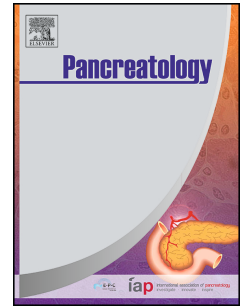# Journal Pre-proof

Opioid burden in patients with inoperable pancreatic adenocarcinoma and the development of a multivariable risk prediction model for opioid use: A retrospective cohort study

A.I. Koulouris, Dr Gabriella Baio, A. Clark, Leo Alexandre

Please cite this article as: Koulouris AI, Baio DG, Clark A, Alexandre L, Opioid burden in patients with inoperable pancreatic adenocarcinoma and the development of a multivariable risk prediction model for opioid use: A retrospective cohort study, *Pancreatology* (2023), doi: https://doi.org/10.1016/j.pan.2023.08.009.

Opioid burden in patients with inoperable pancreatic adenocarcinoma and the development of a multivariable risk prediction model for opioid use: a retrospective cohort study

Authors

A.I.Koulouris[1,2] Gastroenterology specialist registrar and Clinical Research Fellow, University of East Anglia, Dr Gabriella Baio[2] Consultant Radiologist and honorary Clinical Associate Professor, A.Clark[1] Associate Professor in Medical Statistics, Leo Alexandre[1, 2], Clinical Associate Professor in Gastroenterology and honorary Consultant Gastroenterologist

Author Affiliations

[1]Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, Norfolk NR4 7TJ.

[2]Norfolk and Norwich University Hospital. Norwich, Colney Lane, NR4 7UY, United Kingdom

Corresponding author: Dr Andreas Koulouris

Primary email address: andreas.koulouris@nnuh.nhs.uk

Alternative email address: an.koul@hotmail.com

Corresponding address: Department of Gastroenterology, Norfolk and Norwich University Hospital. Norwich, Colney Lane, NR4 7UY, United Kingdom .

Contact number: 01603 597264

1

ABSTRACT

Introduction. Risk prediction models to guide patient selection for early pre-emptive endoscopic ultrasound guided coeliac plexus neurolysis are lacking. This study aimed to determine in patients with inoperable pancreatic cancer: (1) opioid burden, (2) the relationship between opioid use and all-cause mortality, (3) risk factors for opioid use, and aimed to (4) develop and internally validate a risk prediction model for opioid use at three months.

Methods. This was a single-centre retrospective cohort study of patients with confirmed pancreatic cancer. Cox proportional hazard regression estimated the association between opioid use at baseline and all-cause mortality. Logistic regression estimated the associations between clinical and radiological variables with opioid use by three months. Two risk prediction models were developed for opioid use (clinical and clinical-radiological). Model discrimination and calibration was assessed.

Results. In total, 383 patients with inoperable pancreatic cancer were included. Prevalence of pain ranged between 37 to 47% at three monthly intervals in the first year of diagnosis. Opioid use at baseline was associated with poorer survival . Age, pain at presentation, performance status, tumour distance from the right ganglion, the anterior-posterior and the latero-lateral tumour dimensions were independent risk factors for the opioid use at three months. The Area Under Curve (AUC) for the clinical and clinical-radiological models was 0.81 and 0.84, respectively. Models were well calibrated.

Conclusions. Opioid use is prevalent in patients with pancreatic cancer, associated with poor prognosis, and can be predicted based on clinical and radiological variables. External validation of this predictive model is required.

INTRODUCTION

Pancreatic cancer-related abdominal pain is common and can be challenging to manage. Previous research has estimated that approximately 60-80% of the patients are affected by pain at some point during their illness[1]. The pathophysiology of pancreatic pain in patients with pancreatic cancer is likely mediated by a number of mechanisms in the context of pancreatic carcinogenesis, including (1) peri- and endo- neural cancer cell invasion[2], (2) increased nerve density and nerve hypertrophy of the intra-parenchymal nerves[3], (3) over-expression of the vanilloid cation channel receptors, (4) domination of the peri-tumoural inflammation by mast cells[4], (5) expression of neurotrophic growth factors [5] and (6) mechanical obstruction of the pancreatic ductal system[6].

The impact of pain is multi-dimensional and beyond physical distress, pain also negatively affects patients' mood, oral intake, sleep, activity levels and overall quality of life[7]. Pain management in patients with pancreatic cancer is multi-modal, including pharmacological and non-pharmacological approaches[8]. Strong opioid analgesics remain the cornerstone of management and are often used as first line in agents in patients with moderate to severe pain. Balanced against their efficacy and particularly when used at higher doses, adverse effects attributable to opioids are common and include hyperalgesia, gastroparesis, constipation and sedation, all of which can further negatively impact patients' quality of life and may limit dose escalation[9]. In patients with pain which is refractory to opioids, those receiving escalating doses, or those with unacceptable opioid related adverse effects, Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis (EUS-CPN) may be considered{, 2018 #306}. EUS-CPN is an endoscopic modality which provides analgesia through chemical ablation of the coeliac plexus[10]. While, its analgesic efficacy has been demonstrated in a number of trials, it is an invasive procedure associated with some uncommon yet serious risks[11, 12], and uncertainties remain regarding optimal patient selection and the timing of it administration (for example, soon after pain onset or later in opioid refractory cases). The National Institute for Health and Care Excellence (NICE) have recommended a trial comparing early versus on-demand EUS-CPN in patients with unresectable pancreatic cancer{, 2018 #306}.

The natural history and risk factors for pain in patients with pancreatic cancer are unknown. Robust, data-driven methods to optimise patient selection for EUS-CPN (including early pre-emptive administration) are lacking. Risk prediction of opioid use could identify patients most likely to benefit from early EUS-CPN. Against this background we aimed to determine in patients with inoperable pancreatic cancer (1) the incidence and prevalence of opioid use after diagnosis; (2) the absolute and relative survival of opioid users compared with non-users; (3) potential fitness for EUS-CPN among opioid users; (4) the association between demographic, clinical, radiological and cytological characteristics with opioid use by three months in patients with pancreatic cancer; and (5) we aimed to develop and internally validate a multivariable model predictive of opioid use.

METHODS

Study Design and Setting

This is a single-centre, retrospective cohort study, conducted in the Gastroenterology Department at the Norfolk and Norwich University Hospital (NNUH) Foundation Trust, Norwich, United Kingdom. The subjects were identified through the local cancer registry from January 2010 to December 2020[13]. The clinical, radiological and histological data were retrieved from patients' medical records. The study was approved by the West Midlands - Black Country Research Ethics Committee (REC reference: 21/WM/0092).

Study Population

Eligible patients were (1) men and women over 18 years of age with radiological and/or histo-cytological diagnosis of pancreatic adenocarcinoma, confirmed by the multi-disciplinary hepato-pancreatico-biliary meeting, (2) received palliative chemotherapy and/or best supportive care and (3) survived for a minimum of 90 days from diagnosis. Patients were ineligible if they (1) underwent potentially curative surgery; (2) were known to have a chronic pain syndrome and were opioids users prior to diagnosis of pancreatic cancer; (3) received opioids for non-pancreatic pain at baseline; (4) had an incomplete medical record from which opioid use could not be ascertained. Eligibility was restricted to those with at least 90 day's follow-up to enable capture of opioid burden and permit generalisability to the population who may be eligible for EUS-CPN (and would be expected to survive this period of time as a minimum). Patients were followed-up for a minimum of three months and maximum of one year until December 31st 2020 at the latest.

