

ORIGINAL ARTICLE

Development of a clinical score to estimate pancreatitis-related hospital admissions in patients with a new diagnosis of chronic pancreatitis: the trinity score

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Abstract

Background: The clinical course of chronic pancreatitis is unpredictable and there is no globally accepted score to predict the disease course. We developed a clinical score to estimate pancreatitis-related hospitalisation in patients with newly diagnosed chronic pancreatitis.

Methods: We conducted a retrospective cohort study using two clinical chronic pancreatitis databases held in tertiary referral centres in Dublin, Ireland, and in Tarragona, Spain. Individuals diagnosed with chronic pancreatitis between 2007 and 2014 were eligible for inclusion. Candidate predictors included aetiology, body mass index, exocrine dysfunction, smoking and alcohol history. We used multivariable logistic regression to develop the model.

Results: We analysed data from 154 patients with newly diagnosed chronic pancreatitis. Of these, 105 patients (68%) had at least one hospital admission for pancreatitis-related reasons in the 6 years following diagnosis. Aetiology of chronic pancreatitis, body mass index, use of pain medications and gender were found to be predictive of more pancreatic-related hospital admissions. These predictors were used to develop a clinical score which showed acceptable discrimination (area under the ROC curve = 0.70).

Discussion: We developed a clinical score based on easily accessible clinical parameters to predict pancreatitis-related hospitalisation in patients with newly diagnosed chronic pancreatitis.

Received 11 October 2022; accepted 27 April 2023

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Introduction

Chronic Pancreatitis is an inflammatory pancreatic disease characterised by abdominal pain, irreversible pancreatic morphological changes, mechanical complications such as duct distortion and strictures, loss of exocrine pancreatic function, diabetes mellitus and various other complications¹. The incidence of chronic pancreatitis in Europe is 5–10 per 100,000 and there is evidence that it is increasing.^{2,3} Due to its chronic, progressive nature, patients tend to worsen over time, and in the mid and late stages of disease patients frequently develop

malabsorption, chronic abdominal pain, nutrient deficiency, osteoporosis, and pancreatogenic diabetes.⁴ Diagnostic classification systems such as Cambridge or Rosemont describe chronic pancreatitis based on fibrosis. However, the degree of fibrosis correlates poorly with pain, exocrine pancreatic insufficiency, diabetes mellitus, progressive disease, or cancer risk—the main clinical issues. Therefore the clinical course is not amenable to prediction.⁵ Patients with chronic pancreatitis require regular multidisciplinary monitoring. An effective clinical scoring system could facilitate appropriate management in primary care, rationalise secondary and tertiary referral, and allow accurate

planning for service provision demands. A clinical score could also be used for patient classification, as an objective determination of disease severity, and to provide a prognosis.⁶

We first published a systematic review of clinical classification and severity scoring systems in chronic pancreatitis.⁶ In this, 48 papers were reviewed of which 11 described original scoring systems, six described modified scoring systems, and 31 were validation studies. Overall, there was limited evidence for their application in clinical practice or clinical studies.

The aim of the current study was to develop a new clinical score to predict the clinical course of chronic pancreatitis by amalgamating two chronic pancreatitis databases from pancreatic centres in Ireland and Spain. To do this, we identified pancreatitis-related hospital admissions during the six-year follow-up period as the primary outcome of interest, a proxy for disease severity. Secondary outcomes of interest were death and pancreatic cancer.

Methods

Participants

The clinical databases used for this study included a clinical chronic pancreatitis database held in a tertiary pancreatic centre in Dublin (129 adults of both sexes newly diagnosed between 2007 and 2014) and a clinical chronic pancreatitis database held in a tertiary pancreatic centre in Tarragona (63 adults of both sexes newly diagnosed between 2007 and 2014). Both databases enrolled consecutive patients, were prospectively maintained, and collected the same variables so it was not necessary to harmonise the datasets. Of these 192 patients, there were incomplete data for 31 patients and 7 patients in Dublin and Tarragona, respectively. The development cohort therefore comprised 154 patients (Fig. 1). This allowed for a follow-up period of six years (end 2014 to end 2020), this time period

was chosen as patients can live with chronic pancreatitis for many years. Diagnosis of chronic pancreatitis was made based on at least two of the following criteria: patient history (abdominal pain typical of pancreatitis), functional deficits (such as endocrine, exocrine deficiency), and/or findings on imaging studies (computed tomography and/or endoscopic ultrasonography). The Transparent reporting of multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines⁷ were adhered to in study design, data analysis and interpretation, and in the preparation of the manuscript.

Outcomes

Outcomes of interest were number of pancreatitis-related hospital admissions in the 6-year follow-up period (primary outcome), pancreatic cancer, and death (secondary outcomes). A pancreatitis-related hospital admission was included only if confirmed following chart review by a member of the pancreatitis MDT (physician or nurse-specialist) that the reason for admission was management of a complication of chronic pancreatitis, e.g., pain management or other specific interventions. To identify these outcomes, the databases were corroborated by patient charts, physician and nurse-specialist records, in-hospital patient information systems, and public online death notices (www.rip.ie in Ireland). Pancreatic cancer was defined as any pancreatic ductal adenocarcinoma. Follow-up began on the documented date of diagnosis and continued for a six-year period up to end December 2020. As the selected outcomes were objective (length of stay, pancreatic cancer or death), investigators were not blinded to the predictor variables.

