Original article

# Population-based study of the prevalence and management of self-reported high pain scores in patients with non-resected pancreatic adenocarcinoma

S. Tung[1], N. G. Coburn[1,2,5,6], L. E. Davis[5], A. L. Mahar[7], S. Myrehaug[3], H. Zhao[6], C. C. Earle[4,6], A. Nathens[1,2,5,6] and J. Hallet[1,2,5,6]

[1]Division of General Surgery, Department of Surgery, University of Toronto, Divisions of [2]General Surgery, [3]Radiation Oncology and [4]Medical Oncology, Odette Cancer Centre, and [5]Sunnybrook Research Institute, Sunnybrook Health Sciences Centre and [6]Institute for Clinical Evaluative Sciences, Toronto, Ontario, and [7]Department of Community Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

*Correspondence to:* Dr J. Hallet, Department of Surgery, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Room T2 063, Toronto, Ontario, Canada, M4N 3M5 (e-mail: julie.hallet@sunnybrook.ca)

**Background:** **Pain is a common debilitating symptom in pancreatic adenocarcinoma. This cohort study examined the use of, and factors associated with, pain-directed interventions for a high pain score in patients with non-curable pancreatic adenocarcinoma.**

**Methods:** **Administrative databases were linked and patients with non-resected pancreatic adenocarcinoma diagnosed between 2010 and 2016, who reported one or more Edmonton Symptom Assessment System (ESAS) score, were identified. A high pain score was defined as an ESAS score of at least 4. Outcomes were pain-directed interventions: opiates (in patients aged 65 years or more with universal drug coverage), nerve block and radiation therapy for a high pain score. Reduction in pain score of at least 1 point after pain-directed intervention was also evaluated. Modified Poisson regression was used to examine factors associated with pain-directed intervention.**

**Results:** **Among 2623 patients with a median age of 67 years, 1223 (46·6 per cent) were women, and 1621 (61·8 per cent) reported a high pain score at a median of 38 days after diagnosis. Of those with a high pain score, 75·6 per cent (688 of 910) received opiates, 13·5 per cent (219 of 1621) radiation and 1·2 per cent (19 of 1621) nerve block. The pain score decreased in 62·1 per cent of patients after administration of opiates, 73·4 per cent after radiation and all patients after nerve block. In multivariable analysis, no patient factor (age, sex, co-morbidity burden, rurality, income quintile) was associated with receipt of non-opiate pain-directed intervention for a high pain score. In patients aged at least 65 years, advanced age was associated with lower odds of opiate use.**

**Conclusion:** **Opiates are the most common pain-directed intervention for non-curable pancreatic adenocarcinoma, whereas radiation therapy and nerve blocks are seldom used. The lack of association between pain-directed interventions and patient factors points toward practice-driven patterns.**

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## Introduction

Pancreatic adenocarcinoma is a high-fatality cancer representing a considerable societal and healthcare burden; it affects up to 55 000 people and results in 44 000 deaths per year in the USA[1]. The majority of patients present with advanced or metastatic disease and are not eligible for surgery with curative intent[2]. For patients with non-curable disease, survival remains limited at a median of 7 months, despite recent advances in systemic therapy[3]. In addition to systemic therapy, symptom control and optimization of quality of life is particularly important in this population[4].

Pain is one of the cardinal symptoms experienced by patients with pancreatic adenocarcinoma, with up to 80 per cent of patients affected[5,6]. Clinical practice guidelines[7,8] focus on pharmacological therapy, with opiates as the dominant modality used for treatment. Although historical concerns focused on undertreating cancer pain[5,9,10], more recently new concerns have been raised about high and

chronic use of opiates in patients with cancer, despite metastatic status[11]. Frequent use of opiates has been suggested as a chemical coping mechanism for patients with cancer, whereby use of opiates may mask other needs that cannot be addressed adequately[11]. Therefore, the use of opiate-sparing treatments is important[12].

Patient-reported outcome measures (PROMs) have become a growing focus in oncology[13,14]. RCTs demonstrated improvements in patient engagement, outcome and satisfaction with use of PROMs, which led to their routine use in clinical practice[15,16]. In 2007, the province of Ontario initiated population-level routine prospective screening with the Edmonton Symptom Assessment System (ESAS) during outpatient oncology visits[17,18]. However, information regarding the usefulness and actionability of these data to support patients in clinical practice outside of controlled trial settings is limited[19,20]. Therefore, a population-based study was undertaken to examine the use of, and factors associated with, pain-directed interventions for patient-reported high pain scores in the management of non-curable pancreatic adenocarcinoma, and to assess changes in pain scores with intervention.

