Association of multiple patient and disease characteristics with the presence and type of pain in chronic pancreatitis

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Multiple patient and disease characteristics associate with the presence and type of pain in chronic pancreatitis

Short title: Pain risk factors in chronic pancreatitis

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Abstract

Background: Pain is the primary symptom of chronic pancreatitis (CP) and associates with a number of patient and disease characteristics. However, the complex interrelations of these parameters are incompletely understood, and pain treatment remains unsatisfactory in a large proportion of patients.

Objective: We investigated multiple pain risk factors in a large population of CP patients, with a special emphasis on patients' patterns of smoking and alcohol use.

Methods: This was a multicenter, cross-sectional study including 1384 patients with CP. Patient demographics and disease characteristics, as well as current patterns of smoking and alcohol use, were compared for patients with pain (n=801) vs. without pain (n=583). Multivariate logistic regression models were performed to assess the variables associated with the presence and type of pain (constant vs. intermittent pain).

Results: The mean age of participants was 52.1±14.6 years and 914 (66%) were men. Active smoking (odds ratio (OR) 1.6 [95% CI; 1.1–2.2], p=0.005) and alcohol consumption (OR 1.8 [95% CI; 1.1–3.0], p=0.03) were independently associated with the presence of pain. In addition, patients age at diagnosis, pancreatic duct pathology and the presence of pseudocysts, duodenal stenosis and exocrine pancreatic insufficiency were confirmed as pain risk factors (all p≤0.01). Constant pain, as opposed to intermittent pain, was more frequently reported by smokers (p=0.03), while alcohol consumption was associated with intermittent pain (p=0.006).

Conclusion: Multiple patient and disease characteristics, including patterns of smoking and alcohol consumption, associate with the presence and type of pain in patients with CP.

Keywords: Chronic pancreatitis, pain, risk factors, smoking

Introduction

Pain is the primary symptom of chronic pancreatitis (CP) and associates with a poor health-related outcome[1–4]. Unfortunately, successful treatment of pain remains difficult and unsatisfactory in many cases, which is most likely explained by the complex and multifaceted underlying pain mechanisms[5–7]. A better characterization of patient and disease characteristics associated with pain (pain risk factors) may improve the understanding of pain and lead to new targets for therapy.

Past studies for pain risk factors have revealed a number of parameters that associate with the presence of pain. These include patients age at diagnosis[8], etiology and duration of CP[8,9], morphological features of the pancreas including pancreatic duct pathology[10], as well as the presence (or absence) of exocrine pancreatic insufficiency (EPI) and diabetes[9,11,12]. In addition, continued alcohol misuse have been linked to an increased frequency of painful episodes[1,13]. Taken together, these studies have underlined the complexity of pain and unraveled a number of pain risk factors that need consideration for optimal management. However, most past studies have been limited to single centers or focused on few parameters, but the majority of patients with CP present with several pain risk factors that may interact in complex patterns ultimately determining the individual patient´s pain profile[7]. Also, past studies have not investigated the independent impact of smoking on pain symptoms[1,14]. As smoking and alcohol misuse typically occur concurrently, analysis of each variable in an independent approach may lead to bias[15,16].

In a large multicenter cohort of patients with CP we studied pain risk factors, with a special emphasis on patients' current exposure to smoking and alcohol. The aims of the study were: i) to determine the prevalence of pain, ii) to determine risk factors for pain, and iii) to determine associations between pain risk factors and type of pain (intermittent vs. constant pain).

Methods

This was a cross-sectional, multicenter study based on data derived from the Scandinavian Baltic Pancreatic Club (SBPC) database. The SBPC database is an open multicenter prospective registration of patients with CP with continuously recruitment[17]. Data for the present study was derived from the database as of January 1st, 2019 and included data from 11 centers in seven countries in the Scandinavian-Baltic region and Russia (Moscow). The detailed study protocol and methodology of the SBPC database has previously been published[17]. CP was defined according to the M-ANNHEIM classification system and both patients with definitive and probable CP were included[18]. Patients with a current or past history of pancreatic cancer were excluded. The study was approved by the Institutional Review Board (IRB) at each participating center and Aalborg University Hospital served as the coordinating center (2008-58-0028, project ID 2018-19).

Assessment and characterization of pain

The patients´ pain pattern was characterized into the following categories according to a previously published classification[2]: i) no pain, ii) intermittent pain, iii) constant pain, and iv) constant pain with acute pain exacerbations. This classification is based on previous studies in patients with CP and emphasize the importance of distinguishing between patients with intermittent and constant pain[1,2,4,9]. The assessment and categorization of pain patterns was based on the patient's current perception of pain. For example, a patient with a past history of intermittent pain but suffering from continues pain at the time point of pain assessment would be categorized as having continues pain. We choose this approach for pain assessment as the primary aim of the study was to investigate associations between pain and current risk factor exposure (smoking and alcohol use). For the primary analysis the three subgroups of patients with pain were pooled and compared to the patient group without pain. For a secondary analysis, patients with pain were reorganized into two groups according to their type of pain (pain pattern) *viz.* intermittent pain (subgroup ii) and constant pain (subgroups iii and iv).

Patient assessment parameters

Information on patients' demographics (gender and age) and disease characteristics including duration and etiology of CP as well as the presence of diabetes were recorded based on patient interviews and review of medical records including biochemistry. The most likely etiological risk factor(s) were designated by the treating physician according to the M-ANNHEIM system. According to this system more than one etiological risk factor can be ascribed to the individual patient; no risk-thresholds were adopted in this process[18]. Exocrine

pancreatic function was characterized by the fecal elastase concentration test, C13 mixed triglyceride breath test or fecal fat collection according to local practice at the individual sites, and EPI was defined according to previously published criteria[19]. Review of imaging studies were performed as part of routine clinical practice at the individual sites by clinical pancreatologists, expert radiologists or endoscopic ultrasonographers. The presence of pancreatic calcifications, pancreatic duct abnormalities according to the Cambridge classification, pseudocysts and common bile duct or duodenal stenosis were registered in the database[20].

