Pain patterns in chronic pancreatitis: a nationwide longitudinal cohort study

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ORIGINAL RESEARCH

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ABSTRACT

Objective Pain in chronic pancreatitis is subdivided in a continuous or intermittent pattern, each thought to represent a different entity, requiring specific treatment. Because evidence is missing, we studied pain patterns in a prospective longitudinal nationwide study.

Design 1131 patients with chronic pancreatitis (fulfilling M-ANNHEIM criteria) were included between 2011 and 2018 in 30 Dutch hospitals. Patients with continuous or intermittent pain were compared for demographics, pain characteristics, quality of life (Short-Form 36), imaging findings, disease duration and treatment. Alternation of pain pattern and associated variables were longitudinally assessed using a multivariable multinomial logistic regression model.

Results At inclusion, 589 patients (52%) had continuous pain, 231 patients (20%) had intermittent pain and 311 patients (28%) had no pain. Patients with continuous pain had more severe pain, used more opioids and neuropathic pain medication, and had a lower quality of life. There were no differences between pain patterns for morphological findings on imaging, disease duration and treatment. During a median follow-up of 47 months, 552 of 905 patients (61%) alternated at least once between pain patterns. All alternations were associated with the Visual Analogue Scale pain intensity score and surgery was only associated with the change from pain to no pain.

Conclusion Continuous and intermittent pain patterns in chronic pancreatitis do not seem to be the result of distinctly different pathophysiological entities. The subjectively reported character of pain is not related to imaging findings or disease duration. Pain patterns often change over time and are merely a feature of how severity of pain is experienced.

Significance of this study

What is already known on this subject?

- Pain is the most frequent and dominant symptom in chronic pancreatitis.
- It is commonly accepted to subdivide pain in chronic pancreatitis in a continuous or intermittent pattern, each suggested to represent a different entity reflecting different states of pain mechanisms.

What are the new findings?

- No morphological differences on imaging and no association with disease duration were found between pain patterns.
- In most patients, pain patterns alternated during follow-up and were represented by alternating periods of continuous pain perceived as severe with a more negative impact of the pain and bad quality of life, and periods of intermittent pain perceived as less severe.

How might it impact on clinical practice in the foreseeable future?

- This study suggests that continuous and intermittent pain patterns in chronic pancreatitis are not the result of distinctly different pathophysiological entities.
- These data support a clinical focus on severity of pain rather than on a continuous or intermittent character of pain.

INTRODUCTION

Chronic pancreatitis is an inflammatory disease of the pancreas with deterioration of the endocrine and exocrine pancreatic function over time. Pain is the most frequent and dominant symptom, occurring in 80%–90% of patients, with a marked influence on the quality of life.[1 2] In daily practice and international guidelines, the clinical presentation of pain is often subdivided in specific patterns, each proposed as being potentially the result of different entities of chronic pancreatitis, reflection of different states of abnormal pain mechanisms, which could need different treatment strategies.[1 3–5] The commonly accepted subdivision includes the so-called type A pain and type B pain patterns, first

described by Ammann and Muellhaupt.[1] Type A is described as an intermittent pain pattern with short pain episodes of a few days and alternated long pain-free episodes of several months to more than a year. Type B pain is described as a continuous pain, characterised by prolonged periods of pain and/or clusters of recurrent severe pain exacerbations. In a recent cross-sectional study of 414 patients with chronic pancreatitis, the type of pain pattern showed to be a more important determinant of quality of life than the intensity of the pain.[4]

The original study in which the two different pain patterns were proposed was already performed over two decades ago.[1] Recent studies contributed significantly but had a cross-sectional design, which hampers evaluation of the natural disease course in patients with different pain patterns and preclude any assessment whether pain patterns alternate over time.[4 6 7] Moreover, the correlation between morphological findings on imaging and the clinical presentation of pain in chronic pancreatitis remains unclear.[8–10]

More evidence to confirm and better understand these different pain patterns in chronic pancreatitis is needed, because it is suggested that the effect of pharmacological and invasive interventions differs between pain patterns. Patients with different pain patterns may therefore require different diagnostic and therapeutic approaches.[1 4] Here, we hypothesised that continuous and recurrent pain patterns are different entities regarding demographics, imaging findings and long-term clinical course. To test this hypothesis, we analysed an unselected nationwide cohort of more than 1000 patients with chronic pancreatitis to compare continuous and intermittent pain patterns in a longitudinal manner.

METHODS

Design and setting

This is the first prospective longitudinal study using data from the Dutch Chronic Pancreatitis Registry (CARE), which was specifically designed for a study on pain patterns.[11] CARE is a nationwide registry, coordinated by the Dutch Pancreatitis Study Group. Between 2011 and 2018, patients with (suspected) chronic pancreatitis or recurrent acute pancreatitis were included in 30 hospitals and followed up at least yearly. For this study, only patients with a definite diagnosis of chronic pancreatitis were selected. The detailed study protocol and methodology of CARE have been published previously.[11] We adhered to the Strengthening the Reporting of OBservational studies in Epidemiology guidelines.[12]

Patients

For this study, only patients with an established diagnosis of chronic pancreatitis according to the M-ANNHEIM criteria were selected from the CARE registry. According to these criteria, the diagnosis of definite chronic pancreatitis requires a typical clinical history of chronic pancreatitis and at least one of the following criteria: pancreatic calcifications, moderate or marked pancreatic duct lesions, exocrine insufficiency or adequate histology of chronic pancreatitis.[13] Patients were classified for pain pattern in three groups: continuous pain, intermittent pain and no pain.[1] This pain pattern was assessed by a yearly questionnaire including a multiple choice question in which patients were asked to indicate if they had pain and, if pain was present, to choose their course of pain by marking one of the pain pattern pictures (figure 1). Patients with persistent pain with slight fluctuations or pain attacks with persistent pain in between were classified as continuous pain. Patients with pain attacks with pain-free periods between the attacks were classified as intermittent pain.

