TITLE PAGE

Title	Chronic Pancreatitis: A Case Ascertainment Study
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Abbreviations:

CP	Chronic Pancreatitis
EUS	Endoscopic Ultrasound
CT	Computerised Tomography
MRI	Magnetic Resonance Imaging
AXR	Abdominal X-Ray
NHS	National Health Service
ICD 10	International Classification of Diseases, 10th Revision

ABSTRACT

BACKGROUND

Chronic pancreatitis (CP) is a debilitating condition, characterised by chronic inflammation and fibrosis of the pancreas. The population frequency of CP is poorly understood. Therefore, we used a pragmatic approach to estimate the frequency of CP amongst a patient population undergoing investigations at a UK tertiary university hospital.

METHOD

All adult patients who, during 2006 – 2014, underwent abdominal CT MRI, abdominal X-Ray, EUS, faecal elastase testing, received a pancreatin prescription or a recorded primary/comorbid ICD diagnosis of CP were screened (screening cohort) for inclusion. Through applying the well-recognised CT, MRI and EUS criteria to the screening cohort, patients with CP were identified (study cohort). Incidence of diagnosis and point prevalence of CP were calculated, and the change in incidence modelled using Poisson regression.

RESULTS

Screening cohort included 24,271 cases, and 1,003 patients who met the diagnostic criteria for CP were included in the study cohort. The median age of diagnosis was 65 (IQR 50–76); majority were males (n=656, 65.4%); and of European ancestry (n=884, 88.1%). The annual incidence of diagnosis increased by a mean of 4.1% per year (95%CI 0.5–7.8%; p=0.03) over the study period ranging from 8.5 to 13.8 per 100,000 general population. The point prevalence also increased reaching 53.6 (95%CI 48.3 – 59.4) per 100,000 population at the end of the study period.

CONCLUSION

This study provides a clear method of pragmatically identifying patients with CP in a clinical setting. The incidence of CP diagnosis in patients undergoing investigations in hospital increased gradually in Greater Nottingham.

KEY MESSAGES

What is already known about this topic

Chronic pancreatitis (CP) is a progressive, debilitating inflammatory condition. Previous studies have reported varying incidence and prevalence rates in the UK.

What this study adds

This is the largest UK-based clinical study on CP, utilising a multisource case ascertainment method and stringent diagnostic criteria.

The incidence of CP diagnoses increased during the study period, likely reflecting either a genuine rise in disease prevalence or improved case detection.

How this study might influence research, practice, or policy

The findings highlight the need for regional CP services within the NHS to address the rising burden of CP and ensure equitable access to specialised care.

INTRODUCTION

Chronic pancreatitis (CP) is a chronic progressive irreversible disorder characterised by inflammation and fibrosis of the pancreas [1]. The clinical manifestations range from no symptoms to exocrine and/or endocrine insufficiency, cancer and death [2]. CP is associated with diabetes mellitus, metabolic bone diseases, malnutrition and steatorrhea, which lead to reduced quality of life [3-5]. Further, 4%-5% of patients develop pancreatic adenocarcinoma over their lifetime [6-8].

The prevalence of CP in the UK is estimated to be 163 per 100,000 population, while the incidence has increased from 5.9 to 12.8 per year per 100,000 population based on a UK biobank study [9]. A 25-year population-based Danish nationwide study estimated the point prevalence and incidence of CP to be 153.9 per 100,000 population and 12.5 per 100,000 person years, respectively [10]. The overall global incidence of CP is estimated to be 9·62 (95% CI 7·86–11·78) per 100 000 person-years [11]. However, these values may not reflect the true prevalence and incidence, due to difficult and opportunistic nature of the diagnosis of CP [12].

Traditionally, CP is diagnosed using computerised tomography (CT) or magnetic resonance imaging (MRI). However, a wide variety of other modalities are also used in clinical practice to diagnose CP. The lack of rigorous criteria that encompasses various diagnostic tests, has led to a diagnostic dilemma [12]. For example, early changes of CP may not be present or be overlooked on imaging [12, 13]. Imaging findings such as pancreatic duct dilatation and atrophy can occur in other pathologies and may be misinterpreted as CP changes [14]. Endoscopic ultrasonography (EUS) findings are subject to interobserver variability and lack of specificity in early disease [15] . A low faecal elastase, which is sometimes used as a sole diagnostic test, can be a consequence of unrelated medical conditions [16, 17]. Histology remains the gold standard for diagnosing CP, however obtaining tissue for diagnosis is associated with significant complications, some of which are life threatening [14].

