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Review Article

Systematic review of the predictors of health service use in pancreatic cancer

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Abstract: Introduction: Pancreatic cancer (PC) has a dismal prognosis, with identified disparities in survival outcomes based on demographic characteristics. These disparities may be ameliorated by equitable access to treatments and health services. This systematic review identifies patient and service-level characteristics associated with PC health service utilisation (HSU). Methods: Medline, Embase, CINAHL, PsycINFO and Scopus were systematically searched between 1st January, 2010 and 17 May, 2021 for population-based, PC studies which conducted univariable and/or multivariable regression analyses to identify patient and/or service-level characteristics associated with use of a treatment or health service. Direction of effect sizes were reported in an aggregate manner. Results: Sixty-two eligible studies were identified. Most (48/62) explored the predictors of surgery (n=25) and chemotherapy (n=23), and in populations predominantly based in the United States of America (n=50). Decreased HSU was observed among people belonging to older age groups, non-Caucasian ethnicities, lower socioeconomic status (SES) and lower education status. Non-metropolitan location of residence predicted decreased use of certain treatments, and was associated with reduced hospitalisations. People with comorbidities were less likely to use treatments and services, including specialist consultations and palliative care but were more likely to be hospitalised. A more recent year of diagnosis/year of death was generally associated with increased HSU. Academically affiliated and high-volume centres predicted increased treatment use and hospital readmissions. Conclusion: Findings of this review may assist identification of vulnerable patient groups experiencing disparities in accessing and using treatments and therapies.

Keywords: Pancreatic neoplasms, health services, resource allocation

Introduction

Despite representing only 2.5% of cancers across the world, in 2018, pancreatic cancer contributed to 4.5% of all cancer-related deaths worldwide [1]. The prognosis for pancreatic cancer is extremely poor, with 5-year survival rates ranging between 5 to 15%, globally [2]. A poor prognosis is often due to the cancer not displaying any cardinal symptoms during early stages of disease. Coupled with a poor chance of survival, patients also experience high symptom burden and poor quality of life [3, 4].

While surgery is the only curative option for pancreatic cancer, unfortunately most patients do not present until a later stage making them ineligible for surgical resection [5]. Chemotherapy and radiotherapy also form a critical component of tumour management [5]. Given more than 50% of patients present with metastatic disease at diagnosis [6], clinical practice guidelines recommend the provision of supportive care to all patients in need along the care continuum [5]. A recent single-centre randomised controlled trial indicated survival benefits for patients with metastatic solid tumours who received support for symptom management [7].

Significant disparities are prevalent in the survival outcomes of pancreatic cancer patients, with people of minority racial background [8], low SES [9], uninsured [10] and with a higher comorbidity score [11] having poor survival. However, when controlled for treatment, the effects of patient factors on survival may be ameliorated. A recent meta-analysis [12] of sur-

vival disparities among Africa-American and Caucasian patients with pancreatic cancer found that when controlled for treatment type and cancer stage, race did not have an impact on survival outcomes. Similarly, when evaluating treatment modality, grading and comorbidity in a multivariable analysis, treatment modality was found to be the only significant predictor of survival. This may suggest that equitable access to curative-intent, as well as supportive treatments, may in part help to reduce disparities in survival outcomes.

While previous studies have explored specific patient and service-level characteristics associated with treatment use in pancreatic cancer based on data from a single cohort, to our knowledge, there has not been a systematic review of the literature to identify a broad range of characteristics associated with use of treatment as well as other health services, across multiple cohorts, from different countries.

As such, the objective of this systematic review is to identify the specific patient and service-level characteristics which are associated with increased or decreased use of health services and treatments commonly involved in the pancreatic cancer management pathway, based on population-level data. An understanding of the predictors of health service use (HSU), may help to identify certain case-mix factors associated with poorer use and help to guide the delivery of equitable health care to vulnerable patients to minimise variation in care.

Methods

Protocol and registration

A protocol for this review was registered with the International Prospective Register of Systematic Reviews (CRD42020141992). The methods have been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

Medline, Embase, CINAHL, PsycINFO and Scopus were systematically searched between 1st January, 2010 and 17th May, 2021. The search strategy, outlined in Supplementary Material 1, was developed in collaboration with experts in the field of pancreatic cancer management (CP, LI, LtM, JZ and SE) and a medical librarian (LR). HSU included the utilisation of health services commonly involved in the management of pancreatic cancer, as defined by the Optimal Care Pathway for People with Pancreatic Cancer [13]. For the purpose of this review, online/remote health services were not actively searched. The initial search (conducted between 1st January, 2010 and 3rd February, 2020) included terms pertaining to 'oesophagogastric cancers', as the scope of this systematic review was wider. However, due to nuances in health services for oesophagogastric cancers, the predictors of these will be reported separately. Reference lists of included studies and related reviews were searched for additional eligible studies which did not appear in the database search output.

Eligibility criteria

Studies were deemed eligible if they included patients diagnosed with pancreatic cancer, were population-based, cohort or cross-sectional study design, reported patient or service-level characteristics associated with use of a specific health service or the cost(s) incurred and were published in English language. Studies were considered to be population-based if they involved multiple health services and in doing so captured the majority of their eligible cohort. For example, we included studies which used databases such as the Surveillance, Epidemiology and End-Results (SEER), and those conducted in large organisations such as Kaiser Permanente and Department of Defense, which capture a significant proportion of the pancreatic cancer population in their specific region. As this review was focused on understanding the predictors of HSU, inclusion was limited only to studies which conducted univariable and/or multivariable regression analyses to identify patient and/or service-level characteristics associated with use of a specific health service (as outlined by the Optimal Care Pathway for People with Pancreatic Cancer [13]). These included, but were not limited to: diagnostic procedures, chemotherapy, chemoradiotherapy, radiotherapy, immunotherapy, surgery, specialist consultations, primary care, supportive care services (e.g. dietetics, palliative care, psycho-oncology, etc.) and hospital admissions (including intensive care and emergency). Studies involving analyses in which more than one treatment

regime or service type was compared (i.e. predictors of minimally invasive surgery verses open surgery) were excluded as we aimed to identify predictors that were specific to a particular treatment or service. Similarly, studies which focused on use of a specific treatment regime and omitted other common regimes (e.g. focus on gemcitabine use only) were excluded as we intended to identify the predictors of a service (i.e. chemotherapy) use.

Studies were excluded if they focused exclusively on neuroendocrine pancreatic tumours as the prognosis and management differs to that of other pancreatic exocrine tumours. Additionally, studies were excluded if they included multiple cancer types but outcomes of interest were not stratified for pancreatic cancer. Randomised controlled trials and other intervention studies were excluded as these do not provide a real-world view of HSU. Single-centre studies were excluded as they are rarely representative of a population, as were editorials, opinion pieces, letters to the editor, systematic and narrative reviews.

Study selection

Each title and abstract and full text were searched independently by two of three reviewers (NNK, TL and AH) using the Covidence platform [14]. In the event of any discrepancy, a fourth reviewer (SE) was consulted if consensus could not be reached.

Data extraction

A data extraction template was created in consultation with experts in pancreatic cancer management (CP, LI, LtM, JZ and SE) and used to extract data items pertaining to the study characteristics and univariable and multivariable analysis results for associations between patient and/or service-level characteristics and a specific health service. Specifically, unadjusted and adjusted odds ratios (OR) (and in a few cases relative risks (RR) or hazards ratios (HR) in the event an OR was not reported), 95% confidence intervals and *p*-values were extracted. Data items were extracted by NNK, with a random 25% cross-checked by AH and SE to ensure consistency.

Health services and predictor variables

All health services and treatments which are outlined in the clinical practice guidelines for pancreatic cancer management were evaluated [5]. The majority of predictor variables were chosen *a priori* based on existing literature [15] and expert advice. In the event a relevant predictor variable was identified which had not been previously taken into consideration, this was included in the updated data extraction template and extracted studies were checked for the reporting of this variable. For the purpose of this review, hospital volume was treated as a predictor variable rather than a health service.

Risk of bias assessment

The Scottish Intercollegiate Guidelines Network (SIGN) methodology checklist 3 [16] and the Appraisal Tool for Cross-sectional Studies (AXIS) [17] were used to assess the risk of bias of cohort and cross-sectional studies, respectively. Each study was assessed for risk of bias for our outcome(s) of interest. All studies were appraised by NNK with a random 25% independently appraised and cross-checked by TL, with discrepancies resolved through a final consensus discussion.

Synthesis of results

Included studies were categorised broadly into diagnostic procedures, chemotherapy, chemoradiotherapy, radiotherapy, surgery, hospital admissions, specialist consultations and supportive care. With the guidance of clinical experts (CP and JZ), these broader services were categorised further to capture studies with comparable populations. As such, 'chemotherapy' included: neoadjuvant chemotherapy only, adjuvant chemotherapy only, neoadjuvant and adjuvant chemotherapy (in the event this was not clearly specified, it was assumed that studies which included only patients who underwent resectional surgery or patients with early stage or localised disease would have received this form of chemotherapy), and palliative chemotherapy (whereby chemotherapy was provided to patients who were inoperable and/or diagnosed with stage IV pancreatic cancer). 'Chemoradiotherapy' centred studies were distinguished by whether or not the included populations were surgically-treated or inoperable. 'Radiotherapy' was categorised as neoadjuvant and/or adjuvant, or, palliative. 'Surgery' was categorised as curative intent, non-curative intent or pre-operative biliary drainage. 'Hospital admissions' included separate cate-

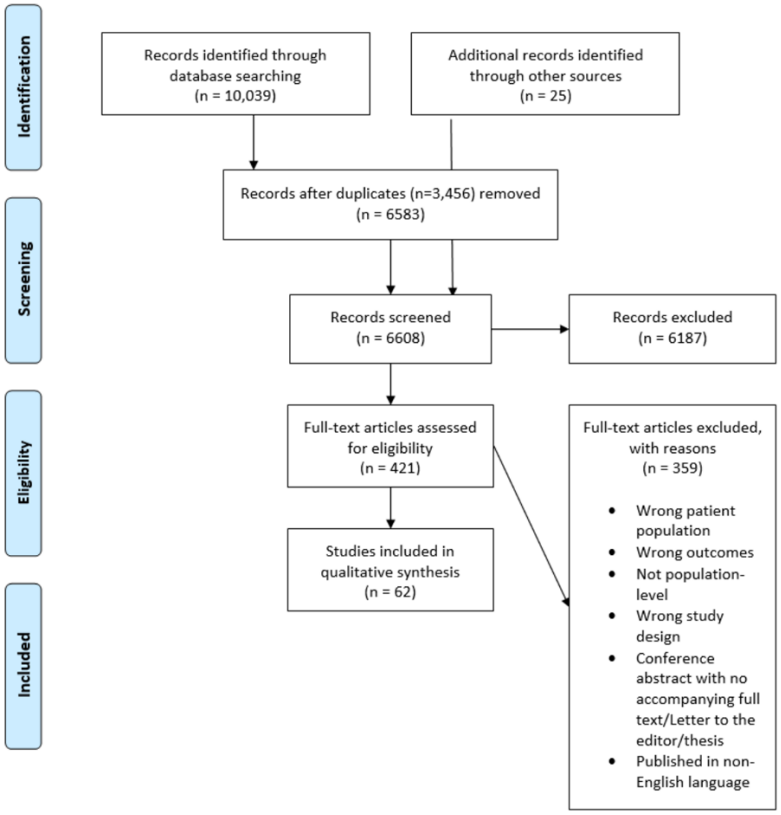

Figure 1. PRISMA flow diagram.

gories of intensive care, emergency, and acute hospitalisation.

Given the heterogeneity of studies, a traditional meta-analysis technique could not be applied to meaningfully synthesise the extracted ORs and confidence intervals. Consequently, according to previously published literature [18], we described the overall direction of effect of a specific characteristic on a specific service, based on the ORs, HRs or RRs of significant associations (i.e. P<0.05). The direction of effect was reported separately for associations explored through univariable and multivariable analyses.

Results

Study selection

A PRISMA flow diagram depicting the selection of studies is shown in **Figure 1**. Our search yielded 6,583 studies for screening of title and abstract, following the removal of duplicates (n=3,456). Cross-checking of the reference lists of eligible full text articles lead to the identification of an additional 25 eligible studies. In total, 62 studies were included.