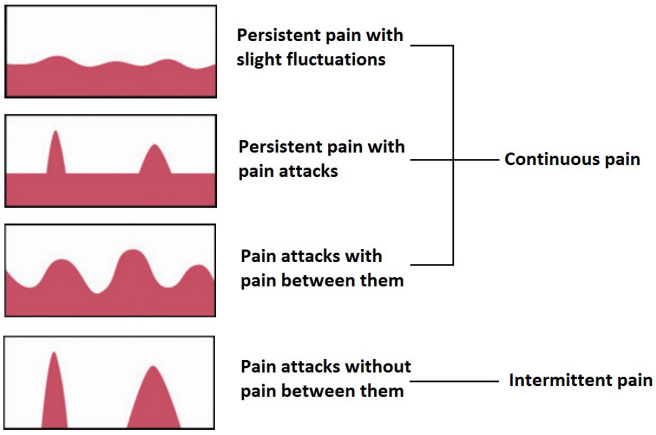

Figure 1 Pain pattern pictures. Pictures adapted from the PainDETECT Questionnaire.[16]

Outcomes

At study inclusion, data were collected using a questionnaire on demographics, diagnosis, risk factors (eg, alcohol, smoking), medication use and pancreatic insufficiency. This questionnaire also included questionnaires as the Izbicki Pain Questionnaire, the PainDETECT Questionnaire for detecting a neuropathic pain component and the Short-Form 36 (SF-36) quality of life questionnaire.[14–17] After inclusion, a yearly follow-up questionnaire was sent out and consisted of questions regarding risk factors, pain (pattern), pancreatic insufficiency, medication use, the Izbicki Pain Questionnaire, the PainDETECT Questionnaire and the SF-36 Questionnaire.[14–17] Medical records were reviewed on site by study nurses at study inclusion and 2 yearly during follow-up for data regarding aetiology (ie, as determined by clinicians in clinical practice), medication, pancreatic function tests, imaging (eg, CT, MRI and endoscopic ultrasonography), hospitalisation, interventional endoscopic (ie, endoscopic retrograde cholangiopancreatography, pancreatic duct stenting, pancreatic cyst drainage) and surgical procedures (ie, longitudinal pancreatojejunostomy, duodenum-preserving pancreatic head resection, pancreatoduodenectomy, (partial) pancreatectomy).

Exocrine insufficiency was registered when patients used pancreatic enzyme replacement therapy and/or had a faecal elastase-1 test <200 µg/g. Endocrine insufficiency was registered when patients were using oral diabetic medication or insulin.

Statistical methods

Three main analyses were performed.

First, in order to compare our results to previous studies on pain patterns in chronic pancreatitis, patients with continuous pain were compared with patients with intermittent pain at study inclusion (ie, in a cross-sectional manner) for the following parameters: demographics, aetiology, alcohol and smoking, pain characteristics, quality of life, treatment and predefined morphological findings on imaging (eg, CT, MRI and endoscopic ultrasonography) performed at diagnosis of chronic pancreatitis and at time of inclusion in CARE.[11] Data on patients without pain are also reported but no statistical tests were used to compare these patients with the continuous and intermittent pain group because this would make it less easy to appreciate the differences between the continuous and intermittent pain group.

Second, alternations of pain pattern in individual patients were investigated longitudinally for each follow-up year. The pain patterns during follow-up were presented in a Sankey diagram, which is a type of flow diagram per follow-up year.

Third, multinomial multivariable logistic regression analysis was performed using generalised estimating equation (GEE) to identify variables that were independently associated with alternations of pain pattern. GEE as multinomial model was used instead of a generalised linear mixed model (GLMM), since too little measurements per patient were present in this study to use GLMM.[18] Change of pain pattern was used as dependent variable, and was categorised in five categories: no pattern change, continuous pain to intermittent pain, intermittent pain to continuous pain, no pain to pain, and pain to no pain. The included potential predicting variables were: age, sex, body mass index, hospital volume, aetiology, smoking status, alcohol status, duration of symptoms, Visual Analogue pain intensity Score (VAS; 0–100), endoscopic and surgical interventions. To assume that the change of pattern could be caused by the intervention, endoscopic and surgical interventions were only included as event when performed within 12 months prior to the follow-up moment. All variables, except age, sex, hospital volume, aetiology and duration of symptoms, were investigated per follow-up year in the GEE regression analyses. As subgroup analyses, change of pain pattern was analysed per category in four separate GEE analyses: continuous pain to intermittent pain, intermittent pain to continuous pain, no pain to pain, and pain to no pain.

Descriptive data were expressed as mean with SD when normally distributed and as median with IQR (P25–P75) when non-normally distributed. Statistical comparison was performed using the X^2 test or Fisher exact test for categorical data and the Student t-test, one-way analysis of variance, Mann-Whitney U test or the Kruskal-Wallis test for continuous data. A p value<0.05 was considered statistically significant. Missing values were not imputed. Data analyses were performed using SPSS V.25.

An additional sensitivity analysis was performed regarding the intensity of pain instead of pain pattern. Patients were classified in two groups according to the intensity of pain based on the Izbicki pain score.[15 17] The intensity groups were as follows: mild pain (ie, no opioid use and a VAS pain score between 10 and 40) and severe pain (ie, use of opioids or a VAS pain score >40 without opioids).