## Methods

A population-based cohort study was undertaken using data linked from prospectively maintained administrative databases stored at the ICES in Ontario, Canada. Under the Canada Health Act, the Ontario population benefits from universally accessible and publicly funded healthcare though the Ontario Health Insurance Plan (OHIP). All residents of Ontario are eligible for OHIP after they have resided in the province for 3 months.

The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board, and met the data confidentiality and privacy guidelines of ICES. It was conducted and reported according to the STROBE statement[21].

### Study population and cohort

The study included patients with a valid OHIP number diagnosed from 2010 to 2016. Patients with a new diagnosis of pancreatic adenocarcinoma were identified in the Ontario Cancer Registry (OCR) using ICD-O.3 codes C25.0–C25.9. Those who did not undergo pancreatectomy with curative intent at any time up to 31 December 2017, and who had contact at a Registered Cancer Centre and reported at least one ESAS score in the 6 months after the date of diagnosis, were retained (*Table S1*, supporting information). Patients who met the following criteria were excluded: invalid or missing unique identification number; date of death missing; death before or on the date of diagnosis; date of last contact missing; another cancer diagnosis before or after the pancreatic adenocarcinoma diagnosis; or aged less 18 years at the time of diagnosis.

### Follow-up

Patients were followed from the time of diagnosis to the end of follow-up, defined as the date of death, last clinical encounter, or end of the study on 31 March 2018, whichever came first.

### Data sources

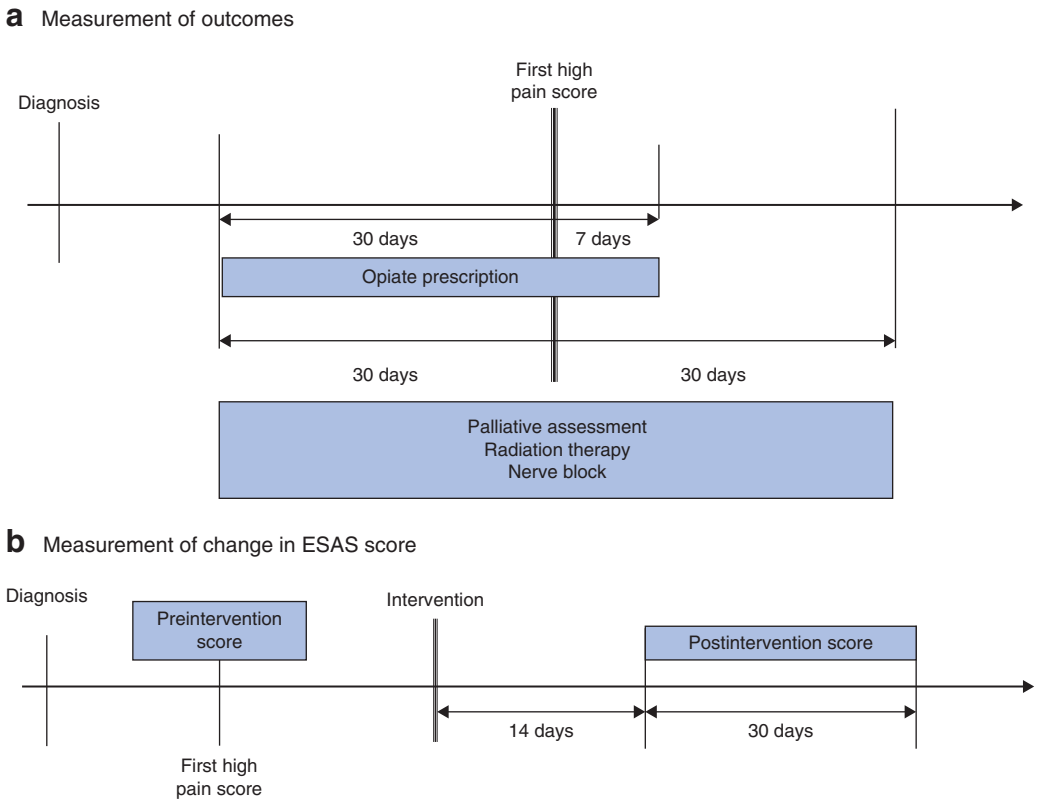
This study used several linked administrative data sets. The OCR includes all patients diagnosed with cancer (excluding non-melanoma skin cancer) in Ontario since 1964[22]. The reliability of its data has been reported previously[23,24]. The Registered Persons Database (RPDB) contains vital status and demographic data on all individuals covered under OHIP[23]. Information regarding health services is included in the Canadian Institute of Health Information Discharge Abstract Database for acute inpatient hospital admissions; the National Ambulatory Care Reporting System for same-day surgery admissions, emergency room visits and oncology clinic visits; and the OHIP Claims Database for billing from healthcare providers, including physicians, groups, laboratories and out-of-province providers. The Cancer Activity Level Reporting (ALR) database is maintained by the OCR, and includes chemotherapy drugs and medications administered to patients with cancer. These databases have been validated for a variety of diagnoses and services[25].