Predictors

The following data were extracted for each patient from the time of diagnosis: sex, date of diagnosis (where month was unknown, date was estimated to be June of that year; in a small

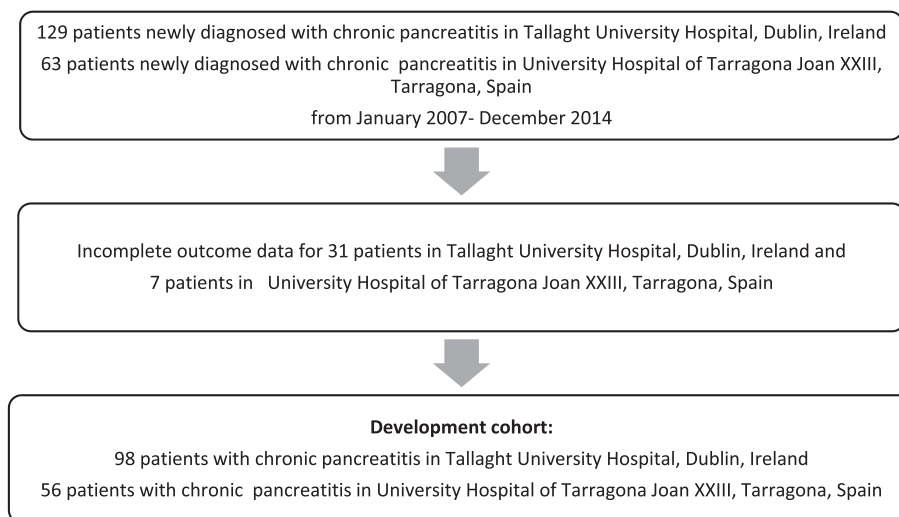


Figure 1 Flow chart for development cohort of Trinity Score

amount of cases where date of diagnosis was recorded as ‘earlier than [year]’, the date was estimated to be the year prior to this), date of birth (to calculate age at diagnosis), aetiology (alcoholic, biliary, idiopathic, other as determined by the medical team at the time of diagnosis), weight and height (within one month of diagnosis; measured without shoes using a calibrated weighing scales and stadiometer respectively; used to calculate body mass index, BMI Kg/M²), smoking history (documented history of smoking), alcohol history (documented history of alcohol excess), history of substance abuse (no mention in the medical notes was taken to mean no history), pain (use of analgesia as per the World Health Organisation Analgesic (WHO) ladder; specifically no regular analgesia, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), weak opioid, strong opioid⁸), exocrine dysfunction (defined as low faecal elastase-1 <200 µg/g or documented prescription of pancreatic enzyme replacement therapy (PERT) or documented clinical malabsorption/steatorrhoea within one month of diagnosis), and endocrine dysfunction (defined as documented diabetes mellitus in medical chart according to the American Diabetes Association⁹ or documented prescription of diabetes medication or record of high HbA1c consistent with diabetes mellitus even if no diagnosis was documented within one month of diagnosis). Bone health defined as dual energy X-ray absorptiometry with T-score reported by a Consultant Radiologist within one year of diagnosis. T-score of -1.0 and -2.5 standard deviations (SD) was osteopenia, and T-scores < -2.5 SD was osteoporosis.¹⁰ However, there were insufficient bone density data within one year of diagnosis from that time period 2007–14 and bone density was excluded as a potential predictor. Fat-soluble vitamin deficiency data were only available in one institution during the time period 2007–14 and therefore deficiency was excluded as a potential predictor. The independence assumption is automatically met for the predictors since the data consists of individual patient records (not time-series data). In addition, we undertook a residual series plot where the deviance residuals of the logit model are plotted against the index numbers of the observations.

Missing data

Missing clinical data for certain predictors such as faecal elastase-1 or HbA1c led to broadening of criteria in the design phase to minimise the need for imputation. For example, for endocrine and exocrine dysfunction we included use of diabetes medications and PERT to confirm a diagnosis as detailed above. Missing data for height to calculate BMI were assumed to be missing at random. To handle missing data, we performed multiple imputations using chained equations with Stata/SE 16 (StataCorp) as it is the preferred imputation method described in the TRIPOD guidelines.⁷ Missing values were predicted based on all other predictors. We created 50 datasets with identical known information but with differences in imputed values reflecting the uncertainty associated with imputations.

Model development

To maximise the power and generalisability of the results, all data that satisfied the inclusion criteria were included from both datasets, and we did not perform a formal sample size calculation as there are no generally accepted approaches to estimate sample size requirements for derivation and validation studies of risk prediction models.⁷ Continuous variables were presented as mean ± SD and were compared using Student’s t-tests for normally distributed data. For skewed distributions, the data were presented as median (interquartile range) and compared using Mann–Whitney U nonparametric test. Categorical variables were presented as percentages and compared using the χ^2 test.

