**Title: The diagnostic value of the Rosemont and Japanese diagnostic criteria for ‘indeterminate’, ‘suggestive’, ‘possible’ and ‘early’ chronic pancreatitis.**

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Abbreviations:

CAPS: Chronic Abdominal Pain Syndrome

CFTR: Cystic Fibrosis Transmembrane conductance Regulator

CONSORT: Consolidated Standards of Reporting Trials

ERCP: Endoscopic Retrograde Cholangio-Pancreatography

EUS: Endoscopic ultrasound of the pancreas

ifMCCP: initial finding of Minimal Change Chronic Pancreatitis

IPMN: Intraductal Papillary Mucinous Neoplasm

IQR: Inter Quartile Range

MCCP: Minimal Change Chronic Pancreatitis

MRCP: Magnetic Resonance Cholangio-Pancreatography

MRI: Magnetic Resonance Imaging

PRSS1: Gene encoding the cationic trypsinogen

SPINK-1: Gene encoding the serine protease inhibitor Kazal-type 1

**ABSTRACT**

**Objective:** There is a lack of consensus on the criteria for diagnosing early chronic pancreatitis. The aim was to review the diagnostic criteria in a longitudinal study.

**Design:** Retrospective observational study in a single centre of the initial evidence for chronic pancreatitis, with reassessment after outpatient follow-up from January 2003 to November 2016.

**Results:** 807 patients were initially diagnosed with chronic pancreatitis. 118 were reclassified, 52 with another diagnosis. Of the remaining 66 patients (whom had 111 chronic pancreatitis associated risk factors identified): 38 were reclassified as chronic abdominal pain syndrome (CAPS) with ‘normal’ imaging and 28 had an initial finding of minimal change chronic pancreatitis (ifMCCP) at endoscopic ultrasound of the pancreas (EUS).

Over a median follow-up of 4.5 (IQR 2.2–6.7) years, there were 266 pancreas-imaging investigations with no progression to chronic pancreatitis in any patient. Using the Japanese diagnostic system, 11 of CAPS group would be classified as ‘possible chronic pancreatitis’ and the remaining 27 patients as ‘normal’. By the Rosemont classification eight patients with ifMCCP would be classed as ‘indeterminate chronic pancreatitis’ and 20 would have been classified as ‘normal’. The same eight patients would have been classified as ‘early chronic pancreatitis’ by the Japanese system using EUS alone and this number would reduce to only 2 if the necessary clinical diagnostic criteria were also applied.

**Conclusion:** There needs to be a more stringent application of the systems used for diagnosing chronic pancreatitis with revision of the current terminology ‘indeterminate’, ‘suggestive’, ‘possible’, and ‘early’ chronic pancreatitis.

**Summary box:**

* **What is already known about this subject?**
* There is no consensus on the threshold number of diagnostic criteria needed to make a diagnosis of chronic pancreatitis in the absence of classical features calcification, dilated and strictured main pancreatic duct, dilated side branches, pseudocyst, necrosis and involvement of adjacent organs such as stricturing.
* There is currently no international consensus on the definition of early chronic pancreatitis, based on clinical, functional or imaging criteria.
* Endoscopic ultrasound of the pancreas may be used to identify features of early chronic pancreatitis but some of these features may also present in people without chronic pancreatitis.
* There are currently three classification systems using endoscopic ultrasound for the diagnosis of chronic pancreatitis, the standard and Rosemont systems use endoscopic ultrasound exclusively and the Japanese system uses both endoscopic ultrasound and clinical criteria. All three systems use overlapping and confusing nomenclature.
* **What are the new findings?**
* After long term clinical follow-up 66 (8.2%) out of 807 patients initially diagnosed with chronic pancreatitis had insufficient criteria to sustain a diagnosis of chronic pancreatitis.
* These 66 patients underwent strict application of established criteria resulting in classification as early, indeterminate, and possible chronic pancreatitis and normal pancreas. After follow up, none of these patients had any progression on imaging to support a diagnosis of chronic pancreatitis and in five cases a repeat endoscopic ultrasound demonstrated complete resolution of initial features ascribed to chronic pancreatitis.
* Patients who had a diagnostic endoscopic ultrasound within 9 months of an acute pancreatitis episode were more likely to have initial findings ascribed to chronic pancreatitis. This suggests that inflammatory endoscopic ultrasound findings within nine months represent resolving features of a single acute pancreatitis attack rather than initial findings of evolving chronic pancreatitis.
* **How might this impact on clinical practice in the foreseeable future?**
* The diagnosis of chronic pancreatitis based on the current terminology ‘indeterminate’, ‘suggestive’, ‘possible’, and ‘early’ chronic pancreatitis is very confusing and is not always understood and correctly applied.
* This study highlights the importance of stringent application of existing systems used for diagnosing chronic pancreatitis.
* Due to the significant implications of a patient receiving a diagnosis of chronic pancreatitis, this diagnostic process should only be undertaken in specialist centres with expertise in chronic pancreatitis and access to other support systems such as chronic pain management teams.
* Ideally, a new consensus is required to unify and simplify the existing systems. There also needs to be a parallel process to agree a consensus on the pathological diagnosis of chronic pancreatitis, including early chronic pancreatitis, which is also lacking.

**INTRODUCTION**

Chronic pancreatitis may be defined as a pathological fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathological responses to parenchymal injury or stress.[1] This will result in varying degrees of parenchymal fibrosis as well as, depending on the severity of the disease, ductal and parenchymal calcifications, inflammatory masses, biliary and duodenal stenosis, parenchymal necrosis and atrophy, islet cell loss, pancreatic fistulae, spleno-portal venous thrombosis and portal hypertension.[2, 3] Symptoms include malnourishment from pancreatic endocrine and exocrine failure and chronic abdominal pain. [2, 3] The annual incidence rates range between 5 and 14.4 cases per 105 with a prevalence of around 50 per 105. [3-7] This prevalence is probably an underestimate for a variety of reasons including disease definition, diagnostic challenges and patient compliance, and may be as high as 120-143 per 105. [7] The median survival time from diagnosis is around 15-20 years and the incidence appears to be rising for reasons that are not entirely clear. There is also an increased risk of developing pancreatic cancer with a standardized incidence of 14.4 to 19.0 in sporadic chronic pancreatitis,[8, 9] and up to 53 fold increase for hereditary pancreatitis. [10-12]

