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Original Research

Risk factors associated with pain and pain relief in patients with chronic pancreatitis

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Abstract

Background: Abdominal pain is one of the most prominent symptoms in patients with chronic pancreatitis (CP) and can manifest intermittently or persistently. The mechanism of pain is not yet clear, and no effective treatment is currently available. This study aimed to explore the risk factors for pain in patients with CP, which may provide new insights for developing effective pain control modalities.

Methods: This clinical study was based on a single-centre research database that included 570 patients with CP. We compared the differences in baseline data, clinical characteristics, and psychophysiology traits between patients with and without pain. Subsequently, patients will be followed up to assess changes in their risk factors and explore their relationship with pain.

Results: In the final risk factor model, young age ($P = .031$; odds ratio [OR] = 0.986 [0.973, 0.999]), prolonged disease duration ($P < .001$; OR = 1.307 [1.127, 1.516]), heavy smoking ($P = .014$; OR = 1.331 [1.060, 1.617]), alcohol consumption ($P = .003$; OR = 1.419 [1.127, 1.788]), low body mass index ($P < .001$; OR = 0.786 [0.703, 0.879]), pancreatic exocrine insufficiency ($P = .040$; OR = 1.683 [1.024, 2.767]), acute pancreatitis attacks ($P = .027$; OR = 1.759 [1.067, 2.902]), anxiety, and depression ($P = .016$; OR = 1.047 [1.009, 1.088]; $P = .014$; OR = 1.068 [1.013, 1.126]) were associated with CP pain. Reducing tobacco and alcohol intake ($P = .001$; OR = 2.367 [1.525, 4.637]; $P = .024$; OR = 2.011 [1.085, 3.199]), increasing the body mass index ($P = .005$; OR = 1.968 [1.265, 3.805]), and improving anxiety ($P = .001$; OR = 1.164 [1.081, 1.340]) were identified to be beneficial for pain relief. Compared to the effects on persistent pain, pancreatic enzyme supplementation ($P = .004$; OR = 1.794 [1.186, 2.502]) had a clear effect on intermittent pain in patients with CP.

Conclusion: We identified a multifactorial model of pain risk factors for CP and confirmed that modifying these risk factors could influence patient pain symptoms.

Key messages:

- **What is already known on this topic?**
  Due to the complex and incompletely understood underlying pain mechanisms of CP, currently, no effective and specific treatment is available for pain control in clinical practice. Previous studies have explored factors associated with painful CP, identifying smoking, alcohol consumption, aetiology, complications, and pathological characteristics as important aspects to consider.
- **What this study adds?**
  Previous cross-sectional studies lacked patient follow-up, which precludes the inference of a causal relationship between risk factors and pain outcomes. Our study supplemented this with long-term patient follow-up. Previous studies have mostly focused on the basic information and clinical characteristics of patients, lacking analysis of their social and psychological factors. We have added analysis in this area to this study.
- **How this study might affect research, practice, or policy?**
  We have confirmed that pain symptoms in patients with chronic pancreatitis are associated with multiple risk factors, and avoiding risk factors can alleviate pain symptoms, which has important implications for long-term management, improvement of quality of life, and avoidance of overuse of painkillers for patients.

Keywords: CP; risk factors; abdominal pain; pain relief; patient management

Introduction

Chronic pancreatitis (CP) is a pathological fibro-inflammatory syndrome of the pancreas characterized by sustained pathological reactions to injury or stress [1]. Clinically, CP manifests as abdominal pain, indigestion, impaired endocrine function, and fatty diarrhoea. The most prominent symptom in patients is pain, primarily located in the upper abdomen, which can present as either intermittent or persistent, ranging from mild to unbearable [2, 3]. Intractable recurrent abdominal pain is the main reason for consultation in >90% of patients and is associated with a poor prognosis. Unfortunately, due to the complex and incompletely understood underlying pain mechanisms of CP, currently, no effective and specific treatment is available for pain control in clinical practice [4]. Therefore, investigating factors related to pain in patients with CP may provide new insights for elucidating the pain mechanisms of CP and identifying effective methods for pain management [5].