Study characteristics

The general characteristics of eligible studies are presented in **Table 1**. All studies used a retrospective cohort design, with the exception of one, which was cross-sectional [19]. Most studies (49/62, 79%) were conducted in the United State of America (USA) (predominantly using either the National Cancer Database (NCDB) (15/49) or the Surveillance Epidemiology and End-Results (SEER) database (23/49)). Four studies were conducted across the Netherlands, two in Australia, three in Canada, and one in Italy, England and Denmark. One study, conducted by Huang et al. [20], reported separate analyses of databases and registries from twelve countries including the USA, Netherlands, Belgium, Norway, Denmark, Slovenia, Estonia, Germany, Italy, Spain, Portugal and Hungary. The recruitment period (defined by most studies as the date of diagnosis of pancreatic cancer) ranged from 1991 to 2017, with sample sizes ranging from 695 to 280,935.

Risk of bias

All retrospective cohort studies were deemed 'acceptable' through evaluation by the SIGN methodology checklist 3, with the exception of Raigani et al. [21], as this study did not present multivariable analysis results for the independent predictors of undergoing curative-intent surgery. As guided by SIGN, an 'acceptable' rating indicated that most of the checklist criteria were met [16]. A few [22-26] either did not adjust their analyses for all relevant variables or did not clearly report which covariates were adjusted for, and as such their results should be interpreted with caution. Despite these shortcomings, the findings of these studies were included in our final analysis. Raviv et al.

Table 1. Characteristics of included studies

Study	Design	Country	Data source	Population			Study Period	Population sample size	Health service/treatment evaluated
				Tumour type	*Stage*	*Treatment status included*			
Abdel-Rahman et al. 2021 [33]	Retrospective cohort	Alberta, Canada	Alberta Cancer registry	Pancreatic adenocarcinoma	Non-metastatic	Upfront surgery	2007-2018	695	Adjuvant chemotherapy
Abraham et al. 2013 [29]	Retrospective cohort	California, USA	California Cancer Registry	Pancreatic adenocarcinoma	n.s	n.s	1994-2008	20312	Adjuvant chemotherapy Palliative chemotherapy Chemoradiotherapy Curative-intent surgery
Amin et al. 2020 [84]	Retrospective cohort	USA	National Cancer Database	Pancreatic ductal adenocarcinoma	Non-metastatic	Definitive surgery	2004-2016	63,154	Immunotherapy
Bakens et al. 2016 [30]	Retrospective cohort	Netherlands	Netherlands Cancer Registry	Pancreatic adenocarcinoma	Non-metastatic	Pancreaticoduodenectomy	2008-2013	1195	Adjuvant chemotherapy
Balzano et al. 2016 [63]	Retrospective cohort	Italy	Directorate of Health Care Planning of the Italian Ministry of Health Database	Pancreas cancer	n.s	Non-resective operation	2010-2012	4366	Non-resective (palliative and exploratory) surgery
Bateni et al. 2019 [64]	Retrospective cohort	California, USA	California Cancer Registry, Office of State-wide Health Planning and Development database	Pancreatic adenocarcinoma	Stages I-II	Resection	2004-2012	2786	Surgical hospitalisation costs
Bergquist et al. 2017 [31]	Retrospective cohort	USA	National Cancer Database Participant User File	Pancreatic ductal adenocarcinoma	n.s	Definitive resection	2004-2012	13501	Adjuvant chemotherapy
Bernards et al. 2015 [38]	Retrospective cohort	Southern Netherlands	Eindhoven Cancer Registry	Pancreatic adenocarcinoma	Metastatic	n.s	1993-2010	1494	Palliative chemotherapy
Bhulani et al. 2018 [68]	Retrospective cohort	USA	SEER-Medicare; Medical Provider Analysis and Review (MEDPAR) file; Outpatient and National Claims History (NCH) files	Pancreatic cancer	n.s	n.s	2000-2009	54130	Palliative care
Burmeister et al. 2016 [48]	Retrospective cohort	Queensland and New South Wales, Australia	Queensland Cancer Registry; New South Wales Cancer Registry	Pancreatic ductal adenocarcinoma	Non-metastatic	n.s	2009-2011	786	Curative-intent surgery
Cerullo et al. 2019 [72]	Retrospective cohort	Michigan, USA	Truven Health Analytics (Ann Arbor, MI) Marketscan Commercial Claims and Encounters Database	Pancreatic cancer	n.s	Total pancreatectomy or pancreaticoduodenectomy	2010-2014	3280	ICU
Chang et al. 2018 [49]	Retrospective cohort	Southern California, USA	Kaiser Permanente Southern California Cancer Registry	Pancreatic ductal adenocarcinoma	n.s	n.s	2006-2014	2103	Medical oncology Curative-intent surgery
Dengso et al. 2020 [85]	Retrospective cohort	Denmark	Danish National Registries	Pancreatic cancer	n.s	n.s	2000-2016	10,793	First anti-depressant use
Dimou et al. 2016 [27]	Retrospective cohort	USA	National Cancer Database	Pancreatic adenocarcinoma	Stage I and II	n.s	2004-2011	39441	Neoadjuvant and adjuvant chemotherapy
Dumbrava et al. 2018 [39]	Retrospective cohort	Australia (QLD & NSW)	Queensland Cancer Registry; New South Wales Cancer Registry	Pancreatic ductal adenocarcinoma or pancreatic cancer of unknown morphological subtype	n.s	Incomplete resection	2009-2011	1173	Palliative chemotherapy Medical Oncology

Ellis et al. 2019 [43]	Retrospective cohort	USA	National Cancer Database	Pancreatic ductal adenocarcinoma	Stage I	n.s	2005-2015	17495	Neoadjuvant chemotherapy and/or radiotherapy Curative-intent surgery
Fergus et al. 2020 [26]	Retrospective cohort	USA	National Cancer Database	Pancreatic adenocarcinoma	Stage I	n.s	2004-2014	20,516	Curative-intent urgery
Forsmark et al. 2020 [86]	Retrospective cohort	USA	IQVIA Legacy PharMetrics Database	Pancreatic cancer	n.s	n.s	2001-2013	32,461	Pancreatic Enzyme Replacement Therapy
Gani et al. 2017 [65]	Retrospective cohort	USA	Nationwide Inpatient Sample	Pancreatic cancer	n.s	Resection	2002-2011	11,081	Surgical hospitalisation costs
Haj et al. 2016 [22]	Retrospective cohort	Netherlands	Netherlands Cancer Registry	Pancreatic adenocarcinoma	Metastatic	n.s	2007-2011	5385	Palliative chemotherapy
He et al. 2015 [50]	Retrospective cohort	Texas, USA	Texas Cancer Registry; SEER-Medicare	Pancreatic adenocarcinoma	Localised	n.s	2001-2009	1501	Curative-intent surgery
Henson et al. 2018 [40]	Retrospective cohort	England	Public Health England's national cancer registration data; Radiotherapy Dataset (RTDS); Systemic Anti-Cancer Therapy (SACT) data	Pancreatic cancer	n.s	n.s	2013-2014	7111	Palliative chemotherapy Palliative radiotherapy Palliative chemoradiotherapy
Huang et al. 2019 [20]	Retrospective cohort	USA, Netherlands, Belgium, Norway, Denmark, Slovenia, Estonia, Germany, Italy, Spain, Portugal and Hungary	Six European national population-based (the Netherlands, Belgium, Norway, Denmark, Slovenia and Estonia) cancer registries and the US (SEER)-18 database and nine institution-based registries from seven European countries	Pancreatic cancer	n.s	n.s	2003-2016	147700	Curative-intent surgery
Hyder et al. 2013 [74]	Retrospective cohort	USA	SEER-Medicare	Pancreatic cancer		Pancreaticoduodenectomy	1998-2005	1488	30-day readmission
Jang et al. 2015 [73]	Retrospective cohort	Ontario, Canada	Ontario Cancer Registry; Ontario Health Insurance Plan (OHIP); Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD); CIHI National Ambulatory Care Reporting System (NACRS); Registered Persons Database (RPDB)	Pancreatic cancer	Advanced	n.s	2005-2010	5381	Chemotherapy within 14 days of days ICU, emergency department and multiple hospitalisation within 30 days of death
Jinkins et al. 2013 [87]	Retrospective cohort	USA	SEER-Medicare	Pancreatic adenocarcinoma	n.s	Pancreatic head resection	1992-2007	2573	Preoperative biliary drainage
Kagedan et al. 2016 [44]	Retrospective cohort	Ontario, Canada	Ontario Cancer Registry (OCR); Institute for Clinical Evaluative Sciences Administrative Database; Ontario Marginalization Database	Pancreatic adenocarcinoma	n.s	n.s	2005-2010	6296	Adjuvant chemotherapy/or chemoradiotherapy Curative-intent surgery

Kutlu et al. 2020 [34]	Retrospective cohort	USA	National Cancer Database	Pancreatic ductal adenocarcinoma	Non-metastatic	Surgical resection	2010-2016	23,494	Adjuvant chemotherapy
Landa et al. 2019 [51]	Retrospective cohort	USA	National Cancer Database	Pancreatic acinar cell carcinoma	n.s	n.s	1998-2012	980	Curative-intent surgery
Lee et al. 2013 [35]	Retrospective cohort	USA	Department of Defense (DoD) Automated Central Tumor Registry (ACTUR)	Pancreatic ductal adenocarcinoma	n.s	n.s	1993-2007	1008	Neoadjuvant and/or adjuvant chemotherapy and radiotherapy Palliative chemotherapy Curative-intent surgery
Lutfi et al. 2016 [28]	Retrospective cohort	USA	National Cancer Database	Pancreatic ductal adenocarcinoma	Stage I and II	Pancreaticoduodenectomy	2006-2012	7881	Neoadjuvant chemotherapy
Mayo et al. 2012 [45]	Retrospective cohort	USA	SEER-Medicare	Pancreatic adenocarcinoma	Non-metastatic	Curative intent resection	1991-2005	2461	Adjuvant chemotherapy and chemoradiotherapy
Mehta et al. 2020 [62]	Retrospective cohort	USA	SEER-Medicare	Pancreatic cancer	Stage I and II	n.s	2004-2015	9125	Surgery
Mirkin et al. 2017 [75]	Retrospective cohort	USA	National Cancer Database	Pancreatic adenocarcinoma or pancreatic carcinoma	Stages I-III	Resection	2003-2011	16,007	30-day readmission
Moaven et al. 2019 [52]	Retrospective cohort	USA	National Cancer Database	Pancreatic adenocarcinoma	n.s	n.s	1998-2012	28,0935	Curative-intent surgery
Ngamruengphong et al. 2010 [66]	Retrospective cohort	USA	SEER-Medicare	Pancreatic cancer	n.s	n.s	1994-2002	8616	EUS
Nipp et al. 2018a [69]	Retrospective cohort	USA	SEER-Medicare	Pancreatic ductal adenocarcinoma	n.s	n.s	2000-2011	16,309	Chemotherapy in last 14 days before death ICU admission and multiple hospitalisation within 30 days of death Hospice
Nipp et al. 2018b [41]	Retrospective cohort	USA	SEER-Medicare	Pancreatic ductal adenocarcinoma	Stage I-IV	n.s	1992-2011	20,896	Non-curative intent surgery Palliative radiotherapy Palliative chemotherapy
Nussbaum et al. 2016 [32]	Retrospective cohort	USA	National Cancer Database	Pancreatic adenocarcinoma	Stage I and II	Pancreaticoduodenectomy	2010-2012	7967	Adjuvant chemotherapy
Paredes et al. 2019 [70]	Retrospective cohort	USA	Medicare Standard Analytic Files	Pancreatic cancer	n.s	Resection	2013-2017	4369	Hospice
Paredes et al. 2021 [71]	Retrospective cohort	USA	Centers for Medicare and Medicaid Services (CMS) 100% Inpatient, Outpatient and Hospice Limited Data Sets Standard Analytic Files (SAFs)	Pancreatic cancer	n.s	Pancreatectomy	2013-2017	14,495	Hospice
Parmar et al. 2014 [36]	Retrospective cohort	USA	SEER-Medicare	Pancreatic adenocarcinoma	Locoregional	n.s	1992-2007	10,505	Neoadjuvant and/or adjuvant chemotherapy
Peluso et al. 2019 [76]	Retrospective cohort	USA	2014 Healthcare Cost and Utilization Project (HCUP) Nationwide Readmissions Database	Pancreatic head cancer	n.s	Pancreaticoduodenectomy	2014	4,445	30-day readmission

