuis Gent, three university medical centres.

All patients with imaging tests (computed tomography [CT] and/or magnetic resonance imaging [MRI]/magnetic resonance cholangiopancreatography [MRCP]) that showed typical features of CP were eligible for the study. The imaging diagnostic criteria were the same at each participating centre and included the identification of pathognomonic pancreatic calcification(s) and/or ductal dilatation(s) and/or parenchymal atrophy. Endoscopic ultrasonography (EUS) criteria were not used as diagnostic criteria for CP in this study. Non-Belgian patients were excluded from the study. This observational study ran for one year from 1/9/2014 until 31/8/2015 and was approved by the institutional review board at each participating hospital. All patients (or their legal guardians) provided written informed consent.

- Methods

Data were gathered by completion of a case report form (CRF) by the patient's physician at the time of an out-patient visit or during admission. Recorded CRF items with their definitions are shown in Table 1. For every CP patient included, physicians had to classify the patient into one of the six etiologic groups of the TIGAR-O classification [7] according to the risk factor that was considered the main contributor to their pancreatic disease (Table 1). CRFs were anonymized and encoded into a database by each participating centre. At the end of the study, the complete database was used to carry out statistical analyses.

- Statistical analysis

SPPS (version 23.0) software was used to perform descriptive, cross-tabs, and non-parametric analyses. Qualitative data are expressed as percentages. Skewed variables are presented as medians and interquartile ranges. Non-parametric tests were used to compare skewed variables: the Mann-Whitney *U* test for two independent variables and the Kruskal Wallis test for multiple independent variables. A two-tailed P value of less than 0.05 was considered significant. Box plots are used to show the distribution of Izbicki Pain Score (IPS) amongst different subgroups.

Results

Patient characteristics

During the one year study period, 815 consecutive CP patients were included. Six were excluded because of missing or incomplete data. Of the remaining 809 cases, 794 were adults (age $\geq$ 16 years old) and 15 were children.

The distribution of the whole population among the eight participating centres was as follows: Erasme Hospital: n = 313 (39%), Cliniques universitaires Saint-Luc: n = 164 (20%), Universitair Ziekenhuis Leuven: n = 141 (18%), the three walloon hospitals (CHU Sart-Tilman, CHR la Citadelle, and CHC Liège): n = 141 (18%), Universitair Ziekenhuis Antwerpen: n = 29 (4%), Universitair Ziekenhuis Gent: n = 6 (1%). All pediatric patients included were from Cliniques universitaires Saint-Luc. Patient characteristics are summarized in Table 2.

The majority of the adult patients were male (74%) and were out-patients at the date of completion of the CRF (69%). The median

Table 1
List of the items included in the case report form (CRF).

Gender
Age at CP diagnosis
Age at onset of symptoms related to CP
Patient type: in-patient/out-patient
Etiology according to TIGAR-O classification [7]:
Toxic:
• Alcohol: consumption of ≥5 units per day for at least 5 years before the study
• Tobacco: Cigarette smoking was defined as smoking at least 5 pack-years. In never-drinkers, smoking of at least 12 pack-years was required [31] to include the patient in the Toxic group.
Idiopathic
• Idiopathic CP is indicated for patients in whom no associated risk factor can be identified
Genetic:
• Genetic CP is indicated if pancreatitis occurs in an individual with a predisposing genetic factor. (PRSS1, CFTR, and SPINK1 mutations).
Auto-immune CP
• requires typical clinical, biological, and imaging characteristics
Recurrent acute and severe pancreatitis
Obstructive
• Obstructive CP is indicated in patients with pancreatic duct dilation proximal to an obstruction such as a pancreatic duct scar, sphincter of Oddi dysfunction, or Groove pancreatitis.
Body mass index (BMI): kg/m^2
Recent weight loss (defined as a loss of ≥10% from baseline): yes or no
Alcohol abuse (defined as a patient who drank ≥5 units per day for at least 5 years) was classified as no, previous, or current.
Tobacco exposure (at least 5 pack-years) was classified as no, previous, or current.
Diabetes mellitus was classified as: no, non-insulin-dependent (NID) or insulin-dependent (ID) according to the American Diabetes Association Classification: HbA1C ≥ 6.5% or fasting plasma glucose ≥7 mmol/L (or ≥126 mg/dl) or 2-h plasma glucose ≥11.1 mmol/L (or ≥ 200 mg/dl) during an oral glucose tolerance test [32].
Clinical Steatorrhea: defined as present if patients presented with typically fatty stools that improved with more than 1 month of treatment with pancreatic enzyme substitution [17].
Izbicki pain score (IPS) was recorded once at the inclusion date but reflected the 12 previous months: IPS is a numerical score based on the pain attack frequency, the Visual Analog Scale (VAS), analgesic use, and the duration of disease-related inability to work [23]
Endoscopic treatment (ET) was recorded as: no, previous, or ongoing. Ongoing endotherapy is applied to patients still being endoscopically treated at the time of inclusion, with a stent in place or requiring stent exchange, or ESWL for obstructive pancreatic duct stones, or endoscopic procedure(s) for treatment of complications (such as biliary strictures, pseudocysts)
Surgical treatment was recorded as: no or previous