There have been major advances in our understanding of chronic pancreatitis most specifically regarding genetic and environmental risk factors.[13-19] Whilst there has been considerable progress in imaging, the definition of and diagnosis of early chronic pancreatitis remains controversial and challenging.[20-21] Established chronic pancreatitis is relatively straightforward to diagnose when pancreatic duct calculi and/or parenchymal calcification are present and are readily identifiable with conventional imaging modalities such as computer tomography. [20-22] Computed tomography also provides information about glandular changes, main pancreatic duct dilatation and stricturing, atrophy, and pseudo-cyst formation as well as involvement of adjacent blood vessels and organs. [20-23] Endoscopic ultrasound of the pancreas (EUS) is a sensitive imaging modality for detecting subtle pancreatic ductal or parenchymal changes, [24] and superseded endoscopic retrograde cholangiopancreatography (ERCP). [25] The EUS Rosemont classification includes many features of the Cambridge classification, which was based on ERCP, but also provides information on the parenchyma. [24,25] The diagnosis of early minimal change chronic pancreatitis (MCCP) remains controversial because the threshold number of EUS criteria needed to establish the diagnosis is unclear. [20] It is now apparent that many of the subtle parenchymal changes seen on EUS are variations of normal and may fluctuate over time with longer term changes influenced by age. [26,27] Progression from MCCP, based on EUS appearances, to definite chronic pancreatitis is uncommon and EUS features of MCCP can revert to completely ‘normal’ appearances. [27] On the other hand, studies from centres undertaking total pancreatectomy and islet auto-transplantation in adults with non-calcific chronic pancreatitis suggest that EUS may under diagnose chronic pancreatitis. [28,29]

A diagnosis of chronic pancreatitis has life changing consequences and is compounded in individuals who suffer from severe chronic abdominal pain without any abnormal imaging findings to explain the symptoms. [30-32] As chronic pancreatitis is a progressive disease we hypothesized that patients with suspected or early chronic pancreatitis would develop clear evidence of the disease over time. [1,3,20,23,27] With evolving concepts of chronic pancreatitis against a background of evolving uncertainty surrounding the diagnosis of early disease, we reviewed a cohort of patients who had been under clinical follow up to determine whether an initial diagnosis remained consistent over time.

# **METHODS**

## **Study design and objectives**

The aim of the study was to review the clinical and imaging criteria on which a diagnosis of chronic pancreatitis was based and, with the benefit of clinical follow-up data, establish if the original diagnosis was correct. This was a single centre study based in the Regional Liverpool Pancreas Centre outpatient clinics at the Royal Liverpool University Hospital.

**Patients and patient selection**

All individuals with a potential diagnosis of chronic pancreatitis who were referred with a suspected diagnosis of chronic pancreatitis between January 2003 and November 2016 were included. All clinical records including demographic, clinical, genetic, radiological, endoscopic and histopathological details were re-reviewed by the senior clinician (J Neoptolemos) and the designated study investigator (A Sheel) between November 2015 and November 2016.

The pre-existing database was enhanced to specify the presenting date and basis for the diagnosis of chronic pancreatitis, imaging results, and risk factors for chronic pancreatitis, including tobacco smoking, and alcohol consumption. The results of genetic tests were checked including those for the serine protease inhibitor Kazal-type 1 (SPINK-1), the cystic fibrosis transmembrane conductance regulator (CFTR) and protease serine 1 (PRSS1). Radiological imaging modalities included computed tomography, EUS, magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and secretin stimulated MRCP. Excess alcohol intake was defined as consumption of ≥62 units (35 drinks) per week for ≥1 year. [33] Details were also recorded of clinical symptoms such as pain and severity, endocrine and exocrine insufficiency, documented hyperamylasaemia (upper limit of normal = 150 IU/L), attack(s) of acute pancreatitis, the type and amount of analgesia, length of follow-up, and the date and reasons for which the diagnosis of chronic pancreatitis was revised. Pancreatic exocrine insufficiency was based on clinical features including patient reported steatorrhoea and use of and response to pancreatic enzyme replacement therapy. Faecal elastase testing was abandoned as the accuracy for early chronic pancreatitis was found to be unreliable. [34, 35] Analgesics were classified into non-opioids (paracetamol and non-steroidal anti-inflammatory agents), adjuvants including neuropathic agents (anti-depressants, anti-epileptics, benzodiazepines, pregabalin and gabapentin), mild opioids (codeine, tramadol and hydrocodone) and strong opioids (morphine, oxycodone, hydromorphone, fentanyl, buprenorphine, and methadone). For simplicity only the use of strong opioids is reported. [36]

Based on all of the information from the initial to the last censored clinic visit, the diagnosis of chronic pancreatitis was either confirmed or rejected by at least two clinicians, including the senior clinician.

In the event of an individual having a diagnosis of chronic pancreatitis revised the individual was counselled by a senior team member. A clear and optimal management plan was developed in agreement with the patient. The exact strategy varied between individuals but may have included patient education, referral to the chronic pain management team for optimisation of analgesia control, further clinical investigation or assessment by gastroenterology which would be overseen and co-ordinated by the pancreatic team, and further pancreatic outpatient follow-up.

## **Diagnostic criteria**

The Japanese system of diagnostic criteria for chronic pancreatitis was adopted for the purpose of this study. [21] There are six main diagnostic criteria: (1) characteristic imaging findings such as parenchymal calcification, ductal calculus, ductal morphological changes, and pseudocyst, (2) characteristic histological findings of loss of exocrine parenchyma with irregular predominantly interlobular fibrosis, (3) repeated upper abdominal pain, (4) elevated pancreatic enzyme levels in serum or urine, (5) reduced pancreatic exocrine function, and (6) continuous heavy drinking > 80g/day (10 units a day), using the Ammann criteria for a diagnosis of chronic pancreatitis secondary to alcohol.[37] A diagnosis of definite chronic pancreatitis requires criteria 1 and/or 2 to be met. Early chronic pancreatitis requires three of four ‘abnormal’ parenchymal findings (i-iv, see Table 1) plus at least three out of clinical criteria 3-6. Possible chronic pancreatitis is diagnosed when patients have at least three of criteria 3-6, in the absence of either criterion 1 or 2, following the exclusion of other pancreatic diseases. A diagnosis of chronic pancreatitis was accepted at any time point during the follow up. This included the development of diagnostic features of chronic pancreatitis from previously normal or equivocal investigations indicative of minimal change chronic pancreatitis (MCCP). For comparison the standard classification, [38] which uses nine equally weighted criteria based on four parenchymal and five ductal features and the Rosemont classification, [24] are shown in (Table 1).