Raigani et al. 2014 [21]	Retrospective cohort	USA	National Cancer Database	Pancreatic adenocarcinoma	Stages I and II	n.s	2003-2010	59094	Curative-intent surgery
Raviv et al. 2017 [19]	Cross-sectional	USA	Healthcare Cost and Utilisation Project; Nationwide Inpatient Sample	Pancreatic caner	n.s	n.s	2007-2011	47836	Curative-intent surgery
Revels et al. 2013 [53]	Retrospective cohort	USA	SEER-Medicare	Pancreatic cancer	Non-metastatic	n.s	2000-2005	6060	Curative-intent surgery
Riall et al. 2010 [54]	Retrospective cohort	USA	SEER-Medicare	Pancreatic adenocarcinoma	Localised or regional	n.s	1992-2002	3777	Curative-intent surgery Surgical consult
Salami et al. 2019 [55]	Retrospective cohort	USA	SEER-18	Pancreatic adenocarcinoma	n.s	n.s	2004-2014	62201	Curative-intent surgery
Schmocker et al. 2017 [67]	Retrospective cohort	USA	SEER-Medicare	Pancreatic adenocarcinoma	n.s	Partial, distal or total pancreatectomy	2000-2007	2782	EUS
Seyedin et al. 2012 [23]	Retrospective cohort	USA	SEER	Pancreatic adenocarcinoma	Localised or regional	n.s	1988-2002	5908	Curative-intent surgery
Shah et al. 2013 [24]	Retrospective cohort	USA	SEER	Pancreatic cancer	Non-metastatic	n.s	1988-2009	35944	Curative-intent surgery
Shapiro et al. 2016 [56]	Retrospective cohort	USA	SEER	Pancreatic adenocarcinoma	Non-metastatic	n.s	2004-2011	17530	Curative-intent surgery
Simons et al. 2010 [46]	Retrospective cohort	USA	SEER-Medicare	Pancreatic cancer	n.s	Resection	1991-2002	1910	Adjuvant chemoradiotherapy
Strohl et al. 2016 [57]	Retrospective cohort	USA	SEER	Pancreatic adenocarcinoma	Localised	No prior cancer-directed surgery	1988-2010	6742	Curative-intent surgery
Swords et al. 2019 [58]	Retrospective cohort	USA	National Cancer Database 2014 Participant User File	Pancreatic ductal adenocarcinoma	Stage I and II	n.s	2004-2014	63640	Curative-intent surgery
Sword et al. 2019b [59]	Retrospective cohort	USA	SEER	Pancreatic ductal adenocarcinoma	Stage I and II	n.s	2007-2015	18100	Curative-intent surgery
Sword et al. 2019c [37]	Retrospective cohort	USA	National Cancer Database	Pancreatic ductal adenocarcinoma	Stage I and II	n.s	2015	39808	Neoadjuvant and/or adjuvant chemotherapy Curative-intent surgery
Sword et al. 2020 [60]	Retrospective cohort	USA	SEER census tract-level SES database	Pancreatic ductal adenocarcinoma	Stage I and II	n.s	2007-2015	17744	Curative-intent surgery
Van der Geest et al. 2017 [42]	Retrospective cohort	Netherlands	Netherlands Cancer Registry	Pancreatic ductal adenocarcinoma	Metastatic	n.s	2005-2013	9407	Palliative chemotherapy
Watson et al. 2020 [61]	Retrospective cohort	USA	National Cancer Database	Pancreatic adenocarcinoma	Stage I	n.s	2010-2016	162,877	Curative-intent surgery
Wright et al. 2019 [25]	Retrospective cohort	USA	SEER	Pancreatic ductal adenocarcinoma		Resection	1998-2014	15585	Neoadjuvant and/or adjuvant chemotherapy
Youngwirth et al. 2017 [47]	Retrospective cohort	USA	National Cancer Database	Pancreatic head/neck adenocarcinoma	Stage I and II	Pancreaticoduodenectomy	1998-2011	18243	Neoadjuvant chemotherapy and/or radiotherapy

Abbreviations: AJCC, American Joint Committee on Cancer; EUS, endoscopic ultrasound; ICU, Intensive care Unit; n.s, not specified; SEER, Surveillance, Epidemiology and End-Results; USA, United States of America.

[19] was a cross-sectional study and addressed all items of the AXIS checklist with the exception of sample size justification and conflict of interest declaration. Please refer to Supplementary Material 2 for detailed risk of bias appraisal results.

Health services and treatments

Most studies conducted univariable and/or multivariable logistic regression analyses to identify predictors of surgery (25 studies) and chemotherapy (23 studies). Others explored the predictors of using radiotherapy (five studies), chemoradiotherapy (five studies), immunotherapy (one study), intensive care admission (three studies), emergency department admission (one study), multiple hospitalisations near death (two studies), medical oncology consultation (two studies), surgical consultation (one study), endoscopic ultrasound (EUS) (two studies), hospice/palliative care (four studies), antidepressant use (one study) and pancreatic enzyme replacement therapy (one study). A single study explored the predictors of costs associated with surgical hospitalisation.

Few studies (10/62) reported univariable regression analyses exploring associations between patient and/or service-level characteristics and a particular health service, with results being reported for palliative chemotherapy, chemoradiotherapy, surgery, palliative care, ICU admission and medical oncology consultation. Results from univariable analyses are presented in Supplementary Material 3.

Independent predictors of health service use

A summary of statistically significant, independent, patient and service-level predictors of health service use in multivariable analyses is summarised below and in accompanying tables within each section. The overall direction of the relationship is indicated with an up (increased use) or down (decreased use) arrow in the 'direction' column. For example, two studies explored predictors of neoadjuvant chemotherapy, of which both explored the effect of age. Of these two studies, only one found a significant association, with older age predicting decreased utilisation of neoadjuvant chemotherapy (**Table 2**). Treatments/services for which evidence exists from multiple studies, are detailed below. **Figures 2** and **3** provide a schematic overview of the overall findings discussed below.

Chemotherapy

Neoadjuvant chemotherapy: Two studies explored the factors associated with exclusive use of neoadjuvant chemotherapy [27, 28] (**Table 2**). Only one of the two studies reported that older age was associated with lower use of neoadjuvant chemotherapy [28]. Both studies reported a significant association between insurance status and neoadjuvant chemotherapy receipt, with those either uninsured or without private insurance less likely to receive it compared to those with some form of insurance. According to a single study, Caucasian racial background (compared to 'missing' or 'other') [27], a T2 or T3 stage (compared to T1) [28], diagnosis after 2004 [27], treatment at a non-community hospital [27] and hospital procedure volume greater than or equal to 15 per year [28] predicted increased utilisation of neoadjuvant chemotherapy. No association was reported for sex, education or CCI score.

Adjuvant chemotherapy: Six studies explored predictors of adjuvant chemotherapy utilisation [29-34] (**Table 2**). All reported that older age was significantly associated with lower likelihood of receiving adjuvant chemotherapy, yet only one of the five studies found a significant association with sex, reporting that females were less likely than males to receive adjuvant chemotherapy [31]. Two of the three studies which explored the impact of race found significantly reduced use among non-Caucasian racial groups [29, 31]. Of three studies which explored the impact of tumour stage, all found that patients with stage II or III tumours were more likely to receive adjuvant chemotherapy than patients with stage I tumour [30-32]. According to three studies, a low CCI score predicted increased utilisation of adjuvant chemotherapy [31, 32]. Two studies which explored health service characteristics found that treatment at an academic hospital [31] or high procedure volume hospital [34] predicted decreased utilisation of adjuvant chemotherapy compared to treatment at a non-academic hospital or low-procedure volume hospital, respectively.

Neoadjuvant and adjuvant chemotherapy: Five studies explored the predictors of undergoing

Table 2. Summary of the evidence for examined significant predictors, on multivariable analysis, of chemotherapy utilisation

Predictor variables	*Chemotherapy*									
	Neoadjuvant chemotherapy only (2 studies) [27, 28]		Neoadjuvant and adjuvant chemotherapy (5 studies) [25, 27, 35-37]		Adjuvant chemotherapy only (6 studies) [29-34]		Palliative Chemotherapy (*i.e. chemotherapy provided to stage IV/inoperable patients*) (8 studies) [22, 29, 35, 38-42]		Chemotherapy in last 14 days of life (2 studies) [69, 73]	
	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*
Patient demographic characteristics										
Age	1/2	↓Older (ref: younger)	5/5	↓Older (ref: younger)	5/5	↓Older (ref: younger)	8/8	↓Older (ref: younger)	2/2	↓Older (ref: younger)
Sex	0/1	n/a	1/5	↑F (ref: M)	1/5	↓F (ref: M)	1/6	↓F (ref: M)	1/2	↓F (ref: M)
Race/ ethnicity	1/1	↓missing/other (ref: Caucasian)	4/5	↓African American or Hispanic (ref: Caucasian)	2/3	*Variable* 1/2: ↓African American (ref: Caucasian) 1/2: ↓other (ref: Caucasian)	3/4	*Variable* 1/2: ↓African American (ref: Caucasian) 1/2: ↓unknown (ref: African American)	0/1	n/a
Education	0/1	n/a	2/2	↑most educated area (ref: least educated area)						
Income	0/1	n/a			1/1	↑highest (ref: lowest)	1/1	↑highest (ref: lowest)	1/1	↑highest (ref: lowest)
Insurance	2/2	*Variable* 1/2: ↑Private, Medicare or Medicaid (ref: uninsured) 1/2: ↓Medicare (ref: private)			2/2	*Variable* ↑insured (ref: uninsured) 1/2: ↑Medicare (ref: uninsured)	1/1	↑non-Medicare/Medicaid, ↓no insurance (ref: Medicaid)		
SES			1/1	↓low SES (ref: high SES)			5/5	↓low SES (ref: high SES)	1/1	↓low SES (ref: high SES)
Location of residence			0/1	n/a			1/2	↓outer regional (ref: major city)	0/2	n/a
Marital status			1/2	↑married (ref: single)			1/1	↑married (ref: unmarried)	1/1	↑married (ref: unmarried)
Disease characteristics										
TNM/ACJJ stage			1/2	↑stage II (ref: stage I)	3/3	↑stage II or III (ref: stage I)	0/1	n/a	1/1	↑stage II or IV (ref: stage I)
Tumour site			1/2	↓body, tail or other/NOS (ref: head)			3/4	↑body/tail (ref: head)	1/1	↑other (ref: head)
Tumour size			1/1	↑2-4 cm (ref: <2 cm)						
Grade/ differentiation					0/2	n/a	0/1	n/a		
Histology							1/1	↓no histology (ref: adenocarcinoma)		
Nodal status					2/2	↑N1 (ref: N0)				

Metastasis			1/1	↑no vascular invasion (ref: vascular invasion)	1/1	↑lymph node mets (ref: no lymph node mets)	1/2	↓≥2 sites or unknown (ref: 1 site)		
T stage	1/1	↑T2 or T3 (ref: T1)								
N stage										
SEER stage										
CCI/ Charlson-Deyo Score	0/1	n/a	2/2	↓increasing CCI (ref: CCI 0)	3/3	*Variable* ↓CCI 1 or 2 (ref: CCI: 0) ↓CCI: 2 (ref: CCI: 0) ↓increasing CCI (ref: CCI: 0)	2/4	↓increasing CCI (ref: CCI 0)	0/2	n/a
Performance status							1/1	↓in bed/bedbound (ref: fully active)		
Year of death									0/1	n/a
Treatment characteristics										
Year of diagnosis/ treatment	1/1	↑post-2004 (ref: 2004)	3/4	↑per year increase (ref: lowest year)	1/1	↑post-2008 (ref: 2008)	5/5	↑per year increase (ref: lowest year)	0/1	n/a
MDT presentation							1/1	↑Yes (ref: no)		
Primary care									0/1	n/a
Radiotherapy			1/1	↓Yes (ref: no)						
Stent			1/1	↓Yes (ref: no)						
Surgery					0/2	n/a				
Palliative care									1/1	↓Yes (ref: no)
Health service characteristics										
Hospital type	1/2	↑teaching, comprehensive, NCI or other (ref: community)	1/1	↑teaching, comprehensive, NCI or other (ref: community)	1/2	↓Academic (ref: non-academic)				
Hospital volume (*i.e. case load per year)*	1/1	↑≥15 (ref: <15)			1/1	↑Lowest procedure volume (ref: highest procedure volume)	1/2	↑treated at high volume incidence centre (ref: not treated at high volume incidence centre)		

*Number of studies = Studies with significant findings in relation to the predictor variable (numerator)/total number of studies evaluating the predictor variable (denominator). Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; EUS, endoscopic ultrasound; ICU, Intensive Care Unit; MDT, Multidisciplinary team meeting; NCI, National Cancer Institute designated centre; Ref, Reference; SEER, Surveillance, Epidemiology and End-Results; SES, Socioeconomic status; TNM, Tumour, Node, Metastasis staging system.