Abbreviations: CP: chronic pancreatitis; PRSS1: cationic trypsinogen-serine protease 1; CFTR: cystic fibrosis transmembrane conductance regulator; SPINK1: serine protease inhibitor, Kazal type 1. ESWL: Extracorporeal shockwave lithotripsy.

age at onset of symptoms was 47 (38–57) years. At the time of inclusion the median duration of disease was 7 [3–13] years and the median IPS was 96 (0–195). Pediatric population characteristics are reported separately at the end of the results section.

Etiological risk factors and comparisons between etiological groups

The main etiological risk factors according to the TIGAR-O classification system [7] were alcohol abuse and tobacco smoking (67%) followed by idiopathic causes in 19% of cases. Recurrent acute and severe pancreatitis, genetic, autoimmune, and obstructive causes were less commonly represented, and accounted for between 2% and 5% of cases each. The etiological risk factor distribution is presented in Fig. 1.

The age at symptom onset was lower in the genetic group compared to the other groups (median age: 17 years [7–24] vs 47 years [39–58], $p < 0.001$). On the other hand, the disease duration up to the inclusion in the study was longer in these patients (median age: 14 years [7–21] vs 7 years [3–13], $p < 0.001$).

Lower body mass index (BMI) (median of 22.3 kg/m^2 [19.7–25] vs 24.2 kg/m^2 [21.3–27], $p < 0.001$), more frequent weight loss of at least 10% from baseline (22% vs 13%, $p < 0.05$), more frequent inclusion in the study as an in-patient (37% vs 21%, $p < 0.001$), and increased IPS (median of 101 [0–210] vs 56 [0–155], $p < 0.001$) were observed in patients from the 'T' group compared to the other groups combined. Seventy-six percent of patients from the 'T 'group compared to 60% from the other etiological groups combined had previously undergone endoscopic treatment (ET) or were still being treated by endoscopy ($p < 0.001$), whereas ET was less often performed in patients belonging to the 'A' and 'I' etiological groups.

Alcohol and tobacco

Associations between clinical parameters regarding nutrition, pain, and ET with alcohol and tobacco abuse are presented in Tables 3 and 4, respectively. Current drinkers presented with a statistically significant lower BMI (21.4 kg/m^2 [19.1–25.6]), higher IPS (110[0–210]), greater inability to work, and a higher rate of ongoing ET (34%) compared to patients who had never drunk alcohol (median BMI: 24.1 kg/m^2 [21.1–27], median IPS: 55.5 [0–155], and rate of ongoing ET: 24%). Similarly, lower BMI (21.5 kg/m^2 [19.2–24.1]), higher IPS (120 [0–235]), and a higher rate of ongoing ET (37%) were observed among current smoking patients compared to non-smoking patients.

Complications: diabetes and clinical steatorrhea

Concerning endocrine insufficiency, 41% of the patients were diabetics (NID: 15% and ID: 26%). Clinical steatorrhea was observed in a similar proportion of patients (36%), and 86% of them received pancreatic enzymes. Diabetes was significantly more frequent in patients from the 'T' group than in patients from the other etiological groups (44% vs 35%, $p < 0.05$), while there was no significant difference between the groups for clinical steatorrhea (36% vs 31%, $p = 0.175$).

Clinical conditions associated with low body mass index

Among the whole adult population, the median BMI was 22.8 kg/m^2 (20.2–25.9), 19% of patients reported a significant weight loss (≥10% from baseline) in the last six months, and 179/794 patients (22.5%) had a BMI <20 kg/m^2.