Drinking and smoking categories

Patients´ current patterns of alcohol consumption were registered as alcohol units (12 g of pure alcohol) consumed per week and organized into the following categories: abstainers (no current alcohol use), light drinkers (≤3 drinks per week), moderate drinkers (4 to 7 drinks per week for women or 4 to 14 drinks per week for men), heavy drinkers (8 to 34 drinks per week for women or 15 to 34 drinks per week for men), and very heavy drinkers (≥35 drinks per week for both sexes) [21]. Patients patterns of smoking were registered according to current smoking status and organized into the following categories: non-smokers, light smokers (<10 cigarettes per day), moderate smokers (10-20 cigarettes per day) and heavy smokers (>20 cigarettes per day).

Statistical analysis

Descriptive analyses are presented as proportions for categorical data and as mean (SD) or median (IQR) values for continuous data. Patient demographics and disease characteristics were compared for patients with pain and without pain using Student´s t-test or Wilcoxon rank-sum test for continuous variables and Fisher's test for categorical variables. Multivariable model development and analyses were performed in agreement with the TRIPOD recommendations[15]. Logistic regression with backward selection was performed to assess the variables associated with the presence of pain (primary analysis) in a multivariable model. Variables were included and removed one at a time according to their significance level ($p<0.15$) until a final model was reached, but variables considered to have clinical relevance were forced back into the model (diabetes)[15]. The presence of calcifications was omitted from the multivariable model due to collinearity with moderate/marked pancreatic duct pathology. Interaction between alcohol intake and smoking was determined using a

nested log-likelihood test, comparing a model containing the variables as single terms with a model also including the interaction term[22]. The final logistic regression model included 1097 of the 1384 enrolled patients with complete data for all variables of interest. Results from multivariate analyses were presented as odds ratios (ORs) with 95% confidence intervals (CI). A sensitivity analysis was performed by stratifying patients into one of four categories based on their current smoking and alcohol exposure and differences in proportions of patients between categories were compared using Fisher's tests. A similar approach as used to for the primary analysis was used to assess the variables associated with the patterns of pain (secondary analysis). A significance threshold of $p<0.05$ was used. The software package STATA version 15.1 (StataCorp LP, College Station, Texas, USA) was used for statistical calculations.

Results

A total of 1550 patients with CP were enrolled in the SBPC database on the date of data extraction. Among these, a pain pattern characterization was available in 1384 patients, which comprised the primary study cohort. Complete datasets were available from 1097 of the 1384 patients in the primary study cohort; missing data were randomly distributed across most variables and confined to one or two variables for >75% of the patients with missing data (supplementary figure1 and Table 1). Demographics and disease characteristics of the study cohort are reported in Table 1. Patients had a mean age of 52.1±14.6 years at the time of CP diagnosis and were predominantly males (66%). A definitive diagnosis of CP was established in 1177 (85%) of patients, and 207 (15%) had a diagnosis of probable CP. According to the treating physician's designation, alcohol was considered an etiological risk factor in 753 (54%) of patients and smoking a risk factor in 819 (59%) of patients. In 580 (42%) of patients, smoking and alcohol were considered coexisting risk factors.

Pain prevalence and pain patterns

Eight hundred-one of the 1384 included patients had pain, while 583 patients had no pain. This corresponds to a pain prevalence of 57.9% (95% CI; 55.2-60.5). The most frequently reported pain pattern was intermittent pain observed in 572 (71%) of patients. This was followed by constant pain with acute exacerbations observed in 151 (19%) of patients, while a constant pain pattern was observed in 78 (10%) of patients.

Pain risk factors (primary analysis)

Patients with painful CP were more likely to be diagnosed with CP at a younger age compared to patients with pain free CP ($p<0.001$). Likewise, patients with long lasting CP were more likely to report pain compared to patients with short lasting disease ($p=0.005$). There were no differences in the proportions of patients with and without pain in relation to gender ($p=0.25$) – Table 1.

Patients patterns of alcohol consumption were associated with the presence of pain ($p=0.003$), but only patients with a very heavy alcohol misuse (>5 units of alcohol per day) had a significantly higher risk of pain compared to alcohol abstainers – figure 1a. In addition, an increased risk of pain was seen with increasing number of daily cigarettes smoked ($p<0.001$) – figure 1b.

Pancreatic exocrine insufficiency was more frequently observed in patients with painful CP ($p=0.007$), while the presence of diabetes was comparable between patients with and without pain ($p=0.27$). With regards to pancreas morphology, moderate or marked pancreatic duct changes ($p<0.001$ and pancreatic calcifications ($p=0.04$) were seen more frequently in patients with pain. In addition, a number of complications to CP including pseudocysts ($p<0.001$), common bile duct stenosis ($p=0.001$) and duodenal stenosis ($p<0.001$) were more frequently seen in the subgroup of patients with pain – Table 1.

Multivariate analysis confirmed the independence and significance of the associations for pain and age at diagnosis ($p<0.001$), current status of smoking ($p=0.005$) and alcohol consumption ($p=0.03$) as well as the presence of EPI ($p=0.01$), pancreatic duct changes ($p=0.001$), pseudocysts ($p<0.001$) and duodenal stenosis ($p<0.001$) – figure 2 and supplementary Table 1. We found no evidence of interaction between alcohol intake and smoking on the risk of pain ($p=0.77$).

Distributions of patients with pain according to current status of smoking and alcohol consumption are illustrated in figure 3 (sensitivity analysis). Active smokers had an increased risk of pain compared to abstainers (61% vs. 43%; $p<0.001$) and patients with active alcohol consumption (61% vs. 46%; $p=0.04$), while the probability of pain was comparable between smokers with and without active alcohol consumption (61% vs. 57%; $p=0.21$). Active alcohol consumers had a risk of pain comparable to that observed in abstainers (46% vs. 43%, $p=0.65$) and alcohol consuming smokers (46% vs. 57%; $p=0.19$).