The first step was to calculate odds ratios (OR) for each variable using univariable logistic regression. All predictors and the number of pancreatitis-related hospital admissions per year were examined for unadjusted associations. The number of pancreatitis-related hospital admissions per year were divided into two categories of those with less than or equal to one hospital admission in the 6 years (or ≤ 0.167 hospital admissions per year) following diagnosis with chronic pancreatitis and those with more than one hospital admission in the 6 years (> 0.167 hospital admissions per year) following diagnosis.

Then, multi-variable logistic regression analysis was performed using predictors that had an odds ratio of <0.7 or >1.2 in the univariable analysis. These cut-points of 0.7 and 1.2 were based on effect size rather than p-values or confidence intervals (CI), as we wanted to prioritise clinical relevance over statistical significance. They were also related to the number of predictors in each cut-point. A score was developed using these significant variables as predictors of the outcome of interest. This score was evaluated using the area under the receiver operating characteristics (ROC) curve (AUC), with an AUC of 0.5 indicating no discrimination, an AUC of 1.0 indicating perfect discrimination and an AUC between 0.7 and 0.8 indicating acceptable discrimination. We assessed internal validity with a bootstrapping procedure to account for over-fitting.

To create an easy-to-use, simplified model, the regression coefficients were multiplied by 3.5 and rounded to the nearest integers to form the scores for each of the predictors. The scores of the predictors were added to calculate the total score, which corresponds to risk of more pancreatitis-related hospitalisation in patients with newly diagnosed chronic pancreatitis.

Only the primary outcome (pancreatitis-related hospital admissions) was used to develop the model. There were 9 deaths and no pancreatic cancer in the Dublin data, and six deaths and no pancreatic cancer in the Tarragona data during the six-year follow-up period post-diagnosis and therefore the event rates were deemed insufficient for analysis. Stata Statistical Software, Release 16 was used to undertake the statistical analysis.

Ethical approval

Ethical approval was obtained from both the Joint Tallaght University Hospital/St James Hospital Ethics Review Board,

Ireland and the Comitè Ètic d'Investigació amb Medicaments, Institut d'Investigació Sanitària Pere Virgili, Spain.

Results

Between January 2007 and December 2014, 129 patients were diagnosed with chronic pancreatitis in Tallaght University Hospital. The following were excluded: 28 patients did not complete their assessment at our centre, one patient was diagnosed in childhood and two duplicate entries were removed from the database. The remaining 98 patients were included in the development cohort (Fig. 1).

In the same time period, 63 patients were diagnosed with chronic pancreatitis in the University Hospital of Tarragona Joan XXIII., of which seven were diagnosed initially at another centre

and did not have outcome data available. The remaining 56 patients were included in the development cohort (Fig. 1).

All patients exhibited the three parts of the diagnostic criteria—patient history, functional deficits, and findings on imaging studies during the study period. Demographics and clinical factors for both cohorts are displayed in Table 1.

Primary outcome

During the six-year follow up period, 24 patients (24%) in the Dublin centre and 25 patients (45%) in the Tarragona centre had no hospital admissions for pancreatitis. The median number of pancreatitis-related admissions was 2 in the Dublin centre and 1 in the Tarragona centre. The median length of stay for these hospital admissions was 17 days in Dublin and 6 days in Tarragona (Table 2).

Table 1 Comparison of Irish (Dublin) group and Spanish (Tarragona) group for demographic and clinical factors

Predictor	Missing Values, n (%)	Combined Cohort (n = 154)	Dublin (n = 98)	Tarragona (n = 56)	P-value
Age, mean (SD)	0	51.29 (13.03)	50.36 (13.35)	52.93 (12.39)	0.239 ^e
Gender male, n (%)	0	105 (68)	61 (62)	44 (79)	0.036 ^{f,*}
Gender female, n (%)	0	49 (32)	37 (38)	12 (21)	
Aetiology, n (%)					
Alcoholic	1 (0.01)	110 (72)	62 (63)	48 (86)	0.003 ^{f,*}
Biliary		14 (9)	14 (14)	0 (0)	
Idiopathic		19 (12)	13 (13)	6 (11)	
Other		10 (7)	8 (8)	2 (4)	
BMI, n (%) ³¹					
Underweight (<18.5 kg/m ²)	23 (15)	12 (9)	5 (6)	7 (14)	0.139 ^f
Normal weight (18.5–24.9 kg/m ²)		58 (44)	33 (40)	25 (51)	
Overweight (25.0–29.9 kg/m ²)		45 (34)	32 (39)	13 (27)	
Obese (>30 kg/m ²)		16 (12)	12 (15)	4 (8)	
Smoking History, n (%) ^a	5 (3)	126 (85)	81 (83)	45 (88)	0.371 ^f
History of Alcohol Excess, n (%) ^a	7 (5)	98 (67)	63 (68)	35 (69)	0.713 ^f
History of Substance Abuse ^a	6 (4)	17 (11)	14 (14)	3 (6)	0.175 ^f
Pain (use of analgesia), n (%) ^b					
No regular analgesia	21 (14)	41 (31)	9 (11)	32 (60)	0.000 ^{f,*}
Paracetamol & NSAIDs		35 (26)	20 (25)	15 (28)	
Weak Opioid		20 (15)	19 (24)	1 (2)	
Strong Opioid		37 (28)	32 (40)	5 (9)	
Exocrine Dysfunction, n (%) ^c	10 (6)	57 (40)	45 (48)	12 (24)	0.004 ^{f,*}
Endocrine Dysfunction, n (%) ^d	5 (3)	44 (30)	23 (24)	21 (41)	0.025 ^{f,*}