The lack of standardisation in establishing the diagnosis, has led to patients being diagnosed based on symptoms alone or inaccurate interpretation of investigations [12]. Identifying those with CP is vital for managing symptoms and service development. Patients with CP are likely to be symptomatic [3, 5] and referred for investigations. We, therefore, used a pragmatic approach to estimate the frequency of CP amongst a patient population undergoing investigations at a tertiary unit in the UK.

METHODS

PATIENT SELECTION AND DATA COLLECTION

A retrospective analysis was undertaken in Nottingham University Hospital to identify patients with CP. All adult patients (≥18 years) who, between 01 January 2006 and 31 December 2014, had (1) CT, MRI or abdominal X-Ray (AXR) and/or (2) EUS and/or (3) faecal elastase testing and/ or (4) received a pancreatin prescription and/or (5) an admission with a recorded primary/comorbid diagnosis of CP (ICD-10 Diagnosis Code K86.0 or K86.1) were screened for inclusion in this study. To ensure completeness of data, the case record of every patient included in the study cohort was searched manually beyond the study period that was used for patient selection. The study was ethically approved by Health Research Authority and Health and Care Research Wales (22/WA/0074).

SEARCH AND DIAGNOSTIC CRITERIA

Imaging modalities (CT/MRI/AXR), EUS, faecal elastase levels, pancreatin prescription and discharge summaries were used to create a Screening Cohort. Cases included in the Screening Cohort were scrutinised systematically with below described CT, MRI, and EUS diagnostic criteria to create the Study Cohort (Figure 1A). AXR, faecal elastase levels, pancreatin prescriptions, and discharge summaries were not used to confirm the diagnosis of CP (i.e., to create Study Cohort), due to their diagnostic limitations.

CT and MRI

Reports of all abdominal CT and MRI (summarised in Supplementary Data 1) scans performed during the study period were searched for the following terminologies: pancreatitis; atrophy; atrophic; calcification; pseudocyst; pancreatic calcification; calcific; pancreatic duct; main duct. Scan reports that were identified to have even one of above search terminologies were included in the Screening Cohort. The reports of those included in the Screening Cohort were re-reviewed to identify diagnostic features of CP [18, 19] (summarised in Supplementary Data 2).

Endoscopic Ultrasound

Reports of all EUS performed during the study period were reviewed using Rosemont criteria (summarised in the Supplementary Data 3) for the confirmation. Rosemont criteria was selected for this study due to its foundation in an international consensus established by a panel of endosonography experts. Moreover, studies indicate that interobserver agreement improves when using the Rosemont criteria rather than standard criteria [20]. All cases deemed definitive and probable CP based on Rosemont criteria were included into the study cohort.

Other Modalities

Reports of all AXR performed during the study period were reviewed for features of CP. Calcification in the epigastric region was considered adequate to be included in the screening cohort. All patients who received prescription for pancreatin during the study period and those who had a recorded primary/comorbid diagnosis of CP (ICD-10 K86.0 and K86.1) on discharge summary during the study period were also included in the screening cohort. All faecal elastase test results during the study period were reviewed and those with less than 200µg/g were included in the screening cohort.

The notes of those included in the screening cohort were searched for CT, MRI, or EUS diagnostic criteria of CP. Those with AXR findings alone or pancreatin prescription alone or diagnostic code of CP alone or faecal elastase less than 200µg/g alone were not included in the study cohort.

CASE DEFINITIONS

History of alcohol excess was defined as current or previous alcohol consumption of more than 14 units per week for both men and women. Current or previous tobacco smoking, irrespective of the quantity or duration, was considered a history of smoking.

DATA PRESENTATION

All data are shown as median (interquartile range) if continuous or number (percentage) if categorical, unless otherwise stated.

PATIENT AND PUBLIC INVOLVEMENT

This study was reviewed by six members of the Patient Advisory Group of Nottingham NIHR Biomedical Research Centre. Their input ensured that the study was relevant to patient needs and that data handling was conducted appropriately. Additionally, they contributed to the development of patient-facing study materials.

STUDY AREA AND DENOMINATOR POPULATION

The annual population of Greater Nottingham was derived from the Office for National Statistics (ONS). The population for a particular year is estimated on 30 June of that particular year by the ONS. These midyear population estimations were used as the denominator populations to calculate the annual incidence of diagnosis and point prevalence of CP.