**Table 1.** Comparison of diagnostic systems using criteria based EUS features that may be associated with chronic pancreatitis.

|  |  |  |  |
| --- | --- | --- | --- |
| Features of Chronic Pancreatitis | StandardCriteria(reference 38) | Japanese Criteria(reference 21) | Rosemont criteria(reference 24) |
| Parenchymal  | Hyperechoic foci  | i. Hyperechoic foci without shadowing | **Major A:** Hyperechoic foci (>2 mm in length/width with shadowing)**Minor:** Hyperechoic foci (>2 mm in length/width, without shadowing) |
| Hyperechoic strands  | ii. Stranding | **Minor:** Hyperechoic strands (≥3 mm in at least 2 different directions with respect to the imaged plane) |
| Lobularity | iii. Lobularity without honey combingiv. Lobularity with honey combing | **Major B:** Lobularity (≥3 contiguous lobules = ‘honeycombing’)**Minor:** Lobularity (>5 mm, non-contiguous lobules) |
| (Pseudo) Cysts | (Pseudo) Cysts | **Minor:** (Pseudo) Cyst (anechoic, round/elliptical with or without septations) |
| Ductal  | Main duct dilatation |  | **Minor:** Dilated duct (≥3.5 mm in body or >1.5 mm in tail) |
| Duct irregularity |  | **Minor:** Irregular duct contour (uneven or irregular outline and ectatic course)  |
| Hyperechoic margins | Hyperechoic main pancreatic duct margin | **Minor:** Hyperechoic duct wall (echogenic, distinct structure >50% of entire main pancreatic duct in the body and tail) |
| Visible side branches | Dilated side branches | **Minor:** Dilated side branch (>3 tubular anechoic structures each measuring ≥1 mm in width, budding from the main pancreatic duct) |
| Intraductal stones |  | **Major A:** Duct calculi (echogenic structure[s] within the main pancreatic duct with acoustic shadowing) |
| Diagnosis  | **Standard Criteria [38]** | **Japanese Criteria [21]** | **Rosemont criteria [24]** |
|  | **High probability for chronic pancreatitis:**5 to 9 criteria | **Definite chronic pancreatitis:**criteria 1 and/or 2(1) characteristic imaging findings (calcifications, calculus, ductal morphological changes),(2) characteristic histological findings of loss of exocrine parenchyma with irregular predominantly interlobular fibrosis | **Consistent with chronic pancreatitis:** 1 Major A feature + ≥3 minor features 1 Major A feature + major B feature 2 Major A features |
|  |  | **Early chronic pancreatitis:**EUS image findings of early chronic pancreatitis (three of i-iv) plus >3 out of criteria 3-6 (3) repeated upper abdominal pain(4) elevated pancreatic enzyme levels (serum or urine)(5) reduced pancreatic exocrine function(6) continuous heavy drinking > 80g/day (10 units a day, Ammann criteria (37) | **Suggestive of chronic pancreatitis:**Major A + <3 minorMajor B + ≥3 minor≥5 minor, no major |
|  | **Indeterminate for chronic pancreatitis:**3-4 criteria  | **Possible** **chronic pancreatitis:** >3 of criteria 3-6, in the absence of criteria 1 or 2, with exclusion of other pancreatic diseases | **Indeterminate for chronic pancreatitis:**Major B + < 3 minor |
|  | **Normal or low probability of chronic pancreatitis:** 0-2 criteria |  | **Normal:**<3 minor, no major |

### **Statistics analysis**

Descriptive data are presented as median with inter quartile range (IQR). Continuous variables were analysed by the two-tailed Mann Whitney U test and categorical variables were compared using the χ2 test and for small numbers a two-tailed Fisher’s exact probability test. Ordered categories (number of risk factors) were analysed with a proportional odds model of cumulative percentages of patients in each group. [39] Significance was set at the 5 per cent level (p<0.05). P values are shown without Bonferroni correction as comparisons were exploratory, except where stated. The statistical package SPSS v22 was used.

**RESULTS**

From approximately 1100 adult patients reviewed for a possible diagnosis of chronic pancreatitis, 807 patients (527 men and 280 women) had sufficient clinical and radiological data to be included in this study. The median (IQR) age was 57 (48-66) years. Following review of the data, the diagnosis of chronic pancreatitis was rejected in 118 (14.6%) patients (Figure 1). An alternative true diagnosis was made in 52 patients: twenty-three patients had post-acute pancreatitis radiological appearances only, 12 had idiopathic recurrent acute pancreatitis, 5 had intraductal papillary mucinous neoplasm and 12 had miscellaneous other diagnoses.

There were sixty-six (8.2%) symptomatic patients who were reclassified as having no diagnosis of chronic pancreatitis or any other alternative physical diagnosis. The clinical details are shown in Table 2. The median (IQR) duration of symptoms was nine (4-14) years. There were 266 specific imaging investigations of the pancreas, a median (interquartile range, IQR) of 4 (3-5) per patient, over a median (IQR) follow-up of 4.5 (2.2 – 6.7) years.

Of the remaining patients, all had definite features of chronic pancreatitis on imaging, including 412 who had histological confirmation.