BMI, body mass index, SD, standard deviation, NSAIDs, non-steroidal anti-inflammatory drugs, DM, diabetes mellitus, PERT, pancreatic enzyme replacement therapy.

* Statistically significant at $P < 0.05$.

^a Defined as 'any documented history' of respective substances.

^b According to the World Health Organisation Analgesic ladder⁸.

^c Defined as 'low faecal elastase-1/documentated use of pancreatic enzyme replacement therapy/documentated clinical malabsorption or steatorrhea'.

^d Defined as 'documented diabetes mellitus in medical chart/use of diabetes medication/abnormal HbA1c consistent with diabetes'.

^e Compared using Student's T-test.

^f Compared using χ^2 analysis.

Table 2 Comparison of outcome data for Irish (Dublin) group and Spanish (Tarragona) group

Outcome	Dublin (n = 98)	Tarragona (n = 56)	P-value
Patients (n) with zero pancreatitis-related admissions in 6 years post diagnosis, n (%)	24 (24)	25 (45)	0.010 ^{b,a}
Number of pancreatic-related hospital admissions	Median (IQR)	Median (IQR)	
Number of pancreatitis-related admissions in 6 years post diagnosis	2 (1–3)	1 (0–3)	0.107 ^c
Number of pancreatic-related admissions per year in 6 years post diagnosis	0.33 (0.16–0.5)	0.17 (0–0.5)	
Hospital LOS for pancreatitis-related admissions	Median (IQR)	Median (IQR)	
Pancreatitis-related hospital LOS in 6 years post diagnosis	17 (2–31)	6 (0–26.5)	0.029 ^{c,a}
Pancreatitis-related hospital LOS per year in 6 years post diagnosis	2.83 (0.33–5.17)	1 (0–4.41)	

LOS, length of stay.

^a Statistically significant.

^b Compared using χ^2 analysis.

^c Compared using Mann–Whitney U test.

Model development

As the first step, all predictors, and the number of pancreatitis-related hospital admissions per year were examined for unadjusted associations (Table 3). The number of pancreatitis-related

hospital admissions per year were divided into two categories of those with less than one hospital admission in the 6 years (or <0.167 hospital admissions per year) following diagnosis with chronic pancreatitis and those with more than one hospital

Table 3 Univariate analysis of the predictors with the number of pancreatitis-related hospital admissions in patients with chronic pancreatitis in the development cohort

Predictor	Odds Ratio	SE	P-value	95% CI
Age	0.96	0.01	0.01 ^a	0.96–0.98
Gender- Male	1.54	0.54	0.22	0.80–3.14
Smoking History	1.01	0.46	0.98	0.42–2.47
History of Alcohol Excess	1.08	0.37	0.83	0.55–2.13
History of Substance Abuse	1.15	0.80	0.43	0.54–4.24
Exocrine Dysfunction	0.83	0.28	0.58	0.43–1.61
Endocrine Dysfunction	0.85	0.30	0.64	0.42–1.71
Aetiology				
Idiopathic & Other	1.00			
Biliary	2.61	1.75	0.16	0.70–9.75
Alcoholic	1.37	0.58	0.45	0.60–3.13
Body Mass Index				
Normal	1.00			
Underweight	2.08	1.33	0.25	0.59–7.31
Overweight	1.95	0.78	0.10	0.89–4.26
Obesity	2.30	1.33	0.15	0.74–7.13
Pain –WHO Analgesic Ladder				
No Regular Analgesia	1.00			
Paracetamol/NSAIDS	3.97	1.95	0.01 ^a	1.51–10.41
Weak opioid	2.79	1.63	0.08	0.89–8.75
Strong opioid	4.75	2.36	0.00 ^a	1.70–12.48

CI; confidence interval; SE; standard error; WHO; world health organisation; NSAIDS; non-steroidal anti-inflammatory drugs.

^a Statistically significant.