ESTIMATION OF ANNUAL INCIDENCE OF DIAGNOSIS AND POINT PREVALENCE

Only patients with confirmed CP from within Greater Nottingham were included in the estimation of annual incidence of diagnosis and point prevalence. Annual incidence of diagnosis was defined as the number of new cases of CP diagnosed over the preceding 12 months to 30 June of a particular year expressed as a rate in the general population of that year. For the year 2006 only, the analysis was limited to 6 months with newly diagnosed cases between 1 January 2006 to 30 June 2006. Point prevalence was defined as the total number of CP patients who were alive on 30 June of a particular year expressed as the proportion of the general population of that year.

The incidence of diagnosis and point prevalence and their respective 95% confidence intervals (95%CI) were calculated using Poisson test in R (Version 4.3.2). The change in incidence of diagnosis with respective 95%CI were calculated using Poisson regression in R (Version 4.3.2). The year 2006 was not included in the Poisson regression analysis as the number of CP cases were available only for the latter 6 months, and not the entire preceding year.

RESULTS

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Screening cohort included 24,271 cases from individual sources. Based on the CT, MRI, and EUS criteria for confirmation of CP, 1,003 patients were included in the study cohort (Figure 1A).

Of the study cohort, two thirds were males (n=656, 65.4%); the median age at diagnosis was 65 years (IQR 50 – 76); majority were of European ancestry (n=884, 88.1%). The commonest risk factors were smoking (current or ex-smoking; n=524, 52.2%) and alcohol (n=388, 38.7%). Demographics and clinical characteristics are summarised in table 1.

CP was confirmed in 876 (87.2%) patients using one modality – 754 (75.2%) patients using CT alone, 78 (7.8%) patients using EUS alone and 44 (4.4%) using MRI alone. In 117 patents (11.7%) CP was confirmed using two modalities; and in 10 patients (1.0%) CP was confirmed using three modalities (Figure 1B).

PERFORMANCE OF OTHER MODALITIES

Based on the presence of calcification in the epigastric region, 84 AXRs were included in the screening cohort; however, only 57 (67.9%) were confirmed to have diagnostic features of CP on CT, MRI and/or EUS.

Based on primary or secondary comorbidity ICD code of K86.0 and K86.1, 233 patients were included in the screening cohort; however, only 123 (52.8%) were confirmed to have CP.

Further, based on pancreatin prescription, 238 were included in the screening cohort. Of which, only 115 (48.3%) were confirmed to have diagnostic features of CP.

Similarly, based on faecal elastase less than 200µg/g, 137 were included in the screening cohort, but only 63 (46.0%) had diagnostic features of CP.

ANNUAL INCIDENCE OF DIAGNOSIS AND POINT PREVALENCE

The annual incidence of diagnosis of CP for Greater Nottingham ranged from 8.5 in 2007 to 13.8 in 2013 per 100,000 general population during the study period. The incidence of CP diagnosis increased by a mean of 4.1% (95%CI 0.5 –7.8) per year (Table 2, Supplementary 2) that was statistically

250 significant (p=0.03). The point prevalence of CP increased by a mean of 16.8% per year (95%CI 15.1 –
251 18.6) reaching 53.6 per 100,000 general population at the end of study period (Table 2, Figure 2).

DISCUSSION

This study utilised multisource case ascertainment to provide a clear method of identifying CP patients in a clinical setting. Using established diagnostic criteria in three different modalities, CP cases were ascertained from a large data set. Multiple modalities were used to establish a screening cohort, however, only three modalities, namely CT, MRI, and EUS, were chosen to confirm the diagnosis, based on their availability, ability to detect changes specific to CP. The incidence of diagnosis of CP in Greater Nottingham increased over the study period.

In line with previous literature, CP was common in middle-aged men in this study [21-24]. CP was also more common in those with European ancestry mirroring the makeup of the general population of a Western country [23, 25]. History of smoking and excess alcohol was common in CP patients in this and previous studies [21, 23, 24]. While oxidative and non-oxidative metabolism of ethanol are said to activate pancreatic stellate cells and lead to the development of CP [26-29], nicotine has been shown to cause widespread changes in the pancreatic exocrine function affecting acinar cells and ductal epithelial cells, increase extracellular matrix and decrease the number of acinar structures [30-32]. Evidence also suggests an interplay between smoking and alcohol in CP development, and smoking seems to accelerate alcohol-induced CP progression [33, 34].