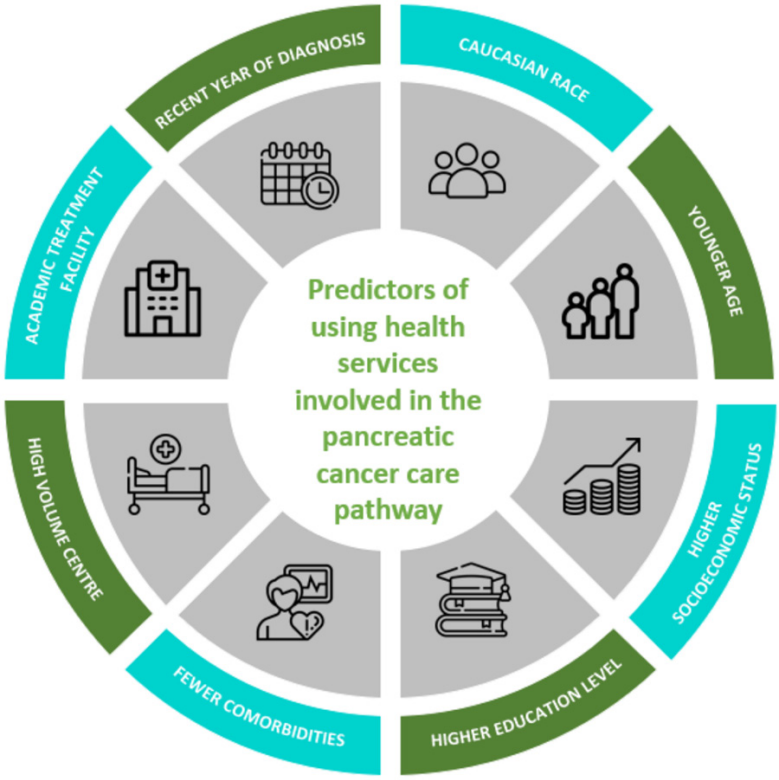

Figure 2. Predictors of using health services involved in the pancreatic cancer care pathway. Note: Image icons sourced from Freepik (https://www.flaticon.com/).

neoadjuvant and adjuvant chemotherapy, with all reporting that older age predicted decreased utilisation [25, 27, 35-37] (**Table 2**). Only one of the five studies found a significant association with sex, reporting increased utilisation among females [37]. Four of the five studies also reported a significant association with race, with people of African American or Hispanic racial background less likely to undergo neoadjuvant and adjuvant chemotherapy compared to Caucasians [25, 27, 36, 37]. A more recent year of diagnosis predicted increased utilisation in three of the four studies [27, 36, 37]. A single study explored the impact of service-level factors and found significantly higher utilisation among non-community hospitals [27].

Palliative chemotherapy: Eight studies conducted multivariable analyses to identify predictors of palliative chemotherapy [22, 29, 35, 38-42] (**Table 2**). Of these, all reported that patients belonging to older age groups were significantly less likely to receive palliative chemotherapy. Only one of six studies found an association with sex, reporting lower utilisation among females [29]. Race was also identified as a significant predictor by three of four studies, with variable associations [29, 40, 41]. Higher SES [38-42] or more recent year of diagnosis [22, 35, 38, 41, 42] were associated with increased utilisation of palliative chemotherapy according to all five studies which explored these predictor variables. In three of four studies, tumour of the body or tail (compared to head) predicted increased utilisation [39, 41, 42]. CCI was found to be a significant predictor by two of four studies, with a CCI≥1 predicting decreased utilisation [40, 41]. Of the two studies which explored the impact of hospital case load volume, one found that treatment at a high-volume incidence centre predicted increased utilisation of palliative chemotherapy [22].

Chemoradiotherapy

Chemoradiotherapy in surgically-treated patients: Seven studies assessed the adjusted effect of patient and/or service-level characteristics on chemoradiotherapy use among surgically-treated patients [29, 35, 43-47] (**Table 3**). Of the six studies which assessed age, five found that older age was significantly associated with decreased use of chemoradiotherapy [29, 35, 45-47]. Only one of the five studies which explored the effect of sex reported lower use among females [43]. Six studies explored the effect of race, with three studies finding a significant, but variable, association [29, 43, 46]. Increasing year of diagnosis was found by four out of six studies to be associated with increased chemoradiotherapy use [43, 45-47]. One of two studies reported significantly lower utilisation of chemoradiotherapy among those with a tumour of the tail (compared to head) [43]. According to two studies, post-operative complications, higher CCI [43, 47] and no insurance or government insurance [29, 47] were associated with lower use.

Figure 3. Predictors of using acute hospital services* by patients diagnosed with pancreatic cancer. *Acute hospital services include emergency department, 30-day hospital readmission and hospitalisation near death. Note: Image icons sourced from Freepik (https://www.flaticon.com/).

Chemoradiotherapy in inoperable patients: Of the two studies which conducted multivariable analyses for predictors of chemoradiotherapy in inoperable patients, both found decreased use among older age groups, with no effect exhibited by sex [29, 40] (refer to **Table 3**). A single study reported decreased use in African American race, compared to Caucasian race [29].

Radiation therapy

Palliative radiation therapy: Two studies explored the adjusted predictors of palliative radiation therapy use among patients with pancreatic cancer [40, 41] (**Table 3**). One reported that patients belonging to older age groups were significantly less likely to receive palliative radiation therapy [41], with both studies noting no associations with sex. Patients who were of Asian race (compared to Caucasian), married, had a tumour in the head of the pancreas and CCI≥2 were significantly more likely to utilise palliative radiation therapy according to one study [41].

Surgery

Curative-intent surgery: Twenty-five studies explored the effect of patient and/or service level characteristics on undergoing curative-intent surgery [19, 20, 23, 24, 26, 29, 35, 37, 43, 44, 48-62] (**Table 4**). Of the 25 studies, one conducted seven separate analyses of data pertaining to different countries [20], such that these analyses could be counted separately, producing 31 stand-alone analyses. Twenty-six analyses assessed the effect of age, with 25 reporting decreased utilisation of curative-intent surgery among older age groups [19, 20, 24, 26, 29, 37, 43, 48-52, 54-59, 61]. A small proportion of (five out of 24) analyses reported significant associations with sex, with the majority indicating an increased likelihood among females [24, 26, 43, 51]. Minority race, which predominantly included African American and Hispanic races, were associated with decreased use of curative-intent surgery, according to 17 of the 21 analyses conducted [19, 23, 24, 26, 29, 37, 43, 51-59, 61]. Nine of the thirteen analyses reported decreased use among lower income groups [19, 23, 24, 26, 44, 52, 58, 59, 61]. Sixteen analyses assessed the effect of year of diagnosis, with 10 finding a significant association, of which the majority reported increased use of curative-intent surgery over time [20, 24, 43, 50, 54, 55]. Of the five analyses which explored health service characteristics, four reported decreased likelihood of curative-intent surgery in community hospitals compared to academic hospitals [26, 51, 58, 61].

Non-curative intent surgery: Two studies explored the predictors of non-curative intent surgery [41, 63] (**Table 4**). Both reported a significant association for tumour site, with tumours of the body or tail, or 'other' site of the pancreas predicting decreased likelihood of

Table 3. Summary of the evidence for examined significant predictors, on multivariable analysis, of chemoradiotherapy, radiotherapy and immunotherapy utilisation

Predictor variables	*Chemoradiotherapy*				*Radiotherapy*				*Immunotherapy*	
	Chemoradiotherapy in surgically-treated patients (7 studies) [29, 35, 43-47]		Chemoradiotherapy in inoperable patients (2 studies) [29, 40]		Neoadjuvant and/or adjuvant radiotherapy (1 study) [35]		Palliative radiation therapy (2 studies) [40, 41]		Immunotherapy in resected patients (1 study) [84]	
	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*
Patient demographic characteristics										
Age	6/6	*Variable* 5/6: ↓Older (ref: younger) 1/6: ↑≥80 (ref: 50-59)	2/2	↓Older (ref: younger)	1/1	↓Older (ref: younger)	1/2	↓Older (ref: younger)		
Sex	1/5	↓F (ref: M)	0/2	n/a	0/1	n/a	0/2	n/a	1/1	↓F (ref: M)
Race/ethnicity	3/6	*Variable* 2/3: ↓African American (ref: Caucasian) 1/3: ↑African American (ref: Caucasian)	1/2	↓African American (ref: Caucasian)	0/1	n/a	1/2	↑Asian (ref: Caucasian)	1/1	↓African American (ref: Caucasian)
Education									1/1	↓Lower education (ref: higher education)
Income	1/2	↓highest (ref: lowest)							0/1	n/a
Insurance	2/3	*Variable* ↓No insurance (ref: Medicaid) ↓government (ref: private)	1/1	↓No insurance (ref: Medicaid)					0/1	n/a
SES	0/2	n/a	0/1	n/a			0/2	n/a		
Location of residence	1/1	↑urban (ref: non-urban)					0/1	n/a	0/1	n/a
Marital status	1/1	↑Married (ref: unmarried)					1/1	↑Married (ref: unmarried)		
Disease characteristics										
TNM/ACJJ stage	0/1	n/a			0/1	n/a				
Tumour site	1/2	↓tail (ref: head)			0/1	n/a	1/1	↓tail/body/other (ref: head)		
Metastasis	1/1	↑lymph node mets (ref: no lymph node mets)								
Grade/differentiation							1/1	↓unknown (ref: low)		
T stage	1/1	↑T2 (ref: T0/T1)								
N stage										
CCI/Charlson-Deyo Score	2/3	*Variable* 1/2: ↓CCI 1 (ref: 0) 1/2: ↓CCI≥2 (ref: 0)	0/1	n/a			1/2	↓CCI≥2 (ref: 0)	1/1	↓Increasing CCI (ref: CCI: 0)
Treatment characteristics										

Year of diagnosis/treatment	4/5	↑per year increase (ref: lowest year)		0/1	n/a	0/1	n/a	1/1	↑2011-2016 (ref: pre-2011)
Medical oncology visit	0/1	n/a							
Chemotherapy								1/1	↑Yes (ref: no)
Radiotherapy								1/1	↑Yes (ref: no)
Surgery	1/1	↑Distal, partial or near-total pancreatectomy (ref: pancreaticoduodenectomy)							
Post-operative complication	2/2	↓Yes (ref: no)							
Readmission following operation	1/1	↓Yes (ref: no)							
Health service characteristics									
Hospital type	1/3	↑teaching hospital (ref: non-teaching hospital)						1/1	↓Community (ref: academic)
Hospital volume *(i.e. no. of procedures per year)*	1/1	↑lowest volume (ref: highest volume)							

*Number of studies = Studies with significant findings in relation to the predictor variable (numerator)/total number of studies evaluating the predictor variable (denominator). Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; Ref, Reference; SES, Socioeconomic status; TNM, Tumour, Node, Metastasis staging system.