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Previous studies have explored factors associated with painful CP, identifying smoking, alcohol consumption, aetiology, complications, and pathological characteristics as important aspects to consider. Olesen *et al.*'s study provides a detailed classification of smoking and drinking patterns and their correlation with pain profiles. Their research demonstrated that a high frequency of pain is observed in heavy smokers and drinkers. Additionally, intermittent pain was most common among drinkers, while smoking was associated with persistent pain [6]. However, their study is primarily applicable to Caucasian patients and requires validation in studies involving diverse ethnic populations. Furthermore, the researchers also noted that similar to previous studies, the cross-sectional study lacked patient follow-up, which precludes the inference of a causal relationship between risk factors and pain outcomes.

Prior studies on acute pancreatitis suggest that removing risk factors, including smoking and drinking cessation, is beneficial for improving the poor prognosis of acute pancreatitis. However, the aim of studying the risk factors of CP is often to mitigate these factors before the development of adverse outcomes. Notably, a lack of studies exists on the correlation between controlling risk factors and symptom relief. Specifically, a critical question in our research is whether pain can be relieved before the disease reaches an advanced stage. Additionally, the mechanisms and risk factors of CP pain are complex, and current research remains controversial and incomplete. Moreover, one ongoing debate centres around the relationship between imaging features and pain. For instance, Steinkohl *et al.*'s study suggests that the progression of CP gland morphology is not related to changes in quality of life or pain symptoms. Although advanced pancreatic imaging techniques may be highly sensitive tools for monitoring the progression of morphological diseases, they cannot directly reflect the disease burden experienced by patients. This inconsistency with previous research perspectives requires further exploration [7, 8].

Previous studies have mostly focused on the basic information and clinical characteristics of patients, lacking analysis of their social and psychological factors. Dunbar *et al.* highlighted that patients with complex and severe pain are likely to have multiple overlapping mechanisms driving pain, anxiety, and depression simultaneously [9]. Therefore, establishing a cohort of patients with CP; achieving long-term follow-up; exploring the influence of social and psychological factors, clinical characteristics, and pancreatic morphology on pain; and analyzing the correlation between risk factors and pain relief would provide valuable insights. This kind of analysis, focusing on the correlation between risk factors and pain relief, represents an innovative and necessary step in advancing CP management [10, 11].

This study was conducted in a stable cohort of patients with CP to:

1. Determine the prevalence of pain and risk factors for pain (including disease characteristics and psychophysiological factors).
2. Explore the correlation between changes in risk factors and pain relief during follow-up.

Materials and methods

Study design

This study was based on a single-centre research database that collects the clinical medical records of all patients who have visited the hospital since its establishment. Patient data diagnosed with CP between 1 June 2012, and 1 December 2017 were extracted from the database. Detailed information was obtained from the medical record system using each patient's unique identification code. After gathering comprehensive patient information, further screening was conducted based on CP as defined by the M-ANNHEIM classification system and guidelines for the diagnosis and treatment of CP. The exclusion criteria were as follows: (i) patients who could not fully meet the diagnostic criteria; (ii) patients currently diagnosed with pancreatic cancer or with a history of pancreatic cancer; (iii) patients with severe underlying conditions and poor general health; and (iv) patients for whom detailed information could not be obtained. Subsequently, a median follow-up of 6 years was conducted on the remaining patients, and their data were collected and statistically analyzed (Fig. 1).

The data collected in the study included basic information [sex, age, body mass index (BMI), dietary habits, age at diagnosis, duration, and aetiology classification], clinical manifestations (including pain and fatty diarrhoea), psychophysiology factors (such as stress and anxiety), complications (such as diabetes and immune system diseases), surgical history, treatment plans (including medication, surgical intervention, and endoscopic treatment), subjective evaluations of efficacy, laboratory examination results, imaging features, pathological data, and other relevant information. This study was approved by the relevant units and received permission from the ethics committee (QYFY WZLL 28588). All participants signed a written informed consent form at the beginning of the study. The participants did not include minors.