RESULTS

Overall, 1450 patients with chronic pancreatitis or recurrent acute pancreatitis were registered in CARE between 2011 and 2018. Of this cohort, 1131 patients had definite chronic pancreatitis according to the M-ANNHEIM criteria and reported a pain pattern, and were therefore included in the current study (online supplemental table A1). Most excluded patients had recurrent acute pancreatitis or a clinical suspicion of chronic pancreatitis without definite chronic pancreatitis morphology according to the M-ANNHEIM criteria (figure 2). Mean age of the included patients was 58±12 years and 69% were men; 54% of patients had an alcoholic aetiology, 34% were current drinkers (of which 33% had an alcoholic aetiology) and 60% were current smokers. Median duration of chronic pancreatitis at inclusion in the CARE registry was 50 months (P25–P75: 17–105). Of the 1131 patients, 589 (52%) had continuous pain, 231 patients (20%) had intermittent pain and 311 patients (28%) had no pain. Of the 1131 patients, 905 (80%) had a longitudinal follow-up, with a median of 47 months after inclusion (P25–P75: 25–64). Of the 226 patients without follow-up, 221 patients were lost to follow-up and 5 patients were recently included in the CARE registry.

Cross-sectional analyses: continuous versus intermittent pain patterns

Patient and disease characteristics at inclusion are presented in table 1. At time of inclusion, the duration of chronic pancreatitis was comparable between the patients in the continuous and intermittent pain pattern groups (51 vs 46 months, p=0.28). There were no differences in demographics, aetiology and risk factors between groups, with the exception of a significant difference in age (2 years less in the continuous pain pattern group (56 vs 58 years, p=0.02)).

Pain characteristics with respect to the intensity of the pain were different between groups. The mean VAS score was higher in the continuous group (57 vs 48, p<0.001) as well as the mean Izbicki pain score (55 vs 41, p<0.001). The presence of a neuropathic pain component, assessed by the PainDETECT Questionnaire, was present in 17% of the continuous group and in 13% in the intermittent group (p=0.08). More patients used opioids and neuropathic pain medication in the continuous group. Quality of life was significantly lower in the continuous group compared with the intermittent group for both the physical and mental component (38 vs 41, p=0.005 and 44 vs 47, p=0.002; a score of 50 represents Dutch population). At inclusion in the CARE registry, 292 patients (26%) had undergone pancreatic surgery and 455 patients (40%) had undergone pancreatic interventional endoscopy. There was no difference in the proportion of patients who had undergone surgery between pain pattern groups (p=0.80). Interventional endoscopy was more often performed in the continuous pain group (p=0.04).

In the 311 patients without pain at inclusion, disease duration, exocrine and endocrine insufficiency were comparable to the patients with pain. Quality of life was 49 points for both the physical as mental component, which is almost comparable with the mean Dutch population score of 50 points. At inclusion in the CARE registry, 39% had undergone pancreatic interventional endoscopy and 24% of the patients had undergone pancreatic surgery.

Morphology on imaging was analysed at diagnosis of chronic pancreatitis and at inclusion in CARE (see online supplemental table A2). Imaging around the date of diagnosis was available in 776 patients (69%) and around date of study inclusion in 427 patients (38%). At study inclusion, 60% of the patients had calcifications in the pancreatic parenchyma and 20% in the pancreatic duct; 62% of the patients had a dilated pancreatic duct (≥5 mm) and 12% an enlarged pancreatic head (≥4 cm). There were no clinically relevant or statistically significant differences regarding morphology on imaging between the continuous and intermittent pain pattern groups (table 2).

Longitudinal analyses: alternations between pain pattern during follow-up

Of the 1131 included patients, 905 (80%) were available for follow-up, with a median of 47 months after inclusion (P25–P75: 25–64). During the entire follow-up period, 552 patients (61%) alternated at least once between pain patterns (figures 2 and 3). When analysed separately per follow-up year, 34% of patients alternated from one pain pattern to another each year (online supplemental figure A1 and table A3). Of the patients that alternated between pain patterns, 294 patients (53%) demonstrated one or more alternations between continuous and