Table 4. Summary of the evidence for examined significant predictors, on multivariable analysis, of surgery utilisation and associated costs

Predictor variables	*Surgery*							
	Curative-intent surgery (25 studies, with 31 analyses[$]) [19, 20, 23, 24, 26, 29, 35, 37, 43, 44, 48-62]		Non-curative intent surgery (2 studies) [41, 63]		Pre-operative biliary drainage (1 study) [87]		Hospitalisation costs following surgery (2 studies) [64, 65]	
	No. of analyses[*]	*Direction*	*No. of studies*[*]	*Direction*	*No. of studies*[*]	*Direction*	*No. of studies*[*]	*Direction*
Patient demographic characteristics								
Age	25/26	↓Older (ref: younger)	0/1	n/a	0/1	n/a	0/2	n/a
Sex	5/24	*Variable* 4/5 ↑F (ref: M) 1/5 ↓F (ref: M)	0/1	n/a	0/1	n/a	1/2	↓F (ref: M)
Race/ethnicity	17/21	↓minority race (ref: Caucasian)	0/1	n/a	0/1	n/a	1/2	↑Non-Hispanic/other (ref: Caucasian)
Preferred language	0/1	n/a						
Education	6/9	*Variable* 5/6↓ lower education (ref: higher education) 1/6↑ lower education (ref: higher education)			0/1	n/a		
Income	9/13	↓lower income (ref: higher income)			0/1	n/a		
Insurance	10/12	*Variable*[&]					0/1	n/a
SES	3/4	↓low SES (ref: high SES)	0/1	n/a			0/1	n/a
Location of residence	2/9	1/2: ↓Unknown (ref: metro) 1/2: ↑Unknown (ref: metro)	0/1	n/a				
Marital status	5/5	↑Married (ref: unmarried)	0/1	n/a	0/1	n/a		
Disease characteristics								
TNM/ACJJ stage	11/12	Variable 1/11: ↑stage II (ref: stage I) 2/11: ↓stage II (ref: stage I) 8/11: ↓stage III-IV (ref: stage I-II)			0/1	n/a	0/1	n/a
Tumour site	16/18	*Variable*[&]	2/2	*Variable* ↓body/tail (ref: head) ↓other (ref: head)				
Tumour size	4/5	↓increasing tumour size (ref: lowest tumour size)			1/1	↓per 10 mm increase (ref: lowest tumour size)		
Grade/differentiation	4/4	*Variable* ↓high or unknown (ref: low) ↑Poor/ungraded (ref: well/moderately diff.)	1/1	↓unknown (ref: low)	0/1	n/a	0/1	n/a
Nodal status	1/1	↓Clinical N0 or Unknown (ref: pathologic N0)			0/1	n/a		
Metastasis	1/1	↓metastatic (ref: non-metastatic)						
T stage	3/3	↑lower T stage (ref: higher T stage)					0/1	n/a
N stage	1/1	↑N1, ↓Nx (ref: N0)					0/1	n/a

CCI/Charlson-Deyo Score	7/10	*Variable* 5/7: ↓increasing CCI (ref: CCI: 0) 2/7: ↑increasing CCI or CCI of 1 (ref: CCI: 0)	1/2	↑increasing CCI (ref: CCI: 0)			1/1	↑CCI≥3
Elixhauser comorbidity index							1/1	↑increasing score (ref: lowest score)
Performance status	1/1	↓Not fully active (ref: fully active)						
Treatment characteristics								
Year of diagnosis/treatment	10/16	8/10: ↑per year increase (ref: lowest year) 2/10: ↓per year increase (ref: lowest year)	0/1	n/a	1/1	↑per year increase (ref: lowest year)		
MDT presentation	1/1	↓Presented at MDT (ref: not presented)						
Pancreas protocol CT	0/1	n/a						
CT	0/1	n/a						
EUS	1/1	↑Yes (ref: no)						
Laparoscopy	0/1	n/a						
MRI/ Cholangiopancreatography	0/1	n/a						
Gastroenterologist	1/1	↓Yes (ref: no)			1/1	↑Yes (ref: no)		
Chemotherapy	1/1	↑Yes, ↓refused (ref: no)			1/1	↑neoadjuvant chemotherapy (ref: no neoadjuvant chemotherapy)	1/1	↓Adjuvant chemotherapy (Ref: none)
Surgery type							2/2	↓Distal pancreatectomy (ref: pancreaticoduode-nectomy)
Length of Stay							1/1	↑Yes (ref: no)
Post-operative complications							2/2	↑Yes (ref: no)
Readmission following operation							1/1	↑Yes (ref: no)
Health service characteristics								
Hospital type	4/5	*Variable* 3/4 ↓Community or comprehensive (ref: academic) 1/4 ↑Comprehensive/academic/integrated network (ref: community)	0/1	n/a			1/2	↑Teaching hospital (ref: non-teaching hospital)
Hospital volume (*i.e. no. of procedures per year*)	1/2	↑≥ pancreatectomies per year (ref: <5 pancreatectomies per year)	1/1	↑decreasing volume (ref: very high volume)			1/2	↓intermediate (ref: low)

*Number of analyses/studies = Studies with significant findings in relation to the predictor variable (numerator)/total number of studies evaluating the predictor variable (denominator). $1 study (Huang et al. 2019) conducted 7 separate analyses of data from different populations. These have been counted separately. &Variable groupings/reference categories have been used by different studies to categorise, therefore it is not possible to comment on overall direction. Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; CT, computed tomography; EUS, endoscopic ultrasound; MDT, Multidisciplinary team meeting; SES, Socioeconomic status; TNM, Tumour, Node, Metastasis staging system.

Table 5. Summary of the evidence for examined significant predictors, on multivariable analysis, of consulting a specialist

Predictor variables	*Specialist consultations*			
	Medical oncology (2 studies) [39, 49]		Surgical (1 study) [54]	
	*No. of studies**	*Direction*	*No. of studies**	*Direction*
Patient demographic characteristics				
Age	2/2	↓Older (ref: younger)	1/1	↓Older (ref: younger)
Sex	1/2	↓F (ref: M)	1/3	
Race/ethnicity	0/1	n/a	1/1	↓African American (ref: Caucasian)
Preferred language	0/1	n/a		
Education	0/1	n/a		
Income	1/1	↓USD$42-700-68,300 (ref: >$76,000)		
Insurance	1/1	↑Medicare (ref: non-Medicare)		
SES	1/1	↓low SES (ref: high SES)		
Location of residence	1/1	↓regional (ref: major city)		
Disease characteristics				
TNM/ACJJ stage	1/1	↑Stage IV (ref: Stages I, II and III)		
Tumour site	0/1	n/a	1/1	↓Not specified (ref: head)
CCI/Charlson-Deyo Score	2/2	↓increasing CCI (ref: CCI: 0)	1/1	↓CCI≥1 (ref: 0)
Performance status	1/1	↓in bed >50%/bedbound (ref: fully active)		
Treatment characteristics				
MDT presentation	1/1	↑Presented at MDT (ref: not presented)		
CT			1/1	↑Yes (ref: no)
Primary care			1/1	↑Yes (ref: no)
Gastroenterologist			1/1	↓Yes (ref: no)
Medical oncology visit			1/1	↑Yes (ref: no)
Health service characteristics				
Hospital volume (*i.e. no. of procedures per year*)	0/1	n/a		

*Number of studies = Studies with significant findings in relation to the predictor variable (numerator)/total number of studies evaluating the predictor variable (denominator). Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; CT, Computed tomography; MDT, Multidisciplinary team meeting; Ref, Reference; SES, Socioeconomic status; TNM, Tumour, Node, Metastasis staging system.

undergoing non-curative intent surgery, compared to tumours of the pancreatic head. One study reported increased likelihood of non-curative intent surgery in patients with higher CCI and those treated at lower volume hospitals [63]. No significant association was found with age, sex and race/ethnicity.

Hospitalisation costs following surgery: Two studies explored the predictors of higher hospitalisation costs following surgery [64, 65] (**Table 4**). No association was found with age, SES, insurance status, or tumour stage. However, males and people belonging to minority racial backgrounds were significantly more likely to incur higher costs, according to one [65] of two studies. Additionally, CCI≥3 [65] or increasing Elixhauser comorbidity index [64] and post-operative complications [64, 65] predicted higher costs. Those who received adjuvant chemotherapy [64], distal pancreatectomy [64, 65] and were treated at an intermediate (compared to low) volume hospital [65], incurred lower costs.

Specialist consultation

Medical oncology: Two studies explored the association between predictor variables and medical oncology visits [39, 49] (**Table 5**). Both studies reported lower use among older age groups and patients with CCI scores above zero, whilst one reported lower utilisation among females [39]. According to a single study, lower SES [39], regional location of residence [39] or a performance status of in bed for more than 50% of the time or bedbound [39] were associated with decreased utilisation of a medical oncologist. Medicare insurance [49], presentation at an MDT meeting [39] and stage IV tumour [39] predicted increased likelihood to consult a medical oncologist, according to one study.

Diagnostic

Endoscopic ultrasound: Two studies assessed the effect of patient and service-level characteristics on use of endoscopic ultrasound (EUS) [66, 67] (refer to **Table 6**). A single study explored the effect of age and found significantly decreased use among those 75 years of age or older [66]. One of two studies which explored the impact of race, reported decreased use among non-Caucasian racial groups [66]. Increased EUS use was reported by one study in married [66], locoregional stage [66] and academic-treatment facility groups [67]. Both studies reported increased EUS use over time [66, 67]. Sex and CCI were not found to have any significant impact on EUS use.

Supportive care

Palliative care: Four studies explored the predictors of palliative or hospice care utilisation [68-71] (refer to **Table 6**). All three studies which explored the effects of sex and age, found that patients who were female and from older age groups were significantly more likely to utilise palliative care [68-70]. Variable significant associations were noted by three studies for race, with one reporting higher utilisation among Asian race [68] and two studies reporting lower utilisation among African American, Hispanic, Asian and other races, in comparison to Caucasian race [69, 71]. Higher SES, metropolitan or urban location of residence (compared to larger metropolitan), CCI score ≤2, tumour of the tail or body and diagnosis after 2005 were found by a single study to predict increased utilisation of palliative care [69]. No significant associations were found between marital status, cancer stage, hospital length of stay, post-operative complication or treatment facility location and palliative care utilisation.

Hospital admissions

Intensive Care Unit (ICU): Three studies conducted multivariable analyses to identify predictors of ICU admission [69, 72, 73], of which two found that patients who were female, older, living in rural areas [69, 73] and had a CCI score ≤1 [69, 72] were significantly less likely to be admitted to ICU (refer to **Table 7**). Lower SES, being married, pancreatic head tumour and year of death post-2005 were associated with significantly increased likelihood of ICU admission [69]. Race, cancer stage, diagnosis year, having a regular primary care physician or receiving chemotherapy did not have any significant impact on ICU admission.

30-day hospital readmission: Three studies explored the association between predictor variables and 30-day hospital readmission [74-76] (**Table 7**). According to two studies which evaluated the effect of hospital volume, variable significant relationships were found with one study indicating decreased re-admission among low volume hospitals compared to very-low volume hospitals [76] and another suggesting increased re-admission among low, medium and high-volume hospitals (compared to very low) [74]. Medicare insurance (compared to private), CCI score of 1 (compared to 0) and treatment at a comprehensive community and academic facility (compared to a community facility), predicted increased likelihood of re-admission, according to one of two studies which evaluated this association [75]. Age, sex, race, tumour stage, year of diagnosis, surgery type, length of stay and post-operative complications were not found to be significantly associated with readmission, however only a proportion of the three studies evaluated these predictors.

Hospitalisation near death

Two studies explored the association between predictor variables and multiple hospitalisations near death [69, 73] (**Table 7**). Both of these found that older and female patients were less likely to be hospitalised near death. One study explored the effect of race and found that those of African American racial background were more likely to be hospitalised near death than those of Caucasian racial background [69]. According to one study, lower SES, metropolitan area of residence, married relationship status, tumour stages II and IV (compared to stage I), CCI score ≥1, diagnosis after 2005 [69] or absence of palliative care enrolment [73] were significantly associated with increased likelihood of being hospitalised near death.

Discussion

Summary of main findings

Most population-based studies included in this review explored predictors of surgery (25/62, 40%) and chemotherapy (23/62, 37%). A small-

Table 6. Summary of the evidence for examined significant predictors, on multivariable analysis, of diagnostic procedures and supportive care utilisation

Predictor variables	*Diagnostic*		*Supportive care*					
	Endoscopic ultrasound (2 studies) [66, 67]		Palliative/hospice care (4 studies) [68-71]		Anti-depressant (1 study) [85]		Pancreatic Enzyme Replacement Therapy (1 study) [86]	
	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*
Patient demographic characteristics								
Age	1/1	↓≥75 (ref: <75)	3/3	↑older (younger)	1/1	↓≥60 (ref: younger)	1/1	↓increasing age (ref: lowest age)
Sex	0/1	n/a	3/3	↑F (ref: M)	0/1	n/a	1/1	↓F (ref: M)
Race/ethnicity	1/2	↓non-Caucasian (ref: Caucasian)	3/3	Variable ↑Asian (ref: Caucasian) ↓African American/Asian/Other (ref: Caucasian) ↓African American/Hispanic (ref: Caucasian)				
Income	1/1	↑highest (ref: lowest)						
SES			1/1	↑High SES (ref: low SES)				
Education					0/1	n/a		
Location of residence			1/1	↑metro/urban (ref: large metro)				
Marital status	1/1	↑Married (ref: unmarried)	0/2	n/a				
Disease characteristics								
TNM/ACJJ stage			0/2	n/a	1/1	↑Advanced stage 0-6 months after diagnosis (ref: not advanced)		
Tumour site			1/1	↑Tail/body (ref: Head)	1/1	↑caput, corpus, cauda or several regions (ref: duodenum)		
Metastasis	1/1	↑locoregional (ref: distant)						
CCI/Charlson-Deyo Score	0/1	n/a	1/1	↓CCI>2 (ref: 0)	0/1	n/a	1/1	↑CCI≥4 (ref: 2-3)
Year of death			1/1	↑post-2005 (ref: pre-2005)				
Treatment characteristics								
Year of diagnosis/treatment	2/2	↑per year increase (ref: lowest year)			1/1	↓2013-2016 (ref: 2000-2004)		
MRI/ Cholangiopancreatography	0/1	n/a						
ERCP	0/1	n/a						
Initial course of treatment					1/1	↓Surgery+chemo <60 days, 0-6 months from diagnosis (ref: no surgery or chemo)		
Chemotherapy	0/1	n/a						

Surgery	1/1	↓Distal or other partial pancreatectomy (ref: Whipple)					1/1	↑Surgery performed (ref: no surgery)
Length of stay			0/1	n/a				
Post-operative complication			0/1	n/a				
Health service characteristics								
Hospital location			0/1	n/a				
Hospital type	1/1	↑Academic (ref: non-academic)						

*Number of studies = Studies with significant findings in relation to the predictor variable (numerator)/total number of studies evaluating the predictor variable (denominator). Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; ERCP, Endoscopic retrograde cholangiopancreatography; MRI, Magnetic resonance imaging; Ref, Reference; SES, Socioeconomic status; TNM, Tumour, Node, Metastasis staging system.