Study parameters and definitions

Based on the presence or absence of pain symptoms, all patients were divided into two groups: (i) those with painless CP and (ii) those with painful CP. The painful CP group was further divided into (a) patients experiencing intermittent pain and (b) patients experiencing persistent pain. Intermittent pain was characterized by brief episodes lasting fewer than 10 days, separated by long pain-free intervals. Persistent pain was defined as prolonged periods of daily pain, punctuated by clusters of recurrent, severe pain exacerbations. Pain relief was defined as complete or partial relief at the end of follow-up which was measured by the Izbicki pain score (complete relief: Izbicki pain score ≤ 10; partial relief: Izbicki pain score > 10 but with >50% reduction compared to the baseline score) [9, 12]. The patients' current drinking patterns were recorded as weekly alcohol consumption (14 g of pure alcohol per unit) and categorized as follows: nondrinkers, light drinkers ($\leq$3 drinks per week), moderate drinkers (4–7 drinks per week for women, 4–14 drinks per week for men), heavy drinkers (8–34 drinks per week for women, 15–34 drinks per week for men), and very heavy drinkers ($\geq$35 drinks per week for both sexes). Based on their current smoking status, patients' smoking patterns were classified into the following categories: nonsmokers, light smokers (<10 cigarettes per day), moderate smokers (10–20 cigarettes per day), and heavy smokers (>20 cigarettes per day). Reduced drinking was defined as a decrease in alcohol intake levels during the follow-up period (e.g. changing from heavy to light drinker), with a similar definition applied to reduced smoking [13–15].

The social and psychological factors affecting the patients were primarily evaluated through two conditions: depression and anxiety. The Hamilton Anxiety Scale and Hamilton Depression Scale were used to assess the severity of these conditions [16, 17].

Endoscopic and imaging manifestations of CP included pancreatic atrophy, pancreatic duct dilation or stenosis, pancreatic