Outcomes

The outcome measures for each of the study aims were: opioid use at baseline, three, six, nine and twelve months (aims 1); all-cause mortality (aim 2); health performance status at baseline (with 0-2 considered definitive fitness for EUS CPN and 3 borderline) (aim 3); opioid use at three months (aims 4 and 5). Detailed definitions are provided in appendix 1. We have assumed that opioid use at three months was a reasonable primary outcome for the risk prediction models to select a patient group most likely to benefit from early EUS-CPN. This is on the basis that patient selection for a future trial of early vs. on demand EUS-CPN would benefit from recruiting a population enriched with individuals at high risk of moderate to severe pain in the short term.

Case Ascertainment and Clinical Measurements

A medical gastroenterologist reviewed each set of case notes to ascertain the prescribed opioids and dose, and confirm that the pain described in patients' correspondence letters was likely to be pancreatic in origin. This was essential as other painful cancer-related complications may also occur, such as gastric outlet obstruction. Likewise, patients with spinal or rib metastases as well as those who were using opioids for other non-malignant reasons, such as osteoarthritis or spondylosis, were excluded. Patients were typically prescribed a fixed, basal opioid dose, as well as additional,

pro re nata (PRN) doses for breakthrough pain. The clinic letters were reviewed to search for statements declaring the exact amount of the PRN prescription used. If a clear statement was not included in the clinic letter, it was assumed that the patient was using 50% of the maximum PRN dose. The doses were converted into morphine dose equivalents[14].

Radiological Assessments

The radiological data were interpreted and extracted by an academic radiologist with a subspecialty interest in pancreato-biliary radiology who was blinded to the outcome of opioid use at three months.

Exposures

The following clinical, biochemical, histological and radiological variables were assessed based on routinely collected data within three months of diagnosis: pancreatic duct diameter (continuous variable; mm), distance of the tumour from the left coeliac ganglion (continuous variable; mm), distance of the tumour from the right coeliac ganglion (continuous variable; mm), volume of the pancreatic tumour (continuous variable, cm^3), the latero-lateral, anterio-posterior and craniocaudal dimensions of the tumour (continuous variables; mm), the location of the pancreatic tumour (categorical variable; head, body, tail), the grade of WHO Histological Classification (categorical variable; poorly differentiated, moderately differentiated, well-differentiated, other WHO variants), the baseline levels of the CA19-9 tumour marker and the prescription of pancreatic enzyme supplements at diagnosis. With the exception of radiological characteristics, it was not possible to blind for the assessment of the remaining exposures for the outcome.

Covariates

Age, gender, abdominal pain at presentation, cancer stage, chemotherapy treatments and major co-morbidities were recorded as plausible co-variates. The prescription of anti-depressant, hypnotic, anxiolytic and anti-psychotic medications were recorded as a surrogate marker of anxiety and/or depression which may confound the association of the above exposures with pancreatic pain.

Statistical Analysis

For all analyses, complete case analysis was conducted. Descriptive analysis was undertaken with the categorical variables reported as frequencies and proportions. Continuous variables were described using means (and standard deviation) or medians (and interquartile range) depending on their distributions. Confidence intervals (CI) for prevalence and incidence were estimated using the binomial exact method[15]. Kaplan-Meier survival curves were plotted to compare those with and without severe pain requiring opioids at three months and statistical significance was examined with log-rank test[15, 16]. Associations between demographic, clinical, radiological and cytological characteristics and the opioid use were estimated by a logistic regression model and expressed in

odd ratios (OR). Both unadjusted and adjusted models are presented. Calculations were conducted using Stata software (Version 16, StataCorp LP, College Station, Texas, USA).

Development of predictive models and evaluation of their performance

We sought to develop a clinical prediction model incorporating all the clinical parameters that a clinician could estimate during an outpatient consultation, in addition to a clinical-radiological prediction model, incorporating imaging measurements which require radiological expertise. The multivariable risk prediction model was conducted and reported in line with TRIPOD guidance[17]. The prediction model was developed using the entire dataset, with internal validation using bootstrapping (a type 1b prediction model). Stepwise selection was used for the construction of the multivariable models. A significance level of 0.25 was used for the selection of the variables for entry into the multivariable model, whilst a significance level of 0.05 was used for elimination from the final model. Discrimination of the two models was measured by calculating the area under the receiver operating characteristic (ROC) curve for models[18]. In addition, sensitivity, specificity and positive (PPV) and negative predictive values (NPV) for a cut-off probability of 50% were reported (PPV defined as the probability of opioid use at three months for probability threshold of 50% or above, and vice versa for NPV). Calibration of the derived model was evaluated by visual assessment of a calibration plot, the ratio of expected to observed events and calibration-in-large and the Hosmer-Lemeshow test[19]. Model optimism was assessed with bootstrap resampling [20]. Bootstrap resampling was also used for bias correction. We estimated the odds ratio (OR) alongside its distributions, expressed as CIs and SD, for each subset and we calculated mean OR of the bootstrap samples. The difference between the mean OR and the OR calculated from the original dataset it is believed to be due to sampling bias, in the context of the internal validation of a prediction model [20].

Sample Size Calculation

The sample size was calculated using the method described by Riley *et al*[21] for clinical prediction models. The study was designed to assess 18 parameters, including exposures and confounding factors. Based on data from a local audit, we expected the outcome to occur in 50% of the cohort. The anticipated model performance, expressed as R-squared (R_{cs}^2), was estimated 0.375. The formula : $R_{cs}^2 = (R_{Neglerkerge} \times Max(R_{cs}^2))$ was used for this calculation, where the $R_{Neglerkerge}$ was defaulted at 0.5 for direct measurements in the absence of existing data[21]. Therefore, a sample size of 385 participants (193 events, 10.69 events per parameter) was deemed sufficient. Unfortunately, due to unexpected and unavoidable issues with research capacity the radiological data was limited to 142 patients.

RESULTS

Study Participants

In total, 1052 patients were identified from the Somerset Cancer Register (SCR) with pancreatic neoplasms (**Figure 1**). From these, 412 (39%) patients were excluded due to survival of 89 days or less. The study cohort was comprised of the remaining 383 (36%) patients who had complete clinical and histological data. Radiological assessment was undertaken in 142 patients. Subjects were followed from their date of diagnosis for a median period of 7.5 months (IQR 5.1 to 11), representing a total follow-up period of 301 years.