Table 4 Multivariate analysis (logistic) of the predictors with the number of pancreatitis-related hospital admissions in patients with chronic pancreatitis in the development cohort

	Regression Coefficient	Odds Ratio	P-value	95% CI
Intercept	-1.97			
Gender				
Female		1.00		
Male	0.38	1.46	0.36	0.65–3.30
Aetiology				
Idiopathic & Other		1.00		
Biliary	0.56	1.75	0.45	0.41–7.40
Alcoholic	0.39	1.48	0.43	0.56–3.90
Body Mass Index				
Normal		1.00		
Underweight	0.77	2.16	0.23	0.62–7.56
Overweight	0.88	2.42	0.03 ^a	1.08–5.44
Obesity	0.45	1.57	0.44	0.50–4.93
Pain –WHO Analgesic Ladder				
No Regular Analgesia		1.00		
Paracetamol/NSAIDS	1.32	3.75	0.01 ^a	1.50–9.37
Weak opioid	0.82	2.26	0.14	0.77–6.61
Strong opioid	1.53	4.60	0.00 ^a	1.80–11.75
ROC area (95% CI)	0.72 (0.64–0.80)			

CI; confidence interval; SE; standard error; WHO; world health organisation; NSAIDS; non-steroidal anti-inflammatory drugs; ROC; receiver-operating characteristic.

^a Statistically significant.

admission in the 6 years (>0.167 hospital admissions per year) following diagnosis.

Predictors that had an odds ratio of <0.7 or >1.2 were included in the multivariable analysis (Table 4), specifically male gender, biliary or alcoholic aetiology, BMI in the underweight, overweight or obese category, and requiring pain medication on any step of the WHO Analgesic Ladder.

Model performance

Discrimination refers to the ability of a prediction model to differentiate between those who do or do not experience the outcome event. We examined this using receiver operating characteristic (ROC) curve analysis. An area under the ROC curve (AUC) of 0.5 indicates no discrimination, whereas an AUC of 1.0 indicates perfect discrimination. An AUC between 0.7 and 0.8 indicates acceptable discrimination. We found an AUC of 0.72 (95%CI: 0.64–0.80) (Fig. 2). We assessed internal validity with a bootstrapping procedure (Table S1). Internal validation allows assessment of performance on the same dataset that was used to develop the prediction model. To complete external validation of model performance, it is planned to test it on an independent cohort of patients.

To create an easy-to-use, simplified model, we multiplied the regression coefficients by 3.5 and rounded them to the nearest

integers to form the scores for each of the predictors. The scores of the predictors are added to calculate the ‘total score’ (Fig. 3). This total score corresponds to risk of more pancreatitis-related hospitalisation in patients with newly diagnosed chronic pancreatitis. In summary, a score between 0 and 3 points represents a 0–25% risk of more than one pancreatitis-related admission in the 6 years following diagnosis, a score of 4–7

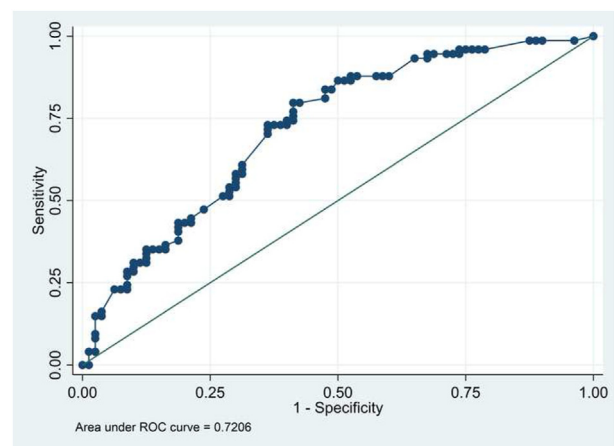


Figure 2 Area under Receiver-Operating Characteristic (ROC) Curve for multivariable model

Aetiology		BMI		Pain Medications	
Idiopathic/Other	0 points	Normal weight	0 points	No regular pain medication	0 points
Alcoholic	1 point	Underweight	3 points	Paracetamol/NSAIDS	5 points
Biliary	2 points	Overweight	3 points	Weak Opioids	3 points
		Obese	2 points	Strong Opioids	5 points
If male gender, add 1 point					
0-3 points		0-3 points		0-6 points	

Figure 3 The Trinity Score—a clinical scoring system for patients with chronic pancreatitis

points the risk is between 25 and 50%, 8–10 points, the risk is 50–75% and a score of 10–12 points the risk is 75–80% (Table S2).

The predicted probability of more pancreatitis-related hospital admissions in the 6 years following diagnosis with chronic pancreatitis was determined by:

$P = 1/[1 + \exp(-1.97 + 0.38 \times \text{Male gender} + 0.56 \times \text{Biliary Aetiology} + 0.39 \times \text{Alcoholic Aetiology} + 0.77 \times \text{Underweight BMI} + 0.88 \times \text{Overweight BMI} + 0.45 \times \text{Obese BMI} + 1.32 \times \text{Paracetamol/NSAIDS} + 0.82 \times \text{Weak Opioid} + 1.53 \times \text{Strong Opioid})]$ (Table 4).