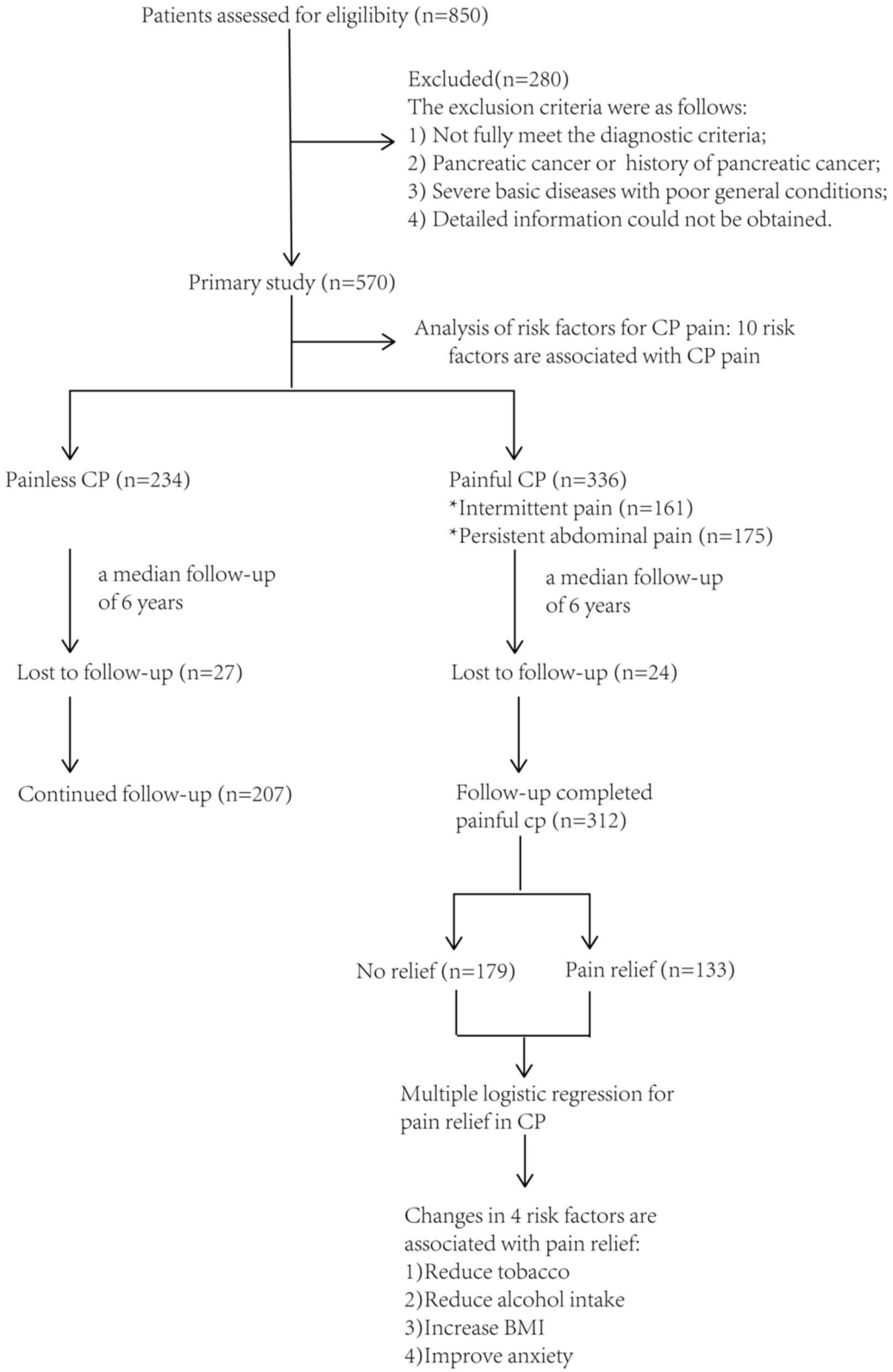

Figure 1 Flowchart of patient screening, classification, and follow-up for identifying risk factors associated with pain relief in CP.

pseudocysts, and pancreatic tissue calcification. These features are often observed using endoscopic ultrasound, computed tomography, magnetic resonance cholangiopancreatography, and abdominal ultrasound. The presence of one or more of the aforementioned characteristics in any prior imaging examination indicated positive imaging features.

Pancreatic exocrine insufficiency is defined as the insufficient or asynchronous secretion of pancreatic enzymes, lead-

Table 1. Univariate logistic regression analysis comparing patients with painful and painless CP.

		Patients with pain ($n = 336$)	Patients with painless CP ($n = 234$)	P- value	OR [95% CI]
Sex	Men	261 (78)	187 (80)	.522	0.875 [0.580, 1.318]
	Women	75 (22)	47 (20)		
Age of diagnosis	Mean ± SD	53.32 ± 14.13	57.51 ± 15.35	.001	0.981 [0.969, 0.992]
Duration	Mean ± SD	7.39 ± 1.64	6.87 ± 1.07	<.001	1.317 [1.156, 1.500]
Smoking	Nonsmoker	121 (36)	143 (61)	<.001	1.684 [1.388, 2.043]
	<10 cigarettes per day	111 (33)	53 (22)		
	10–20 cigarettes per day	75 (22)	27 (12)		
	>20 cigarettes per day	29 (9)	11 (5)		
Drinking	Nondrinker	133 (78)	142 (61)	<.001	1.720 [1.411, 2.097]
	Light use	98 (39)	59 (25)		
	Heavy use	75 (67)	26 (11)		
	Very heavy use	30 (67)	7 (3)		
BMI	Mean ± SD	21.26 ± 1.71	21.82 ± 1.72	<.001	0.825 [0.746, 0.911]
HAMA scores	Mean ± SD	15.02 ± 4.79	13.38 ± 5.21	<.001	1.068 [1.033, 1.105]
HAMD scores	Mean ± SD	7.34 ± 3.99	6.61 ± 3.31	.023	1.055 [1.007, 1.106]
Past history	Acute pancreatitis	113 (34)	41 (17)	<.001	2.385 [1.589, 3.580]
		223 (66)	193 (83)		
	DM	52 (16)	35 (15)	.865	1.041 [0.654, 1.658]
		284 (84)	199 (85)		
	Biliary tract	111 (33)	73 (32)	.650	1.088 [0.761, 1.556]
		225 (67)	61 (68)		
Image feature	Positive	219 (65)	133 (57)	0.045	1.421 [1.009, 2.002]
	Negative	117 (35)	101 (43)		
Pancreatic exocrine insufficiency	Insufficient	130 (39)	40 (17)	<.001	3.061 [2.041, 4.589]
		206 (61)	194 (83)		

ing to symptoms of poor nutritional digestion and absorption [18]. The diagnosis was based on a comprehensive evaluation of the patient's clinical symptoms, underlying diseases, nutritional status, and other factors that meet the diagnostic criteria for pancreatic exocrine insufficiency.

Statistical analysis

Statistical results were expressed as proportions for categorical data and as means [standard deviation (SD)] or medians (interquartile range) for continuous data. Continuous variables were analyzed using Student's *t*- and Wilcoxon rank-sum tests. Fisher's exact and Pearson's chi-square tests were employed for categorical variables. Possible exposure factors in cross-sectional studies, changes in exposure in cohort studies, and intervention factors were included in the multivariate logistic regression analysis, with the model adjusted according to the significance levels of the variables. Two-tailed *P*-values <.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 26.

Results

As of the data extraction, a total of 850 patients with CP were enrolled. After screening, 570 patients demonstrated high data completeness, which comprised the primary study cohort.