**Table 2**. Clinical features of patients reclassified into the chronic abdominal pain syndrome group and the initial finding minimal change chronic pancreatitis group.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Clinical Variables | Chronic Abdominal Pain SyndromeN= 38 | Initial finding of Minimal Change Chronic PancreatitisN=28 | \*Pvalue | TotalN=66 |
| Gender (Male: Female) | 19:19 | 17:11 | 0.388 | 36:30 |
| Age at first symptoms Median (IQR) years | 43 (31-47.5) | 38 (24.25-44.25) | 0.143 | 40 (30-46) |
| Duration of pain Median (IQR) years | 10 (4.25-14.75) | 9 (4.0-12.75) | 0.460 | 9 (4-14) |
| Clinical exocrine insufficiency | 6(15.8%) | 5(17.9%) | 0.539 | 11(16.7%) |
| Pancreatic enzyme supplements | 25(65.8%) | 15(53.6%) | 0.315 | 40(60.6%) |
| Insulin dependent diabetes mellitus | 3(7.9%) | 2(7.1%) | 0.644 | 5(7.6%) |
| Oral hypoglycaemics for diabetes mellitus | 4(10.5%) | 0(0%) | 0.102 | 4(6.1%) |
| Consumed ≥62 units per week of alcohol for ≥1 year | 13 (34.2 %) | 7 (25.0%) | 0.421 | 20 (30%) |
| Alcohol units consumption per week in excess drinkersMedian (IQR) | 160 (82-315) | 112 (70-560) | 0.968 | 116 (85-297.5) |
| Ever smoker  | 25 (65.8%) | 18 (64.3%) | 0.899 | 43 (65%) |
| Current smoker (%) | 12(31.6%) | 6(21.4%) | 0.360 | 18(27.3%) |
| Number of pack years in ever smokers Median (IQR) | 20(11.25-30) | 10(6-18) | **0.021** | 15(10-25) |
| Gainful employment | 6(15.8%) | 10 (35.7%) | 0.062 | 16(24.2%) |
| Regular morphine and/or other strong opiate(s) | 31 (86.1) | 14 (50%) | **0.006** | 40 (60.6%) |
| Daily morphine or strong opiate(s) | 21 (55.3%) | 8 (28.6%) | **0.031** | 29 (43.9%) |
| Cholecystectomy | 11 (28.9) | 8 (28.6%) | 0.839 | 19 (28.8%) |
| One attack of acute pancreatitis | 13(34.2%) | 21(75.0%) | **\*\*0.001** | 34(51.5%) |
| Deaths during study period  | 2 (5.3%) | 0(0%) | 0.328 | 2 (3.0%) |

\*P values are shown without Bonferroni correction as exploratory, except where stated.

\*\*P value with Bonferroni correction is significant, p<0.0029.

Thirty-eight (4.7%) patients were diagnosed with chronic abdominal pain syndrome (CAPS) all without any abnormal pancreas findings. [31,32,40,41] Patients who were reclassified as CAPS, either did not demonstrate any features of chronic pancreatitis on any radiological investigation performed, or did not have sufficient EUS features to be classified as possible/probable or early chronic pancreatitis, even when including clinical features. There were 28 EUS examinations in twenty-five (65%) of these 38 patients all with normal EUS examinations. Patients in this group also had 120 computed tomography examinations and 14 MRCPs and secretin stimulated MRCPs. According to the Japanese diagnostic system, eleven patients would have been classified as ‘possible chronic pancreatitis’ based on three or more of the following four criteria: repeated upper abdominal pain, elevated pancreatic enzyme levels, clinical features of reduced pancreatic exocrine function and heavy alcohol consumption. The remaining 27 patients would be classified as normal by the Japanese system. [21]

There were 28 (3.5%) patients with initial findings of MCCP on EUS without any progression of radiological features. In order to differentiate this group of patients from those with true MCCP they are called ifMCCP. All patients with ifMCCP had at least one report stating there were EUS features consistent with a diagnosis of chronic pancreatitis. According to the Rosemont classification no patients had a major A criterion, three patients had one major B plus one minor criterion, four had four minor features, four had three minor features, five patients had two minor features, and seven patients had one minor criterion. None of these findings would give a diagnosis of chronic pancreatitis if the Rosemont classification was strictly applied. Eight patients would be classed as ‘indeterminate chronic pancreatitis’ and 20 would have been classified as ‘normal’. One patient was told that they had a diagnosis of chronic pancreatitis immediately following an EUS examination plus targeted parenchymal biopsy. On microscopy, the pancreas biopsy was normal. According to the Japanese system, the same eight patients would have been classified as ‘early chronic pancreatitis’ based on EUS features only. However, with the additional application and consideration of clinical features, only two fulfilled the criteria.

There were 34 (51.5%) patients who had had one attack of acute pancreatitis 13 (34.2%) in the CAPS group and 21 (75.0%) in the ifMCCP group, which was significant with a Bonferroni correction shown in Table 4. Clinical characteristics comparing those with and without a history of acute pancreatitis in either group or as a whole showed no major differences (Table 3).

**Table 3.** Clinical characteristics comparing those with and without a history of acute pancreatitis in the chronic abdominal pain syndrome group and the initial finding minimal change chronic pancreatitis group.