Figure 1. Flow chart of study participants.
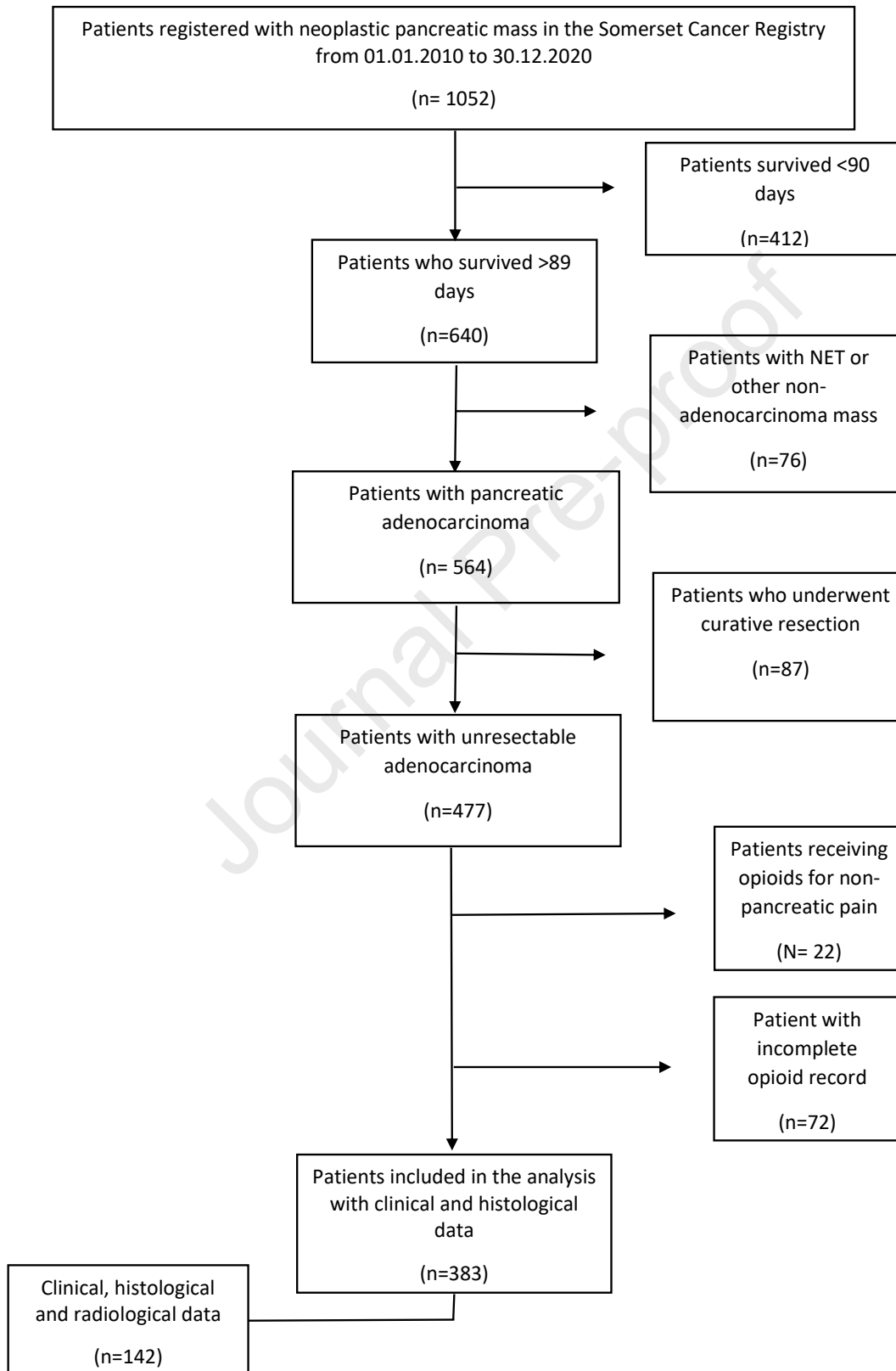
Clinical Characteristics

Baseline characteristics of study participants are summarised in **Table 1**. The mean age was 70.8 years (SD 10.4) and 198 (52%) were male. Several variables were affected by missing values. The tumour histological differentiation was not available in 241 (63%) patients. Smoking history was missing from the clinical notes in 96 (24%) patients. Finally, missing values of the CA19-9 was observed in 111 (29%) patients.

Table 1. Clinical characteristics of the cohorts.

	Total (n=383)	Cases with missing values
Age (mean, SD)	70.8 (10.4)	-
Gender (n, %)		-
Male	198 (51.7%)	-
Female	185 (48.3%)	-
Major Co-morbidities (n, %)		17 (4.4%)
Neurological	45 (12%)	-
Cardiovascular	127 (35%)	-
Respiratory	25 (7%)	-
Type 2 Diabetes Mellitus	86 (24%)	-
Renal Disease	20 (5%)	-
Presenting Symptoms (n, %)		-
Jaundice	155 (42%)	13 (3.4%)
Abdominal Pain[1]	165 (43%)	-
Weight Loss or Anorexia	184 (48%)	13 (3.4%)
Nausea or Vomiting	46 (12%)	13 (3.4%)
Diarrhoea or Steatorrhea	50 (13%)	13 (3.4%)
Incidental	44 (12%)	13 (3.4%)
Other[2]	21 (6%)	13 (3.4%)
Health Performance Status (n, %)		17 (4.4%)
0	119 (32%)	-
1	111 (30%)	-
2	61 (17%)	-
3	62 (17%)	-
4	13 (3%)	-
Smoking History (n, %)		96 (25%)
Current smokers	44 (15%)	-
Ex- smokers	57 (20%)	-
Never smoked	186 (65%)	-
CA19-9 (media, IQR)	503 (95, 2476)	111 (28.9%)
Cancer Stage (n,%)		4 (1.0%)
I	22 (7%)	-
II	31 (8%)	-
III	128 (33%)	-
IV	198 (52%)	-
T stage		11 (2.9%)
T_1	5 (1.5%)	-
T_2	54 (15%)	-
T_3	68 (18%)	-
T_4	245 (66%)	-
N stage		5 (1.3%)
N_0	176 (46%)	-
N_1	202 (54%)	-
M stage		4 (1.0%)
M_0	181 (48%)	-
M_1	198 (52%)	-
Histological Differentiation (n, %)		141 (39%)
Poorly- differentiated	35 (10%)	-
Moderately- differentiated	48 (13%)	-
Well-differentiated	10 (3%)	-
Adeno-squamous differentiation	6 (2%)	-
Acinar differentiation	3 (0.8%)	-
Mucinous differentiation	22 (6%)	-
Unclassified	100 (27%)	-
Biopsy not available	141 (39%)	-
Chemotherapy Treatment (n,%)		13 (3.4%)
No chemotherapy	152 (41%)	-
FOLFIRINOX	103 (28%)	-
Gemcitabine	94 (25%)	-
Other	21 (5%)	-
Chronic Pancreatitis (n, %)	24 (6%)	10 (2.6%)
Pancreatic Enzyme Therapy (n, %)		11 (2.9%)
Prescribed	243 (65%)	-
Not prescribed	129 (35%)	-
Depression or Anxiety (n,%)	102 (27%)	11 (2.9%)

[1] **This refers to abdominal pain or discomfort which may be controlled with or without opioids.**

[2] **Thromboembolic events, acute pancreatitis, haematuria, ascites, new onset diabetes, breathlessness.**

Radiological Characteristics

Radiological assessment was undertaken in 142 (38%) sequential patients, diagnosed between 2014 and 2018. The generic radiological characteristics illustrated in **Table 2**.

Table 2. Radiological characteristics of the pancreatic tumours.

Radiological Characteristics	Total
Tumour location (n, %)	
Head/Neck/Uncinate Process	256 (67%)
Body	74 (19%)
Tail	49 (13%)
Unclassified or unavailable	4 (1%)
Main Pancreatic Duct Diameter in mm (mean, SD)[1]	5.95 (3.08)
Tumour Dimensions in mm (mean, SD) [1]	
Anterior-posterior	32.4 (12.8)
Latero-lateral	34.9 (15.6)
Cephalo-caudal	32.4(11.4)
Tumour Total Volume cm³ (mean, SD) [1]	4.9 (6.5)
Distance from the Left Coeliac Ganglion in mm (mean, SD) [1]	
Overall	26.9 (21.4)
Head/neck/uncinate process tumours	31.7 (20.5)
Body tumours	5.7 (9.1)
Tail tumours	23.2 (20.9)
Distance from the Right Coeliac Ganglion in mm (mean, SD) [1]	
Overall	25.7 (21.3)
Head/neck/uncinate process tumours	27.0 (19.7)
Body tumours	8.1 (11.3)
Tail tumours	40.6 (26.6)

[1]The radiological characteristics were available for 142 patients who were diagnosed between 2014 to 2018.