Associations between pain risk factors and pain patterns (secondary analysis)

Compared to patients with intermittent pain, patients with constant pain were more likely to be diagnosed with CP at a younger age ($p=0.06$) and to have long lasting CP ($p=0.02$), while

the distribution of gender was proportionate between patients with intermittent and constant pain (p=0.45) – Table 2.

Patients current exposure to alcohol was associated with the patients' pain patterns, with active alcohol consumers being more likely to report intermittent pain (p=0.06). In contrast, smoking was not associated with the patients' pain pattern on univariable analysis (p=0.34) – Table 2.

Patient with EPI (p=0.006), diabetes (p=0.03), pancreatic calcifications (p=0.04) and common bile duct stenosis (p=0.004) were more likely to have constant pain as opposed to intermittent pain, while the presence of pancreatic duct lesions (p=0.18), pseudocysts (p=0.28) and duodenal stenosis (p=0.84) were not associated with the patients´ pain patterns – Table 2.

Multivariate analysis revealed a significant and independent association between the patients´ pain pattern and smoking status, with constant pain being more frequently reported in moderate (p=0.06) and heavy smokers (p=0.03). The association for alcohol and intermittent pain was also confirmed on multivariable analysis, with the most notable association seen for heavy alcohol consumers (p=0.006). In addition, moderate to marked pancreatic duct changes (p=0.07) and EPI (p=0.06) trended to associate with constant pain, while none of the remaining variables were associated with patients' pain pattern on multivariate analysis – figure 4 and Supplementary Table 2.

Discussion

In a large multicenter cohort comprising of almost 1400 patients with CP we studied risk factors for pain. Sixty percent of patients had pain and intermittent pain was the most frequently reported pain pattern. Patients current patterns of smoking and alcohol use were independently associated with the presence of pain, with higher pain frequencies observed in heavy smokers and excessive alcohol consumers. Furthermore, smoking and drinking behavior were associated with patients' pain patterns; intermittent pain was most frequently observed in alcohol consumers, while smoking was associated with constant pain. In keeping with previous studies, a number of disease complications were confirmed as pain risk factors. Taken together these findings have important clinical implications: First, the increased risk for pain associated with active smoking and alcohol use underlines the importance of smoking and alcohol cessation in this context. Second, our findings emphasize the importance of a systematic clinical work-up of patients to exclude complications potentially amendable for therapy[10].

Pain prevalence and pain patterns

Sixty percent of patents reported pain in our cohort, which is a lower pain prevalence compared to that reported in the North American Pancreatitis Study 2 (85%)[1]. Also, the distribution of pain patterns differed between the two study cohorts, with constant pain being the most prevalent pain pattern in North America, while intermittent pain was most frequently seen in our North European cohort[1]. The differences between the two study cohorts may relate to different methods for pain assessment[1,2], ethnical differences in the underlying patient populations[23], differing patterns of alcohol and tobacco consumption [1] and different disease stages of the enrolled patients[24].

Risk factors for pain

A notable finding of our study was the independent association between smoking and pain with a nearly twofold increased risk of pain in heavy smokers compared to non-smokers. Smoking is a well-established risk factor for CP and accelerates the development of pancreatic insufficiency and calcifications[14,21,22]. However, the association between smoking and pain is less clear. In a previous study by Mullady et al. smoking was associated with a higher prevalence of constant pain as opposed to intermittent pain[1]. However, dose-risk relationships were not explored, and analysis was not adjusted from influence of other pain risk factors including alcohol consumption. Furthermore, a group of CP patients without pain was not included in the study by Mullady et al. which makes it difficult to ascertain if smoking was associated with the presence of pain *per se*[1]. In another study, continued smoking was associated with a poor outcome to surgical treatment of pain in CP patients, which is in keeping with the findings from our study[25].

The relationship for alcohol consumption and pain was complex and only patients with a very heavy alcohol use had a significantly increased risk for pain compared to alcohol abstainers. Along this line, alcohol did not convey an increased risk of pain in the sensitivity analysis, where only patient subgroups including active smokers had an increased risk of pain, implying that smoking rather than alcohol is a risk factor for pain in CP. This is in opposition to findings from past studies where active alcohol consumption was associated with pain[1,13]. However, alcohol and smoking effects were not isolated in those studies and consequently the previous observed associations for alcohol and pain may be explained by residual confounding by smoking.

In addition to smoking and alcohol consumption, a number of known pain risk factors were confirmed in our study. Moderate to severe pancreatic duct abnormalities according to the Cambridge classification were independently associated with the presence of pain, which is conceivable as ductal pathology provides the morphological substrate for most invasive procedures used for pain management in CP[10,26]. Also, the presence of EPI, pseudocysts and duodenal stenosis were confirmed as pain risk factors thus emphasizing the importance of a systematic clinical work-up of patients, as these complications are often treatable[10,19]. No association between disease duration and pain was observed on multivariate analysis, thus questioning the "burn-out" phenomenon of pain in CP[9]. However, the cross-sectional nature of our study precludes any definitive conclusions in relation to the temporal aspect of pain evolution.

Associations between pain risk factors and pain patterns

The multivariate risk estimates for constant vs. intermittent pain were directionally lower for all alcohol categories, while they were directionally higher for all smoking categories. This implies that smoking associates with constant pain, while alcohol use associates with an intermittent pain pattern. The finding may be explained by observations from a recent publication from our group where smoking was associated with development of fibrosis related complications, while alcohol was associated with inflammatory driven complications[16]. Hence, it is likely that fibrotic complications (for example a pancreatic duct stricture) will result in a more constant pain pattern, as opposed to inflammatory complications that in many patients relate to an acute, but reversible, deterioration in the patient`s clinical state (acute on chronic pancreatitis). This observation has important implications as constant pain often lead to sensitization of the pain system as a consequence of continued nociceptive input on central pathways, which may ultimately result in an autonomous and self-perpetuating pain state that has become independent of the peripheral nociceptive drive[5–7,26]. Consequently, constant pain becomes more difficult to treat than intermittent pain and is associated with impaired quality of life, more lost work days and an increased frequency of hospitalizations compared to intermittent pain[1,3]. In keeping with this, constant pain and continued smoking are predictors of failed surgical treatment for painful CP[25,27].