Table 2
Patient characteristics.

Characteristics	Adult Patients (n = 794)	Pediatric Patients (n = 15)
Gender male (%)	589/794 (74)	4 (27)
Out-patients n (%)	545/794 (69)	15 (100)
Age at inclusion (years) [median (IQR)]	56 (47–64)	7 (4–10)
Age of CP diagnosis (years) [median (IQR)]	48 (39–58)	4 (0–14)
Age at onset of symptoms (years) [median (IQR)]	47 (38–57)	3 (1–7)
Disease duration (years) [median (IQR)]	7 (3–13)	2 (2–5)
BMI (kg/m^2) [median (IQR)]	22.8 (20.2–25.9)	NA
Weight loss n (%)	149/775 (19)	NA
Smoking n (%)		
- No	197/792 (25)	0
- Previous	169/792 (21)	0
- Current	426/792 (54)	0
Alcohol n (%)		
- No	272/790 (35)	0
- Previous	374/790 (47)	0
- Current	144/790 (18)	0
Diabetes n (%)		
- No	465/787 (59)	0
- NID	114/787 (15)	0
- ID	208/787 (26)	0
Clinical steatorrhea n (%)	283/778 (36)	0
- Pancreatic enzyme treatment n (%)	266/773 (34)	0
Izbicki pain score [median (IQR)]	96 (0–195)	150(135–275)
- Frequency of pain	25 (0–50)	25 (25–25)
- VAS-score	30 (0–80)	85(70–94)
- Analgesic medication	1 (0–15)	15(15–100)
- Inability to work	0 (0–50)	25 (25–50)
Treatment		
- Endoscopy n (%)		
➢ No	228/790 (29)	9/15 (60)
➢ Previous	308/790 (39)	5/15 (33)
➢ Ongoing	254/790 (32)	1/15(7)
- Surgery n (%)	116/794 (15)	0

Abbreviations: BMI: Body mass index; NID: Non-insulin-dependent; ID: Insulin-dependent; NA: Not available; VAS: visual analog scale.

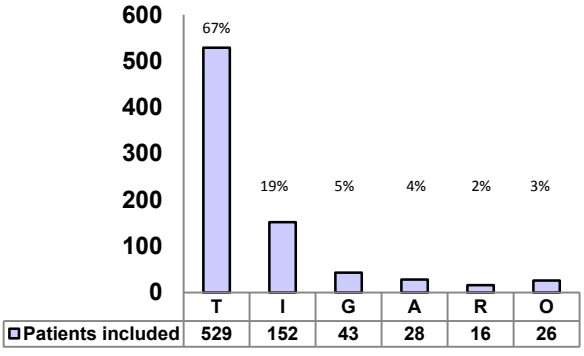

Fig. 1. Etiological risk factor distribution according to the TIGAR-O classification system.
Included patients were classified into one of the six etiological categories according to the TIGAR-O classification system: toxic (T), idiopathic (I), genetic (G), autoimmune (A), recurrent acute and severe pancreatitis (R), or obstructive cause (O) [7].

Table 5 summarizes the clinical conditions associated with a low BMI, defined as <20 kg/m^2. More patients with a low BMI had clinical steatorrhea (45% vs 34%, p < 0.001) and weight loss (32% vs 16%, p < 0.001) compared to patients with a BMI ≥20 kg/m^2. In the group of patients with a low BMI, a higher IPS was recorded (median 146 [50–245] vs 70 [0–176], p < 0.001). The proportions of patients currently smoking and drinking were also significantly higher in the low BMI group compared to patients with a BMI ≥20 kg/m^2 (78% and 30% vs 47% and 15%, respectively, p < 0.001).

Treatment: differences between endoscopic and surgical approaches

Fig. 2 and Table 6 show IPS according to the type of treatment (endoscopy and/or surgery). In the subgroup of patients without surgery, patients with ongoing endotherapy (G5, n = 233) reported a significantly higher IPS (median of 160 [85–250]) compared to patients with previous (G3, n = 243) or no endoscopic treatment (G1, n = 198) (46 [0–131] and 1 [0–156], respectively, p < 0.001).

Table 3
Clinical conditions associated with alcohol consumption.