Prevalence and Incidence of Pain Requiring Opioid Treatment

The prevalence, incidence and daily morphine doses are displayed in **Table 3**. The prevalence of opioid use remained almost constant throughout the first year from the diagnosis, ranging from 37% to 47%. Of a total of 241 opioid-free patients at month one, 46 (19%) were opioid users (i.e. became incident cases) by month three. The mean daily morphine dose started from 54 (SD 44) mg at baseline to climb progressively to 126mg (SD 125) by the end of the first year from diagnosis.

Table 3. Point prevalence, incidence and daily morphine doses

Follow-up	Total number of alive patients at risk[1] (n)	Absolute number of patients on opioids[1] (n)	Point prevalence (%, CI)	Absolute number of new opioid-recipients (n)	Incidence[2] (%, CI)	Missing data (n)	Daily morphine dose in mg (mean, SD)
Month 1	383	142	37% (32%-42%)	-	-	-	54 (44)
Month 3	383	183	47% (43%-53%)	46	19% (14%-25%)	-	90 (84)
Month 6	238	111	46% (40%-53%)	24	12% (8%-17%)	36	105 (83)
Month 9	137	63	46% (37%-55%)	15	12% (7%-19%)	51	114 (128)
Month 12	88	34	39% (29%-50%)	2	3% (0.3%-9%)	45	126 (125)

[1]The figures represent the alive population who has no missing values.

[2]Incident cases are defined as the subjects in receipt of new opioid prescription, who were opioid-free in their previous three-month follow-up period.

Fitness for Endoscopic Analgesia

Of a total of 176 opioid users with recorded performance status at diagnosis, definitive fitness for EUS-CPN (defined as performance status scores of 0 to 2) was observed in 137 (77%). Borderline fitness, with a score of 3, was observed in 36 (20%) whilst lack of fitness was only observed in 3 (1.7%) of the patients (**Table**). In total, 125 (67%) of the opioid users pursued diagnostic (EUS or gastroscopy) or therapeutic endoscopy (ERCP) in the days to weeks following diagnosis. Finally, chemotherapy was administered in 107 (58.5%) of the opioid users.

Survival Analysis stratified by opioid use at three months

Overall, median survival was 7.5 (IQR 5.1 to 11) months. In total, 33 out of 383 patients were alive by the end of the study. The median survival was shorter in patients treated with opioids [median survival 5.9 (IQR 4.3 to 8.8) versus 9.3 (IQR 6.6 to 14) months, log rank test p<0.001] (Appendix 2). The following covariates were associated with survival at a significance level of 0.250 in the univariable analysis were included in the multivariable model: age, cardiovascular and renal co-morbidities, health performance status, CA19-9, cancer stage, chemotherapy, total tumour volume and location (Appendix 2). Opioid users were at higher risk of death than non-users (HR 1.83, 95% CI, 1.14 to 2.95, p=0.012). Retained variables independently associated with mortality were: chemotherapy treatment (HR 0.44, 95% CI, 0.26 to 0.76, p=0.003), the total tumour volume per cm^3 (HR 27.29, 95% CI, 2.06 to 360.86, p=0.012) and cancer stage (HR for trend across categories 1.40, 95% CI, 1.01 to 1.95, p=0.001).

Multivariable risk prediction models

Univariate analysis determined eight clinical variables (age, gender, pain at presentation, type 2 diabetes mellitus, health performance status, cancer stage, smoking history and anxiety/depression) and six radiological variables (pancreatic duct diameter, the anterioposterior and laterolateral tumour dimensions, tumour location, tumour distance from left and right ganglia) which were associated with opioid use at three months at a significance level of 0.250 (**Table 4** and **Table 5**). In contrast, there was no evidence of association with CA19-9 levels, grade of histological differentiation, use of pancreatic enzyme therapy, chronic pancreatitis, chemotherapy, total tumour volume, cephalocaudal tumour dimension. Due to high missing value rates, smoking history and anxiety/depression was not included in the multivariable model.

The multivariable analysis of the clinical parameters included 366 patients (with 183 events). Age (OR per year: 0.97 95% CI, 0.94 to 0.99, p<0.001), performance status (3 vs 0-2) (OR: 2.57, 95% CI, 1.32 to 5.00, p = 0.006), presentation with pain (OR 9.57, 95% CI 5.78 to 15.85, p<0.001) were independently associated with opioid use at three months. (**Table 6**). The model combining clinical and radiological variables was developed in a total of 138 patients (with 73 events). In addition to the associations with the age, performance status and pain at presentation, it also revealed an associations for latero-lateral tumour dimension (OR 1.04, 95% CI, 1.00 to 1.08 , p= 0.048), anterior-posterior dimension (OR 0.94, 95% CI, 0.89 to 0.99, p= 0.042) and tumour distance from the right ganglion (OR per mm of distance: 0.96, 95% CI, 0.94 to 0.9, p=0.004) (**Table 6**).

Table 4. Univariate analysis of clinical parameters predictive of opioid use at three months.

	Patients on opioids at 3 months (n=183)	Patients not on opioid at 3 months (n=200)	Odd Ratio (95% CI)	P-value
Age (mean, SD)	68.5 (10.6)	73.0 (9.7)	0.96 (0.94–0.98)	**<0.001[1]**
Gender (n,%)				
Male	87 (47.5%)	111 (55.5%)	1.00	**-**
Female	96 (52.4%)	89 (44.5%)	0.73 (0.49–1.09)	**0.120[1]**
Abdominal Pain at diagnosis (n/%)				
Yes	129 (70.5%)	164 (82%)	10.89 (6.73-17.6)	**<0.001[1]**
No	54 (29.5%)	36 (18%)	1.00	
Major Co-morbidities (n,%)				
Neurological	21 (11%)	24 (14%)	1.29 (0.69–2.40)	0.430
Cardiovascular	58 (33%)	69 (36%)	0.88 (0.57–1.35)	0.549
Respiratory	14 (8%)	11 (6%)	1.42 (0.63–3.22)	0.398
Diabetes Mellitus Type 2	36 (21%)	50 (27%)	0.84 (0.66–1.08)	**0.169[1]**
Renal	9 (5%)	11 (6%)	0.89 (0.36–2.19)	0.796
Health Performance Status (n,%)			1.16 (0.98–1.39)	**0.086[1]**
0	44 (25%)	75 (39%)	1.00	-
1	60 (34%)	51 (27%)	2.01 (1.18–3.40)	**0.010[1]**
2	33 (19%)	28 (15%)	2.01 (1.07–3.76)	**0.029[1]**
3	36 (20%)	26 (14%)	2.36 (1.26–4.42)	**0.007[1]**
4	3 (1.7%)	10 (5%)	0.51 (0.13–1.96)	0.328
Smoking History (n,%)			1.27 (0.93–1.75)	**0.123[2]**
Current smokers	24 (17%)	20 (13%)	1.52 (0.79–2.95)	**0.212[2]**
Ex- smokers	31 (23%)	26 (17%)	1.51 (0.83–2.74)	**0.174[2]**
Never smoked	82 (60%)	104 (69%)	1.00	-
CA19-9 per 1000 units (mean, SD)	12745 (88536)	4042 (13258)	1.02 (0.98–1.05)	0.342
Cancer Stage (n,%)			1.29 (1.01–1.64)	**0.039[1]**
I	7 (4%)	15 (7%)	1.00	**-**
II	13 (7%)	18 (9%)	1.55 (0.49–4.87)	0.455
III	58 (32%)	70 (35%)	1.78 (0.68–4.65)	**0.242[1]**
IV	103 (57%)	95 (48%)	2.32 (0.91–5.94)	**0.079[1]**
Histological Differentiation (n,%)			0.89 (0.70–1.13)	0.345
Poorly- differentiated	19 (11%)	16 (8%)	1.00	-
Moderately- differentiated	27 (15%)	21 (11%)	1.08 (0.45–2.60)	0.859
Well-differentiated	5 (3%)	5 (3%)	0.84 (0.20–3.43)	0.811
Adeno-squamous differentiation	2 (1%)	4 (2%)	0.42 (0.07–2.61)	0.985
Acinar differentiation	1 (0.5%)	2 (1%)	0.42 (0.03–5.08)	0.496
Mucinous differentiation	12 (7%)	10 (5%)	1.01 (0.35–2.94)	0.985
Unclassified	42 (24%)	58 (31%)	-	-
Biopsy not available	67 (38%)	74 (39%)	-	-
Pancreatic Enzyme Therapy (n,%)				
Not prescribed at the 1st month	65 (36%)	64 (33%)	1.00	-
Prescribed at the 1st month	115 (64%)	128 (67%)	0.89 (0.58–1.36)	0.574
Anti-depressant or anxiolytic (n,%)				
Not prescribed	120 (66%)	150 (78%)	1.00	-
Prescribed	59 (34%)	43 (22%)	1.72 (1.08–2.72)	**0.022[2]**
Chronic Pancreatitis (n,%)				
No	167 (94%)	182 (93%)	1.00	-
Yes	10 (5%)	14 (7%)	0.78 (0.33-1.80)	0.558
Chemotherapy Treatment (n,%)				
No chemotherapy	76 (43%)	76 (39%)	1.00	-
FOLFIRINOX	45 (25%)	58 (30%)	0.78 (0.47 – 1.28)	0.322
Gemcitabine	45 (25%)	49 (25%)	0.92 (0.55- 1.54)	0.675
Other	11 (6%)	10 (5%)	-	-