Study limitations

Our study has several limitations that are important to emphasize. First, the cross-sectional nature precludes any causal inference of the observed findings. To confirm a causal relationship between smoking, alcohol exposure and pain, well-designed prospective studies are needed. Likewise, prospective studies including patient reported outcome measures (PROMS) as well as proxies of disability (hospitalization, ability to work) and other clinically relevant outcome parameters, are needed to investigate the clinical relevance of the observed differences in pain prevalence between smokers and non-smokers. Second, no assessments of pain intensity or pain medication were obtained. Adjusting for these parameters may have influenced our findings. On the other hand, the patients´ pain pattern, as opposed to pain severity, has previously been shown to be the most important determinant of pain related outcome[1]. Third, recall bias may have some relevance for our findings in particular for the quantification of alcohol and smoking exposure. To minimize this bias, we intentionally focused our assessments on current patterns of alcohol and tobacco consumption (i.e. modifiable risk factors) as opposed to patients' past history of alcohol consumption and smoking. Fourth, our study may be subject to response and selection bias. Hence, an appropriate assignment of pain phenotype was not obtained in all enrolled patients, and 166 of 1550 (11%) were excluded from our final study cohort. Our response rate was, however, higher than that obtained in the North American Pancreatitis Study II (77%)[1]. Also, patients failing to assign pain assessment responses have generally been shown to have less pain (according to the treating physician and analysis of pain medication utilization) compared to questionnaire responders[1]. Finally, our findings largely apply to Caucasian patients and need to be confirmed in studies including patent populations with different ethnical backgrounds[23].

Conclusions

Several patient and disease characteristics, including patterns of smoking and alcohol consumption, associate with the presence and type of pain in patients with CP. These findings underlines the complexity of pain and specifically emphasize the importance of smoking and alcohol cessation in this context.

References

1. Mullady DK, Yadav D, Amann ST, O'Connell MR, Barmada MM, Elta GH, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut. 2011 Jan;60(1):77–84.
2. Olesen SS, Juel J, Nielsen AK, Frøkjær JB, Wilder-Smith OHG, Drewes AM. Pain severity reduces life quality in chronic pancreatitis: Implications for design of future outcome trials. Pancreatology [Internet]. 2014;14(6):497–502. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25455540
3. Machicado JD, Amann ST, Anderson MA, Abberbock J, Sherman S, Conwell DL, et al. Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities. Am J Gastroenterol [Internet]. 2017;112(4):633–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28244497
4. Olesen SS, Poulsen JL, Broberg MCH, Madzak A, Drewes AM. Opioid treatment and hypoalbuminemia are associated with increased hospitalisation rates in chronic pancreatitis outpatients. Pancreatology [Internet]. 16(5):807–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27320721
5. Olesen SS, Brock C, Krarup AL, Funch-Jensen P, Arendt-Nielsen L, Wilder-Smith OH, et al. Descending inhibitory pain modulation is impaired in patients with chronic

pancreatitis. Clin Gastroenterol Hepatol [Internet]. 2010 Aug [cited 2012 Mar 17];8(8):724–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20304100

6. Frøkjær JB, Bouwense S a W, Olesen SS, Lundager FH, Eskildsen SF, van Goor H, et al. Reduced cortical thickness of brain areas involved in pain processing in patients with chronic pancreatitis. Clin Gastroenterol Hepatol [Internet]. 2012 Apr 7 [cited 2012 Mar 17];10(4):434–8.e1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22155560

7. Olesen SS, Krauss T, Demir IE, Wilder-Smith OH, Ceyhan GO, Pasricha PJ, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. Pain reports [Internet]. 2017 Nov;2(6):e625. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29392239

8. Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology. 1994 Nov;107(5):1481–7.

9. Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. Gastroenterology [Internet]. 1999 May [cited 2014 May 3];116(5):1132–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10220505

10. Drewes AM, Bouwense SAW, Campbell CM, Ceyhan GO, Delhaye M, Demir IE, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology. 2017;17(5).

11. Ammann RW, Akovbiantz A, Largiader F, Schueler G. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. Gastroenterology [Internet]. 1984 May;86(5 Pt 1):820–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6706066

12. Lankisch PG, Löhr-Happe A, Otto J, Creutzfeldt W. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. Digestion [Internet]. 1993;54(3):148–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8359556

13. de las Heras G, de la Peña J, López Arias MJ, Gonzalez-Bernal AC, Martín-Ramos L, Pons-Romero F. Drinking habits and pain in chronic pancreatitis. J Clin Gastroenterol [Internet]. 1995 Jan [cited 2014 Mar 26];20(1):33–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7884174

14. Maisonneuve P, Lowenfels AB, Müllhaupt B, Cavallini G, Lankisch PG, Andersen JR, et al. Cigarette smoking accelerates progression of alcoholic chronic pancreatitis. Gut [Internet]. 2005 Apr;54(4):510–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15753536

15. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med [Internet]. 2015 Jan 6;162(1):W1-73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25560730

16. Olesen SS, Nøjgaard C, Poulsen JL, Haas SL, Vujasinovic M, Löhr M, et al. Chronic Pancreatitis Is Characterized by Distinct Complication Clusters That Associate With Etiological Risk Factors. Am J Gastroenterol [Internet]. 2019 Feb 5; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30741740

17. Olesen SS, Poulsen JL, Drewes AM, Frøkjær JB, Laukkarinen J, Parhiala M, et al. The Scandinavian baltic pancreatic club (SBPC) database: design, rationale and characterisation of the study cohort. Scand J Gastroenterol. 2017;52(8).