CT was the most common modality for identifying patients and confirming the diagnosis. This may be due to CT being a common cross-sectional radiological modality used in both acute and chronic clinical settings [Diagnostic Imaging Dataset Statistical Release, version 1, 18 May 2023, NHS England]. It is also likely due to CT being a reliable tool for assessing pancreatic morphology [12, 35]. It demonstrates a high sensitivity in detecting parenchymal changes characteristic of advanced CP, such as parenchymal and ductal calcifications, with sensitivity levels reaching up to 90% [36, 37], which makes CT a valuable primary diagnostic tool [12].

Unlike advanced CP, which is detected easily on CT imaging, detection of early stage CP is challenging as the classical parenchymal changes are not readily visible [18, 36, 38]. In such instances EUS appears superior to CT [12, 39]. EUS has a sensitivity of 84% and a specificity of 100% of diagnosing CP compared to the gold standard, histopathology [40]. However, EUS is not without its diagnostic pitfalls. In the above study, of the 256 patients who met any EUS criteria of CP, only 159 (62%) fulfilled the benchmark Rosemont's EUS criteria [41]. Such discrepancy has also been demonstrated in other studies [20]. The use of more stringent Rosemont's criteria has also been shown to improve the

interobserver agreement in diagnosing CP [20, 42]. Other EUS diagnostic criteria appear to vary widely depending on institutions and operators [43].

MRI is also a sensitive modality in the diagnosis of early stage CP as it can detect initial parenchymal and ductal changes and able to exclude other diagnoses such as IPMN, which may be misdiagnosed as CP [44, 45]. The use of secretin-enhancement has been shown to further increase the diagnostic yield of MRI/MRCP in detecting early CP changes [46].

The additional investigations which aided Screening Cohort included AXR. Coarse calcifications in the epigastric region projecting over the pancreas are a recognised AXR feature of CP. However, the sensitivity of AXR is as low as 30% in diagnosing CP [47]. Whilst these calcifications are specific, they have to be differentiated from calcifications of other organs, tissues or vascular structures. These limited the use of AXR as a sole diagnostic tool in determining CP, and thus it was only used as a screening modality in this study. Similarly, prescription of pancreatin and the discharge summaries with ICD codes K86.0 and K86.1 were only used as screening modalities due to the inherent low sensitivity and specificity [16, 48, 49].

This study provides an insight into the clinical incidence and prevalence of CP in a UK population and will be instrumental in organising and improving regional CP services in the National Health Service (NHS). This indicates a potential impact on the NHS and the urgent need of specialist regional CP services. The reported figures of incidence and prevalence of CP of this study are in keeping with previously reported figures from a multi-ethnic Western [50-52] and a more mono-ethnic Eastern [24, 53] countries. However, a UK biobank based cohort study reports a higher prevalence rate of 163 per 100,000 population [9]. The likely reasons for this difference in prevalence can be attributed to various factors. Firstly, individuals diagnosed with CP prior to our study commencement were only included if they had a hospital episode during the study period, potentially resulting in an underestimation of CP prevalence in Greater Nottinghamshire. Secondly, while our study relied on meticulous clinical data, the identification of CP patients in the UK Biobank study was solely based on reported diagnoses without verification through appropriate investigations. Notably, in our study, almost half of those identified using ICD-10 code did not exhibit features of CP on CT, MRI, or EUS examinations. This underscores the inadequacy of relying solely on ICD-10 coding for identifying CP patients, a practice that likely led to an overestimation of CP prevalence in the aforementioned UK Biobank study.

This study has its own strengths and limitations. Though this is the largest study to date, it is reasonable to consider the inherent biases of this being a single centre study as a major limitation and can only be generalised with caution. Given that CT was the commonest modality used and CT is less sensitive at detecting early stage CP changes, it is likely that the study cohort is biased towards detecting those with clinically relevant CP. Furthermore, although the CT and MRI criteria used in this study are well-recognised and widely accepted diagnostic features, relying on a single feature does risk overestimating the presence of chronic pancreatitis, which is a limitation of this study. Ideally, studies of this nature, where diagnostic ambiguity exists, should be conducted prospectively, with diagnoses confirmed using multiple criteria across different modalities. However, this approach carries the drawback of potentially prolonging the study duration significantly. It is likely that the study duration of 9 years is relatively short, and this may have impacted the estimation of point prevalence estimate. However, it is unclear, from the literature, what the optimal study duration should be to estimate the 'true' prevalence with certainty, especially given that the incidence of CP is also increasing.