|  |  |  |  |
| --- | --- | --- | --- |
| Clinical Variables | Chronic Abdominal Pain SyndromeN= 38 | Initial finding of Minimal Change Chronic PancreatitisN=28 | All CombinedN=66 |
| **No Pancreatitisn=25** | **Previous pancreatitis=13** | **\*P Value** | **No Pancreatitisn=7** | **Previous pancreatitisn=21** | **\*P Value** | **No Pancreatitisn=32** | **Previous pancreatitisn=34** | **\*P Value** |
| Gender: Men | 10(40.0%) | 9(69.2%) | 0.087 | 4(57.1%) | 13(61.6%) | >0.999 | 14(43.8%) | 22(64.7%) | 0.087 |
| Age at first symptoms Median (IQR) years | 41(30-46) | 45.5(36.8-48.3) | 0.249 | 31(22.5-36) | 39(30.3-45) | 0.114 | 38.5(28-45.3) | 41(34.3 -46.5) | 0.304 |
| Duration of pain Median (IQR) years | 10(6-14.0) | 10(4-15) | 0.711 | 13(9.5-15) | 6(3-9) | **0.026** | 10(4-15) | 7(4.5-11.5) | 0.259 |
| Clinical exocrine insufficiency | 3(12.0%) | 3(23.1%) | 0.392 | 0(0%) | 5(23.8%) | 0.290 | 3(9.4%) | 8(23.5%) | 0.123 |
| Pancreatic enzyme supplements | 18(72.0%) | 7(53.8%) | 0.301 | 6(85.7%) | 9(42.9%) | 0.084 | 24(75.0%) | 16(47.1%) | **0.020** |
| Insulin dependent diabetes mellitus | 0(0%) | 3(23.1%) | **0.034** | 0(0%) | 2(9.5%) | >0.999 | 0(0%) | 5(14.7%) | 0.054 |
| Oral hypoglycaemics for diabetes mellitus | 3(12.0%) | 1(7.7%) | >0.999 | 0(0%) | 0(0%) | N/A | 3(9.4%) | 1(2.9%) | 0.348 |
| Consumed ≥62 units per week of alcohol for ≥1 year | 11(44.0%) | 2 (15.4%) | 0.148 | 1(14.3%) | 6(28.6%) | 0.639 | 12(37.5%) | 8(23.5%) | 0.217 |
| Alcohol units consumption per week in excess drinkers Median (IQR) | 160(100-240) | 221(143.3-299.8) | >0.999 | 90(90-90) | 116(80.5-450) | 0.611 | 130(97.5-220) | 116(70-423.5) | 0.816 |
| Ever smoker  | 16(64.0%) | 9(69.2%) | >0.999 | 5(71.4%) | 13(61.9%) | >0.999 | 21(65.6%) | 22(64.7%) | 0.938 |
| Current smoker | 8(32.0%) | 4(30.8%) | >0.999 | 3(42.9%) | 3(14.3%) | 0.144 | 11(34.4%) | 7(20.6%) | 0.209 |
| Number of pack years in ever smokers Median (IQR) | 18(13.8-30) | 25(12.5-30) | 0.705 | 10(7.5-18) | 11(6.5-17) | 0.884 | 16(10-28) | 13.5(8.5-20) | 0.364 |
| Gainful employment | 5(20.0%) | 1(7.7%) | 0.643 | 2(28.6%) | 8(38.1%) | >0.999 | 7(21.9%) | 9(26.5%) | 0.663 |
| Regular strong opiates | 19(76.0%) | 12(92.3%) | 0.385 | 6(85.7%) | 8(38.1%) | 0.077 | 25(78.1%) | 20(58.8%) | 0.092 |
| Daily strong opiates | 13(52.0%) | 8(61.5%) | 0.575 | 3(42.9%) | 5(23.8%) | 0.371 | 16(50.0%) | 13(38.2%) | 0.336 |
| Cholecystectomy | 5(20.0%) | 5(38.5%) | 0.263 | 3(42.9%) | 5(23.8%) | 0.371 | 8(25.0%) | 10(29.4%) | 0.688 |
| Deaths during study period  | 1(4.0%) | 1(7.7%) | >0.999 | 0(0%) | 0(0%) | N/A | 1(3.1%) | 1(2.9%) | >0.999 |

\*P values are shown without a Bonferroni correction

The EUS appearances in these patients are shown in Table 4. The EUS for thirteen patients was performed within 9 months of an episode of acute pancreatitis (4 in the CAPS group and 9 in the ifMCCP group) with a median (IQR) of 2 (1.25-2.75) EUS features compared to the 21 patients who had an EUS after a longer interval with a median (IQR) of 1 (0-2) features per patient (p=0.091). Within the CAPS group those with an attack of acute pancreatitis within 9 months of the EUS examination had a median (IQR) of 1 (1-1.25) EUS features whereas all patients with acute pancreatitis more than 9 months previously had nil EUS features (p=0.006).

**Table 4.** EUS features in patients with a history of acute pancreatitis in the chronic abdominal pain syndrome group and the initial finding minimal change chronic pancreatitis group.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| EUS StandardCriteria(reference 38) | Acute Pancreatitis in Chronic Abdominal Pain Syndrome | Acute Pancreatitis in Initial finding of Minimal Change Chronic Pancreatitis | \*Pvalue | Total |
| Patients with history of acute pancreatitis | 13 (34.2%) of 38 | 21 (75.0%) of 28 | **\*\*0.001** | 34 (51.5%) of 66 |
| Patients with acute pancreatitis who underwent EUS | 9 (69.2%) | 21 (100%) |  | 30 (88.2%) |
| EUS reports diagnosing MCCP without listing specific EUS criteria | 0 (0%) | 7 (33.3%) |  | 7 (23.3%) |
| EUS reports listing specific features including negative features | 9 (100%) | 14 (66.7%) |  | 23 (76.6%) |
| PARENCHYMAL FEATURES |  |  |  |
| Hyperechoic foci | 1 (11.1%) | 8 (57.1%) | **0.040** | 8 (34.8%) |
| Hyperechoic strands  | 1 (11.1%) | 5 (35.7%) | 0.340 | 6 (26.1%) |
| Lobularity 1. Without honey combing
2. With honey combing
 | 3 (33.3%)0 (0%) | 6 (42.9%)3 (21.4%) | >0.9990.253 | 9 (39.1%)3 (13.0%) |
| (Pseudo) Cysts | 2 (22.2%) | 3 (21.4%) | >0.999 | 5 (21.7%) |
| DUCTAL FEATURES |  |  |  |  |
| Main duct dilatation | 0 (0%) | 0 (0%) | - | 0 (0%) |
| Duct irregularity | 0 (0%) | 2 (14.3%) | 0.502 | 2 (8.7%) |
| Hyperechoic margins | 0 (0%) | 6 (42.9%) | **0.048** | 6 (26.1%) |
| Visible side branches | 0 (0%) | 0 (0%) | - | 0 (0%) |
| Intraductal stones | 0 (0%) | 0 (0%) | - | 0 (0%) |
|  |  |  |  |  |
| Number of patients any EUS feature | 5 (55.6%) | 14 (100%) | **0.014** | 16 (82.6%) |

\*P values are shown without Bonferroni correction as exploratory, except where stated.

\*\*P value with Bonferroni correction is significant, p<0.0029.

None of the patients with EUS appearances of ifMCCP demonstrated radiological progression in any imaging modality over a median (IQR) follow-up period of 4.9 (2.9-6.2) years. Five patients underwent repeat EUS at a median (IQR) of 3.0 (2.1-6.0) years between tests, with all five showing resolution of ifMCCP related changes. The remaining 23 patients were followed up using other imaging modalities and these were normal. Examples of radiological imaging in these patients, including regression of ifMCCP changes at EUS, are shown in Figures 2 and 3, and a comparative example of radiological progression from MCCP at EUS is shown in Figure 4.

Forty patients underwent genetic testing for alterations in SPINK-1, CFTR and, if a family history of pancreatitis was present, PRSS1 genes. There were four positive results; three patients had heterozygous CFTR ΔF508 mutation (frequency = 7.5%) and one patient had a heterozygous SPINK-1 N34S variant (frequency = 2.5%). Three of these patients had previously had one episode of acute pancreatitis (two with a CFTR ΔF508 mutation and one with SPINK-1 N34S).