18. Schneider A, Löhr JM, Singer M V. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol [Internet]. 2007 Feb [cited 2014 Mar 25];42(2):101–19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17351799

19. Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J. 2017 Jan;205064061668469.

20. Sarner M, Cotton PB. Classification of pancreatitis. Gut [Internet]. 1984 Jul;25(7):756–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6735257

21. Yadav D, Hawes RH, Brand RE, Anderson M a, Money ME, Banks P a, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med [Internet]. 2009 Jun 8;169(11):1035–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19506173

22. Tolstrup JS, Kristiansen L, Becker U, Gronbaek M. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. Arch

Intern Med. 2009 Mar;169(6):603–9.

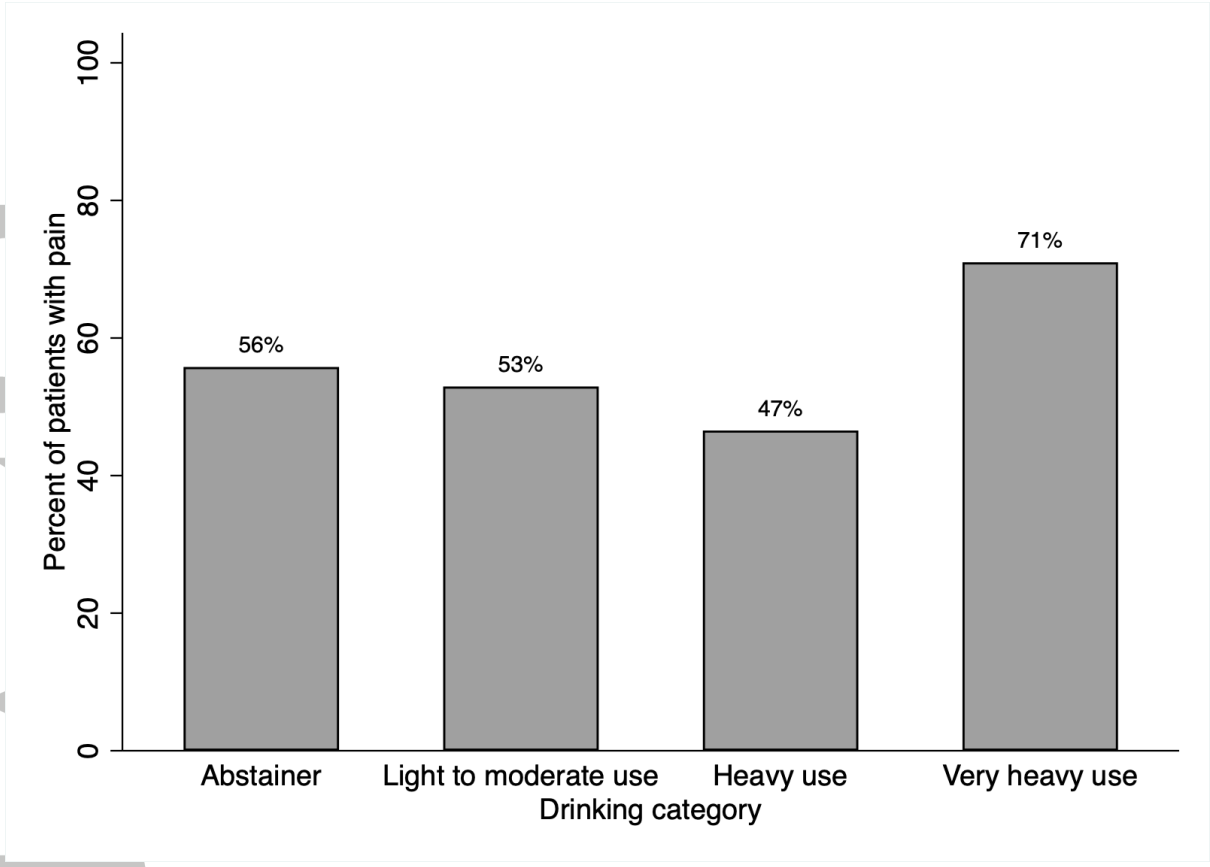
23. Wilcox CM, Sandhu BS, Singh V, Gelrud A, Abberbock JN, Sherman S, et al. Racial Differences in the Clinical Profile, Causes, and Outcome of Chronic Pancreatitis. Am J Gastroenterol [Internet]. 2016 Oct;111(10):1488–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27527745

24. Bellin MD, Whitcomb DC, Abberbock J, Sherman S, Sandhu BS, Gardner TB, et al. Patient and Disease Characteristics Associated With the Presence of Diabetes Mellitus in Adults With Chronic Pancreatitis in the United States. Am J Gastroenterol [Internet]. 2017 Sep;112(9):1457–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28741615

25. Bordaçahar B, Couvelard A, Vullierme M-P, Bucchini L, Sauvanet A, Dokmak S, et al. Predicting the efficacy of surgery for pain relief in patients with alcoholic chronic pancreatitis. Surgery [Internet]. 2018 Nov;164(5):1064–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30029988

26. Drewes AM, Kempeneers MA, Andersen DK, Arendt-Nielsen L, Besselink MG, Boermeester MA, et al. Controversies on the endoscopic and surgical management of pain in patients with chronic pancreatitis: pros and cons! Gut [Internet]. 2019 May 25; Available from: http://www.ncbi.nlm.nih.gov/pubmed/31129569

27. Negi S, Singh A, Chaudhary A. Pain relief after Frey's procedure for chronic pancreatitis. Br J Surg. 2010 Jul;97(7):1087–95.