[1]Covariates included in the multivariable analysis based on significance level of 0.250.
[2]Smoking history and Anxiety/depression were not included in the multivariable model due to high missing value rates.

Table 5. Univariate analysis of radiological parameters predictive of opioid use at three months post-diagnosis.

Radiological Characteristic	Patients on opioids at 3 months	Patients not on opioids at 3 months	Odd Ratio	P-value
Pancreatic Duct Diameter mm (mean, SD)	5.66 (3.09)	6.26 (3.07)	0.94 (0.84–1.04)	**0.238[1]**
Total tumour volume in cm³	5.3 (4.8)	4.6 (7.9)	5.1 (0.02-1083)	0.548
Tumour Dimensions in mm (mean, SD)				
Anterior-posterior	33.9 (11.9)	30.9 (13.4)	1.02 (0.99–1.05)	**0.159[1]**
Latero-lateral	37.5 (14.9)	32.1 (16.0)	1.03 (1.00–1.05)	**0.044[1]**
Cephalo-caudal	33.1 (11.0)	31.7 (11.9)	1.01 (0.98–1.04)	0.453
Tumour location (n, %)				
Head tumours	114 (62%)	142 (71%)	0.67 (0.44–1.03)	**0.071[1]**
Body tumours	44 (24%)	30 (15%)	1.79 (1.07–3.00)	**0.026[1]**
Tail tumours	21 (11%)	28 (14%)	0.79 (0.43–1.45)	0.461
Unclassified or unavailable	4 (2%)	-	-	-
Distance from the Right Coeliac Ganglion in	22.2 (21.0)	31.7 (20.7)	0.96 (0.95–0.98)	**0.001[1]**
Distance from the Left Coeliac Ganglion in mm (mean, SD)	19.6 (19.8)	32.0 (21.2)	0.97 (0.96–0.99)	**0.008[1]**

[1]Covariates included in the multivariable analysis based on significance level of 0.250.

Table 6. Multivariable logistic regression analysis of the clinical and the radiological predictors of opioid use at three months post-diagnosis.

Clinical model		
Characteristics	**Odd Ratio (95% CI)**	**P-value**
Age in years	0.97 (0.94-0.99)	<0.001
Presentation with Abdominal Pain	9.57 (5.78-15.85)	<0.001
Performance status 3	2.57 (1.32-5.00)	0.006
*The clinical parameters were analysed in a total of 366 patients		

Clinical-radiological model		
Characteristics	**Odd Ratio (95% CI)**	**P-value**
Age in years	0.94 (0.89-0.99)	0.008
Presentation with Abdominal Pain	8.33 (3.36-20.66)	<0.001
Performance status 3	5.42 (1.50-19.79)	0.010
Anterior-posterior tumour dimension in mm	0.94 (0.89-0.99)	0.042
Latero-lateral tumour dimension in mm	1.04 (1.00-1.08)	0.048
Tumour distance from the right ganglion in mm	0.96 (0.93-0.98)	0.001
*The clinical-radiological was developed in 138 patients.		

19

Model Performance

The discriminatory ability of the two models, assessed based on their AUC, was estimated at 0.81 (95% CI 0.76 to 0.85) and 0.84 (95% CI 0.78 to 0.92), for the clinical and the clinical-radiological models, respectively (Appendix 3). Sensitivities, specificities, PPVs and NPVs remained at moderate levels. Assessments of calibration and internal validation were also undertaken and the results are provided in the Appendix 4.

Case example

A 70 year old patient is presenting with a health performance less than three, with no pain at diagnosis. His tumour is located 5mm away from the right coeliac ganglion, it has an anterior-posterior dimension of 20mm and a latero-lateral dimension of 20mm. This patient has a 44% probability (95% CI 22% to 66%, p<0.001) of requiring opioids. If the same patient had a 30 mm latero-lateral tumour dimension his probability increases to 55% (95% CI 33% to 77%, p<0.001) and if this dimension increased to 40 mm his probability climbs to 65% (95% CI 41% to 89%, p<0.001).

DISCUSSION

Main Findings

This retrospective single-centre cohort study demonstrated that opioid use is prevalent in 37% to 47% of patients with pancreatic cancer during the first year of their diagnosis. Opioid use at three months is associated with poorer survival (HR for death 1.83, 95% CI, 1.14 to 2.95, p=0.012). The mean daily morphine increased over time for from 54 mg (SD 44) in the first month to 126 mg (SD 125) at one year. We sought to develop predictive models based on clinical and radiological characteristics to identify patients at risk of requiring opioids at three months. We investigated a series of candidate predictors of opioid use at three months. Based on those associations, we firstly developed a predictive model based exclusively on clinical parameters. Age, presentation with pain and health performance status were the three parameters retained in this clinical model. The discrimination of the clinical model was good (AUC: 0.81; sensitivity: 70.9%; specificity: 80.4%; PPV: 77.0%; NPV: 74.9%). We then added a series of radiological parameters, of which the distance of the tumour from the right ganglion, the latero-lateral and the anterior-posterior tumour dimensions reached statistical significance. The discrimination ability of this radio-clinical model improved further (AUC: 0.84, sensitivity: 78.9%, specificity: 69.2%, PPV: 73.7%, NPV: 75.0%). Both models were well calibrated. Based on the reported health performance status of the cohort patients, 77% met the assumed fitness criteria for endoscopic analgesia whilst 20% had borderline fitness.