The data sets were linked using unique encoded identifiers and analysed at the ICES. The research team's analyst had complete access to all data sets used in this study in order to create the study cohorts, proceed to linkage and perform the analyses.

### Exposure

The main exposure was a patient-reported high pain score, defined as a moderate-to-severe pain score on the ESAS. The ESAS is a validated and reliable patient-reported outcome assessing the severity of nine common cancer-associated symptoms, including pain[17,18]. Patients are asked to rate each symptom on a 11-point numeric scale, from 0 (absence of symptom) to 10 (worst possible symptom)[17] (*Fig. S1*, supporting information). The first ESAS score of 4 or higher within the first 6 months after diagnosis[26] was captured to avoid reflecting high pain scores at the end of life.

**Fig. 1 Time windows used for measurement of outcomes and change in pain scores**




**a** Measurement of outcomes and **b** measurement of change in Edmonton Symptom Assessment System (ESAS) scores.

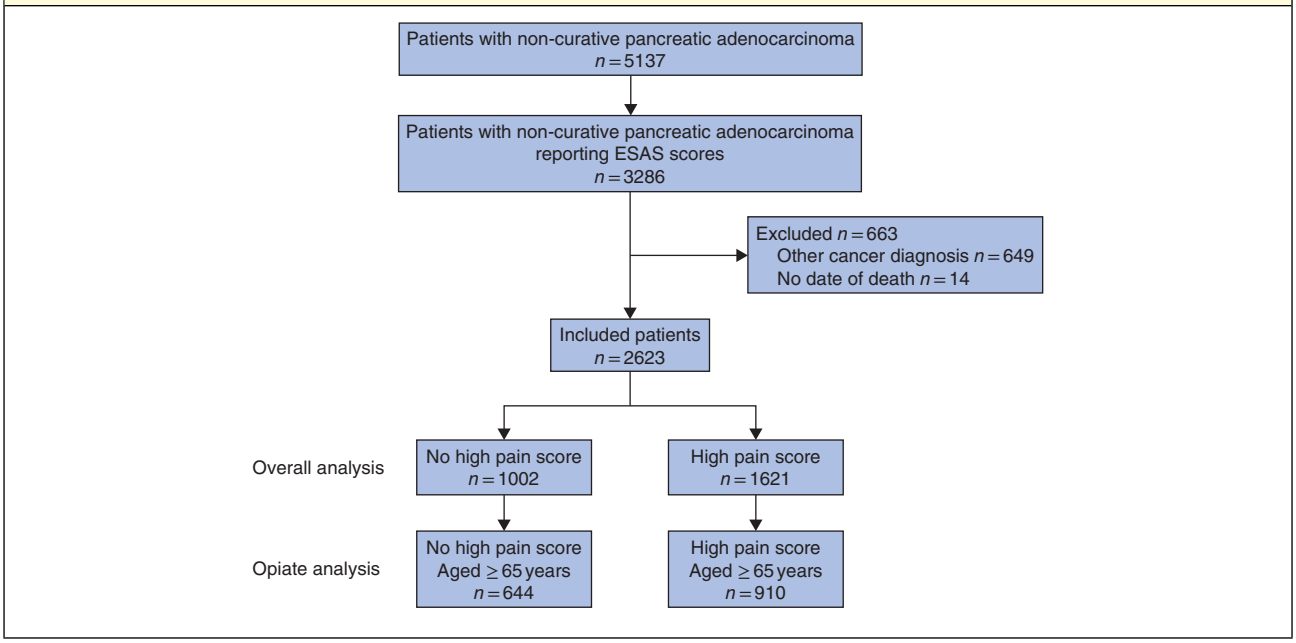
## Outcome measures

The primary outcome of interest was receipt of a pain-directed intervention, subdivided into receipt of radiation therapy, nerve block and opiates. Receipt of radiation therapy was defined by ALR codes, and nerve block by OHIP physician claims. Opiate medication use was defined by filling of a prescription for opiates according to the Ontario Drug Benefit (ODB), using drug identification numbers. The ODB covers all patients in Ontario aged at least 65 years with OHIP. Therefore, for assessment of opiate use the cohort was restricted patients aged 65 years or older.