The baseline data and disease characteristics of the study population are presented in Table 1. The proportion of men in the cohort (79%) was significantly higher than that of women (21%). The average age of patients diagnosed with CP was 55.04 ± 14.78 years. Regarding pain patterns in patients with CP, a total of 336 patients (59%) reported abdominal pain symptoms, including 161 (48%) with intermittent and 175 (52%) with persistent abdominal pain.

The results of the final multiple logistic regression analysis identified 10 significant risk factors for pain (Table 2). Compared to patients who did not perceive pain, those with painful CP were often diagnosed at a young age ($P = .031$, 0.986 [0.973, 0.999]). Correspondingly, the duration of painful CP was long ($P < .001$, 1.307 [1.127, 1.516]). In terms of lifestyle habits, heavy smoking ($P = .014$, 1.331 [1.060, 1.617]) and alcohol consumption ($P = .003$, 1.419 [1.127, 1.788]) were both identified as risk factors for CP pain. A reduced BMI was also associated with CP pain ($P < .001$, 0.786 [0.703, 0.879]). Pancreatic exocrine dysfunction was prevalent in patients with painful CP ($P = .040$, 1.683 [1.024, 2.767]), whereas endocrine dysfunction (mainly manifested as diabetes) was not ($P = .865$, 1.041 [0.654, 1.658]).

In the final model, no correlation was identified between imaging manifestations and pain ($P = .278$, 1.238 [0.842, 1.822]). No significant differences were observed in other imaging manifestations between the groups. Regarding medical history, patients with a history of acute pancreatitis were prone to abdominal pain ($P = .027$, 1.759 [1.067, 2.902]), while those with a history of biliary tract disease were not ($P = .650$, 1.088 [0.761, 1.556]). Regarding social and psychological factors, anxiety and depression status scores were associated with pain, with significant levels of both considered key risk factors ($P = .016$, 1.047 [1.009, 1.088]; $P = .014$, 1.068 [1.013, 1.126]).

Follow-up was conducted on 570 patients with complete baseline data. The median follow-up time was 6 years. Among the 570 patients, 9 died (from tumour, cardiovascular disease, kidney disease, and unknown causes), 25 were lost to follow-up, 17 refused to provide follow-up information, and 519 completed the follow-up, resulting in a response rate of 91%. According to the pain pattern at the time of the initial recording, 312 of

Table 2. The multiple logistic regression results for pain in CP.

		Patients with pain ($n = 336$)	Patients with painless CP ($n = 234$)	P-value	OR [95% CI]
Sex	Men	261 (78)	187 (80)		
	Women	75 (22)	47 (20)		
Age of diagnosis	Mean ± SD	53.32 ± 14.13	57.51 ± 15.35	.031	0.986 [0.973, 0.999]
Duration	Mean ± SD	7.39 ± 1.64	6.87 ± 1.07	<.001	1.307 [1.127, 1.516]
Smoking	Nonsmoker	121 (36)	143 (61)	.014	1.331 [1.060, 1.617]
	<10 cigarettes per day	111 (33)	53 (22)		
	10–20 cigarettes per day	75 (22)	27 (12)		
	>20 cigarettes per day	29 (9)	11 (5)		
Drinking	Nondrinker	133 (78)	142 (61)	.003	1.419 [1.127, 1.788]
	Light use	98 (39)	59 (25)		
	Heavy use	75 (67)	26 (11)		
	Very heavy use	30 (67)	7 (3)		
BMI	Mean ± SD	21.26 ± 1.71	21.82 ± 1.72	<.001	0.786 [0.703, 0.879]
HAMA scores	Mean ± SD	15.02 ± 4.79	13.38 ± 5.21	.016	1.047 [1.009, 1.088]
HAMD scores	Mean ± SD	7.34 ± 3.99	6.61 ± 3.31	.014	1.068 [1.013, 1.126]
History	Acute pancreatitis	113 (34)	41 (17)	.027	1.759 [1.067, 2.902]
		223 (66)	193 (83)		
	DM	52 (16)	35 (15)		
		284 (84)	199 (85)		
	Biliary tract	111 (33)	73 (32)		
		225 (67)	61 (68)		
Image feature	Positive	219 (65)	133 (57)	.278	1.238 [0.842, 1.822]
	Negative	117 (35)	101 (43)		
Pancreatic exocrine insufficiency	Insufficient	130 (39)	40 (17)	.040	1.683 [1.024, 2.767]
		206 (61)	194 (83)		