Table 7. Summary of the evidence for examined significant predictors, on multivariable analysis, of hospital utilisation

Predictor variables	*Hospital admissions*							
	ICU (3 studies) [69, 72, 73]		30-d hospital readmission (3 studies) [74-76]		Hospitalisations near death (2 studies) [69, 73]		ED near death (1 study) [73]	
	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*	*No. of studies**	*Direction*
Patient demographic characteristics								
Age	2/3	↓Older (ref: younger)	0/2	n/a	2/2	↓Older (ref: younger)	1/1	↓≥80 (ref: <50)
Sex	2/3	↓F (ref: M)	0/1	n/a	2/2	↓F (ref: M)	0/1	n/a
Race/ethnicity	0/1	n/a	0/1	n/a	1/1	↑African American (ref: Caucasian)		
Income	0/1	n/a	0/2	n/a	0/1	n/a	0/1	n/a
Insurance			1/2	↑Medicare (ref: private)				
SES	1/1	↓High SES (ref: low SES)			1/1	↓High SES (ref: low SES)		
Location of residence	2/2	↑metro (ref: rural)	0/1	n/a	1/2	↓rural (metro)	1/1	↑Rural (ref: non-rural)
Marital status	1/1	↑Married (ref: unmarried)			1/1	↑Married (ref: unmarried)		
Disease characteristics								
TNM/ACJJ stage	0/1	n/a	0/1	n/a	1/1	↑II & IV (ref: I)		
Tumour site	1/1	↓Tail/body (ref: Head)			0/1	n/a		
SEER stage			0/1	n/a				
CCI/Charlson-Deyo Score	2/3	*Variable* ↑1 (ref: 0) ↑2+ (ref: 0)	1/2	↑1 (ref: 0)	1/2	↑≥1 (ref: 0)	0/1	n/a
Year of death	1/1	↑post-2005 (ref: pre-2005)			1/1	↑post-2005 (ref: pre-2005)		
Treatment characteristics								
Year of diagnosis/treatment	0/1	n/a	0/1	n/a	0/1	n/a	0/1	n/a
Primary care	0/1	n/a			0/1	n/a	0/1	n/a
Medical oncology visit	1/1	↑Yes (ref: No)			0/1	n/a	0/1	n/a
Neoadjuvant therapy	0/1	n/a						

Chemotherapy	0/1	n/a			0/1	n/a	1/1	↓Yes (ref: no)
Surgery			0/1	n/a				
Vascular reconstruction	1/1	↑Yes (ref: No)						
Perioperative transfusion	1/1	↑Yes (ref: No)						
Palliative care					1/1	↓Yes (ref: no)	1/1	↓Yes (ref: no)
Length of stay			0/2	n/a				
Post-operative complication			0/1	n/a				
Health service characteristics								
Hospital location			0/1	n/a				
Hospital type			1/2	↑comprehensive community & academic (ref: community)				
Hospital volume (*i.e. no. of procedures per year*)			2/2	*Variable* ↓low (ref: very low) ↑low, medium & high (ref: very low)				

*Number of studies = Studies with significant findings in relation to the predictor variable (numerator)/total number of studies evaluating the predictor variable (denominator). Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; Ref, Reference; SEER, Surveillance, Epidemiology and End-Results; SES, Socioeconomic status; TNM, Tumour, Node, Metastasis staging system.

er proportion investigated the predictors of hospital admissions (6/62, 10%), radiotherapy (5/62, 8%) and chemoradiotherapy (5/62, 8%), specialist consultations (3/62, 5%), and EUS (2/62, 3%). Very few explored the predictors of palliative care (4/62, 6%) or other forms of supportive care (2/62, 3%). The findings of this review suggest some unexpected disparities in the use of treatment and health services by people diagnosed with pancreatic cancer.

As expected, older age significantly predicted decreased use across all health services including EUS, chemotherapy, chemoradiotherapy, radiotherapy, surgery, hospital admissions and specialist consultations. Palliative care was the only exception whereby older age predicted increased use of the service. Few studies reported significant associations between sex and HSU. Minority groups (particularly African American individuals), those from lower SES and those with low education attainment were often less likely to access treatments such as chemotherapy and curative-intent surgery. Non-metropolitan location of residence was found in a few studies to predict decreased use of certain treatments, however, was associated with reduced ICU use and multiple hospital admissions (excluding emergency department).

With regard to disease-related characteristics, a stage II tumour predicted increased use of neoadjuvant and adjuvant chemotherapy as well as curative-intent surgery, in line with treatment recommendations [5]. People presenting with more comorbidities were generally less likely to receive specialist consultations, chemotherapy, chemoradiotherapy, radiotherapy, curative-intent surgery and palliative care, yet were more likely to be admitted to hospital and incur higher hospitalisation costs.

A more recent year of diagnosis/year of death was generally associated with a greater likelihood of undergoing EUS, chemotherapy, chemoradiotherapy, curative-intent surgery, preoperative biliary drainage as well as utilising palliative care. ICU admissions and multiple hospitalisations near death also increased over time. Minimal studies explored health-service characteristics. However, hospitals with academic affiliations generally predicted increased use of EUS, neoadjuvant and adjuvant chemotherapy and radiotherapy, chemoradiotherapy and curative-intent surgery. Higher volume hospitals were generally associated with increased utilisation of neoadjuvant and palliative chemotherapy. Interestingly, academically-affiliated and higher volume hospitals were both associated with a greater likelihood of hospital readmission, which may be due to more complex patients presenting to these facilities.

Comparison of findings with existing literature

The findings of this review are similar to an existing narrative review of studies published in USA exploring disparities in pancreatic cancer treatment, which reported that patients of African-American race, lower SES status and uninsured were less likely to receive treatment [15]. The findings from the previous review add robustness to our findings in that minority race and lower SES status were the most commonly reported significant predictors of decreased HSU. Insurance status was also found to be a significant predictor for utilisation of multiple health services, however, it is difficult to comment on the directionality of this effect as the groupings for insurance status or type varied widely across studies.

In addition to race and SES, several demographic characteristics, including education attainment, insurance status, and to a lesser extent, sex, were found to predict HSU. The direction of this association is of no surprise as those of minority racial backgrounds, lower SES and lower education groups commonly experience difficulties in accessing health services. However, the association between patient characteristics and HSU may be more nuanced as a recent multivariable analysis in patients with early-stage pancreatic cancer reported that patients who were older, female, on non-Private insurance, had a higher CCI score or were treated at a non-academic facility were more likely to refuse recommended surgery [77]. Consequently, there may be several inter-dependant factors, such as personal choice, cultural beliefs, uncertainty about treatment, hopelessness or denial about illness, as well as patient-physician communication [78] which may also influence HSU.

Non-metropolitan location of residence was associated with under-use of certain treatments and health services, including palliative care. This is concerning as patients from non-

metropolitan areas often experience poorer outcomes [79]. Under-use may be due to a lack of treatment facilities and services available in close proximity, creating barriers to access. Nurse navigation programs may be particularly beneficial for regional-dwelling patients, as they have been shown to produce more streamlined care and improve patient experience [80]. Interestingly, rural location of residence was protective against ICU admission, which may be explained by a lack of ICU facilities in these areas, as well as hospitalisations near death, however the opposite was observed with ED admissions.

While few studies identified in this review explored the independent effect of service-level factors on HSU, it appeared however that hospital volume and academic affiliation were associated with greater likelihood of undergoing treatment. It is well established that treatment at high volume centres as well as centres with academic affiliations are associated with improved outcomes, including mortality [81, 82]. Hospital re-admission, however, was more common in higher volume and academically-affiliated facilities. This may be due to more complex patients presenting to these types of facilities.

Implications and future directions

Given the dismal prognosis of pancreatic cancer, timely access to treatment, both curative and supportive in nature, is critical for all patients. However, this systematic review has demonstrated that several patient, disease and service-level characteristics are independently associated with variations in utilisation of critical treatments and health services. However, it is important to note that there may be several inter-dependant factors which may contribute to decreased use of health services and treatments amongst certain groups, and these require further exploration.

This review has highlighted that a lack of health equity persists in pancreatic cancer management. These findings may be utilised by policy makers and health services to guide the delivery of equitable health care, particularly to patients belonging to older age groups, minority races as well as from low SES backgrounds. Equitable access to treatment may help to reduce current disparities in survival outcomes.

Given the lack of studies focussed on supportive care services, future research should focus on exploring potential disparities in supportive care utilisation in pancreatic cancer, as this forms a critical component of the cancer management pathway. Additionally, greater understanding is required around more nuanced patient variables, such as personal preferences or belief systems, which may also influence HSU.

Methodological considerations

To our knowledge, this is the first systematic review which provides a detailed synthesis of the predictors of HSU in the pancreatic cancer population. Rather than being limited to specific variables only, our review encompasses a wide-range of predictor variables, including patient demographic, disease, treatment and health service characteristics. Additionally, limiting inclusion to studies which captured a large proportion of the pancreatic cancer population in their specific region(s), aids the generalisability of our findings. The screening, data extraction and appraisal phases of this review were independently conducted by two separate reviewers, increasing the consistency of our results and reducing random error.

Due to pragmatic reasons, publication in English-language was an inclusion criterion for this review. This limited our ability to include potential studies which may have been conducted in non-English speaking cohorts. Consequently, our findings may not be generalisable across non-Western countries. The inclusion of population-level data only also limits the generalisability of our findings to affluent countries and regions, where systems support capture of population-level data. Additionally, the majority of included studies were conducted in USA, which has a unique health care system that may contribute to disparities in HSU. However, similar predictors of HSU were identified in other Western countries, suggesting that our findings may indeed be generalisable across Western regions.

While we included studies which were apparently population-level, we recognise that many of the databases (i.e. SEER-Medicare), do not capture the entire pancreatic cancer population, but rather a subset (i.e. those aged over 65 years and in receipt of Medicare). These databases however were deemed eligible for

inclusion as they capture a significant proportion of the population and have been shown to be comparable to the general population [83].

Given the inclusion of a variety of health services as well as a broad range of population-level datasets which each have their unique inclusion criteria, there is a high level of inter-study heterogeneity. Future reviews may limit their focus to specific health services or more strictly define their cohort of interest to reduce inter-study heterogeneity.

Additionally, no studies examined the impact of cultural and psychological factors on the utilisation of treatments and health services, which may play a significant role in whether certain treatments are offered to or accepted by patients with pancreatic cancer.

Conclusion

Several patient and service-level factors are associated with HSU in pancreatic cancer, with race, SES (including income, education level and location of residence), year of diagnosis, tumour stage, CCI score, hospital type and volume being strong predictors. The findings of this review may assist health services and clinicians in identifying vulnerable patient groups who are prone to experiencing disparities in accessing treatments and therapies. However, the delivery of equitable health care must be supported by relevant policies which enable all patients with pancreatic cancer to access health services to optimise their outcomes.

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Disclosure of conflict of interest

None.

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Supplementary Material 1: Search Strategy

INITIAL SEARCH: Conducted Monday 3rd Feb 2020

**Note: Terms for oesophageal and gastric cancer were included in the original search due to the initial wider scope of the systematic review. Cochrane Central Register of Controlled Trials was searched prior to the exclusion of randomised controlled trials from the review.*

MEDLINE

1. exp Esophageal Neoplasms/

2. exp Stomach Neoplasms/

3. ((pancrea* or oesophag* or esophag* or stomach or gastric or upper GI or upper gastrointestinal) adj3 (cancer* or malignan* or carcinoma* or adenocarcinoma* or tumo?r* or neoplasm*)).mp.