	Current Alcohol Abuse (n = 144)	Previous Alcohol Abuse (n = 374)	No Alcohol Abuse (n = 272)	P[a]
BMI (kg/m^2)	21.4 (19.1–25.6)	22.6(20.2–25)	24.1(21.1–27)	*P < 0.001*
Weight loss n (%)	35 (24)	77(21)	35 (13)	*P < 0.05*
Izbicki score (/400)	110(0–210)	101(0–216)	56(0–155)	*P < 0.01*
Izbicki sub-score (/100)				
➢ Inability to work	0 (0–75)	0 (0–75)	0(0–25)	*P < 0.05*
Ongoing endotherapy n (%)	49 (34)	139 (37)	64(24)	*P < 0.001*

Abbreviations: BMI: Body Mass Index.
Skewed variables are presented as median (interquartile range). Qualitative data are expressed as percentages.
[a] The P value represents the comparison of Current vs No.

Table 4
Clinical conditions associated with smoking.

	Current Smoking (n = 426)	Previous Smoking (n = 169)	No Smoking (n = 197)	P[a]
BMI (kg/m^2)	21.5 (19.2–24.1)	24 (22–27.5)	25 (22–27)	*P < 0.001*
Izbicki pain score (/400)	120 (0–235)	46(0–140)	30 (0–75)	*P < 0.001*
Ongoing endotherapy n (%)	156 (37)	53 (32)	45 (23)	*P < 0.001*

Abbreviations: BMI: Body Mass Index.
Skewed variables are presented as median (interquartile range). Qualitative data are expressed as percentages.
[a] The P value represents the comparison of Current vs No.

Table 5
Clinical conditions associated with a low BMI defined as < 20 kg/m.^{2}.

	BMI <20 kg/m^2 (n = 179)	BMI ≥20 kg/m^2 (n = 614)	P-value
Clinical Steatorrhea(%)	45	34	*P < 0.001*
Weight loss (%)	32	16	*P < 0.001*
Smoking (n/p/c) (%)	12/10/78	28/25/47	*P < 0.001*
Alcohol (n/p/c) (%)	21/49/30	38/47/15	*P < 0.001*
Izbicki score (/400)	146 (50–245)	70 (0–176)	*P < 0.001*

Abbreviations: BMI: Body Mass Index; n: no; p: previous; c: current.
Skewed variables are presented as median (interquartile range). Qualitative data are expressed as percentages.

However, patients treated with previous surgery and with ongoing endotherapy (G6, n = 20) at the date of inclusion reported the highest IPS (280 [151–350]). One-hundred and sixteen out of the 794 adult patients (15%) had previous surgery and, among them, 84 patients (72%) had CP related to toxic risk factors. CP complications such as diabetes and clinical steatorrhea were more frequently observed in these 116 patients compared to the whole population, 58% and 56% vs 41% and 36%, respectively, p < 0.01.

Thirty patients (30/116 [26%]) had a surgical intervention alone without endoscopic treatment. Twenty-one of them (70%) underwent pancreas-related interventions, two underwent biliary-