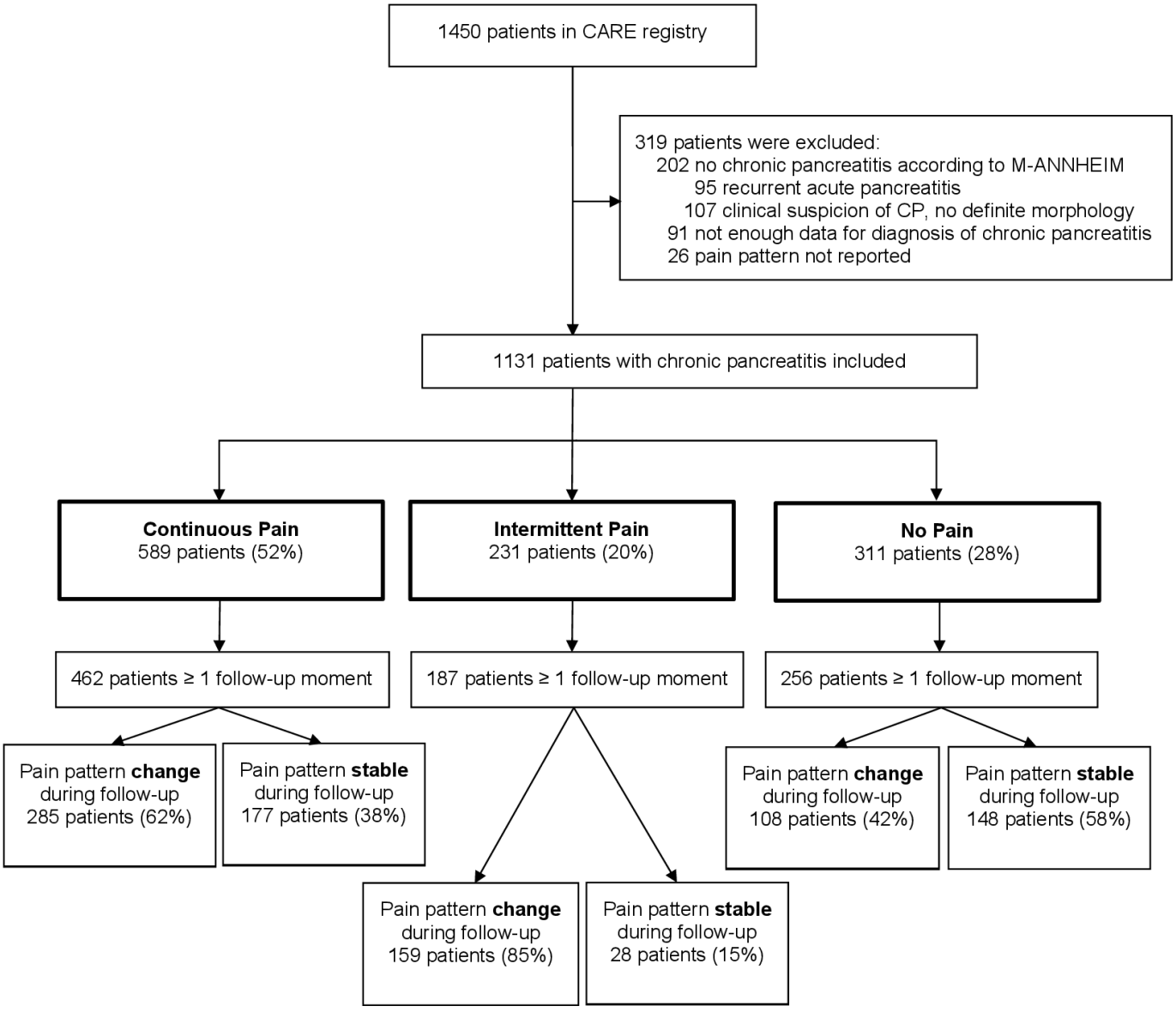

Figure 2 Flowchart of patient inclusion and follow-up. CARE, Dutch Chronic Pancreatitis Registry; CP, chronic pancreatitis.

intermittent pain patterns, and 333 patients (60%) alternated one or more times between no pain and pain. Pain patterns remained unchanged in a minority of patients (39%); 177 patients (20%) had consistently stable continuous pain and 28 patients (3%) had stable intermittent pain. Of the 311 included patients without pain, 256 (82%) were available for follow-up. During follow-up, 148 (58%) had stable no pain, and 108 (42%) alternated between pain patterns.

Longitudinal analyses: associated parameters with alternations between pain pattern

Multivariable multinomial regression analysis was performed to analyse which parameters were associated with alternations between pain patterns. Subgroup regression analyses for alternating of pain pattern per category are presented together with the multinomial analysis in table 3. Only the intensity of pain presented as VAS pain score (0–100) was associated with all types of alternations (OR: 0.97, 95%CI 0.94 to 0.99; p=0.04). During the follow-up, 148 patients (16%) underwent interventional endoscopy and 106 (12%) surgery. Interventional endoscopy during follow-up was not associated with any type of alternation. Surgery was associated with alternating of pain pattern (OR: 1.90, 95%CI 1.05 to 3.42; p=0.03) and specifically with the change from pain to no pain (OR: 11.83, 95%CI 4.40 to 31.82, p<0.001).

Sensitivity analysis

Since differences in pain pattern appeared to be independently associated with the intensity of pain (VAS pain score), the same cross-sectional comparison of continuous pain and intermittent pain pattern was done for severe pain (ie, use of opioids or a VAS pain score >40 without opioids) and mild pain (ie, no opioid use and a VAS pain score between 10 and 40) at inclusion in the registry. Results did not change, with two exceptions: patients with severe pain were more often current smokers and more often had intraductal calcifications on imaging, as compared with patients with mild pain (online supplemental tables A4 and A5).

DISCUSSION

Pain in chronic pancreatitis is a pathophysiological and clinical phenomenon that is poorly understood, and difficult to

Table 1 Cross-sectional patient and disease characteristics at CARE registry inclusion