Considering the opportunistic nature of ESAS collection, it was possible that patients may have been experiencing pain before their index assessment and so, because of possible delays in initiating therapy, receipt of therapy was measured during time windows around the date on which the high pain score was registered (*Fig. 1a*)[27]. Alternative time windows were tested and did not alter the proportion of patients receiving the intervention. The use of opiates was captured from 30 days before to 7 days after the date of the high pain score (*Fig. 1a*). This approach has been validated previously, and other time windows have been tested with no change in the results[28].

The secondary outcomes were: palliative care assessment; and change in ESAS score following receipt of pain-directed intervention, categorized as increased, stable or decreased. Palliative care assessments were defined by OHIP billing codes and examined for the entire cohort of patients with a high pain score (*Table S1*, supporting information). The change in ESAS score was examined in a subgroup analysis of patients with a high pain score who received pain-directed therapy. A clinically significant increase or decrease was defined as a change in score of at least 1 of 10 compared with the preintervention score[29]. The postintervention ESAS pain score was captured during a 30-day time window starting from 14 days after the intervention, to allow time for the treatment to take effect (*Fig. 1b*). In this analysis, the denominator was the number of patients receiving the interventions and recording an

**Fig. 2 Flow diagram of cohort inclusion and exclusion**




ESAS, Edmonton Symptom Assessment System.

ESAS score during the postintervention score observation time window.

## Co-variables

Age and sex were abstracted from the RPDB. Rural living was determined based on postal code of residence[30]. Income quintile was assessed by means of an ecological measure based on the median income of a patient's postal code of residence using national census data[25]. The co-morbidity burden was measured using the Johns Hopkins Adjusted Clinical Groups system score. The 32 Aggregated Diagnosis Groups were summed to create a total score, then dichotomized, with a cut-off of 10 indicative of a high co-morbidity burden, consistent with previous reports[31]. Patients who received chemotherapy were identified as those with at least one chemotherapy infusion billed from the date of diagnosis to the end of follow-up; this strategy was demonstrated previously to have 90 per cent concordance with patient medical records (ALR)[32].

Finally, the prevalence of concomitant high patient-reported scores (score at least 4) for ESAS symptoms other than pain at the time the high pain score was recorded was analysed.

## Statistical analysis

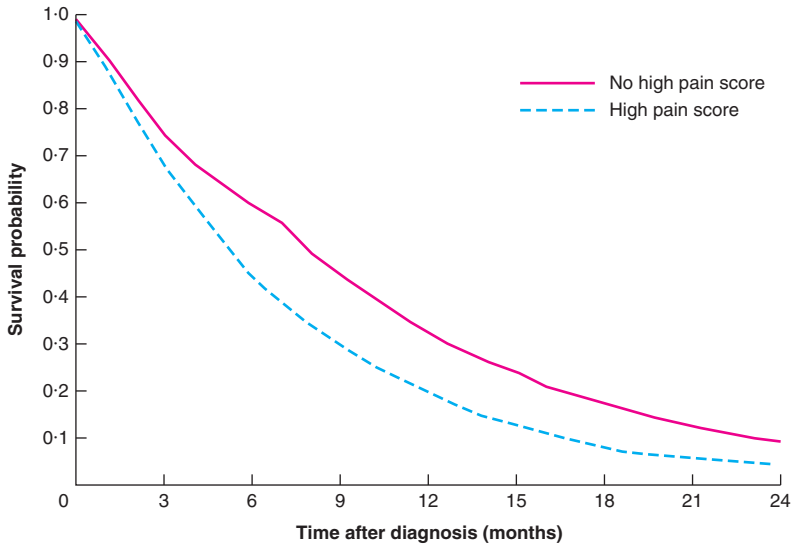
Categorical variables are reported as numbers with percentages, and continuous variables as median (i.q.r.).