Example: A male patient with alcoholic aetiology, overweight BMI, and requiring a weak opioid at time of diagnosis with chronic pancreatitis would have a predicted probability of:

$$P = 1/[1 + \exp(-1.97 + 0.38 \times 1 + 0.39 \times 1 + 0.88 \times 1 + 0.82 \times 1)]$$

$$P = 1/[1 + \exp(-0.5)]$$

$$P = 1/1 + 0.61$$

$$P = 1/1.61$$

$$P = 0.62$$

$$\% = 62$$

Discussion

We investigated a database of patients with chronic pancreatitis in Ireland and in Spain who were diagnosed between 2007 and 2014 and observed the number of pancreatitis-related hospitalisations they had in the following six years. Using this data, we developed a clinical score to predict the risk of pancreatitis-

related hospitalisation in newly diagnosed patients with chronic pancreatitis using routine clinical parameters—age, gender, aetiology, smoking history, history of alcohol excess or substance abuse, BMI, use of pain medication, endocrine and exocrine dysfunction. We found that male gender, use of pain medication, underweight, overweight or obese BMI and alcoholic or biliary aetiology were associated with increased risk of pancreatitis-related hospital admission. These findings were consistent with the findings of a study from Denmark who reported that male gender, opioid use, and underweight BMI were associated with increased annual hospitalisation.¹¹

No one national database exists for patients with chronic pancreatitis, to our knowledge, to assess the representativeness of our cohort. However, we have used a development cohort that we consider reflects real-world practice experience in relation to clinical phenotype and spectrum of disease. For example, our patients with chronic pancreatitis had been diagnosed at a mean age of 51 years which is comparable to a recent Danish study that found the mean age at time of diagnosis of 55.9 years.¹² Male patients made up the majority (68%) of our development cohort consistent with a male majority for chronic pancreatitis seen in many other studies.^{13–16}

The most common aetiology for chronic pancreatitis was alcohol, with 63% of the Irish cohort and 86% of the Spanish cohort having an alcoholic aetiology, consistent with a study from six Spanish hospitals where 74.8% of individuals with chronic pancreatitis had an alcohol or tobacco aetiology.¹⁷ A recent study found that alcohol consumption or smoking significantly accelerated disease progression with alcohol consumption and age of onset of CP independent risk factors for the development of diabetes, and male sex and smoking predictors of steatorrhea.¹⁸

A recent systematic review found that weight loss affects 22% of patients with chronic pancreatitis at the time of diagnosis.¹⁹ Of our patients 9% had an underweight BMI at the time of diagnosis. The systematic review also noted that 28% of patients had

diabetes at the time of diagnosis. Similarly, 30% of patients in our development cohort had endocrine dysfunction.

Patients with chronic pancreatitis may be managed as out-patients, and in our development cohort 45% of the Spanish cohort and 24% of the Irish cohort were managed as out-patients for the six years following diagnosis. A group from Denmark followed 170 patients for a median of 11 months and found that 34% required hospitalisation.¹¹

Outcome

While chronic pancreatitis is a condition that patients can live with for many years, this study had a follow-up period of six years following diagnosis, and investigated admissions to hospital for a pancreatitis-related reason in that time as a marker of the clinical course of the disease. The number of pancreatitis-related admissions was higher, and the length of stay was longer, in the Dublin centre than in the Tarragona centre. The reasons for this are unclear, but may reflect differences in out-patient care or societal variations between the two countries. Researchers in Germany followed 91 patients with chronic pancreatitis for one year, and reported (a mean of) 1.5 pancreatic hospital admissions in a 12 month follow up study.²⁰ However, these data are not directly comparable to our cohort as the patients in Germany were not newly diagnosed at the time of the study.

Comparison to other prediction models

Previous classification systems for chronic pancreatitis, such as the Cambridge classification and the Rosemont criteria, are based on morphological changes. Our clinical score excluded morphology due to its limited correlation with clinical symptoms.²¹ The M-ANNHEIM system included diagnostic criteria, a multifactorial risk factor classification and presents a severity score for clinical staging; however, it does not include malnutrition or BMI.^{22,23} The inclusion of BMI in our clinical score identifies patients who require dietary and clinical interventions at the time of diagnosis to address this modifiable risk factor. Multiple issues such as exocrine and endocrine dysfunction can contribute to an abnormal BMI.

The more recently-developed CP Prognosis Score does include BMI and has been prospectively validated to be able to predict admission to hospital and days spent in hospital in the following 12 months.^{20,24} However, it has been claimed that the follow-up of 12 months is too short to represent the prognosis of chronic pancreatitis or the risk for complications.²⁵ Our outcome of pancreatitis-related hospital admissions only, in the six years following diagnosis may be more representative of the prognosis and complications of patients with chronic pancreatitis.