**Table 5.** The number of recognised risk factors for chronic pancreatitis identified in the population, including significant alcohol consumption, tobacco smoking, previous episode of acute pancreatitis, and altered predisposing gene(s).

|  |  |
| --- | --- |
| Patient Group | Number of Risk Factors |
|  | **0**  | **1**  | **2**  | **3**  | **4**  |
| Chronic Abdominal Pain Syndrome |
| Number of patientsN=38 | 6(15.8%) | 11(28.9%) | 16(42.1%) | 5(13.2%) | 0(0%) |
| Total number of risk factorsN=58 | 0(0%) | 11(19.0%) | 32(55.2%) | 15(25.8%) | 0(0%) |
| Initial finding of Minimal Change Chronic Pancreatitis |
| Number of patientsN=28 | 2(7.1%) | 10(35.7%) | 6(21.4%) | 9(32.1%) | 1(3.6%) |
| Total number of risk factorsN=53 | 0(0%) | 10(18.9%) | 12(22.6%) | 27(50.9%) | 4(7.5%) |
| Total number of patientsN=66 | 8(12.1%) | 21(31.8%) | 22(33.3%) | 14(21.2%) | 1(1.5%) |
| Total number of risk factorsN=111 | 0(0%) | 21(18.9%) | 44(39.6%) | 42(37.8%) | 4(3.6%) |

All patients reported severe abdominal pain as their main symptom. The analgesic requirements were substantial. Forty patients (60.6%) required regular morphine and other strong opiates and 29 (43.3%) required this daily. More patients in the CAPS group had greater analgesic requirements than the ifMCCP group and many more were not in gainful employment. Five patients required repeated ketamine infusions for pain control, three of whom had a previous EUS diagnosis of ifMCCP. Two of these underwent a further EUS demonstrating a ‘normal’ pancreas. Fifteen patients reported symptoms that could be attributed to pancreatic exocrine insufficiency, which was mostly occasional diarrhoea, although 40 of the patients had been prescribed pancreatic enzyme supplementation during their follow-up regardless of the presence or absence of diarrhoea/steatorrhoea in their history.

Fifty-eight (87.9%) of the combined CAPS and ifMCCP individuals had at least one recognised risk factor for chronic pancreatitis and all reported symptoms of abdominal pain (Tables 2 and 3). As shown in Table 5, there were no significant differences in the number of risk factor categories between the ifMCCP and the CAPS groups (Fishers exact probability test, p= 0.102), nor in the differences in the overall number of risk factors by ordered categories (odds ratio = 1.84, 95% confidence interval = 0.75, 4.53; p-value = 0.255).

There were 23 surgical or endoscopic interventions undertaken. Eighteen patients had a cholecystectomy of whom two had no gallstones. Three had a limited pancreatic necrosectomy for necrotising acute pancreatitis, and two underwent an ERCP and sphincterotomy for suspected sphincter of Oddi dysfunction. Only 16 individuals were gainfully employed (24.2%), 38 (57.6%%) were unemployed, and 6 (9.1%) were retired. Two (3.0%) patients had died (one unemployed and one retired at the time of death) and data was missing in four (6.1%) patients. The two deaths occurred in a current smoker died from metastatic lung cancer, and the other in a patient with a history of significant alcohol excess from the complications from portal hypertension.

**DISCUSSION**

This study found that 118 (14.6%) of 807 patients had been misdiagnosed with chronic pancreatitis, 52 with an alternative diagnostic pathological process and 66 without an alternative physical diagnosis. Thirty-eight patients had severe chronic abdominal pain with normal imaging of the pancreas, of whom 32 also had between one and three risk factors associated with chronic pancreatitis. These patients were therefore reclassified as having chronic abdominal pain syndrome. As well as having more strong opioid analgesic requirements than the ifMCCP group, they also smoked significantly more pack years and had trend towards a higher rate of unemployment. Eleven of these patients would have been classified as ‘possible chronic pancreatitis’ according to the Japanese diagnostic criteria but did not evolve into chronic pancreatitis with follow-up. [21] The remaining 27 patients would have been classified as normal.

A further 28 patients were diagnosed with chronic pancreatitis based on EUS findings in the presence of abdominal pain. Strict adherence to the Rosemont classification resulted in eight patients being re-classed as ‘indeterminate chronic pancreatitis’ and 20 would have been re-classified as ‘normal’. With further follow-up and a median of four investigations per patient, no patient from either group displayed any imaging evidence of progression to chronic pancreatitis and in 5 cases EUS imaging reversed to normal. Both groups of patients had a similar number and distribution of risk factors, so the presence or absence of one or more risk factors alone cannot be used to infer a diagnosis of chronic pancreatitis in the absence of characteristic imaging findings or histopathology.

Features of post-acute pancreatitis seen on co-axial imaging and EUS can take 12 months or more to resolve (in the absence of necrotising pancreatitis at the initial attack), usually lagging behind the resolution of symptoms. In the present series 23 of the 52 patients with no clinical or radiological evidence of chronic pancreatitis had resolving post-acute pancreatitis imaging findings and another 12 patients had recurrent acute pancreatitis with resolution of symptoms and imaging in between attacks. Amongst the 66 patients misdiagnosed with chronic pancreatitis there were 34 patients with a single attack of acute pancreatitis of whom three had a predisposing gene alteration (two with a CFTR ΔF508 mutation and one with SPINK-1 N34S). These patients were more likely to have EUS initial findings suggestive of MCCP when EUS performed within 9 months of the single attack of acute pancreatitis. This suggests that these EUS findings within nine months represent resolving features of a single attack of acute pancreatitis rather than the initial findings of evolving chronic pancreatitis.