the 336 patients with painful CP completed the follow-up (96%). Subsequently, multiple logistic regression analysis was conducted on the changes in parameters related to risk factors and pain patterns in 312 patients with painful CP, as demonstrated in Table 3. The analysis indicated that reducing tobacco and alcohol intake (or persistently avoiding them) can alleviate pain symptoms in patients with painful CP ($P = .001$, 2.659 [1.525, 4.637]; $P = .024$, 1.863 [1.085, 3.199]). Additionally, an increase in the BMI correlated with pain relief ($P = .005$, 2.194 [1.265, 3.805]). Furthermore, a decrease in anxiety scores was also associated with pain relief ($P = .001$, 1.203 [1.081, 1.340]), indicating that improving anxiety levels can improve patients' pain symptoms. However, improvement in depressive status did not exhibit a correlation with pain relief ($P = .139$, 1.053 [0.983, 1.128]).

Treatment with pancreatic enzymes was classified based on its duration of administration as follows: <1 month, 1–3 months, 3–6 months, and > 6 months. The results of multivariate regression analysis indicated that treatment with pancreatic enzymes did not correlate with pain relief ($P = .300$, 1.137 [0.892, 1.449]). Subsequently, painful CP was divided into persistent and intermittent pain groups based on pain patterns. The results of the subgroup analysis revealed that treatment with pancreatic enzymes had a pain-relieving effect on patients with intermittent pain ($P = .004$, 1.723 [1.186, 2.502]). In the persistent pain group, no correlation was observed between pancreatic enzyme treatment and pain relief ($P = .341$, 0.835 [0.575, 1.211]).

Discussion

This study screened 570 eligible patients with CP based on a single-centre scientific research data platform and examined the pain risk factors associated with CP. We established a stable patient cohort, conducted a 6-year follow-up on patients, and studied the correlation between changing risk factors and pain relief in patients with CP. In our cohort, 59% of patients reported pain, representing a lower prevalence compared to that reported in the North American Pancreatitis Study (85%) [19] and one that is similar to the prevalence reported in a North European pancreatitis study (60%) [6]. Additionally, the distribution of pain patterns varies among the three research cohorts; constant pain is the prevalent pain pattern in North America, while intermittent pain was observed frequently in our North European cohort. Interestingly, in our group, the proportions of these two pain types were relatively similar. These variations could be attributed to differences in medical approaches, differing methods of pain assessment, ethnic differences in the underlying patient populations, patterns of alcohol and tobacco consumption, and varying disease stages among the enrolled patients.

In our model of risk factors for pain, we included assessments of patient anxiety and depression status, which have been lacking in previous studies, in addition to lifestyle habits, disease course, imaging, and other factors. The final statistical analysis results suggested that age at diagnosis, disease course, smoking, drinking, BMI, depression and anxiety status, previous history of acute pancreatitis, and pancreatic exocrine dysfunction were related to CP pain, whereas sex, previous biliary diseases, diabetes, and patients' imaging performance were not associated with pain.

Reducing tobacco and alcohol intake, increasing BMI, improving anxiety, and alleviating pain are interconnected factors that significantly influence health outcomes. Particularly, when comparing the effects on persistent pain, pancreatic enzyme supplementation has a significant effect on intermittent pain in patients with CP. Moreover, smoking is highly correlated with multiple types of chronic pain and is an independent risk factor for the onset of CP [20]. Previous studies have confirmed that smoking is associated with persistent CP in a dose-dependent

Table 3. The multiple logistic regression results for pain relief in CP.

		Patients with pain relief ($n = 133$)	Patients with no relief ($n = 179$)	P-value	OR [95% CI]
Smoking	Consistent or increased	30 (23)	100 (69)	0.001	2.659 [1.525, 4.637]
	Reduced or no intake	103 (77)	79 (44)		
Drinking	Consistent or increased	37 (28)	95 (53)	0.024	1.863 [1.085, 3.199]
	Reduced or no intake	96 (72)	84 (47)		
Treatment with pancreatic enzymes	<1 month	37 (28)	64 (35)	0.300	1.137 [0.892, 1.449])
	1–3 months	19 (14)	51 (29)		
	3–6 months	57 (43)	39 (22)		
	>6 months	20 (15)	25 (14)		
BMI	No increase	35 (26)	91 (51)	0.005	2.194 [1.265, 3.805]
	Increase	98 (74)	88 (49)		
HAMA[a]	Mean ± SD	3.00 ± 2.68	1.23 ± 2.40	0.001	1.203 [1.081, 1.340]
HAMD[b]	Mean ± SD	4.41 ± 3.66	3.36 ± 3.72	0.139	1.053 [0.983, 1.128]