**Table 1 Demographic and clinical characteristics of included patients, stratified by reporting of a high pain score**

| | No high pain score (*n* = 1002) | High pain score (*n* = 1621) | *P** |
|---|---|---|---|
| **Age (years)** | | | < 0·001 |
| < 65 | 358 (35·7) | 711 (43·9) | |
| 65–70 | 189 (18·9) | 351 (21·7) | |
| 71–80 | 299 (29·8) | 396 (24·4) | |
| ≥ 81 | 156 (15·6) | 163 (10·1) | |
| **Sex ratio (F : M)** | 457 : 545 | 766 : 855 | 0·410 |
| **Rural residence** | 104 (10·4) | 155 (9·6) | 0·490 |
| **High co-morbidity burden (ADG ≥ 10)** | 269 (26·8) | 544 (33·6) | 0·002 |
| **Income quintile** | | | 0·060 |
| 1 (lowest) | 159 (15·9) | 285 (17·6) | |
| 2 | 169 (16·9) | 307 (18·9) | |
| 3 | 210 (21·0) | 348 (21·5) | |
| 4 | 229 (22·9) | 373 (23·0) | |
| 5 (highest) | 235 (23·5) | 308 (19·0) | |
| **Time interval of diagnosis** | | | 0·410 |
| 2010–2013 | 494 (49·3) | 826 (51·0) | |
| 2014–2016 | 508 (50·7) | 795 (49·0) | |
| **Receipt of chemotherapy** | | | 0·606 |
| No | 366 (36·5) | 576 (35·6) | |
| Yes | 636 (63·5) | 1045 (64·4) | |

Values in parentheses are percentages. ADG, Aggregated Diagnosis Group. *$\chi^2$ test.

**Fig. 3 Overall survival after diagnosis of non-curable pancreatic adenocarcinoma, stratified by patient-reporting of high pain score**

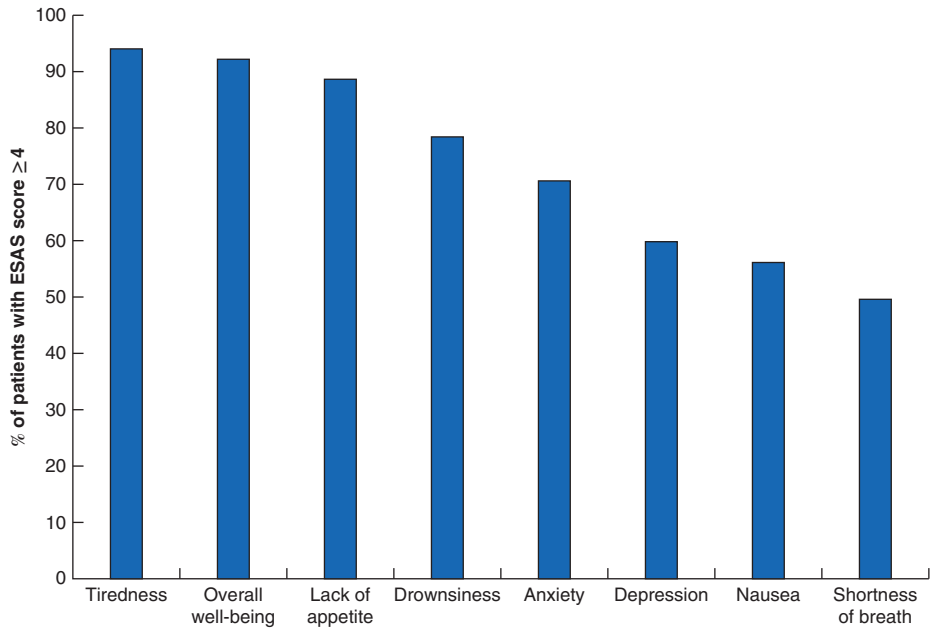



**No. at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No high pain score | 1002 | 829 | 640 | 481 | 358 | 255 | 181 | 118 | 80 |
| High pain score | 1621 | 1265 | 841 | 538 | 359 | 223 | 139 | 85 | 63 |