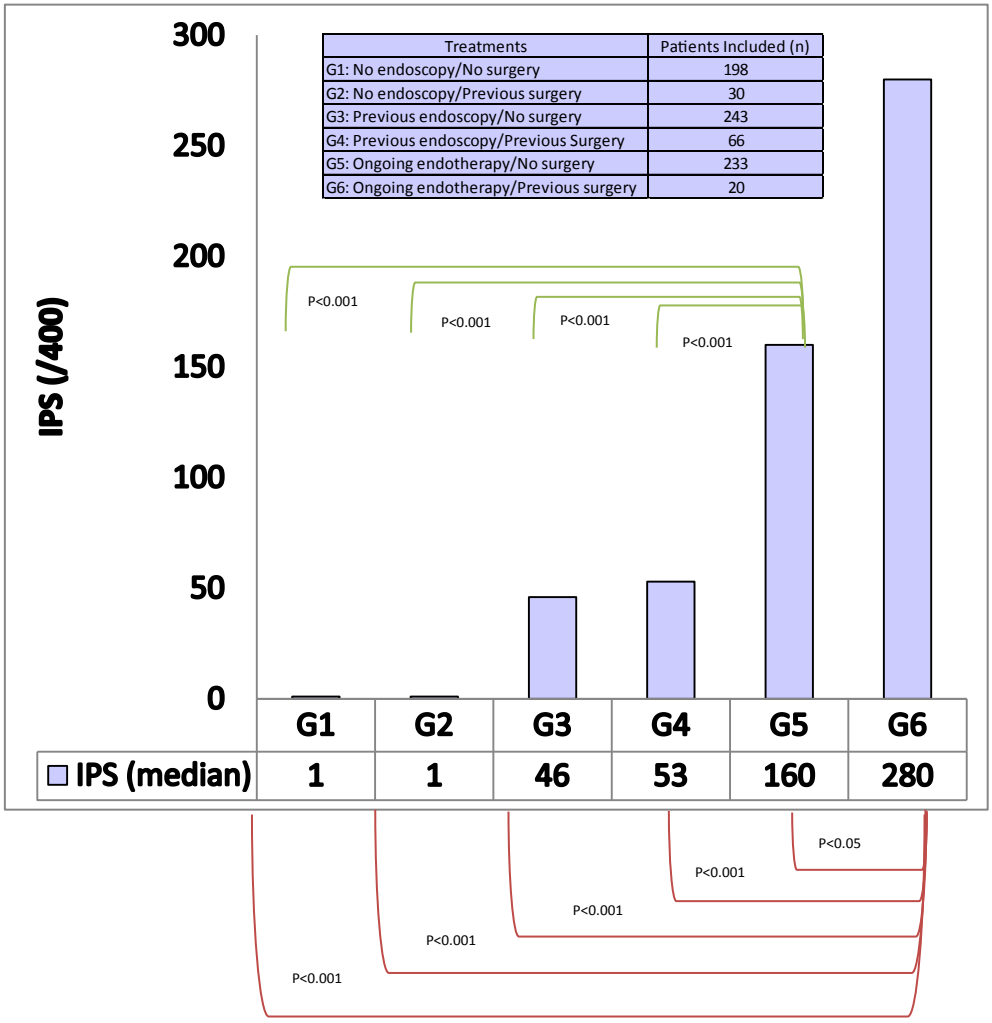

Fig. 2. Comparison of IPS levels according to the type of treatment.
Included patients were classified into one of six different groups depending on the type of treatment performed: G1: No endoscopy/No Surgery; G2: No Endoscopy/Previous Surgery; G3: Previous Endoscopy/No Surgery; G4: Previous Endoscopy/Previous Surgery; G5: Ongoing Endotherapy/No Surgery; G6: Ongoing Endotherapy/Previous Surgery. Izbicki pain score (IPS), expressed as median values, was significantly higher for patients from groups G5 and G6 compared to patients from groups G1,G2,G3, and G4.

Table 6
Izbicki Pain score according to the type of treatment.

6a. Izbicki Pain Score distribution according to the treatment(s) performed

Treatments	Patients n (%)	IPS Median (IQR)
G1: No endoscopy/No Surgery	198 (25)	1 (0–156)
G2: No Endoscopy/Previous Surgery	30 (4)	1(0–165)
G3: Previous Endoscopy/No Surgery	243 (31)	46(0–131)
G4: Previous Endoscopy/Previous Surgery	66 (8)	53(0–125)
G5: Ongoing Endotherapy/No Surgery	233 (29)	160(85–250)
G6: Ongoing Endotherapy/Previous Surgery	20 (3)	280(151–350)

Abbreviations: IPS: Izbicki pain score IQR: Interquartile range
Variables are presented as median (IQR).

6b. Comparisons between the different groups of patients treated with or without endoscopy and with or without surgery.

Versus	G1	G2	G3	G4	G5	G6
G1	–	NS	NS	NS	*P < 0.001*	*P < 0.001*
G2	NS	–	NS	NS	*P < 0.001*	*P < 0.001*
G3	NS	NS	–	NS	*P < 0.001*	*P < 0.001*
G4	NS	NS	NS	–	*P < 0.001*	*P < 0.001*
G5	*P < 0.001*	*P < 0.001*	*P < 0.001*	*P < 0.001*	–	*P < 0.05*
G6	*P < 0.001*	*P < 0.001*	*P < 0.001*	*P < 0.001*	*P < 0.05*	–