[a]Represents the changes in Hamilton Depression Scale scores. [b]Represents the changes in Hamilton Anxiety Scale scores.

manner. Compared with non-smokers, heavy smokers have a 2-fold increased risk [6]. In another study, continued smoking was associated with poor outcomes following surgical treatment for pain in patients with CP [21]. These findings are consistent with those of our research. Nevertheless, the underlying mechanisms of CP pain due to tobacco exposure remain inconclusive; however, they may involve increased sensitivity of central and peripheral receptors, along with the regulation of neural processing of sensory information by nicotine and other tobacco chemicals. Harmful substances such as carbon monoxide in tobacco can damage the inner walls of blood vessels, leading to increased interstitial pressure in the pancreas, insufficient tissue blood supply, and tissue acidosis—similar to a 'compartment-like syndrome' [22]. Importantly, these pathological and physiological changes can be repaired after smoking cessation, which aligns with the results of our study.

Consistent with previous studies, excessive alcohol consumption is significantly associated with pain in CP. *In vivo* experiments have demonstrated that excessive alcohol exposure can induce progressive visceral pain-like behaviours in rats with CP. This is mainly because ethanol directly damages pancreatic tissue, causing tissue oxidative stress, increasing endogenous opioid and enkephalin levels, and leading to a sustained increase in peripheral nerve input [23]. Similarly, after reducing ethanol intake, these reactions can be significantly alleviated, with reducing the intake of fat and nicotine having a synergistic effect [24]. Shah *et al.*'s study revealed that in the CP cohort, patients with recurrent acute pancreatitis were more likely to experience abdominal pain (89% vs. 67.9%) and were inclined to use opioids (58.4% vs. 32.3%) and gabapentinoids (56.6% vs. 34.8%) compared to patients without acute pancreatitis attacks. Although the patient groupings and statistical methods of the aforementioned two studies were different, the finding that recurrent acute pancreatitis is a risk factor for CP pain was similar [25].

Acute pancreatitis and CP may be interrelated, and some patients with CP may present with a history of recurrent acute pancreatitis. However, the initial pancreatic damage caused by acute pancreatitis can be reversed through the regeneration of exocrine acinar cells. This regeneration process involves transient phases of inflammation, acinar-to-ductal metaplasia, and acinar redifferentiation. Moreover, a correlation exists between the initial severity of tissue damage and the degree of acinar-to-ductal metaplasia formation [26]. The inflammatory response in acute pancreatitis leads to significant harmful peripheral stimuli and tissue and nerve damage, resulting in an increase in the synaptic efficiency of sensory neurons in the spinal dorsal horn (and/or upper spinal cord), a phenomenon known as central sensitization [27]. This explains our observation that patients with CP who experience acute pancreatitis are likely to experience pain.

Clinical studies have demonstrated that psychological fragility is a risk factor for long-term pain. Specifically, when patients encounter new sources of social and psychological stress, their potential for mild chronic pain may aggravate [28]. Yadav *et al.* investigated the association between the pain characteristics of CP and physical, psychological, and social health. Compared with participants with no pain, those with severe pain from CP (but not mild to moderate pain) displayed great decrements in each PROMIS domain in multi-variable models (effect sizes, 2.54–7.03) and a high prevalence of clinically significant depression, anxiety, sleep disturbance, and physical disability (odds ratios, 2.11–4.74 [29]. Furthermore, research by Phillips *et al.* also suggests that psychiatric comorbidities are prevalent in CP and are associated with pain and quality of life [30]. Our research results align with these findings; however, the aforementioned studies were primarily cross-sectional, making it difficult to explain the causal relationships between the variables.