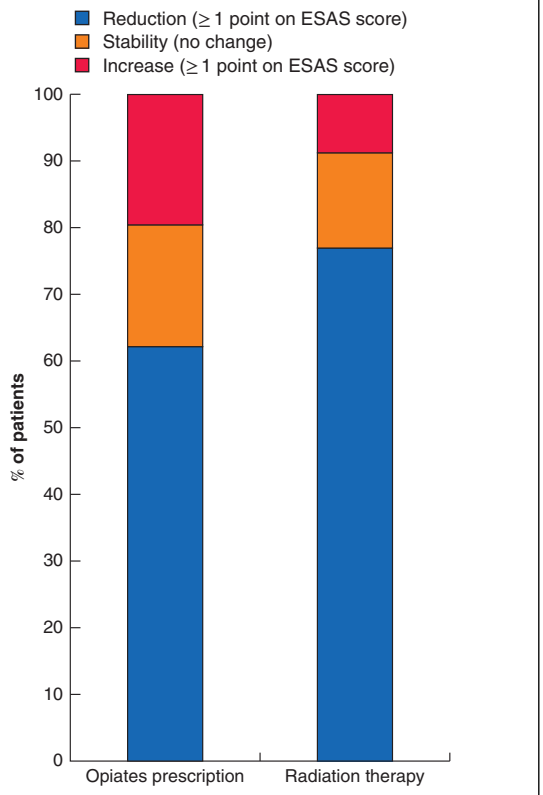
$P < 0{\cdot}001$ (log rank test).

**Fig. 4 Proportion of patients reporting moderate-to-severe symptoms at the time of recording a high pain score**




Moderate-to-severe symptoms were defined as those with an Edmonton Symptom Assessment System (ESAS) score of at least 4.

**Fig. 5 Change in pain score in patients stratified by receipt of opiate prescription and radiation therapy, among patients with a high pain score**




Change in Edmonton Symptom Assessment System (ESAS) pain score stratified by receipt of opiate prescription (354 patients) and radiation therapy (109).

Comparisons were undertaken using the $\chi^2$ test for categorical variables and the Kruskal–Wallis or *t* test for continuous variables. Median survival from the time of diagnosis was computed as actual survival.

Predictors of receipt of pain-directed intervention for a high pain score were examined using modified Poisson regression with robust error variance. Relevant demographic and clinical characteristics were identified *a priori* as potential predictors of pain-directed intervention based on clinical relevance (markers of complexity of cancer care) and existing literature (known relationship with symptom burden in pancreatic adenocarcinoma). The following variables were included: age (categorical), sex, co-morbidity burden, income, rural living and time interval of diagnosis (categorical). As opiate data were available only for patients aged 65 years or older, three models were constructed. The first included all patients with a high pain score and examined predictors of receiving radiation therapy and nerve blocks (opiate-sparing interventions). The second model was restricted to patients aged at least 65 years with a high pain score for whom opiate prescription data were available, and assessed predictors of combined radiation therapy, nerve block and opiates (all interventions). The third model was restricted to patients aged at least 65 years with a high pain score, and examined predictors of opiate use (opiate-only intervention). These models were designed to elucidate the different patterns of patient selection for opiate and non-opiate interventions for a high pain score. Results are reported as relative risks with 95 per cent confidence intervals.

All analyses were two-sided and statistical significance was set at $P \leq 0{\cdot}050$. Analyses were conducted using SAS® Enterprise Guide® 6.1 (SAS Institute, Cary, North Carolina, USA).

## Results

A total of 3286 patients diagnosed with pancreatic adenocarcinoma between 2010 and 2016, and reporting at least one ESAS score in the 6 months following diagnosis, were identified (*Fig. 2*). Of these, 2623 patients, with a median age of 67 years, were included in the analysis. A high pain score was reported by 1621 patients (61·8 per cent), of whom 910 were aged 65 years or older. Overall, 64·1 per cent of patients received chemotherapy, and the remainder received best supportive care. The characteristics of patients with and without a high pain score are shown in *Table 1*. Younger patients and those with a higher co-morbidity burden were more likely to report a high pain score. Median follow-up from the time of diagnosis was 263 (117–453) days for patients without and 185 (96–329) days for patients with a high pain score. Median survival from the time of diagnosis was 8 (4–14) and 6 (3–11) months respectively (*Fig. 3*). The median time from diagnosis to first registering a high pain score was 38 (21–69) days and the median time from recording a high pain score to death was 119 (49–258) days. The proportions of moderate-to-severe patient-reported symptoms concomitant with the index high pain score are shown in *Fig. 4*.

Of all patients with a high pain score, 13·5 per cent (219 of 1621) received radiation therapy and 1·2 per cent (19 of 1621) nerve block around the time they reported a high pain score. Of patients aged at least 65 years, 75·6 per cent (688 of 910) filled a prescription for opiates (*Fig. 5*). Overall, 74·0 per cent of patients had a palliative care assessment around the time the high pain score was registered.