A number of studies have taken patients with a single episode of non-gallstone acute pancreatitis, recurrent non-gallstone acute pancreatitis, chronic pancreatitis with a background of acute pancreatitis, and chronic pancreatitis per se, [1-3, 20, 23] and grouped these together into a single study population causing difficulties in interpretation. [23,28,29] The problem is further compounded by the lack of consensus as to the pathological definition of early chronic pancreatitis. In 1996 Ammann, Heitz and Klöppel compared a histological fibrosis scoring system (range 0-12) with a pancreatic function index based on (1) the faecal chymotrypsin test, and (2) diabetes mellitus (range 0–5) in patients with alcohol related chronic pancreatitis. [42] In this system a fibrosis score of 2 could derive from mild focal perilobular and mild focal interlobular fibrosis whilst a function index of 1 could derive simply from a marginal reduction in faecal chymotrypsin or a normal faecal chymotrypsin value but prescribed an oral hypoglycaemic. There were 10 (12.0%) out of 83 patients investigated with fibrosis scores of 0-3 and a mean function index of 1 and another 16 (19.3%) with a fibrosis score of 4-6 with a mean function index of just above one. [42] A step change occurred at a fibrosis score of 7-9 when the mean function score jumped to two. [42]

Despite the lack of validation and consensus as to the diagnostic threshold of the fibrosis score for chronic pancreatitis a number of studies have used a fibrosis score of >2 as being indicative of chronic pancreatitis. [28,29,43,44] In a series of 50 adults with non-calcific chronic pancreatitis who underwent total pancreatectomy and islet auto-transplantation 42 had a fibrosis score of >2, but in eight (16%) patients the score was only 0-1. [29] None of these patients had a diagnosis of chronic pancreatitis using the Rosemont classification. In the group with a fibrosis score of >2, the Rosemont criteria classified 5 as normal, 12 as indeterminate and 25 as suggestive of chronic pancreatitis and in the patients with a score of only 0-1, EUS classified 4 as normal, 3 as indeterminate and one as suggestive. [29] It was unexplained why 84% were women and nearly three quarters of these patients had a history of acute pancreatitis needing hospitalization. In the patients with recurrent acute pancreatitis, EUS was performed 6-8 weeks after an episode of acute pancreatitis. [29] Therefore, it remains unclear whether the fibrosis (and pancreatic function) as well as the EUS features observed in this study reflect post-acute pancreatitis sequelae rather than underlying chronic pancreatitis.

A study by LeBlanc et al of 100 surgical patients identified an increased odds ratio for severe pancreatic fibrosis (score 9-12) associated with hyperechoic foci with and without shadowing, lobularity with honeycombing, main pancreatic duct dilation or irregularity, and dilated side branches.[43] They also found a relatively poor accuracy of EUS for early chronic pancreatitis with a sensitivity and specificity of >3 EUS criteria for mild fibrosis (score 1-4) of 54% and 22% respectively in the head of the pancreas, and 63% and 15% respectively in the body and tail of the pancreas. [43] In another surgical series Chong et al also reported a poor correlation between EUS criteria and the fibrosis score. [44].

In the present study no patient demonstrated any progression on imaging to features of chronic pancreatitis and all five patients with ifMCCP who had a repeat EUS showed complete resolution to normal appearances within a median follow-up of 3 years, consistent with findings from Japan. [27]

This study has highlighted the challenges in clinically and radiologically diagnosing early chronic pancreatitis in patients with risk factors for chronic pancreatitis and abdominal pain. Especially in those with a documented single attack of acute pancreatitis, EUS criteria were often overcalled in making a presumptive diagnosis of chronic pancreatitis. With follow-up, none of the patients developed features of chronic pancreatitis. Using the Japanese diagnostic system, [21] eleven of 38 patients in the CAPS group would have been classified as ‘possible chronic pancreatitis’ and the remaining 27 patients would be classified as normal. In patients with ifMCCP, using the Rosemont classification,[24] eight patients would be classed as ‘indeterminate chronic pancreatitis’ and 20 would have been classified as ‘normal’. The Japanese system, would have classified the same eight patients as ‘early chronic pancreatitis’ using EUS alone and only two if the necessary clinical diagnostic criteria were also applied.

Caution is needed in managing patients with the Rosemont diagnosis of ‘indeterminate chronic pancreatitis’ or ‘suggestive of chronic pancreatitis’, [24] and similarly the revised Japanese diagnosis of ‘possible chronic pancreatitis’ or ‘early chronic pancreatitis’. [21] The application of a time factor for follow-up (for example, 24 months) should be applied in patients with an uncertain diagnosis to determine whether there is complete resolution to normal or progression to chronic pancreatitis. Consensus is also required for the diagnosis of early chronic pancreatitis by histopathological criteria as the use of a fibrosis score of >2 is not convincing from the published studies.

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**LEGENDS TO FIGURES**

**Figure 1.** CONSORT diagram of the study. CP = chronic pancreatitis, IPMN = intraductal papillary mucinous neoplasm, CAPS = chronic abdominal pain syndrome, MCCP = minimal change chronic pancreatitis, EtOH = alcohol.

**Figure 2.** Imaging from two patients (2(A) and 2(B)) previous diagnosed with chronic pancreatitis, now reclassified as chronic abdominal pain syndrome.

**Figure 3.** Representative images from a patient reclassified as ‘initial finding of minimal change chronic pancreatitis’. These images were collected during long-term follow up and show no disease progression in addition to demonstrating regression of the initial findings which were deemed to be consistent with minimal change chronic pancreatitis on EUS examination.