Clinical scores for other conditions have been developed in a similar way to the Trinity score. For example, the Model for End-stage Liver Disease (MELD) score commonly used in liver disease was developed on a subset of variables which were shown to be significantly and independently correlated to outcome by multivariable analysis.²⁶ It accurately predicts mortality in

patients with cirrhosis and is used commonly to rank candidates for liver transplantation.²⁷ The Framingham Atrial Fibrillation (AF) risk score was developed using 4764 participants from the Framingham Heart Study using multivariable regression to examine clinical variables and 10-year AF incidence.²⁸ The external validation study showed that this score predicted AF well across all race and ethnic cohorts²⁹

Limitations and strengths

We acknowledge several limitations. Firstly, the pancreatitis databases in both centres existed as patient registries before the development of the Trinity score therefore the score was developed using retrospective data. Some predictors would have been recorded with more detail if the study was designed prospectively, for example, it would have been helpful to have a standardised method of quantifying alcohol intake and smoking history at the time of diagnosis. The definition of endocrine and exocrine dysfunction was broadened as HbA1c and faecal elastase were not available at the time of diagnosis for all patients. We intended to investigate the effects of malabsorption in more detail, however data on fat soluble vitamin levels and bone density were not available at time of diagnosis for all patients, and therefore these elements were not part of the final score. Missing data was a limitation of this study; however, we used multiple imputation which predicted values on the basis of all other predictors in 50 datasets. The small sample size was a limitation that meant it was not possible to analyse our secondary endpoints of death and pancreatic cancer. However the sample size used in this development study was comparable to the size of the development cohort used in the CP Prognosis Score²⁰ and in the pancreatic cancer disease impact (PACADI) score.³⁰ Finally, this model requires external validation in an independent cohort of patients with chronic pancreatitis.

This study was strengthened by the fact that the score was developed using databases from two European countries which may increase the representativeness of the development sample. Furthermore, the database was not limited to either inpatients or outpatients only. We developed this model using similar methodology to widely used clinical scores such as MELD²⁶ and the Framingham Atrial Fibrillation (AF) risk score.²⁸

Conclusion

We developed a clinical score for newly-diagnosed patients with chronic pancreatitis that predicts their risk of pancreatitis-related hospitalisation in the six years following diagnosis. This score has the potential to identify patients at the time of their diagnosis that have risk factors for future hospital admission. This information can then be used to stratify risk, inform treatment, and to allow for timely referrals to the wider multidisciplinary team such as dietetics, pain management and endocrinology. Using the clinical score to highlight those who are at high risk of hospital admission can facilitate planning interventions to reduce or

avoid costly hospital admissions. Managing patients with chronic pancreatitis as out-patients or reducing length of hospital stay could prevent physical deconditioning and improve the quality of life. Further prospective research is needed to evaluate the utility and validity of this scoring system in other clinical settings.

Acknowledgments

Funding: This work was supported in part by an unrestricted research grant from the Meath Foundation [Grant Ref RG107/2018] (www.meathfoundation.com).

The Meath Foundation has no part in the design, execution, analysis or write-up of the study, or the decision to submit for publication. No other entity has a role in funding, writing, designing, analysing, or sponsoring the study.

Conflict of interest

None to declare.