Comparison with previous research

The prevalence of pain and opioid use has been reported in three previous studies[22-24]. A previous retrospective cohort study included 103 patients with stage IV pancreatic cancer who underwent chemotherapy[22]. Overall, 78% of the patients received opioids at baseline, of whom 66% were on doses exceeding 5mg per day. Morphine was associated with reduced survival; patients on less than 5mg/daily of morphine equivalents survived longer than those on doses greater than 5mg/daily (median survival: 315 versus 150 days, p<0.01, HR= 1.79; 95% CI, 1.13 to 2.84) which is similar to the association demonstrated in our study (HR= 1.83; 95% CI, 1.14 to 2.95, p=0.012)[22]. A second retrospective cohort study examined 566 patients with stage III and IV inoperable pancreatic cancer. Only 9.7% of the patients treated with chemotherapy. The mean opioid dose at their first opioid prescription was 55.9 (SD 53.8) mg whilst the mean opioid dose in their last month of their life was 162.8 (SD 131.6) mg. These figures approximate our results. The mean survival time from diagnosis was 284 (SD 328) days. The mean duration of the opioid-free period for patients were 97 (SD 234) days whilst the mean survival from the first opioid prescription was 187 (SD 212) days. A third retrospective cohort study included 109 male patients with adenocarcinoma and non-adenocarcinoma tumours which were identified from a US army veterans' registry[24]. In total, 58% of them had pain at diagnosis. Patients with abdominal pain had a 6.77-fold (p<0.01) higher odds for early death in comparison to those who were pain free[24]. To the best of our knowledge there are no other published risk prediction models for patients

Strengths

To the best of our knowledge, this is the first clinical study to evaluate associations between clinical and radiological parameters with opioid use in patients with advanced pancreatic cancer. The study was conducted in a large UK tertiary centre and covered a period of 10 years. The cases were identified from the cancer registry, so missing cancer cases are unlikely. It is likely our results are representative of the general population of patients with pancreatic cancer, as demonstrated by the representative epidemiology of this cohort (for example the mean age in this cohort is 71 years and 52% of them are males which match exactly the UK cancer statistics[25]). The radiological results demonstrate face validity, showing that the latero-lateral and the anterior-posterior tumour dimension is associated with pain, as opposed to the superior-inferior dimension. These associations are plausible considering the relative anatomical associations of the ganglia with the pancreas.

Limitations

Case note review, used to ascertain opioids use, may have introduced measurement error as we were unable to fully establish the exact opioid doses administered, especially when PRN prescriptions were issued. We anticipate significant loss to follow-up during the period from 6 to 12 months, likely resulted in selection bias and a likely underestimate of opioid use at these time points. Nevertheless, this does not detract from the key findings that burden of opioids use in the cohort is substantial (and increases over time) and would not have influenced the primary outcome for the risk prediction models. While the sample for the clinical model was sufficient, the sample for the model incorporating radiological characteristics was less than the pre-specified sample size (138 available vs 383 required). Although for the six predictors in this model, there were more than 10 events per parameter, the limited sample size likely precluded inclusion of additional predictors. The models were developed in a single centre, and while we suspect the models are likely representative of patients in other UK centres, this inevitably limits generalisability.

Interpretation and implications for future research

Opioid use is common in patients with inoperable pancreatic cancer. Opioid doses on average escalates to 126mg per day in the first year of diagnosis. The association between opioid use at three months and poorer prognosis is likely explained by unmeasured confounding (by tumour burden / advanced disease), rather than a causal explanation. A previous meta-analysis investigating the risk of unintentional opioid overdose showed that doses of at least 50mg per day (compared with lower doses) were associated with an approximate four-fold (Relative Risk 3.87, 95% CI, 2.36 to 6.33, p<0.001) risk of overdoses in comparison to doses of ≤50mg[26]. This indicates that patients with pancreatic cancer are likely to be at elevated risk of opioid-related harms. Therefore, benefits and risks of opioids need to be carefully balanced, and strategies to mitigate risk while conferring analgesic efficacy should be considered. EUS-CPN can be considered in selected cases, however there is uncertainty regarding optimal patient selection and timing for this intervention. NICE have recommended the conduct of a trial comparing early vs. on demand EUS-CPN. Our study provides additional evidence to justify such a trial. Risk prediction models for opioid use could have clinical utility in identifying patients most likely to benefit from early EUS-CPN and could be used to inform patient eligibility in such a trial. Extension of derivation cohort to other centres with external validation is required. To empirically demonstrate the potential

22

for improved decision making based on the risk prediction models, a net benefit approach would be informative[27].

Conclusion

Nearly half of patients with inoperable pancreatic adenocarcinoma require opioids within a year of diagnosis. Mean opioid doses double in the first year. Opioid use by three months is associated with poorer prognosis. The clinical and radiological risk factors identified and the risk prediction models could be helpful in identifying patients at risk of requiring opioids by three months. Expansion of the derivation cohort and external validation of this predictive model is required.

REFERENCES

1.   !!! INVALID CITATION !!! 1-3.
2.   Bapat AA, Hostetter G, Von Hoff DD, et al. Perineural invasion and associated pain in pancreatic cancer. Nature Reviews Cancer 2011;11:695-707.
3.   Ceyhan GO, Bergmann F, Kadihasanoglu M, et al. Pancreatic neuropathy and neuropathic pain--a comprehensive pathomorphological study of 546 cases. Gastroenterology 2009;136:177-186.e1.
4.   Demir IE, Schorn S, Schremmer-Danninger E, et al. Perineural mast cells are specifically enriched in pancreatic neuritis and neuropathic pain in pancreatic cancer and chronic pancreatitis. PLoS One 2013;8:e60529.
5.   Zhu Z, Friess H, diMola FF, et al. Nerve growth factor expression correlates with perineural invasion and pain in human pancreatic cancer. J Clin Oncol 1999;17:2419-28.
6.   Costamagna G, Mutignani M. Pancreatic stenting for malignant ductal obstruction. Digestive and Liver Disease 2004;36:635-638.
7.   Drewes AM, Campbell CM, Ceyhan GO, et al. Pain in pancreatic ductal adenocarcinoma: A multidisciplinary, International guideline for optimized management. Pancreatology 2018;18:446-457.
8.   Lahoud MJ, Kourie HR, Antoun J, et al. Road map for pain management in pancreatic cancer: A review. World journal of gastrointestinal oncology 2016;8:599-606.
9.   McNicol E. Opioid side effects and their treatment in patients with chronic cancer and noncancer pain. J Pain Palliat Care Pharmacother 2008;22:270-81.
10. Wyse MS, V. Endoscopic Ultrasound-Guided Management of Pain in Chronic Pancreatitis and Pancreatic Cancer: an Update. Curr Treat Options Gastroenterol 2018;16:417-427.
11. Wyse JM, Carone M, Paquin SC, et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol 2011;29:3541-6.
12. Koulouris AI, Alexandre L, Hart AR, et al. Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) technique and analgesic efficacy in patients with pancreatic cancer: A systematic review and meta-analysis. Pancreatology 2021;21:434-442.
13. Somerset Cancer Register (SCR), 2020.
14. Strong Opioids: Palliative cancer care - pain. National Institute of Clinical Excellence (NICE), 2021.
15. Fagan T. Exact 95% confidence intervals for differences in binomial proportions. Comput Biol Med 1999;29:83-7.
16. Clark TG, Bradburn MJ, Love SB, et al. Survival analysis part I: basic concepts and first analyses. British journal of cancer 2003;89:232-238.
17. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.
18. Peacock J, Peacock PJ. Oxford handbook of medical statistics: Oxford University Press, 2011.
19. Hosmer DW, Hosmer T, Le Cessie S, et al. A comparison of goodness-of-fit tests for the logistic regression model. Stat Med 1997;16:965-80.
20. Neeman T. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating by Ewout W. Steyerberg. International Statistical Review 2009;77:320-321.
21. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. BMJ 2020;368:m441.
22. Steele GL, Dudek AZ, Gilmore GE, et al. Impact of Pain, Opioids, and the Mu-opioid Receptor on Progression and Survival in Patients With Newly Diagnosed Stage IV Pancreatic Cancer. American Journal of Clinical Oncology 2020;43.