Previous studies have predominantly focused on the psychological impact of pain on quality of life; our study is more concerned with whether improving psychological factors is beneficial for pain relief. We discovered that improvements in anxiety can alleviate pain in patients with CP. However, in our study, no correlation was observed between improvements in depressive states and pain relief, indicating that further research is needed to explore this point. Considering the above findings comprehensively, a potential bidirectional relationship exists among chronic pain, depression, and anxiety. To explain the correlation at the psychological factor level, the most prominent model of pain is the fear-avoidance model. In the context of pain, pain catastrophizing and catastrophic thinking (such as anxiety and depression) can lead to emotional distress, subsequently amplifying the subjective intensity of the pain experience [31]. Additionally, patients with chronic pain exhibit changes in brain structure and function. Some studies have confirmed that pain catastrophizing, anxiety, and depression can enhance the sensitivity of pain-processing brain regions to pain, emotion, and motor activity while simultaneously reducing the inhibition of pain from the central to peripheral regions, which can be demonstrated through resting-state functional magnetic resonance imaging data [32].

Exocrine pancreatic insufficiency (EPI) refers to a reduction in pancreatic enzyme activity, primarily pancreatic lipase, in the intestinal lumen below the threshold required for proper digestive functions. EPI can negatively impact the digestion, absorption, and metabolism of carbohydrates, fats, and proteins, leading to malnutrition, low BMI levels, complications, and a poor quality of life [33]. According to a general belief, the pancreas must lose 90% of its function before significant exocrine dysfunction occurs. Consequently, some scholars argue that when EPI develops, pancreatic damage indicative of CP is already severe. This may contribute to the high incidence of pain experienced by patients with CP and EPI [35].

Among the various causes of CP, EPI is often attributed to chronic obstructive pancreatitis. In such cases, intrapancreatic hypertension tends to present with abdominal pain symptoms [33]. Fortunately, pancreatic enzyme replacement therapy can effectively treat EPI and the associated malnutrition. However, a debate is ongoing regarding whether pancreatic enzyme replacement can alleviate pain. In a review of clinical trials examining the effects of pancreatic enzymes on pain relief, two trials indicated that supplementation with pancreatic enzyme tablets can improve pain, while the results of four other studies demonstrated no influence on pain relief. Notably, previous research on pancreatic enzyme replacement therapy did not classify the types of pain experienced by patients, but our study has refined this aspect [36–42].

In our analysis, we did not obtain meaningful results when analyzing the relationship between pain relief and pancreatic enzyme supplementation in a general context. However, our classification of pain patterns revealed that pancreatic enzyme supplementation affects intermittent pain in CP, while its effect on persistent pain remains uncertain [43]. Intermittent abdominal pain in patients with CP is primarily caused by indigestion resulting from EPI, which can be alleviated by pancreatic enzyme supplementation. In contrast, persistent pain typically originates in the pancreas, and the relationship between this type of pain and pancreatic enzyme therapy has yet to be established. This suggests that clinical management can be personalized based on the type of pain experienced by the patient. A precise classification of clinical symptoms can enhance treatment effectiveness and reduce the burden on medical resources [44,45].

Limitations

Our study had certain limitations. First, it was a single-centre study with a limited sample size; some patients exhibited low compliance, resulting in a loss to follow-up. Additionally, the follow-up period was relatively short, making it difficult to explore risk factors for slow changes, including imaging and pathological alterations in the pancreas. Moreover, while our study provided a unified analysis of risk factors for eligible patients with CP, we focused on analyzing the impact of changes in risk factors on the symptoms of patients with painful CP, as patients initially classified as painless exhibited few changes in clinical symptoms during follow-up. Lastly, our research needs to be confirmed in populations with diverse racial backgrounds to enhance its generalizability.

Conclusion

We identified a multifactorial model of pain risk factors for CP and confirmed that modifying the corresponding risk factors could influence pain symptoms.

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Author contributions

B.L. conceptualization, data curation. Y.C. and X.W. investigation, methodology. P.M., L.F., and Z.T. project administration, writing—review & editing. X.L. funding acquisition, resources.

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Data availability

The individual deidentified participant data (including data dictionaries) will be shared. The shared data content includes individual participant data that underlie the results reported in this article, after deidentification. Study Protocol, Statistical Analysis Plan and Analytic Code can also be shared. Data can be shared from 3 months to 5 years after the publication. Anyone who wants to obtain data for scientific research purposes can apply to the corresponding author (lixiaoyu05@163.com). To gain access, data requestors will need to sign a data access agreement. After obtaining consent, the data will be sent to the requester via email.

Research ethics approval

This study involves human participants and was approved by the Ethics Committee of Qingdao University Affiliated Hospital. NO.16 Jiangsu Road, Shinan District, Qingdao, Shandong Province, China. ID: QYFY WZLL 28588.

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