	Continuous pain N=589	Intermittent pain N=231	No pain N=311	P value Continuous versus intermittent
Age (year), mean±SD	56±11	58±12	62±11	0.02
Duration of CP (months), median (P25–P75)	51 (17–109)	46 (14–90)	50 (19–107)	0.28
Duration of symptoms (months), median (P25–P75)	87 (45–167)	78 (34–151)	93 (37–181)	0.11
Male sex, no. (%)	402 (68)	147 (64)	235 (76)	0.21
Body mass index, mean±SD	23±4	24±5	24±4	0.09
Aetiology, no. (%)				0.12
Alcoholic	277 (57)[n]	101 (54)[l]	119 (50)[m]	
Idiopathic	102 (21)	42 (22)	54 (23)	
Autoimmune	7 (1)	9 (5)	17 (7)	
Hereditary	19 (4)	7 (4)	3 (1)	
Other	84 (17)	28 (15)	44 (19)	
Smoking, no. (%)				0.39
Never	59 (10)[b]	29 (13)	41 (13)[a]	
Past	147 (25)	63 (27)	113 (37)	
Current	381 (65)	139 (60)	156 (50)	
Pack years, median (P25–P75)	26 (11–38)	27 (11–37)	26 (11–28)	0.82
Alcohol, no. (%)				0.13
Never	62 (10)[b]	35 (15)	26 (8)[b]	
Past	351 (60)	124 (53)	141 (46)	
Current	174 (30)	72 (32)	142 (46)	
Units/day, median (P25–P75)	5 (1–11)	5 (1–10)	5 (2–8)	0.34
Exocrine insufficiency, no. (%)	411 (70)[a]	152 (66)	165 (54)[c]	0.28
Pancreatic enzyme therapy, no. (%)	306 (52)	118 (51)	139 (45)[a]	
Faecal elastase-1 (µg/g), median (P25–P75)	27 (14–176)	23 (14–165)	15 (14-107)	
Endocrine insufficiency, no. (%)	209 (36)	88 (38)	155 (50)	0.48
Insulin dependent, no. (%)	126 (21)	40 (17)	79 (25)	
Oral antidiabetic medication, no. (%)	83 (14)	48 (21)	76 (24)	
VAS pain score, mean±SD*	57±28	48±29	0±0	<0.001
Izbicki pain score, mean±SD*	55±24[i]	41±21[e]	8 ± 11[g]	<0.001
Pain attacks, median (P25–P75)†				
Frequency (times per week)	4 (1–26)	1 (0.5–7)	0 (0–0)	<0.001
Duration (hours per attack)	2 (1–24)	2 (1–24)	0 (0–0)	0.18
Radiating pain, no. (%)	382 (65)[d]	127 (55)[a]	0 (0)	0.007
Neuropathic pain (PainDETECT), no. (%)				0.08
No	320 (56)[j]	144 (64)[f]	287 (100)[k]	
Unclear	151 (27)	51 (23)	0 (0)	
Yes	99 (17)	28 (13)	0 (0)	
Quality of life scores (SF-36), mean±SD				
Physical health scale‡	38±11[e]	41±10[d]	49±9[h]	0.005
Mental health scale‡	44±12[e]	47±11[d]	49±11[h]	0.002
Hospital of inclusion				0.303
High-volume centre (≥50 patients with CP)	391 (66)	162 (70)	194 (62)	
Low-volume centre (<50 patients with CP)	198 (34)	69 (30)	117 (38)	
Pain medication, no. (%)				
Strong opioids	215 (37)[b]	37 (16)[a]	4 (1)[b]	<0.001
Weak opioids	147 (25)	35 (15)	5 (2)	0.002
Non-opioids	378 (64)	140 (61)	32 (10)	0.35
No medication	105 (18)	64 (28)	273 (88)	0.002
Neuropathic medication	62 (11)	8 (4)	10 (3)	0.001
Endoscopy before inclusion, no. (%)	252 (43)	81 (35)	122 (39)	0.04
Surgery before inclusion, no. (%)	153 (26)	62 (27)	77 (24)	0.80

Missing patients: a=1, b=2, c=3, d=4, e=6, f=8, g=9, h=14, i=15, j=19, k=24, l=44, m=74, n=100.
*Scale of 0–100, increasing with severity.
†In the continuous group, patients could have continuous pain with pain attacks. In the intermittent group, patients had pain attacks without pain in between. See figure 1.
‡Scale from 0 (maximum disability) to 100 (no disability), score of 50 represents Dutch population. Only summary component scales are reported. Subdomain scores are presented in the online supplemental table A6.
CARE, Dutch Chronic Pancreatitis Registry; CP, chronic pancreatitis; SF-36, Short-Form 36; VAS, Visual Analogue Scale.

Table 2 Morphology characteristics on imaging*

	Continuous pain	Intermittent pain	No pain	P value
Diagnosis	N=408	N=161	N=207	Continuous versus intermittent
Calcifications, n/n (%)	285/408 (70)	114/161 (71)	147/207 (71)	0.82
Intraductal	117/408 (29)	48/161 (30)	60/207 (29)	0.79
Parenchyma	259/408 (64)	104/161 (65)	136/207 (66)	0.80
Enlarged pancreatic head, n/n (%)	90/408 (22)	34/161 (21)	43/207 (21)	0.81
Pseudocysts, n/n (%)	204/408 (50)	79/161 (49)	92/207 (44)	0.84
PD dilatation, n/n (%)				0.92
Dilated (≥5 mm)	230/371 (62)	89/146 (61)	114/177 (64)	
Slightly dilated (2–4 mm)	53/371 (14)	20/146 (14)	25/177 (14)	
Non-dilated (<2 mm)	88/371 (22)	37/146 (25)	38/177 (22)	
CBD involvement†, n/n (%)	141/408 (35)	52/161 (32)	65/207 (31)	0.61
Vascular complications‡, n/n (%)	73/408 (18)	34/161 (21)	33/207 (16)	0.41
Liver cirrhosis, n/n (%)	3/408 (1)	4/161 (3)	2/207 (1)	0.10
Duodenal stenosis, n/n (%)	19/408 (5)	11/161 (7)	12/207 (6)	0.30
Study inclusion	N=251	N=84	N=92	
Calcifications, n/n (%)	145/251 (58)	50/84 (60)	61/92 (66)	0.78
Intraductal	53/251 (21)	16/84 (19)	20/92 (22)	0.69
Parenchyma	134/251 (53)	48/84 (57)	56/92 (61)	0.55
Enlarged pancreatic head, n/n (%)	32/251 (13)	10/84 (12)	7/92 (8)	0.84
Pseudocysts, n/n (%)	93/251 (37)	28/84 (33)	31/92 (34)	0.54
PD dilatation, n/n (%)				0.76
Dilated (≥5 mm)	127/205 (62)	40/66 (61)	43/69 (62)	
Slightly dilated (2–4 mm)	27/205 (13)	11/66 (17)	9/69 (13)	
Non-dilated (<2 mm)	51/205 (25)	15/66 (23)	17/69 (25)	
CBD involvement†, n/n (%)	84/251 (34)	27/84 (32)	25/92 (27)	0.82
Vascular complications‡, n/n (%)	34/251 (14)	15/84 (18)	13/92 (11)	0.37
Liver cirrhosis, n/n (%)	1/251 (0.4)	0/84 (0)	2/92 (2)	>0.99
Duodenal stenosis, n/n (%)	5/251 (2)	3/84 (4)	0/92 (0)	0.42