23.   Oh TK, Do S-H, Yoon Y-S, et al. Association Between Opioid Use and Survival Time in Patients With Unresectable Pancreatic Cancer: 10 Years of Clinical Experience. Pancreas 2018;47.
24.   Kim D, Zhu H, Nassri A, et al. Survival analysis of veteran patients with pancreatic cancer. Journal of digestive diseases 2016;17:399-407.
25.   Cancer Research UK. Pancreatic Cancer Statistics, 2016.
26.   Adewumi AD, Hollingworth SA, Maravilla JC, et al. Prescribed Dose of Opioids and Overdose: A Systematic Review and Meta-Analysis of Unintentional Prescription Opioid Overdose. CNS Drugs 2018;32:101-116.
27.   de Hond AAH, Steyerberg EW, van Calster B. Interpreting area under the receiver operating characteristic curve. Lancet Digit Health 2022;4:e853-e855.

APPENDICES

Appendix 1 – Definitions of epidemiological and other terms

Opioid use was defined as receipt of opioid medications for the treatment of pancreatic cancer-related pain. The prevalence of opioid use at each time-point was defined as the fraction of opioid users to the total number of at risk (alive) subjects without missing data regarding their opioid use. The incidence was the proportion of patients with a new opioid prescription to the total number of patients who were alive and opioid-free in the previous three-month period. Fitness for endoscopy was determined based on the health performance status recorded in patients' notes assuming that scores 0 to 2 represented definitive fitness, scores of 3 represented borderline fitness, and scores of 4 represented lack of fitness. Other indirect measures of the fitness for endoscopy were diagnostic or therapeutic endoscopies performed at diagnosis and the administration of chemotherapy.

Appendix 2 - Survival analysis supplementary material

Kaplan-Meier survival curves of the patients with inoperable pancreatic cancer stratified by their opioid use.
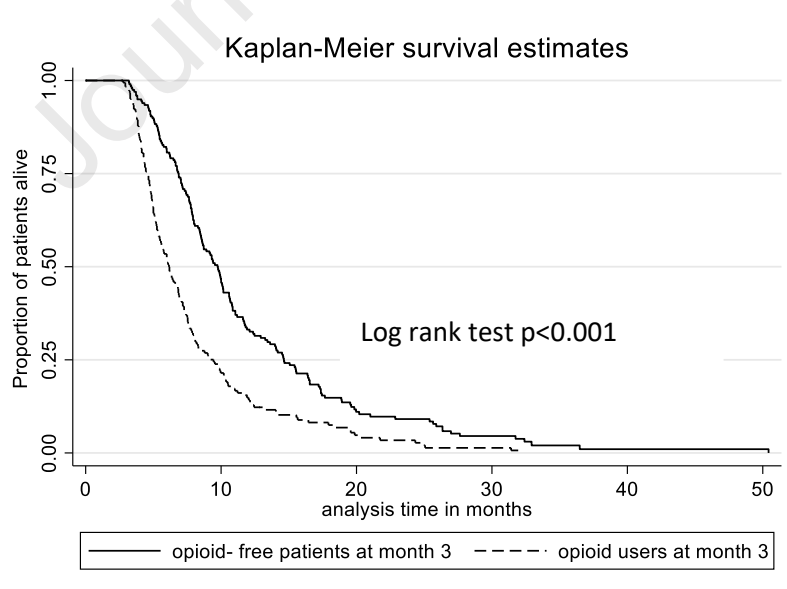
Uni- and multi-variable associations between demographic, clinical, radiological characteristics and all-cause mortality.

Univariable model

Characteristics	Hazard Ratio (95% CI)	P-value
Opioid use (Y/N)	1.89 (1.53–2.34)	**<0.001[1]**
Age per year	1.02 (1.01–1.03)	**<0.001[1]**
Sex (male)	0.99 (0.81–1.23)	0.952
Major Co-morbidities (Y/N)		
Neurological	0.95 (0.69–1.32)	0.760
Cardiovascular	1.44 (1.15–1.80)	**0.002[1]**
Respiratory	1.18 (0.77–1.80)	0.457
Diabetes Mellitus Type 2	0.92 (0.70–1.19)	0.512
Renal	1.86 (1.18–2.93)	**0.007[1]**
Health Performance Status[2]	1.32 (1.21–1.44)	**<0.001[1]**
Smoking History[2]	1.09 (0.93–1.29)	0.285
CA19-9 per 1000 units/mm	1.02 (1.01–1.04)	**<0.001[1]**
Cancer Stage[2]	1.31 (1.13–1.51)	**<0.001[1]**
Histological Differentiation[2]	0.93 (0.81–1.06)	0.77
Chemotherapy Treatment (Y/N)	0.50 (0.408–0.62)	**<0.001[1]**
Pancreatic Enzyme Therapy (Y/N)	1.13 (0.90–1.41)	0.299
Depression or Anxiety (Y/N)	1.12 (0.89–1.42)	0.341
Total tumour volume per cm³	11.36 (1.73–74.80)	**0.011[1]**
Tumour location	1.16 (0.99–1.35)	**0.052[1]**

[1]Covariates included in the multivariable analysis
[2]Variables analysed as trends across categories.

Multivariable model

Characteristics	Hazard Ratio (95% CI)	P-value
Opioid use	1.83 (1.14–2.95)	0.012
Chemotherapy Treatment	0.44 (0.26–0.76)	0.003
Total tumour volume per cm³	27.29 (2.06–360.86)	0.012
Cancer Stage[1]	1.40 (1.01–1.95)	0.001

[1]Variable analysed as trends across categories.

Predicting use of opioids in patients with inoperable pancreatic cancer

Appendix 3 - Model Discrimination

Figure 3. Receiver Operator Curve (ROC) analysis for the clinical and the radio-clinical prediction models.

Area under ROC curve = 0.8056

Area under ROC curve = 0.8436
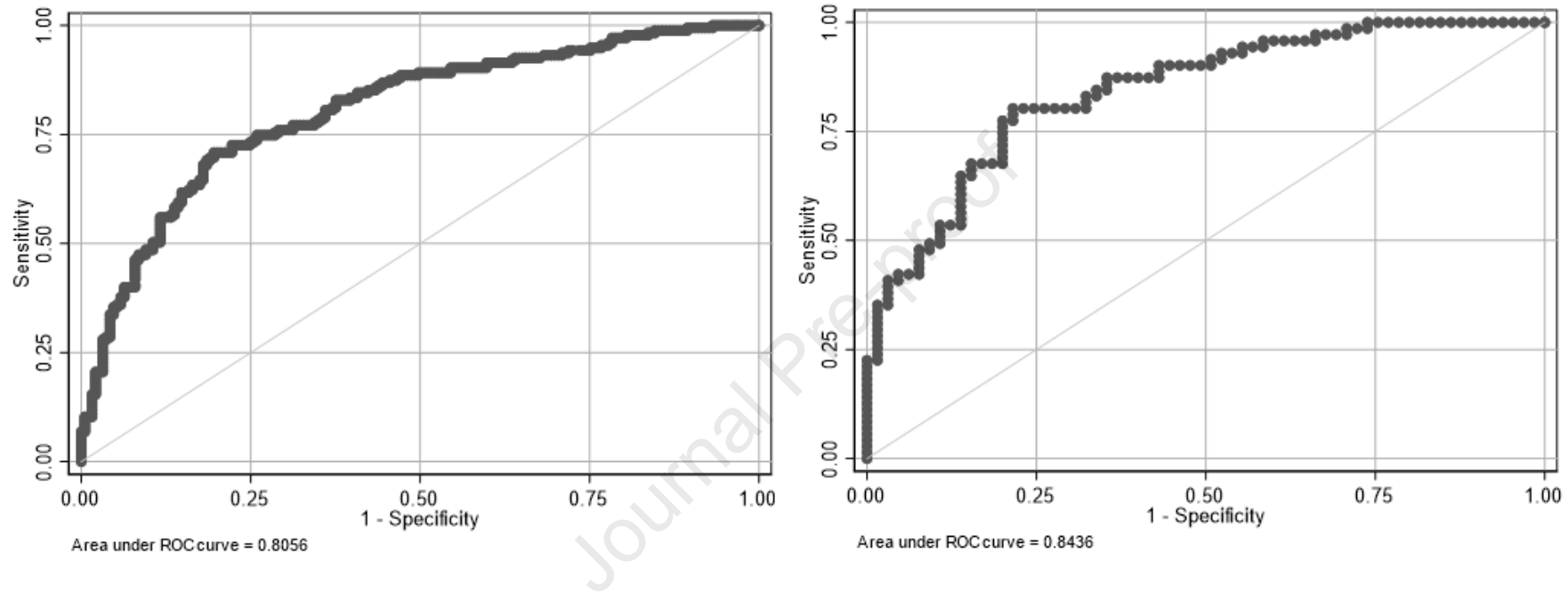
Table 9. Predictive performance of the clinical and the radio-clinical models at a cut-