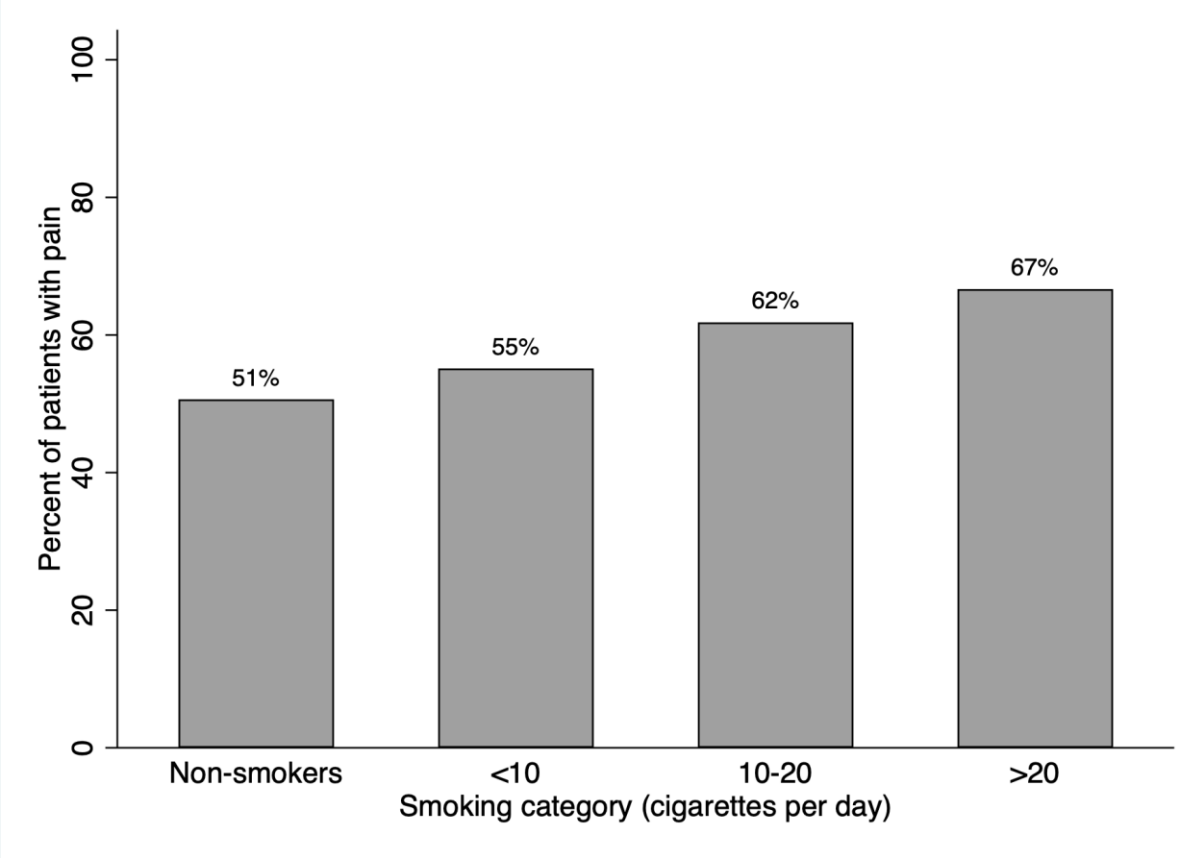


Figure 1. Distribution of chronic pancreatitis patients with pain stratified by patterns of alcohol use (A) and smoking (B)

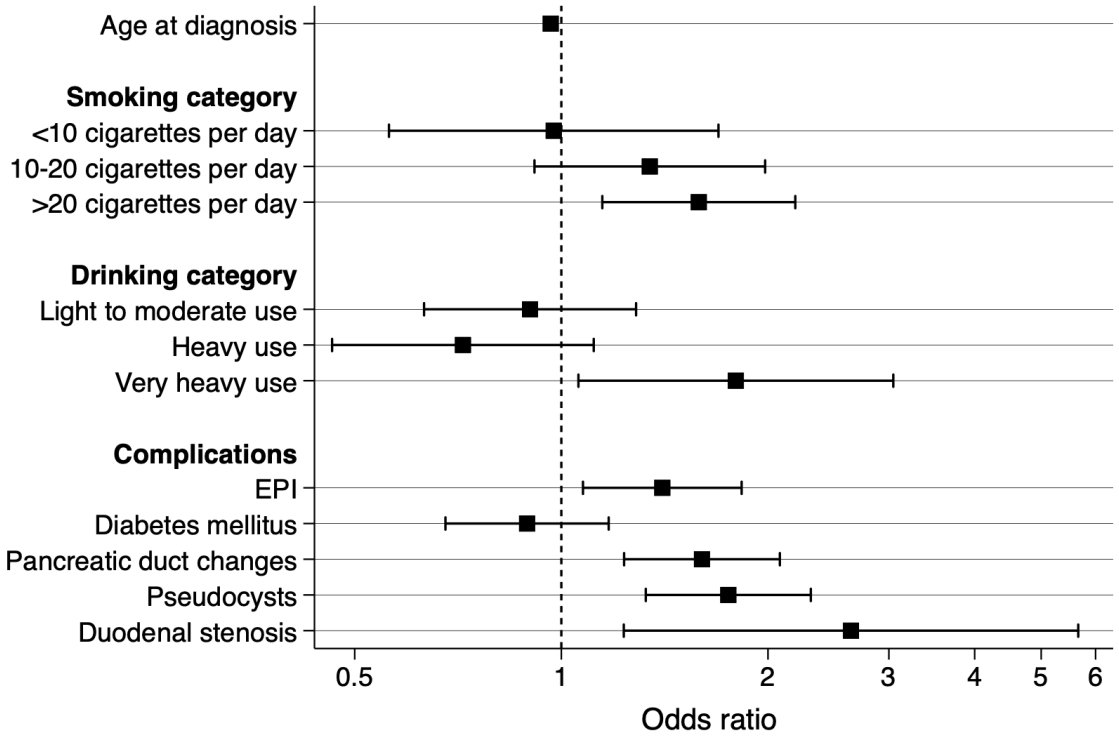


Figure 2. Forest plot of the multivariable logistic regression model for the presence of pain vs. no pain in patients with chronic pancreatitis. Non-smokers served as reference group for smoking categories and alcohol abstainers served as reference group for alcohol categories. Whiskers represent 95% confidence intervals. EPI; exocrine pancreatic insufficiency