This study illustrates the use of CT, MRI and EUS in identifying patient with CP in a clinical setting. CT seems to be the most reliable modality that identifies the majority of patient with CP. It is crucial that rigorous diagnostic criteria are applied in the diagnosis of CP for better understanding of the disease and avoid harm to the patients from unnecessary disease labelling and treatment.

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TABLES

Table 1: Clinical and demorgraphic characteristics of patients diagosed with chronic pancreatitis

			All Confirmed Chronic Pancreatitis (n=1,003) median (IQR) / number (%)
Age at diagnosis			65 (50 – 76)
Male sex			656 (65.4%)
Ethnicity	European ancestry		884 (88.1%)
	African ancestry		14 (1.4%)
	South Asian ancestry		11 (1.1%)
	East/South East Asian ancestry		1 (0.1%)
	Unknown		91 (9.1%)
Smoking	Current		477 (47.6%)
	Ex		47 (4.7%)
	Never		121 (12.1%)
	Unknown		358 (35.7%)
History of alcohol excess			388 (38.7%)
Diagnostic modality*		CT	872 (86.9%)
		MRI	108 (10.8%)
		EUS	160 (16.0%)

*since 179 patients with chronic pancreatitis were confirmed of the diagnosis using more thatn one modality, the total number and percentate will be higher that the study cohort of 1,003 and 100%. **Abbreviatoins**: CT computerised tomography, MRI magnetic resonance imaging, EUS endoscopic ultrasonography.

Table 2: Yearly Incidence of Diagnosis and Point Prevaence of Chronic Pancreatitis

Year	General Population	New CP Cases	Total Number of CP Cases	Incidence (per 100,000) with 95%CI	Prevalence (per 100,000) with 95%CI
2006*	644903	21*	75*	3.3 (2.0 – 5.0)*	11.6 (9.1 – 14.6)*
2007	647571	55	117	8.5 (6.4 – 11.1)	18.1 (14.9 – 21.7)
2008	651966	62	160	9.5 (7.3 – 12.2)	24.5 (20.9 – 28.7)
2009	658028	71	206	10.8 (8.4 – 13.6)	31.3 (27.2 – 35.9)
2010	664843	63	235	9.5 (7.3 – 12.1)	35.3 (31.0 – 40.2)
2011	670751	73	272	10.9 (8.5 – 13.7)	40.6 (35.9 – 45.7)
2012	676809	64	300	9.5 (7.3 – 12.1)	44.3 (39.5 – 49.6)
2013	682412	94	340	13.8 (11.1 – 16.9)	49.8 (44.7 – 55.4)
2014	688521	75	369	10.9 (8.6 – 13.7)	53.6 (48.3 – 59.4)

Incidence of diagnosis was defined as the number of new cases of CP diagnosed over the preceding 12 months to 30 June of a particular year expressed as a proportion of the general population of that year. *Data for the year 2006 only included cases of CP between 1 January 2006 to 30 June 2006. Point prevalence was defined as the total number of CP patients who were alive on 30 June of a particular year expressed as the proportion of the general population of that year. **Abbreviations**: CP chronic pancreatitis; CI confidence interval.

FIGURE LEGEND

Figure 1 – Screening Cohort and Study Cohort

Figure 1A illustrates the selection of participants for the study. The Screening Cohort was initially identified based on CT, MRI, EUS, abdominal X-ray features, faecal elastase levels, Creon prescription records, and discharge summaries with ICD-10 codes K86.0 or K86.1. The Screening Cohort was further refined by evaluating only CT, MRI, and EUS features to identify cases with chronic pancreatitis. Individuals confirmed to have chronic pancreatitis comprised the Study Cohort, which underwent detailed analysis. Figure 1B illustrates the distribution of patients within the Study Cohort diagnosed with chronic pancreatitis, identified through CT, MRI, and/or EUS modalities. Each section represents the number of patients diagnosed by one or more of these methods, highlighting the overlap and individual contribution of each modality in identifying chronic pancreatitis cases.

Figure 2 – Incidence and Prevalence of Chronic Pancreatitis in Greater Nottingham

This graph presents the annual incidence of diagnosis and the prevalence of chronic pancreatitis per 100,000 individuals in the general population of Greater Nottingham during the study period (2006 to 2014).

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