References

- Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D *et al.* (2016) Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology* 16:218–224. <https://doi.org/10.1016/j.pan.2016.02.001>.
- Majumder S, Chari ST. (2016) Chronic pancreatitis. *Lancet* 387: 1957–1966. [https://doi.org/10.1016/s0140-6736\(16\)00097-0](https://doi.org/10.1016/s0140-6736(16)00097-0).
- Joergensen M, Brusgaard K, Crüger DG, Gerdes AM, de Muckadell OB. (2010) Incidence, prevalence, etiology, and prognosis of first-time chronic pancreatitis in young patients: a nationwide cohort study. *Dig Dis Sci* 55:2988–2998. <https://doi.org/10.1007/s10620-009-1118-4>.
- Ramsey ML, Conwell DL, Hart PA. (2017) Complications of chronic pancreatitis. *Dig Dis Sci* 62:1745–1750. <https://doi.org/10.1007/s10620-017-4518-x>.
- Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. (2020) ACG clinical guideline: chronic pancreatitis. *Am J Gastroenterol* 115:322–339. <https://doi.org/10.14309/ajg.0000000000000535>.
- Rahman A, O'Connor DB, Gather F, Kosci S, Gilgan J, Mockler D *et al.* (2019) Clinical classification and severity scoring systems in chronic pancreatitis: a systematic review. *Dig Surg*, 1–11. <https://doi.org/10.1159/000501429>.
- Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW *et al.* (2015) Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 162:W1–W73. <https://doi.org/10.7326/m14-0698>.
- Ventafriidda V, Saita L, Ripamonti C, De Conno F. (1985) WHO guidelines for the use of analgesics in cancer pain. *Int J Tissue React* 7: 93–96. Published 1985/01/01.
- Association AD. (2004) Diagnosis and classification of diabetes mellitus. *Diabetes Care* 27(suppl_1):s5–s10. <https://doi.org/10.2337/diacare.27.2007.S5>.
- Kanis JA. (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int* 4:368–381. <https://doi.org/10.1007/bf01622200>.
- Olesen SS, Poulsen JL, Broberg MC, Madzak A, Drewes AM. (2016) Opioid treatment and hypoalbuminemia are associated with increased hospitalisation rates in chronic pancreatitis outpatients. *Pancreatology* 16:807–813.
- Olesen SS, Mortensen LH, Zinck E, Becker U, Drewes AM, Nojgaard C *et al.* (2021) Time trends in incidence and prevalence of chronic pancreatitis: a 25-year population-based nationwide study. *United European Gastroenterology Journal* 9:82–90. <https://doi.org/10.1177/2050640620966513>.
- Drake M, Dodwad S-JM, Davis J, Kao LS, Cao Y, Ko TC. (2021) Sex-related differences of acute and chronic pancreatitis in adults. *J Clin Med* 10:300. <https://doi.org/10.3390/jcm10020300>.
- Kempeneers MA, Issa Y, Verdonk RC, Bruno M, Frockens P, van Goor H *et al.* (2021) Pain patterns in chronic pancreatitis: a nationwide longitudinal cohort study. *Gut* 70:1724. <https://doi.org/10.1136/gutjnl-2020-322117>.
- De La Iglesia D, Vallejo-Sendra N, López-López A, Iglesias-García J, Larieno-Noia J, Nieto-García L *et al.* (2019) Pancreatic exocrine insufficiency and cardiovascular risk in patients with chronic pancreatitis: a prospective, longitudinal cohort study. *J Gastroenterol Hepatol* 34: 277–283. <https://doi.org/10.1111/jgh.14460>.
- Whitcomb DC, Yadav D, Adam S, Hawes RH, Brand RE, Anderson MA *et al.* (2008) Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatology* 8:520–531.
- Lucendo AJ, Carballo F, Tenías JM. (2014) A Spanish multicenter study to estimate the prevalence and incidence of chronic pancreatitis and its complications. *Rev Esp Enferm Dig* 2014:239–245.
- Ru N, Xu X-N, Cao Y, Zhu J-H, Hu L-Hao, Wu S-Y *et al.* (2022) The impacts of genetic and environmental factors on the progression of chronic pancreatitis. *Clin Gastroenterol Hepatol* 20:e1378–e1387. <https://doi.org/10.1016/j.cgh.2021.08.033>.
- Thompson BS, Philcox S, Devereaux B, Metz AJ, Croagh D, Gray A *et al.* (2022) Prodromal signs and symptoms of chronic pancreatitis: a systematic review. *J Clin Gastroenterol* 56:e1–e10.
- Beyer G, Mahajan UM, Budde C, Bulla TJ, Kohlmann T, Kuhlmann L *et al.* (2017) Development and validation of a chronic pancreatitis prognosis score in 2 independent cohorts. *Gastroenterology* 153: 1544–1554. <https://doi.org/10.1053/j.gastro.2017.08.073>, e1542.
- Wilcox CM, Yadav D, Ye T, Gardner TB, Gelrud A, Sandhu BS *et al.* (2015) Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. *Clin Gastroenterol Hepatol* 13:552–560. <https://doi.org/10.1016/j.cgh.2014.10.015>, quiz e528–559.
- Duggan SN, Smyth ND, Murphy A, Macnaughton D, O'Keefe SJ, Conlon KC. (2014) High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 12:219–228. <https://doi.org/10.1016/j.cgh.2013.06.016>.
- Duggan SN, Ewald N, Kelleher L, Griffin O, Gibney J, Conlon KC. (2017) The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. *Eur J Clin Nutr* 71:3–8. <https://doi.org/10.1038/ejcn.2016.127>.
- Maheshwari A, Patra PS, Ray S, Dhali GK, Das K. (2022) External validation of chronic pancreatitis prognosis score (COPPS): a prospective cohort study. *Dig Liver Dis* 54:654–662. <https://doi.org/10.1016/j.dld.2021.08.022>.
- Hao L, Liao Z, Hu L-H. (2018) Chronic pancreatitis prognosis score system is not ready yet. *Gastroenterology* 154:1852–1853. <https://doi.org/10.1053/j.gastro.2017.11.297>.

- 26.** Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. (2000) A model to predict poor survival in patients undergoing trans-jugular intrahepatic portosystemic shunts. *Hepatology* 31:864–871. <https://doi.org/10.1053/he.2000.5852>.
- 27.** Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, *et al.* (2001) A model to predict survival in patients with end-stage liver disease. *Hepatology* 33:464–470. <https://doi.org/10.1053/jhep.2001.22172>.
- 28.** Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino Sr RB *et al.* (2009) Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 373:739–745. [https://doi.org/10.1016/s0140-6736\(09\)60443-8](https://doi.org/10.1016/s0140-6736(09)60443-8).
- 29.** Shulman E, Kargoli F, Aagaard P, Hoch E, Di Biase L, Fisher J *et al.* (2016) Validation of the Framingham Heart study and CHARGE-AF risk scores for atrial fibrillation in hispanics, african-Americans, and non-hispanic whites. *Am J Cardiol* 117:76–83. <https://doi.org/10.1016/j.amjcard.2015.10.009>.
- 30.** Heiberg T, Nordby T, Kvien TK, Buanes T. (2013) Development and preliminary validation of the pancreatic cancer disease impact score. *Support Care Cancer* 21(6):1677–1684. <https://doi.org/10.1007/s00520-012-1713-3>.
- 31.** Organization WH. (1995) *Physical status: the use of and interpretation of anthropometry, Report of a WHO Expert Committee*. World Health Organization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.hpb.2023.04.014>.