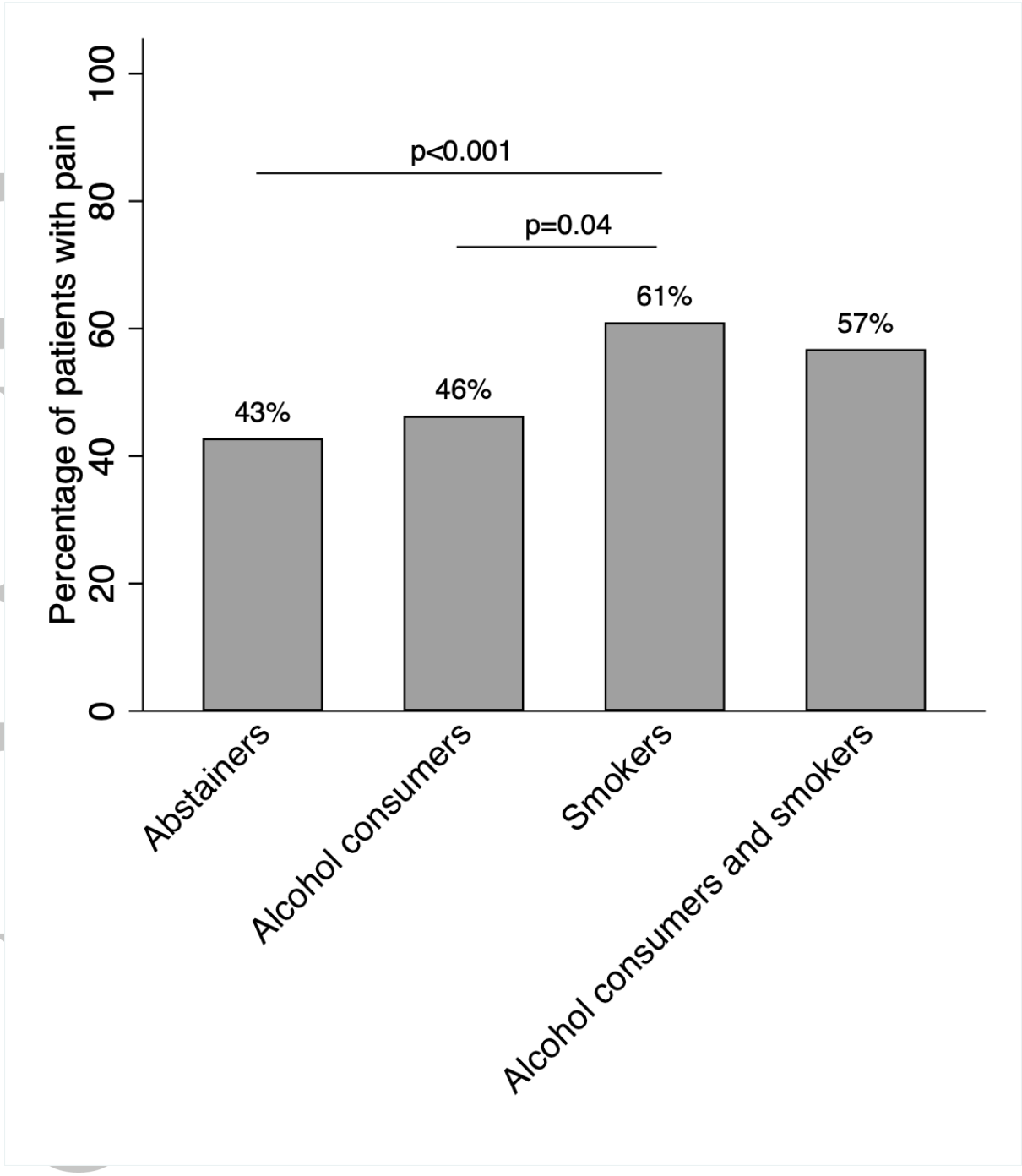


Figure 3. Distribution of chronic pancreatitis patients with pain according to status (yes/no) of alcohol use and smoking