**Figure 4.** Example of a patient with disease progression to chronic pancreatitis.

**REFERENCES**

1. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. *Pancreatology* 2016;16:218-24.
2. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001;120:682-707.
3. Majumder S, Chari ST. Chronic pancreatitis. *Lancet* 2016; 387, 1957-66.
4. Yadav D, Timmons L, Benson JT, et al. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. *Am J Gastroenterol* 2011; 106: 2192-9.
5. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013;144: 1252-61.
6. Hirota M, Shimosegawa T, Masamune A, et al.; Research Committee of Intractable Pancreatic Diseases. The seventh nationwide epidemiological survey for chronic pancreatitis in Japan: clinical significance of smoking habit in Japanese patients. *Pancreatology* 2014; 14: 490-6.
7. Levy P, Dominguez-Munoz E, Imrie C, et al. Epidemiology of chronic pancreatitis: burden of the disease and consequences. *United European Gastroenterol J* 2014; 2: 345-54.
8. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993;328:1433-7.
9. Malka D, Hammel P, Maire F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. *Gut* 2002;51:849-52.
10. Lowenfels AB, Maisonneuve P, DiMagno EP, et al.; International Hereditary Pancreatitis Study Group.Hereditary pancreatitis and the risk of pancreatic cancer. *J Natl Cancer Inst.* 1997 ; 89(6):442-6.
11. Howes N, Lerch MM, Greenhalf W, et al.; European Registry of Hereditary Pancreatitis and Pnacreatic Cancer (EUROPAC). Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clinical Gastroenterology and Hepatology* 2004; 2(3):252–261.
12. Grocock CJ, Rebours V, Delhaye M, et al. [The variable phenotype of the p.A16V mutation of cationic trypsinogen (PRSS1) in pancreatitis families.](http://www.ncbi.nlm.nih.gov/pubmed/19951905?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1) *Gut* 2010; 59: 357-63.
13. Pfützer RH, Barmada MM, Brunskil APJ, et al. SPINK1/PSTI Polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. *Gastroenterology* 2000; 119: 615-623.
14. Threadgold J, Greenhalf W, Ellis I, et al. The N34S mutation of SPINK1 (PSTI) is associated with a familial pattern of idiopathic chronic pancreatitis but does not cause the disease. *Gut* 2002;50:675-81.
15. Cohn JA, Neoptolemos JP, Feng J, et al. Increased risk of idiopathic chronic pancreatitis in cystic fibrosis carriers. *Human Mutation* 2005; 26(4):303-307.
16. Whitcomb DC, Larusch J, Krasinskas AM, et al. Common genetic variants in the *CLDN2* and *PRSS1-PRSS2* loci alter risk for alcohol-related and sporadic pancreatitis. *Nat Genet.* 2012; 44(12):1349-54.
17. Witt H, Beer S, Rosendahl J, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. *Nat Genet.* 2013;45(10):1216-20.
18. Whitcomb, D.C. Genetic risk factors for pancreatic disorders. *Gastroenterology* 2013;144: 1292-302.
19. Fjeld K, Weiss FU, Lasher D, et al. A recombined allele of the lipase gene CEL and its pseudogene CELP confers susceptibility to chronic pancreatitis. *Nat Genet.* 2015;47(5):518-22.
20. Conwell DL, Lee LS, Yadav D, et al*.* American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. *Pancreas* 2014;43:1143-62.
21. Shimosegawa T, Kataoka K, Kamisawa T, et al. The revised Japanese clinical diagnostic criteria for chronic pancreatitis. *J Gastroenterol* 2010;45:584-91.
22. Dimastromatteo J, Brentnall, T, Kelly, KA. Imaging in pancreatic disease. *Nat Rev Gastroenterol Hepatol* 2017;14(2):97-109.
23. Otsuki M. Chronic pancreatitis. The problems of diagnostic criteria. *Pancreatology* 2004**;**4:28-41.
24. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009;69:1251-61.
25. Sarner M, Cotton PB. Classification of pancreatitis. *Gut* 1984;25:756-9.
26. Lee LS, Conwell, D.L. Update on advanced endoscopic techniques for the pancreas: endoscopic retrograde cholangiopancreatography, drainage and biopsy, and endoscopic ultrasound. *Radiol Clin North Am* 2012;50: 547-61.
27. Masamune A, Kikuta K, Nabeshima T*,* et al. Nationwide epidemiological survey of early chronic pancreatitis in Japan. J Gastroenterol 2017. Jan 27. doi: 10.1007/s00535-017-1311-8.
28. Trikudanathan G, Vega-Peralta J, Malli A, et al. Diagnostic Performance of Endoscopic Ultrasound (EUS) for Non-Calcific Chronic Pancreatitis (NCCP) Based on Histopathology. *Am J Gastroenterol* 2016;**111**, 568-74.
29. Trikudanathan G, Munigala S, Barlass U, et al. Evaluation of Rosemont criteria for non-calcific chronic pancreatitis (NCCP) based on histopathology - A retrospective study. *Pancreatology* 2017;17(1):63-69.
30. Demir I.E., Friess, H.Ceyhan, G.O. Neural plasticity in pancreatitis and pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 2015;12: 649-59 .
31. Drewes AM, Krarup AL, Detlefsen S, et al. Pain in chronic pancreatitis: the role of neuropathic pain mechanisms. *Gut* 2008;57: 1616-27.
32. Poulsen JL, Olesen SS, Malver LP, et al. Pain and chronic pancreatitis: a complex interplay of multiple mechanisms. *World J Gastroenterol* 2013;19:7282-91 .
33. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009;169(11):1035-45.
34. Siegmund, E., Lohr, J.M. Schuff-Werner, P. The diagnostic validity of non-invasive pancreatic function tests--a meta-analysis. *Z Gastroenterol* 2004;42:1117-28.
35. Sabater L, Ausania F, Bakker OJ, et al. Evidence-based guidelines for the management of exocrine pancreatic insufficiency after pancreatic surgery. *Ann Surg.* 2016;264:949-58.
36. National Institute for Clinical Excellence. Pharmacological Management of Cancer Pain in Adults. *National Clinical Guideline No. 9*. Published November, 2015. ISSN 2009-6259.
37. Ammann RW. A clinically based classification system for alcoholic chronic pancreatitis: summary of an international workshop on chronic pancreatitis. *Pancreas* 1997;14:215-21.
38. Savides TJ, Gress FG, Zaidi SA, et al. Detection of embryologic ventral pancreatic parenchyma with endoscopic ultrasound. *Gastrointest Endosc* 1996;43:14-9.
39. McCullagh P. Regression models for ordinal data. *Journal of the Royal Statistical Society. Series B (Methodological)* 1980: 109-42.
40. Drewes AM, Bouwense SAW, Campbell CM, et al; Working group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis. Guidelines for the understanding and management of pain in chronic pancreatitis. *Pancreatology.* 2017 Jul 13. pii: S1424-3903(17)30515-X. doi: 10.1016/ j.pan. 2017.07.006.
41. Keefer L, Drossman DA, Guthrie E, et al. Centrally Mediated Disorders of Gastrointestinal Pain. *Gastroenterology.* 2016;150:1408–1419.
42. Ammann RW, Heitz PU, Klöppel G. Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. *Gastroenterology* 1996; 111: 224 – 31.
43. LeBlanc JK, Chen JH, Al-Haddad M, et al. Endoscopic ultrasound and histology in chronic pancreatitis: how are they associated? *Pancreas* 2014;43:440-4.
44. Chong AK, Hawes RH, Hoffman BJ, et al. Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. *Gastrointest Endosc* 2007;65:808-14.