*Imaging within 6 months of diagnosis and within 12 months prior to inclusion.
†Dilatation, obstruction or stenting of the biliary tract.
‡Pseudoaneurysms, thrombosis and collaterals of the vascular system related to the pancreas.
CBD, common bile duct; PD, pancreatic duct.

interpret. This is the first longitudinal cohort study comparing continuous and intermittent pain patterns in chronic pancreatitis, with a long-term follow-up of around 900 patients. In the cross-sectional analyses of data at study inclusion, patients with continuous pain experienced a more severe pain, with increased use of opioids and neuropathic pain medication, and a lower

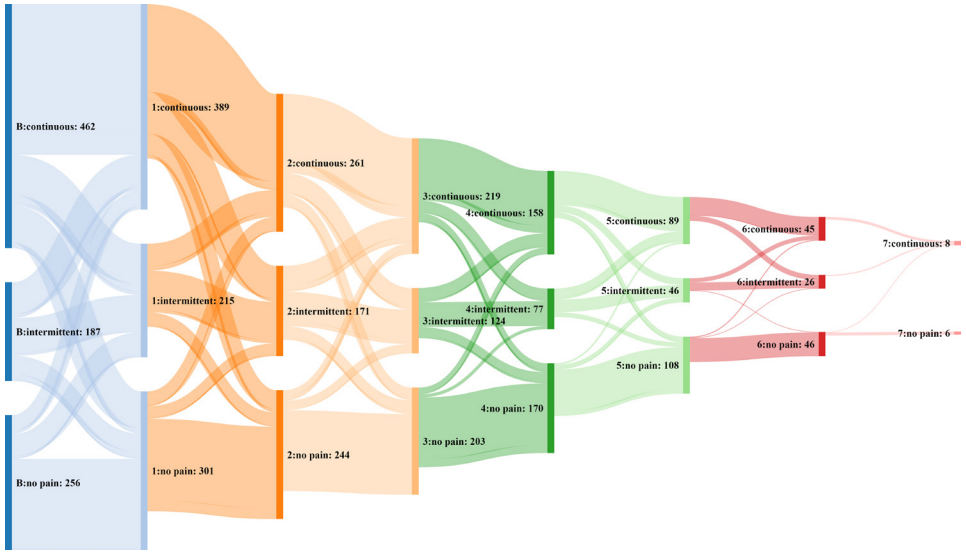

Figure 3 Sankey diagram of pain patterns during follow-up. Sixty-one per cent of patients had at least one pain pattern alteration.

Table 3 Multivariable multinomial logistic regression analysis of changes in pain pattern over time

			Subgroups							
	Multinomial regression n=905*		Continuous to intermittent n=489†		Intermittent to continuous n=292‡		Pain to no pain n=736§		No pain to pain n=420¶	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.00 (0.99 to 1.02)	0.7	1.01 (0.99 to 1.03)		0.99 (0.97 to 1.02)		0.99 (0.97 to 1.01)		1.01 (0.97 to 1.06)	
Sex		0.58								
Male	1		1		1		1		1	
Female	0.93 (0.73 to 1.20)		1.06 (0.70 to 1.60)		0.85 (0.50 to 1.44)		0.82 (0.49 to 1.37)		0.90 (0.41 to 1.97)	
Body mass index	0.99 (0.96 to 1.02)	0.38	0.99 (0.94 to 1.03)		0.98 (0.91 to 1.05)		1.02 (0.95 to 1.10)		1.02 (0.92 to 1.14)	
Hospital volume		0.9								
High (≥50 patients with CP)	1		1		1		1		1	
Low (<50 patients with CP)	1.02 (0.80 to 1.29)		0.98 (0.65 to 1.48)		0.72 (0.42 to 1.23)		0.88 (0.54 to 1.43)		0.78 (0.33 to 1.85)	
Aetiology		0.6								
Alcoholic	1		1		1		1		1	
Idiopathic	1.15 (0.86 to 1.55)		1.03 (0.64 to 1.66)		0.85 (0.40 to 1.79)		0.54 (0.28 to 1.02)		2.76 (1.23 to 6.23)	
Autoimmune	0.72 (0.34 to 1.55)		1.19 (0.38 to 3.71)		0.49 (0.09 to 2.60)		0.68 (0.19 to 2.40)		0.90 (0.26 to 3.09)	
Hereditary	1.29 (0.64 to 2.61)		0.82 (0.20 to 3.33)		0.52 (0.12 to 2.25)		0.71 (0.24 to 2.09)		1.26 (0.28 to 5.68)	
Other	0.94 (0.65 to 1.36)		0.79 (0.45 to 1.39)		0.83 (0.36 to 1.92)		0.50 (0.27 to 0.94)		1.32 (0.37 to 4.74)	
Smoking status		0.37								
Current	1		1		1		1		1	
Past	0.99 (0.75 to 1.29)		0.99 (0.63 to 1.55)		0.71 (0.35 to 1.42)		0.91 (0.53 to 1.55)		1.07 (0.46 to 2.51)	
Never	0.82 (0.61 to 1.11)		1.03 (0.61 to 1.74)		1.08 (0.53 to 2.22)		0.94 (0.50 to 1.78)		0.65 (0.27 to 1.59)	
Alcohol status	NA**	NA**	NA**		NA**		NA**		NA**	
Duration of symptoms	0.99 (0.99 to 1.00)	0.17	0.99 (0.99 to 1.00)		1.00 (0.99 to 1.00)		1.00 (0.99 to 1.00)		0.99 (0.99 to 1.00)	
VAS pain score††	0.97 (0.94 to 0.99)	0.035	0.89 (0.83 to 0.95)	0.001‡‡	1.18 (1.07 to 1.31)	0.002§§	0.27 (0.22 to 0.34)	<0.001‡‡	18.36 (2.68 to 125.9)	0.003§§
Endoscopy¶¶		0.25								
Yes	1.30 (0.83 to 2.05)		1.05 (0.48 to 2.28)		0.66 (0.26 to 1.71)		1.03 (0.42 to 2.56)		0.93 (0.22 to 3.93)	
No	1		1		1		1		1	
Surgery¶¶		0.033		0.59		0.54		<0.001***		NA††
Yes	1.90 (1.05 to 3.42)		1.42 (0.39 to 5.14)		1.71 (0.31 to 9.36)		11.83 (4.40 to 31.82)		NA††	
No	1		1		1		1		NA††	