off probability of 50%.

Model Discrimination	Clinical Model	Radio-clinical Model
Sensitivity	70.9%	78.9%
Specificity	80.4%	69.2%
Positive predictive value*	77.0%	73.7%
Negative predictive value^	74.9%	75.0%

Appendix 4 - Model Calibration

Calibration of the derived model (i.e. how well the predicted probabilities agree with the observed probabilities) was evaluated by visual assessment of a calibration plot, in conjunction with the estimation of the relevant metrics expressing the degree of discordance between observed and expected probabilities[20]. These metrics were: a. the calibration slope (i.e. odd ratio of the mean predicted and the mean observed probability), b. the ratio of expected to observed events (E:O) and c. the calibration-in-large (CITL) (i.e. a one-sample t-test of the difference between the mean predicted and the mean observed probability). We also applied the Hosmer-Lemeshow test, which is the statistical analogue of the calibration plot[19]. The calibration plot showed evidence of goodness-of-fit for the radio-clinical model based on the calibration plot below and the Hosmer-Lemeshow test confirmed (p=0.636).

Calibration plot for prediction of opioid use at three months. The diagonal line represents the ideal calibration, the light blue line (known as Lowess curve) represents the actual predictions and the green circles are the outcomes by deciles of risk. Visual assessment of the plot indicates that Lowess curve runs close to the diagonal line, hence the model is well-calibrated.
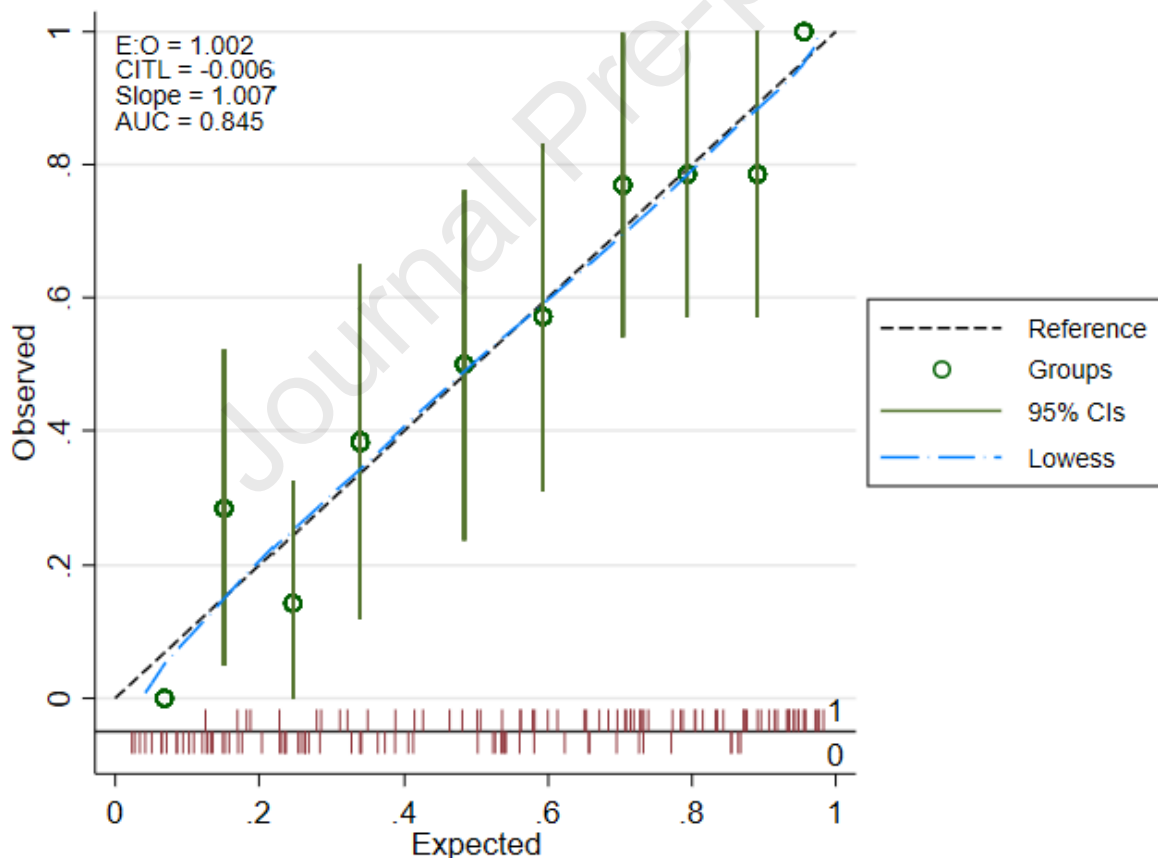
Appendix 5 - Internal validation with bootstrap resampling

Bootstrap resampling was used for bias correction[20]. Our derivation cohort may hypothetically fit differently in a different (external) dataset due to sampling bias. As for this study an external dataset was not available, we performed bootstrapping to correct for such bias. Bootstrapping revealed low level of sampling bias proportionally to the estimated effect sizes (**Table 10 Appendix 3**).

<table>
<tr><td colspan="5" align="center">**Table 10. Bias estimation and correction, using bootstrap resampling technique**</td></tr>
<tr><td></td><td>**Observed Odds Ratio**</td><td>**Bias**</td><td>**Bias-corrected 95% CI**</td><td>**p-value**</td></tr>
<tr><td>**Age in years**</td><td>0.93</td><td>-0.010</td><td>0.88–0.99</td><td>0.019</td></tr>
<tr><td>**Presentation with Abdominal Pain**</td><td>10.05</td><td>2.489</td><td>4.03-37.8</td><td><0.001</td></tr>
<tr><td>**Performance Status 3**</td><td>11.46</td><td>4.012</td><td>1.41–83.96</td><td>0.012</td></tr>
<tr><td>**Latero-lateral tumour dimension**</td><td>1.05</td><td>0.017</td><td>0.99-1.11</td><td>0.211</td></tr>
<tr><td>**Anterior-posterior tumour dimension**</td><td>0.94</td><td>-0.012</td><td>0.88-1.02</td><td>0.087</td></tr>
<tr><td>**Distance of the Tumour from the Right Ganglion in mm**</td><td>0.96</td><td>-0.004</td><td>0.93–0.98</td><td>0.029</td></tr>
</table>