4. pancreatic neoplasms/or carcinoma, pancreatic ductal/or pancreatic intraductal neoplasms/

5. 1 or 2 or 3 or 4

6. ((health resource* or health service* or health care or procedure* or technique* or facilit*) adj3 (utili#e or utili#ation or “use” or us? age)).mp.

7. ((general practi* or primary care physician or family physician or emergency service or emergency department or Intensive care or critical care or surg* or gastroenterolog* or oncolog* or palliative care or terminal care or hospice care or end of life care or patholog* or pharmacy or pharmacist or nurs* care or dieti#ian or nutritionist or nutrition therapy or psycholog* or psychiatr* or counsel* or speech language patholog* or speech therap* or social work* or occupational therap* or physiotherap* or exercise physiolog* or physical therap* or chemotherapy or radiotherapy) adj3 (utili#e or utili#ation or “use” or us?age)).mp.

8. health services/or community health services/or exp community health nursing/or counseling/or home care services/or home care services, hospital-based/or parenteral nutrition, home/or hospices/ or dietary services/or emergency medical services/or emergency service, hospital/or nursing care/or critical care/or exp hospitalization/or palliative care/or perioperative care/or preoperative care/or subacute care/or terminal care/or hospice care/or pharmaceutical services/or diagnostic services/or exp rural health services/or exp social work/or urban health services/

9. (utili#e or utili#ation or “use” or us?age).tw.

10. 8 and 9

11. exp Health Care Costs/

12. ((health care or direct service or drug or hospital or out of pocket) adj3 cost*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. 6 or 7 or 10 or 11 or 12

14. 5 and 13

15. exp animals/not humans.sh.

16. 14 not 15

17. limit 16 to english language

18. limit 16 to (case reports or comment or editorial or letter or meta-analysis or “review” or “systematic review” or systematic reviews as topic)

19. 17 not 18

EMBASE

1. exp pancreas cancer/

2. exp esophagus cancer/

3. exp stomach cancer/

4. ((pancrea* or oesophag* or esophag* or stomach or gastric or upper GI or upper gastrointestinal) adj3 (cancer* or malignan* or carcinoma* or adenocarcinoma* or tumo?r* or neoplasm*)).mp.

5. 1 or 2 or 3 or 4

6. exp health care utilization/

7. ((health resource* or health service* or health care or procedure* or technique* or facilit*) adj3 (utili#e or utili#ation or “use” or us?age)).mp.

8. ((general practi* or primary care physician or family physician or emergency service or emergency department or Intensive care or critical care or surg* or gastroenterolog* or oncolog* or palliative care or terminal care or hospice care or end of life care or patholog* or pharmacy or pharmacist or nurs* care or dieti#ian or nutritionist or nutrition therapy or psycholog* or psychiatr* or counsel* or speech language patholog* or speech therap* or social work* or occupational therap* or physiotherap* or exercise physiolog* or physical therap* or chemotherapy or radiotherapy) adj3 (utili#e or utili#ation or “use” or us?age)).mp.

9. Health service/or Clinical pharmacy/or emergency health service/or hospital emergency service/or genetic counselling/or health care/or “drug use”/or prescription/or medical care/or emergency care/or general practice/or outpatient care/or pharmaceutical care/or primary medical care/or nursing/or cancer rehabilitation/or occupational therapy/or rural health care/or rural health nursing/or terminal care/or hospice care/or nutrition service/or occupational health service/or mental health service/

10. (utili#e or utili#ation or “use” or us?age).tw.

11. 9 and 10

12. exp “health care cost”/

13. ((health care or direct service or drug or hospital or out of pocket) adj3 cost*).mp.

14. 6 or 7 or 8 or 11 or 12 or 13

15. 5 and 14

16. (exp animal/or nonhuman/) not exp human/

17. 15 not 16

18. limit 17 to english language

19. limit 18 to (conference abstract or editorial or letter or “review”)

20. (case report* or comment or meta-analysis or systematic review).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

21. 19 or 20

22. 18 not 21

COCHRANE CENTRL REGISTER OF CONTROLLED TRIALS

1. exp Esophageal Neoplasms/

2. exp Stomach Neoplasms/

3. ((pancrea* or oesophag* or esophag* or stomach or gastric or upper GI or upper gastrointestinal) adj3 (cancer* or malignan* or carcinoma* or adenocarcinoma* or tumo?r* or neoplasm*)).mp.

4. pancreatic neoplasms/or carcinoma, pancreatic ductal/or pancreatic intraductal neoplasms/

5. 1 or 2 or 3 or 4

6. ((health resource* or health service* or health care or procedure* or technique* or facilit*) adj3 (utili#e or utili#ation or “use” or us?age)).mp.

7. ((general practi* or primary care physician or family physician or emergency service or emergency department or Intensive care or critical care or surg* or gastroenterolog* or oncolog* or palliative care or terminal care or hospice care or end of life care or patholog* or pharmacy or pharmacist or nurs* care or dieti#ian or nutritionist or nutrition therapy or psycholog* or psychiatr* or counsel* or speech language patholog* or speech therap* or social work* or occupational therap* or physiotherap* or exercise physiolog* or physical therap* or chemotherapy or radiotherapy) adj3 (utili#e or utili#ation or “use” or us?age)).mp.

8. health services/or community health services/or exp community health nursing/or counseling/or home care services/or home care services, hospital-based/or parenteral nutrition, home/or hospices/ or dietary services/or emergency medical services/or emergency service, hospital/or nursing care/or critical care/or exp hospitalization/or palliative care/or perioperative care/or preoperative care/or subacute care/or terminal care/or hospice care/or pharmaceutical services/or diagnostic services/or exp rural health services/or exp social work/or urban health services/

9. (utili#e or utili#ation or “use” or us?age).tw.

10. 8 and 9

11. exp Health Care Costs/

12. ((health care or direct service or drug or hospital or out of pocket) adj3 cost*).mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]

13. 6 or 7 or 10 or 11 or 12

14. 5 and 13

15. exp animals/not humans.sh.

16. 14 not 15

17. limit 16 to english language

PSYCHINFO

1. exp Pancreas/

2. exp Esophagus/

3. exp Stomach/

4. 1 or 2 or 3

5. exp Neoplasms/

6. 4 and 5

7. ((pancrea* or esophag* or oesophag* or stomach or gastric or upper GI or upper gastrointestinal) adj3 (cancer* or malignan* or carcinoma* or adenocarcinoma* or tumo?r*)).mp.

8. 6 or 7

9. exp Health Care Utilization/or exp Mental Health Services/or exp Community Mental Health Services/ or exp Health Care Services/

10. ((general practi* or primary care physician or family physician or emergency service or emergency department or Intensive care or critical care or surg* or gastroenterolog* or oncolog* or palliative care or terminal care or hospice care or end of life care or patholog* or pharmacy or pharmacist or nurs* care or dieti#ian or nutritionist or nutrition therapy or psycholog* or psychiatr* or counsel* or speech language patholog* or speech therap* or social work* or occupational therap* or physiotherap* or exercise physiolog* or physical therap* or chemotherapy or radiotherapy) adj3 (utili#e or utili#ation or "use" or us?age)).mp.

11. ((health resource* or health service* or health care or procedure* or technique* or facilit*) adj3 (utili#e or utili#ation or "use" or us?age)).mp.

12. exp Health Care Costs/

13. ((health care or direct service or drug or hospital or out of pocket) adj3 cost*).mp.

14. 9 or 10 or 11 or 12 or 13

15. 8 and 14

16. limit 15 to english language

17. limit 16 to (comment/reply or editorial or letter or reviews)

18. (case report* or meta-analysis or systematic review).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

19. 17 or 18

20. 16 not 19

SCOPUS

(LIMIT-TO (LANGUAGE, "English")) AND (EXCLUDE (DOCTYPE, "re") OR EXCLUDE (DOCTYPE, "ed") OR EXCLUDE (DOCTYPE, "no") OR EXCLUDE (DOCTYPE, "le") OR EXCLUDE (DOCTYPE, "sh") OR EXCLUDE (DOCTYPE, "ch") OR EXCLUDE (DOCTYPE, "bk"))

10 #1 AND #8

8 #2 OR #3 OR #4 OR #5 OR #6 OR #7

7 TITLE-ABS-KEY (((“health care” OR “direct service” OR drug OR hospital OR “out of pocket”) W/3 cost*))

6 TITLE-ABS-KEY (((physiotherap* OR “exercise physiolog*” OR ”physical therap*” OR chemotherapy OR radiotherapy) W/3 (utili#e OR utili#ation OR “use” OR us?age)))

5 TITLE-ABS-KEY (((psycholog* OR psychiatr* OR counsel* OR “speech language patholog*” OR “speech therap*” OR “social work*” OR “occupational therap*”) W/3 (utili#e OR utili#ation OR “use” OR us?age)))

4 TITLE-ABS-KEY (((oncolog* OR “palliative care” OR “terminal care” OR “hospice care” OR “end of life care” OR patholog* OR pharmacy OR pharmacist OR “nurs* care” OR dieti#ian OR nutritionist OR “nutrition therapy”) W/3 (utili#e OR utili#ation OR “use” OR us?age)))

3 TITLE-ABS-KEY (((“general practi*” OR “primary care physician” OR “family physician”” OR “emergency service*” OR “emergency department” OR “Intensive care” OR “critical care” OR surg* OR gastroenterolog*) W/3 (utili#e OR utili#ation OR “use” OR us?age)))

2 TITLE-ABS-KEY (((“health resource*” OR “health service*” OR “health care” OR procedure*OR technique* OR facilit*) W/3 (utili#e OR utili#ation OR “use” OR us?age)))

1 TITLE-ABS-KEY (((pancrea* OR oesophag* OR esophag* OR stomach OR gastric OR “upper GI” OR “upper gastrointestinal”) W/3 (cancer* OR malignan* OR carcinoma* OR adenocarcinoma* OR tumo?r* OR neoplasm*)))

CINAHL

S1 (MH “pancreatic neoplasms”) OR (MH “esophageal neoplasms”) OR (MH “stomach neoplasms”)

S2 (pancrea* or esophag* or stomach or gastric or upper gastrointestinal or upper GI) N3 (cancer* or malignan* or carcinoma* or adenocarcinoma* or tumo#r*)

S3 S1 OR S2

S4 (health resource* or health service* or health care or procedure* or technique* or facilit*) N3 (utili#e or utili#ation or “use” or us#age)

S5 (general practi* or primary care physician or family physician or emergency service or emergency department or Intensive care or critical care or surg* or gastroenterolog* or oncolog* or palliative care or terminal care or hospice care or end of life care or patholog* or pharmacy or pharmacist or nurs* care or dieti#ian or nutritionist or nutrition therapy or psycholog* or psychiatr* or counsel* or speech language patholog* or speech therap* or social work* or occupational therap* or physiotherap* or exercise physiolog* or physical therap* or chemotherapy or radiotherapy) N3 (utili#e or utili#ation or “use” or us#age)

S6 MH “health care costs”

S7 (health care or direct service or drug or hospital or out of pocket) N3 cost*

S8 (MH “Health Services”) OR (MH “Community Health Nursing”) OR (MH “Home Health Care+”) OR (MH “Diagnostic Services+”) OR (MH “Community Health Services”) OR (MH “Community Mental Health Services”) OR (MH “Counseling”) OR (MM “Emergency Service”) OR (MM “Health Services, Indigenous”) OR (MH “Hospitalization+”) OR (MM “Interpreter Services”) OR (MH “Mental Health Services+”) OR (MH

"Nursing Care+") OR (MH "Nutrition Services+") OR (MM "Rehabilitation, Cancer") OR (MM "Rural Health Services") OR (MH "Social Work+") OR (MM "Urban Health Services")

S9 S4 OR S5 OR S6 OR S7 OR S8

S10 S3 AND S9

S11 Limit S10 to English Language

S12 Limit S10 to Publication Type: Case Study, Commentary, Editorial, Letter, Meta-Analysis, Review, Systematic Review

S13 S11 NOT S12

UPDATED SEARCH: ***conducted on 17th May, 2021***

*Note: Search strategy excluded terms pertaining to 'oesophageal' and 'gastric' cancers. Cochrane Central Register of Controlled Trials not searched due to exclusion of randomised controlled trials.