Abbreviations: NS: non-significant. G1: No endoscopy/No Surgery; G2: No Endoscopy/Previous Surgery; G3: Previous Endoscopy/No Surgery; G4: Previous Endoscopy/Previous Surgery; G5: Ongoing Endotherapy/No Surgery; G6: Ongoing Endotherapy/Previous Surgery.

related surgeries, and seven underwent both pancreas and biliary-related surgery or infected pseudocyst management. For the remaining 86 patients, pancreas-related surgery was performed in 55 of the 86 cases (64%). The comparison between the 30 patients treated with surgery alone and the 86 patients treated with the combination of surgery and endoscopy was significantly different regarding the age at inclusion (51 years [41–58] vs 54 years [48–63], $p < 0.05$), BMI (20 kg/m^2 [18–24] vs 22.4 kg/m^2 [20.2–25.5], $p < 0.05$), the proportion of patients with weight loss (10/30 cases [33%] vs 12/86 cases [14%], $p < 0.05$), the proportion of current smokers (22/30 [73%] vs 50/86 [58%]), VAS-score (median VAS: 0 [0–70] vs 28 [0–76], $p < 0.05$) and the score for analgesic medication (median 0 [0–1] vs 0 [0–100], $p < 0.05$).

Pediatric cohort results

Fifteen children aged less than sixteen were enrolled in this study, the majority of them were girls (73%). Table 2 summarizes pediatric patient characteristics. The median age at CP diagnosis was 4 (0–14) years and the duration of the disease was 2 [2–5] years. All of them were included as out-patients. Genetic and idiopathic causes were the main risk factors identified in 40% and 34% of cases, respectively. Most of the pediatric patients were under the P50 range on the BMI percentiles curve for their age. No diabetes or clinical steatorrhea were reported. No surgical treatments were performed. Children who underwent endoscopic treatment (previous [n = 5] or ongoing [n = 1]) reported higher pain levels than children without endoscopic treatment: median IPS was 159/400 (with VAS of 92/100) and 300/400 (with VAS of 100/100) versus 145/400 (with VAS of 80/100).

Discussion

This is the first national Belgian study that aimed to prospectively collect epidemiology, evolution, complications, and treatment data regarding CP.

This prospective multi-centre study showed that alcohol and tobacco were the main etiological risk factors of CP in Belgium (67% of cases), similar to what has been shown in earlier studies performed in other areas around the world (around 70–80% of cases) [6,7]. This study showed that current drinkers had lower BMIs, while 25% of them had experienced a significant weight loss. Moreover, they suffered higher pain levels, leading to an inability to work. Similarly, current smokers presented with lower BMIs and also reported being in greater pain. Therefore, efforts should be made to encourage these patients to stop drinking alcohol and smoking tobacco. In addition, it has already been shown that drinking and smoking cessation are associated with improved outcomes [17,18].

This study also demonstrated the important role of malnutrition that is often observed in CP patients [19,20]. In a study performed in a rehabilitation centre, 32% of CP patients with a BMI <20 kg/m^2 had ongoing maldigestion [19]. In our study, 22.5% of patients had a BMI <20 kg/m^2. Several clinical conditions were associated with low BMI including higher rates of clinical steatorrhea, more frequent significant weight loss, and higher pain scores. Moreover, patients who continued to drink and smoke were twice as likely to have a BMI <20 kg/m^2. These patients should be followed to ensure that their dietary and nutritional needs are taken into account. Management strategies should include treatment plans that contain pancreatic enzymes for cases of associated clinical steatorrhea, as well as support in making a real effort to control addictions, with the help of counseling if needed.

Pain is well recognized as one of the most dominant and disabling symptoms of the disease [21,22]. Currently, there is no perfect system to assess pain in patients with CP. IPS is used widely and has been validated in several comparable studies [15,23]. It is easy to use and has the advantage of evaluating several aspects of pain, namely, the frequency with which it occurs, its intensity/severity (VAS), the type of analgesics needed, and the impact of the disease on work disability, and takes into account a period of 12 months before scoring. Interestingly, patients with ongoing endotherapy with or without previous surgery had the highest IPS with scores of 280 (G6) and 160 (G5), respectively. When groups G5 and G6 were combined, the IPS remained significantly higher in patients with ongoing endotherapy, independently of surgery, compared to patients who completed ET (166 vs 50, $p < 0.001$). These results suggest that in some of these patients (G5 and G6), endoscopic therapy, which focuses on decreasing intraductal pressure, did not provide complete pain relief, and that there might be potential interference from a neuropathic pain component as an additional mechanism of pain [21,24].