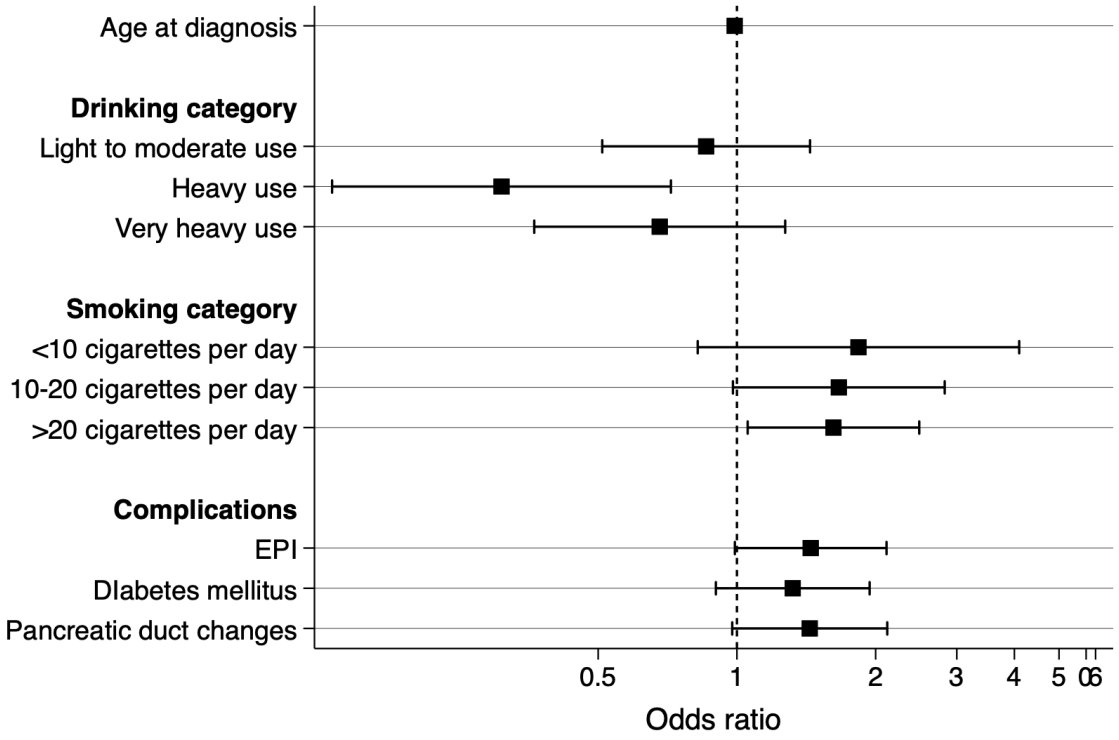


Figure 4. Forest plot of the multivariable logistic regression model for the presence of constant vs. intermittent pain in patients with chronic pancreatitis. Non-smokers served as reference group for smoking categories and alcohol abstainers served as reference group for alcohol categories. Odds ratios <1.0 reflect an association with intermittent pain and Odds ratios >1.0 reflect and association with constant pain. Whiskers represent 95% confidence intervals. EPI; exocrine pancreatic insufficiency

Table 1. Patient and disease characteristics of the study cohort and stratified by the presence of pain

		All patients [a] (n=1384)	Painful CP (n=801)	Pain free CP (n=583)	P-value
Gender	Female	470 (34)	282 (35)	188 (32)	0.25
	Male	914 (66)	519 (65)	395 (68)	
Age at diagnosis	mean ± SD	52.1±14.6	48.8±13.5	56.8±14.7	<0.001
Age category	<30 Years	106 (8)	71 (9)	35 (6)	<0.001
	30-40 Years	175 (13)	129 (16)	46 (8)	
	40-50 Years	307 (22)	219 (27)	88 (15)	
	50-60 Years	339 (25)	213 (27)	126 (22)	
	60-70 Years	284 (21)	113 (14)	171 (29)	
	>70 Years	173 (13)	56 (7)	117 (20)	
Duration of CP	median (IQR)	2 (1-7)	3 (1-8)	2 (0-6)	<0.001
Duration of CP category	<5 years	852 (63)	464 (60)	388 (68)	0.005
	5-10 years	306 (23)	186 (24)	120 (21)	
	>10 years	185 (14)	123 (16)	62 (11)	
Current drinking status	Abstainers	796 (66)	444 (66)	352 (65)	0.003
	Light to moderate use	204 (17)	108 (16)	96 (18)	
	Heavy use	116 (10)	54 (8)	62 (12)	
	Very heavy use	100 (8)	71 (11)	29 (5)	
Current smoking status	Non-smokers	705 (54)	357 (48)	348 (62)	<0.001
	<10 cigarettes per day	78 (6)	43 (6)	35 (6)	
	10-20 cigarettes per day	186 (14)	115 (16)	71 (13)	
	>20 cigarettes per day	336 (26)	224 (30)	112 (20)	
EPI		649 (48)	396 (52)	253 (44)	0.007
Diabetes		465 (36)	257 (35)	208 (38)	0.27
Pancreatic duct changes	Moderate / marked [b]	744 (55)	466 (60)	278 (49)	<0.001
Calcifications		836 (61)	502 (64)	334 (58)	0.04
Pseudocysts		494 (36)	345 (43)	149 (26)	<0.001
Common bile duct stenosis		251 (19)	162 (21)	89 (16)	0.01
Duodenal stenosis		57 (4)	47 (6)	10 (2)	<0.001

[a] Data are reported as number (percentage) of patients unless otherwise specified; all percentages presented are based on effective numbers. Information was missing from the following data categories: Duration of CP (41), drinking category (168), smoking category (79), recurring AP (119), EPI (44), diabetes (91), pancreatic duct changes (37), calcifications (20), pseudocysts (10), common bile duct stenosis (60) and duodenal stenosis (61)

[b] According to the Cambridge classification

Table 2. Patient and disease characteristics stratified by pain patterns

		Intermittent pain [a] (n=572)	**Constant pain** (n=229)	**P-value**
Gender	Female	206 (36)	76 (33)	0.45
	Male	366 (64)	153 (67)	
Age category	<30 Years	55 (16)	16 (7)	0.06
	30-40 Years	84 (15)	45 (20)	
	40-50 Years	144 (25)	75 (33)	
	50-60 Years	161 (28)	52 (23)	
	60-70 Years	87 (15)	26 (11)	
	>70 Years	41 (7)	15 (7)	
Duration of CP	<5 years	349 (63)	122 (54)	0.02
	5-10 years	129 (23)	57 (25)	
	>10 years	76 (14)	47 (21)	
Drinking category	Abstainer	302 (63)	142 (71)	0.06
	Light to moderate use	79 (17)	29 (15)	
	Heavy use	46 (10)	8 (4)	
	Very heavy use	51 (11)	20 (10)	
Smoking category	Non-smokers	267 (50)	90 (43)	0.34
	<10 cigarettes per day	29 (5)	14 (7)	
	10-20 cigarettes per day	78 (15)	37 (18)	
	>20 cigarettes per day	156 (29)	68 (33)	
EPI		269 (49)	127 (60)	0.006
Diabetes		168 (32)	89 (41)	0.03
Pancreatic duct changes	Moderate / marked [b]	325 (59)	141 (64)	0.18
Calcifications		350 (62)	152 (68)	0.04
Pseudocysts		240 (42)	105 (46)	0.28
Common bile duct stenosis		101 (19)	61 (28)	0.004
Duodenal stenosis		33 (6)	14 (6)	0.84

[a] Data are reported as number (percentage) of patients; all percentages presented are based on effective numbers as reported in Table1.

[b] According to the Cambridge classification