Supplementary Material 2: Quality of included studies

Table S1. SIGN methodology checklist 3 items: cohort studies

Study	Internal validity							Overall assessment		
	1.1 Clear study question	1.2 Comparable groups	1.7 Clear outcomes	1.10 Reliable exposure assessment	1.11 Outcome assessment valid and reliable	1.13 Main confounders considered	1.14 Confidence intervals provided	2.1 Overall acceptability	2.2 Evidence of Association between exposure and outcome	2.3 Result applicable to population
Abdel-Rahman et al. 2021 [20]	√	√	√	√	×	√	√	Acceptable	√	√
Abraham et al. 2013 [21]	√	√	√	√	×	√	√	Acceptable	√	√
Amin et al. 2020 [22]	√	√	√	√	×	√	√	Acceptable	√	√
Bakens et al. 2016 [23]	√	√	√	√	×	√	√	Acceptable	√	√
Balzano et al. 2016 [24]	√	√	√	√	×	√	√	Acceptable	√	√
Bateni et al. 2019 [25]	√	√	√	√	√	√	√	Acceptable	√	√
Bergquist et al. 2017 [26]	√	√	√	√	×	√	√	Acceptable	√	√
Bernards et al. 2015 [27]	√	√	√	√	×	√	√	Acceptable	√	√
Bhulani et al. 2018 [28]	√	√	√	√	×	√	√	Acceptable	√	√
Burmeister et al. 2016 [29]	√	√	√	√	×	√	√	Acceptable	√	√
Cerullo et al. 2019 [30]	√	√	√	√	√	√	√	Acceptable	√	√
Chang et al. 2018 [31]	√	√	√	√	×	√	√	Acceptable	√	√
Dengso et al. 2020 [32]	√	√	√	√	√	√	√	Acceptable	√	√
Dimou et al. 2016 [33]	√	√	√	√	×	√	√	Acceptable	√	√
Dumbrava et al. 2018 [34]	√	√	√	√	×	√	√	Acceptable	√	√
Ellis et al. 2019 [35]	√	√	√	√	√	√	√	Acceptable	√	√
Fergus et al. 2020 [36]	√	√	√	√	×	?*	√	Acceptable	Can't say	√
Forsmark et al. 2020 [37]	√	√	√	√	√	√	√	Acceptable	√	√
Gani et al. 2017 [38]	√	√	√	√	√	√	√	Acceptable	√	√
Haj et al. 2016 [39]	√	√	√	√	×	?*	√	Acceptable	√	√
He et al. 2015 [40]	√	√	√	√	×	√	√	Acceptable	√	√
Henson et al. 2018 [41]	√	√	√	√	√	√	√	Acceptable	√	√
Huang et al. 2019 [19]	√	√	√	√	√	√	√	Acceptable	√	√
Hyder et al. 2013 [42]	√	√	√	√	√	√	√	Acceptable	√	√
Jang et al. 2015 [43]	√	√	√	√	√	√	√	Acceptable	√	√
Jinkins et al. 2013 [44]	√	√	√	√	×	√	√	Acceptable	√	√
Kagedan et al. 2016 [45]	√	√	√	√	√	√	√	Acceptable	√	√
Kutlu et al. 2020 [46]	√	√	√	√	√	√	√	Acceptable	√	√
Landa et al. 2019 [47]	√	√	√	√	×	√	√	Acceptable	√	√
Lee et al. 2013 [48]	√	√	√	√	×	√	√	Acceptable	√	√

Lutfi et al. 2016 [49]	√	√	√	√	×	√	√	Acceptable	√	√
Mayo et al. 2012 [50]	√	√	√	√	√	√	√	Acceptable	√	√
Mehta et al. 2020 [51]	√	√	√	√	√	√	√	Acceptable	√	√
Mirkin et al. 2017 [52]	√	√	√	√	×	√	√	Acceptable	√	√
Moaven et al. 2019 [53]	√	√	√	√	×	√	√	Acceptable	√	√
Ngamruengphong et al. 2010 [54]	√	√	√	√	×	√	√	Acceptable	√	√
Nipp et al. 2018a [55]	√	√	√	√	√	√	√	Acceptable	√	√
Nipp et al. 2018b [56]	√	√	√	√	√	√	√	Acceptable	√	√
Nussbaum et al. 2016 [57]	√	√	√	√	×	√	√	Acceptable	√	√
Paredes et al. 2019 [58]	√	√	√	√	√	√	√	Acceptable	√	√
Paredes et al. 2021 [59]	√	√	√	√	√	√	√	Acceptable	√	√
Parmar et al. 2014 [60]	√	√	√	√	√	√	√	Acceptable	√	√
Peluso et al. 2019 [61]	√	√	√	√	×	√	√	Acceptable	√	√
Raigani et al. 2014 [62]	√	√	√	√	×	×	×	Low quality *Multivariable analyses not conducted therefore unable to determine true association*.	×	√
Raviv et al. 2017 [18]	√	√	√	√	√	√	√	Acceptable	√	√
Revels et al. 2013 [63]	√	√	√	√	√	√	√	Acceptable	√	√
Riall et al. 2010 [64]	√	√	√	√	×	√	√	Acceptable	√	√
Salami et al. 2019 [65]	√	√	√	√	×	√	√	Acceptable	√	√
Schmocker et al. 2017 [66]	√	√	√	√	√	×	√	Acceptable	Can't say	√
Seyedin et al. 2012 [67]	√	√	√	√	×	×	√	Acceptable	Can't say	√
Shah et al. 2013 [68]	√	√	√	√	×	√	√	Acceptable	√	√
Shapiro et al. 2016 [69]	√	√	√	√	√	√	√	Acceptable	√	√
Simons et al. 2010 [70]	√	√	√	√	×	√	√	Acceptable	√	√
Strohl et al. 2016 [71]	√	√	√	√	×	√	√	Acceptable	√	√
Swords et al. 2019 [72]	√	√	√	√	√	√	√	Acceptable	√	√
Sword et al. 2019b [73]	√	√	√	√	√	√	√	Acceptable	√	√
Sword et al. 2019c [74]	√	√	√	√	√	√	√	Acceptable	√	√
Sword et al. 2020 [75]	√	√	√	√	×	√	√	Acceptable	√	√
Van der Geest et al. 2017 [76]	√	√	√	√	×	√	√	Acceptable	√	√
Watson et al. 2020 [77]	√	√	√	√	×	×	√	Acceptable	Can't say	√
Wright et al. 2019 [78]	√	√	√	√	√	√	√	Acceptable	√	√

*Unable to determine if main potential confounders were identified and taken into account in the design and analysis as specific variables included in regression analysis models have not been specified.
?Analyses were not adjusted for comorbidities.

AXIS cross-sectional studies checklist items

	1 Clear aims	2 Appro-priate study design	3 Sample size justi-fied	4 Clearly defined popula-tion	5 Repre-senta-tive sample	6 Appro-priate sample selection	7 Non-re-spond-ers	8 Appro-priate out-comes	9 Appropriate outcome measure-ment	10 Statis-tical meth-ods	11 Repro-ducible statistical methods	12 Data de-script-ion	13 Re-sponse rate	14 Non-re-spon-ders	15 Internal consis-tency	16 Re-port-ing	17 Justi-fied conclu-sions	18 Limi-ta-tions	19 Fund-ing/ COI	20 Ethics approval
Raviv et al. 2017	√	√	×	√	√	√	n/a	√	√	√	√	√	n/a	n/a	√	√	√	√	?	√

?Unable to comment as no funding was provided and conflicts of interest were not explicitly declared.

Supplementary Material 3: Univariable predictors

Table S2. Summary of the evidence for examined significant predictors, on univariable analysis, of palliative chemotherapy, chemoradiotherapy and surgery in patients with pancreatic cancer

Predictor variables	*Palliative chemotherapy (3 studies)* [27, 34, 76]		*Chemoradiotherapy in surgically-treated patients (1 study)* [50]		*Curative-intent surgery (5 studies)* [40, 62, 63, 69, 77]		*Non-curative-intent surgery (1 study)* [24]	
	No. of studies	*Direction*	*No. of studies*	*Direction*	*No. of studies*	*Direction*	*No. of studies*	*Direction*
Patient demographic characteristics								
Age	3/3	↓Older (ref: younger)	1/1	↓>72 (ref: ≤72)	4/4	↓Older (ref: younger)		
Sex	2/3	↓F (ref: M)	0/1	n/a	3/3	↓F (ref: M)	0/1	n/a
Race/ethnicity			0/1	n/a	3/4	↓African American (ref: Caucasian)		
Country of birth								
Preferred language								
Education					2/2	↑most educated area (ref: least educated area)		
Income					2/2	↑highest (ref: lowest)		
Insurance					2/3	↑Private (ref: government)		
SES	2/3	↓low SES (ref: high SES)						
Location of residence	0/1	n/a	0/1	n/a	1/1	↓Urban (ref: metro)		
Marital status					1/1	↑married (ref: single)		
Disease characteristics								
TNM/ACJJ stage	1/1	↑stage IV (ref: stage I, II and III)						
Tumour site	2/2	↑body/tail (ref: head)			2/2	↑body/tail (ref: head)	1/1	↓body/tail (ref: head)
Tumour size					2/2	↓increasing/unknown size (ref: lowest size)		
Grade/differentiation					1/1	↓unknown (ref: grade I)		
Histology	1/1	↓no histology (ref: adenocarcinoma)						
Nodal status					1/1	↓clinical N0 or unknown (ref: pathologic N0)		
Metastasis	1/2	↓unknown (ref: 1 site)	1/1	↑lymph node mets (ref: no lymph node mets)				
CCI/Charlson-Deyo Score	2/2	↓CCI≥1 (ref: 0)			3/3	*Variable* 2/3 ↓≥2 (ref: 0) 1/3 ↓≥3, á1 (ref: 0)	1/1	↑increasing CCI (ref: CCI 0)
Performance status	1/1	↓Limited activity, in-bed or bedbound (ref: fully active)						
Treatment characteristics								
Year of diagnosis/treatment	2/2	↑per year increase (ref: lowest year)	1/1	↑post-2003 (ref: 1991-96)	0/1	n/a		
MDT presentation	1/1	↑presented at MDT (ref: not presented)						

Surgery			1/1	↓total pancreatectomy (ref: pancreaticodudenectomy)				
Post-operative complication			1/1	↓Yes (ref: no)				
Health service characteristics								
Hospital type					2/2	↓community (ref: Academic/teaching)		
Hospital volume (*i.e. no. of procedures per year*)	1/1	↓low volume (ref: high volume)					1/1	↓increasing volume (ref: lowest volume)
Public v. private hospital							1/1	↓private (ref: public)

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; MDT, Multidisciplinary team meeting; Ref, Reference; SES, Socioeconomic status; TNM, Tumour, Node, Metastasis staging system.

Table S3. Summary of the evidence for examined significant predictors, on univariable analysis, of medical oncology consultation, palliative/hospice care and ICU utilisation

Predictor variables	*Medical oncology consult (1 study)* [34]		*Palliative/hospice care (1 study)* [28]		*ICU (1 study)* [30]	
	No. of studies	*Direction*	*No. of studies*	*Direction*	*No. of studies*	*Direction*
Patient demographic characteristics						
Age	1/1	↓≥70 (ref: <60)	1/1	↓80-84 (ref: ≥85)	0/1	n/a
Sex	1/1	↓F (ref: M)	1/1	↑F (ref: M)	0/1	n/a
Race			1/1	↑Asian (ref: white)		
SES	0/1	n/a				
Location of residence	1/1	↓inner regional (ref: major city)				
Marital status			0/1	n/a		
Disease characteristics						
TNM/ACJJ stage	1/1	↑Stage IV (ref: I, II and III)	0/1	n/a		
Tumour site	1/1	↑body/tail (ref: head)				
CCI/Charlson-Deyo Score	1/1	↓CCI≥1 (ref: CCI 0)			1/1	↑CCI: 1 (ref: CCI 0)
Performance status	1/1	↓in bed/bedbound (ref: fully active)				
Treatment characteristics						
Year of diagnosis/treatment					1/1	↓2010-2014 (Ref: pre-2010)
Neoadjuvant therapy					1/1	↑Yes (ref: no)
Surgery					1/1	↑Whipple (ref: total pancreatectomy)
Vascular reconstruction					1/1	↑Yes (ref: no)
Perioperative transfusion					1/1	↑Yes (ref: no)
MDT presentation	1/1	↑presented at MDT (ref: not presented)				
Health service characteristics						
Hospital volume (*i.e. no. of procedures per year*)	1/1	↑increasing volume (ref: lowest volume)				

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; ICU, Intensive Care Unit; MDT, Multidisciplinary team meeting; Ref, Reference; SES, Socioeconomic status; TNM, Tumour, Node, Metastasis staging system.