Current guidelines recommend using endoscopy as the first line of treatment and considering surgery for clinical and/or technical failures of endoscopy, for long term biliary drainage, for duodenal obstruction, or when there is a pancreatic inflammatory mass in the head of the pancreas where malignancy could not be ruled out [10,13]. Our observational study was not designed to assess the application of the above guidelines. However, two randomized studies have suggested that initial surgery would yield better results than endoscopy. Dite et al. [14] showed that 34% of surgical patients were pain-free after 5 years versus 15% after endoscopic therapy. A second study from Cahen et al. [15,16] showed that surgery improved pain in 75% of patients compared to 32% of the endoscopically-treated patients. In our study, we didn't observe a significant difference in terms of IPS between patients who had surgery alone and patients who were treated exclusively endoscopically. However, the high IPS scores recorded in patients with ongoing endotherapy should be considered in line with the previously identified unfavorable risk factors for achieving post-operative pain relief, i.e. more than five endoscopic procedures prior to surgery, duration of the disease longer than three years, and preoperative opioid treatment [25]. These factors and our

results should be taken into account when discussing the best timing to perform surgery and when to continue endoscopic therapy.

Overall, our CP population is comparable to the recently published CP registry from the Dutch Pancreatitis Study Group [9] and other previously reported epidemiological studies [2,26] in terms of gender, age at onset of symptoms, and duration of the disease, as well as rates of complications such as diabetes and clinical steatorrhea. However, contrary to these previous studies, our work has thoroughly investigated the potential associations between alcohol and tobacco abuse, malnutrition, and the different treatments applied with a validated pain score established on a 12-month period before patient inclusion.

In children, until recently, the main etiological risk factor for CP was idiopathic. With the discovery of CP-associated gene mutations, it seemed obvious that genetic causes would rise as the most frequent etiologic risk factor for pediatric CP [27–29], as we observed in our study. The majority of pediatric cases had weight/size ratios below the 50th percentile mark on the BMI percentile curve for the patient's age suggesting that nutritional support is also very important in this subgroup of patients. In contrast to the adult population, no diabetes or clinical steatorrhea was observed in the pediatric cohort and the disease duration was significantly shorter. The evaluation of pain can be difficult in children and, except for the VAS sub-category, IPS was not suitable for evaluation of this group of patients [30].

One of the limitations of this study was the selection of some subjective items (i.e. alcohol and tobacco consumption). Detailed consumption of alcohol, tobacco, and the benefits of alcohol/tobacco withdrawal on pain evolution and on nutritional status would be of interest during the follow-up of these patients. We should also acknowledge that national recruitment remained incomplete, with only 8 hospitals involved from the entire country: an estimation of the prevalence and incidence of CP in Belgium seems unreasonable based on our results. Moreover, an unknown proportion of patients with no pain (IPS: 0/400) after previous treatment were not included in this study because the interval of time between out-patient visits in such patients sometimes exceeded one year. This could have negatively impacted our overall results. As data retrieval was done only once at the time of inclusion of the patient in the study with no data recorded during follow-up, it is difficult to determine causality between the different factors and only significant associations can be observed. Regarding pain, we didn't assess its temporal nature (intermittent vs constant) although Mullady et al. [22] have demonstrated that this is a more important determinant of quality of life than pain intensity.

This study has several strengths. It is the first Belgian prospective registry on CP and the population size is representative, providing data from the main hospitals across the country, where expertise is focused on the management of CP patients.

To conclude, this multi-centre Belgian study on 809 CP patients provides a useful tool for assessing the management of these patients in terms of complications and treatment. This study showed that current alcohol drinking and smoking were significantly associated with pain and malnutrition. Moreover, pain scores were higher in patients with ongoing endotherapy, independently of surgery. However, further studies, including follow-up data for these patients, could provide a deeper assessment of the causal relationships between environmental factors, treatment modalities, and clinical outcomes associated with CP in the coming years.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

No source of funding.

Acknowledgment

The authors would like to acknowledge the contribution of a medical writer, Sandy M. Field, PhD, to this publication.

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