*704 pain pattern changes in 2020 cases.
†253 events in 1093 cases.
‡226 events in 527 cases.
§306 events in 1926 cases.
¶208 events in 980 cases.
**Due to amount of missings not possible in GEE model.
††ORs were presented per 10 points difference of the VAS pain score. VAS pain score was chosen instead of Izbicki pain score. The Izbicki pain score is related to pain pattern since frequency of pain is part of this score.
‡‡VAS score decreases concomitant with change.
§§VAS score increases concomitant with change.
¶¶Intervention performed within 12 months prior to follow-up moment.
***Surgery in the last 12 months is positively associated with change from pain to no pain.
CP, chronic pancreatitis; GEE, generalised estimating equation; NA, not applicable; VAS, Visual Analogue Scale.

quality of life, as compared with patients with intermittent pain. No differences for any morphological finding on imaging or for disease duration were found between patients reporting continuous or intermittent pain patterns. During the longitudinal follow-up of median 47 months, the majority of patients (61%) alternated at least once between pain patterns. When analysed separately per follow-up year, 34% of patients alternated from one pain pattern to another each year. Strikingly, alternations between continuous and intermittent pain were not associated with endoscopic or surgical interventions, but only the VAS pain score was independently associated with these alternations. Thereby, only surgery and not interventional endoscopy was associated with the change from pain to pain. These results altogether suggest that the continuous and intermittent pain patterns in chronic pancreatitis are not specific pathophysiological entities requiring different treatment strategies, but rather a feature that plays a role in how the severity of pain is experienced in patients with chronic pancreatitis. Changes in pain patterns seem to be represented by alternating periods of continuous pain that is severe and periods of intermittent pain that patients experience as less severe. Potentially, alternations in pain pattern could better reflect changes in social and behavioural conditions than physical changes.

Continuous versus intermittent pain

Ammann and Muellhaupt first defined the intermittent (type A: intermittent pain episodes) and continuous (type B: prolonged periods of persistent pain) pain pattern in a prospective cohort of 207 patients in 1999. Ever since, this subdivision of clinical presentation of pain is used in daily practice, clinical studies and international guidelines.[3–5 19] In the original study, continuous pain appeared to be associated with end-stage severe disease with local complications, which responded well to surgical intervention. Intermittent pain was seen in early stage chronic pancreatitis without complications. Based on these findings,

the authors suggested further development on defining pain mechanisms, with a strategy for surgical interventions.[1] A more recent cross-sectional study with 540 patients demonstrated that patients with continuous pain have significantly poorer quality of life and greater rates of disability, as compared with patients with intermittent pain.[4] Because pain severity appeared to have little to no effect on these outcomes, the authors concluded that the pain pattern seems more important than the pain severity. The effect of pharmacological and invasive interventions potentially differs between pain patterns and therefore may require specific therapeutic approaches.[4]

We first performed a cross-sectional analysis of data at registry entry to generate data that can be compared with previous studies.[1 4 6 7] Our results were mostly similar, with more pain medication use and a lower quality of life in patients with continuous pain. These results did, however, not change in the sensitivity analysis looking at pain intensity (severe pain vs mild pain, based on opioid use and VAS score). In our longitudinal follow-up analyses, pain patterns did not seem to represent distinct entities of chronic pancreatitis since most of the patients alternated between patterns during follow-up, with changes from continuous to intermittent and vice versa. Our findings in the regression analysis showed that pain patterns were more a representation of severity of pain, since alternations between continuous and intermittent pain was only associated with the VAS score (intensity of pain) and with use of opioids. Another recent cross-sectional study showed that active smoking and alcohol use were independently associated with the presence of pain. In this study, there was an independent association between pain pattern and smoking and alcohol status, with continuous pain being more reported in heavy smokers and intermittent pain in heavy drinkers.[7] In our cross-sectional results and longitudinal analysis, we could not find an association between alcoholic aetiology, alcohol use smoking and pain patterns. Although there is homogenous evidence that alcohol use and smoking are associated with pain in chronic pancreatitis, the evidence on the association with pain patterns remains contradictory.