**Table 2 Predictors of receipt of pain-directed intervention in patients with a high pain score**

| | Relative risk | | |
|---|---|---|---|
| | Radiation therapy and nerve block (all patients) | Radiation therapy, nerve block and opiates (aged ≥ 65 years) | Opiates only aged ≥ 65 years) |
| **Age (years)** | | | |
| < 65 | 1·00 (reference) | – | – |
| 65–70 | 1·31 (0·98, 1·75) | 1·00 (reference) | 1·00 (reference) |
| 71–80 | 0·81 (0·58, 1·14) | 0·92 (0·86, 1·00) | 0·92 (0·85, 1·00) |
| ≥ 81 | 1·36 (0·94, 1·97) | 0·89 (0·79, 0·99) | 0·89 (0·79, 1·00) |
| **Female sex (*versus* male)** | 0·90 (0·71, 1·13) | 0·96 (0·89, 1·03) | 0·94 (0·87, 1·02) |
| **High co-morbidity burden (ADG ≥ 10 *versus* < 10)** | 0·97 (0·90, 1·05) | 0·97 (0·90, 1·10) | 0·96 (0·88, 1·04) |
| **Rural residence (*versus* urban)** | 1·02 (0·68, 1·51) | 0·96 (0·84, 1·10) | 0·93 (0·81, 1·08) |
| **Income quintile** | | | |
| 1 (lowest) | 0·79 (0·52, 1·20) | 1·01 (0·89, 1·14) | 1·02 (0·90, 1·15) |
| 2 | 1·22 (0·85, 1·74) | 1·01 (0·90, 1·14) | 0·99 (0·88, 1·12) |
| 3 | 1·01 (0·70, 1·45) | 1·06 (0·96, 1·18) | 1·05 (0·94, 1·17) |
| 4 | 0·89 (0·61, 1·29) | 1·01 (0·90, 1·13) | 0·97 (0·86, 1·10) |
| 5 (highest) | 1·00 (reference) | 1·00 (reference) | 1·00 (reference) |
| **Diagnosis in 2014–2016 (*versus* 2010–2013)** | 0·63 (0·50, 0·81) | 1·02 (0·95, 1·10) | 1·04 (0·96, 1·12) |

Values in parentheses are 95 per cent confidence intervals. ADG, Aggregated Diagnosis Group. All factors shown are included in the model as potential predictors (multivariable modified Poisson regression).

Changes in ESAS pain score following a pain-directed intervention for a high pain score are shown in *Fig. 5*. A reduction in ESAS pain score was identified in 73·4 per cent of all patients receiving radiation therapy (80 of 109) and 62·1 per cent of those aged 65 years or more who received opiates (220 of 354). All nine patients who received nerve blocks and reported a postintervention score had a reduction in ESAS pain score (not shown in figure owing to small numbers).

The results of the multivariable analyses examining factors associated with receipt of pain-directed interventions are detailed in *Table 2*. There was no patient factor associated with receipt of non-opiate intervention. The only patient-level factor associated with receipt of opiate-based intervention was older age; patients aged 81 years or older had a lower odds of receiving a composite of radiation, nerve block and opiates, or opiates alone, compared with patients aged 65–70, in an analysis restricted to patients aged 65 years or older.

## Discussion

This study provides insight into patient-reported pain for non-curable pancreatic adenocarcinoma based on population-based, validated, prospectively collected data. Opiates are the most common pain-directed intervention for non-curable pancreatic adenocarcinoma, whereas radiation therapy and nerve blocks are seldom used. Decision-making for pain-directed interventions appears to be dependent on provider and practice patterns, rather than patient factors. These findings are important to raise awareness about the need to optimize use of opiates and guide oncology practice, to increase the use of non-opiate interventions where appropriate[33]. This is highly relevant to surgeons, who are often the first specialists to see patients with non-curable pancreatic adenocartcinoma[34]. As one of the key specialists orienting patients for both curative and palliative care, participating in multidisciplinary case conferences, and having the ability to perform nerve blocks during staging or exploratory procedures, surgeons have a unique role to play in improving the multimodal management of patient-reported pain for non-curable pancreatic adenocarcinoma.

Patients with non-curable pancreatic adenocarcinoma experience a high symptom burden, with pain as one of the cardinal symptoms[6,9,35]. Pain is one of the most distressing symptoms for patients and has a significant impact on quality of life[36]. Routine screening with PROMs has been integrated into clinical practice to improve the care experience and symptom management for patients with cancer[37,38]. However, the value of such symptom screening is contingent on following up with interventions, which has been an issue in implementing routine screening programmes; a minority of physicians look at symptom scores or use them to direct management[20].

Beyond describing the frequency of high pain scores, the authors connected this knowledge to a detailed analysis of patterns of care for pain. The literature focuses mostly on the effectiveness of isolated pain strategies, and there are no data on whether or not such therapies are actually delivered to patients in practice[39–41]. The present study provides a real-life assessment of how PROM information can be leveraged to gain insight into patient care. It provides an important understanding of the management of a high level of pain associated with non-curable pancreatic adenocarcinoma so that routine PROM screening can be followed effectively by intervention, multimodal management improved, and patients better supported.

The present results indicate that current management of pain in pancreatic adenocarcinoma is dominated by opiate therapy. Opiates are highly effective analgesics, but can represent a health concern, even in patients with non-curable cancer. There might be a tendency to over-rely on the use of opiates owing to traditional practice patterns, comfort and knowledge with this therapy, and ease of use, but data suggest that cancer pain may remain undertreated with opiates[42,43]. Additional issues pertain to chemical coping, referring to non-medical opioid use by patients with cancer as a means of coping with the stresses of their cancer journey, including psychological or spiritual distress[11]. It affects up to one in five patients with cancer and can lead to addictive behaviours as well opioid misuse[11]. It may also mask undertreatment of pain as well as inadequate management of other cancer-related symptoms. Therefore, non-opiate or opiate-sparing pain interventions should be used when available and feasible, to optimize pain and overall management of patients with cancer.

Although their prognosis remains guarded, patients with non-curable pancreatic adenocarcinoma now live longer with the disease, and symptom palliation should take into account opiate-related side-effects and chemical coping[11]. Non-opiate pain interventions showed a reduction in patient-reported pain scores in this study. Of note, the results regarding nerve blocks should be interpreted with caution as they relate to a small sample. Coeliac nerve blocks have been shown to provide effective and sustained pain relief in phase III trials[39–41]. They can also improve sleep and appetite disturbances[44]. Radiation therapy has also been established as an effective pain treatment in pancreatic adenocarcinoma, with results sustained up to a median of 6 months and a concomitant reduction in need for opiates[45–47]. Despite their effectiveness, these pain interventions were used rarely for patients with a high pain score in the present study. Enhanced use of nerve blocks and radiation therapy could result in better pain control overall for more patients, while optimizing the use of opiates. It may also result in better management of other cancer-related symptoms, by concomitant management pathways or avoidance of chemical coping.

Factors associated with the use of pain interventions for a high pain score were examined to understand the selection process for pain management. There were no patient factors associated with receipt of non-opiate pain-directed intervention. Among patients aged at least 65 years, advanced age was associated with a lower odds of opiate interventions, probably owing to the different risk profile of older patients with regard to opiates. This suggests that decision-making is more practice- or provider-driven than patient-based. Additional work is warranted to understand the reasons underlying the underuse of non-opiate pain interventions in non-curable pancreatic adenocarcinoma; this fell beyond the scope of the present study.

The study has some limitations. This retrospective cohort study used healthcare administrative data sets that were not collected specifically to address the research question. As such, some patient and disease details were lacking. The opiate analysis included only patients aged 65 years or older who benefited from drug coverage under the ODB, which could have led to underestimation or overestimation of the actual use of opiates in the entire cohort. However, the rates reported are consistent with previous studies investigating the use of opiates in cancer care[48]. In addition, there is variation in rates of patient-reported symptom screening in the population, which may limit the generalizability of the results to patients well enough to visit outpatient cancer clinics. The reporting of ESAS scores is opportunistic; although a high pain score is captured on a specific date, manifestations of pain and reporting to healthcare providers might happen before this time. Therefore, interventions were assessed during time windows encompassing the period before and after ESAS score acquisition[28]. Finally, it was not possible to determine the details of the patient's pain experience to decipher the eligibility for each pain intervention. Some patients may not have been candidates for radiation or nerve block. Nevertheless, the number of patients receiving non-opiate interventions was very small; even if this represents a worst-case scenario in patterns of care, it highlights a potential underuse rather than simply a lack of an appropriate indication.

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## Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.