Alternations of pain pattern

It is known that pain in chronic pancreatitis has a very unpredictable course. In our study, patients alternated between pain patterns regardless of any endoscopic or surgical intervention. Only with the change from pain to no pain, surgical intervention in the past year was associated. On basis of the results of this exploratory study, it cannot be concluded that interventions have no effect on pain, particularly since surgery was associated with the change from pain to no pain. Changes in pain patterns seem to be represented by alternating periods of continuous pain that is severe and periods of intermittent pain which patients experience as less severe. Severity of pain in chronic pancreatitis should therefore not only be measured by the intensity of pain (VAS pain score), but also the frequency of pain and use of opioids should be included, such as by using the Izbicki pain score. This pain score is specifically designed for chronic pancreatitis and shows its effectiveness in many robust studies.[17 19 20] However, the higher VAS and Izbicki pain score in the continuous group could reflect a shortcoming of these tools, since patients with chronic pain could report higher pain scores due to the chronic character of the pain.

Pain pattern versus morphology

A cross-sectional comparison of imaging findings did not show any difference between patients with continuous and intermittent pain for a wide array of morphological changes that can be observed in chronic pancreatitis, including (intraductal) calcifications, ductal dilatation and pseudocysts. Only in the sensitivity analysis, intraductal calcifications were more often present in patients with severe pain compared with patients with mild pain. Potentially there is limited or even no correlation between pain and morphology in chronic pancreatitis and this was also suggested by previous studies.[8 10 21] A recent study compared imaging characteristics in 518 patients with different pain patterns, including 91 patients (16%) without pain.[21] Their results were comparable with our results, finding no difference in morphology between pain patterns, including presence of calcifications, ductal obstruction and dilatation, atrophy and pseudocysts.[21] However, an actual correlation between morphological findings and pain is difficult to rule out since interventional therapy relieving ductal obstruction leads to a high percentage of pain relief in many high-quality intervention studies.[17 19 22–24]

Burn-out theory

Decades ago the 'burn-out' theory was introduced by several small studies that showed a relation between pain relief and a longer disease duration with loss of pancreatic function in chronic pancreatitis.[1 25 26] This theory proclaims that severe pain is provoked by inflammation and that spontaneously pain relief will occur after long-standing disease with extensive fibrosis. However, the scientific ground for this 'burn-out' theory is doubtful. Present study and several other large studies with long-term follow-up showed that disease duration is not associated with pain relief.[4 27] Furthermore, present study showed that, during the disease, changes from pain to no pain are very heterogeneous and not associated with disease duration nor with exocrine and endocrine insufficiency. Our study therefore adds to the body of evidence to refute the so-called 'burn-out' theory.

Thereby, in all analyses, duration of chronic pancreatitis was comparable between continuous and intermittent pain, suggesting that these patterns are not associated with rather an early or end-stage of chronic pancreatitis, as was proposed by Ammann and Muellhaupt[1]

Post-hoc power analysis

It could be possible that our study was underpowered, with the result that the rejection of the hypothesis that continuous and recurrent pain patterns are different entities could be due to a statistical type II error. We, therefore, performed a post-hoc power analysis based on the Izbicki pain score, since this outcome involves different aspects of pain, including frequency, and is one of the most important outcome in this and other important studies.[17 19 22] The difference in Izbicki pain score between the continuous and intermittent pain pattern group was 14 points. With a two-sided alpha level of 0.05 and group size of, respectively, 589 and 231 patients, the power was >99%.

Limitations

This study evaluated long-term longitudinal data over 4 years on pain in a cohort of about 900 patients with chronic pancreatitis, therefore providing better insight in pain in chronic pancreatitis than the often used cross-sectional designs. It has also limitations. First, only physical outcomes are investigated in this study and outcomes regarding psychological, social and behavioural factors and treatment are missing. Potentially, alternations in pain pattern could better reflect changes in these mental conditions than the investigated physical changes. Thereby, outcomes regarding employment, hospital admissions and mortality are

missing. Second, although patients were prospectively included in this study, data collection on the time period between diagnosis of chronic pancreatitis and study inclusion were collected retrospectively. Moreover, time of inclusion in the CARE registry was random in the disease course of chronic pancreatitis, with already a median chronic pancreatitis duration of 50 months, and a reasonable proportion of patients had already been treated with pain medication and interventional therapy before study inclusion. This obviously influenced the evaluation of the natural disease course in these patients. Thereby, duration of follow-up may still be too limited to assess the development of pain to its full extent, since our median follow-up was around 4 years. Third, all analyses regarding morphology on imaging were cross-sectional and only apply to 38% of the patients who were included. Possibly, these imaging findings are not generalisable to the general population of patients with chronic pancreatitis. At last, although the pain questionnaires included in this study are all state-of-the-art and commonly used instruments, they have never been validated and standardised in chronic pancreatitis. Also, the diagnosis of exocrine insufficiency with the faecal elastase-1 test and enzyme therapy is limited, since the faecal elastase-1 test is not completely accurate.[28]

Future studies should focus on a standardised method of pain measurement like the Izbicki score, with intensity, frequency and use of opioids as main elements. Thereby, the contrary that there seems no relation between morphology and (pain) symptoms, but treating morphological abnormalities leads to pain relief has to be further explored, since the understanding and a robust explanation is still missing.

CONCLUSION

In conclusion, the results of this study suggest that continuous and intermittent pain patterns in chronic pancreatitis are not the result of distinctly different pathophysiological entities. The subjectively reported character of pain is not related to imaging findings, disease duration or treatment. Pain patterns often change over time, by alternating periods of continuous pain perceived as severe and periods of intermittent pain perceived as less severe. Pain patterns are therefore merely a feature of how severity of pain is experienced in patients with chronic pancreatitis.

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