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Manuscript title: The symptom experience of patients with advanced pancreatic cancer: An integrative review

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ABSTRACT

Background: Pancreatic cancer is a devastating disease with limited treatment options. Over 80% of pancreatic cancers are diagnosed in advanced stages and often have debilitating symptoms, making symptom management paramount; yet, the symptom experience of patients with advanced pancreatic cancer (APC) is not well understood.

Objective: The purpose of this integrative review was to synthesize the current evidence regarding the symptom experience of patients with APC.

Method: An integrative literature review was conducted to identify the patient symptom experience in studies published from 2005 to 2015.

Results: Sixteen studies met the inclusion criteria. All studies used a quantitative approach; 44% were quasi-experimental, 31% were descriptive, and 25% were correlational. Physical symptoms, especially pain, were the primary focus in most studies. Fatigue, loss of appetite, and impaired sense of well-being were prevalent and reported by patients to be of high intensity. Few studies examined psychological symptoms in patients with APC, though anxiety and depression were noted.

Conclusion: Findings suggest that physical and psychological symptoms are prevalent, some with high intensity. Pre-selection of symptom inventories limits our ability to fully understand the symptom experience of patients with APC. Future qualitative work is needed to provide a more in-depth understanding of symptoms, especially symptom quality and distress level, from patients' perspectives. More studies are needed to explore psychological symptoms and the interaction of physical and psychological symptoms.

Implications for practice: Findings help health care givers to better understand the symptom experience of their APC patients.

**THE SYMPTOM EXPERIENCE OF PATIENTS WITH ADVANCED PANCREATIC
CANCER: AN INTEGRATIVE REVIEW**

Introduction

Pancreatic cancer is one of the most challenging types of cancer because there are no effective prevention or early detection methods and treatment options are limited. Pancreatic cancer ranks fourth as a cause of cancer deaths, with over 40,500 estimated deaths for 2015 in the United States.¹ By 2030, scientists predict that pancreatic cancer will be the second leading cause of cancer death.² Despite significant improvement in survival rates for many types of cancer, the death rate for pancreatic cancer has slowly increased over the past decade. In fact, the overall five-year survival rate for patients in the advanced stage is approximately only 2%.^{1, 3}

The complexity of the disease and treatment and the rapid physical deterioration pose special challenges to symptom management for patients with advanced pancreatic cancer (APC). Symptoms, which are the “perceived indicators of change in normal functioning as experienced by patients,”^{4(pp68)} may be both complex and severe and significantly impact health related quality of life (HRQOL). For patients with APC and their caregivers, symptom management is the primary goal of care. Yet, though some studies have begun to focus on special symptoms or symptom clusters among different critically ill cancer populations, such as leukemia and lung and ovarian cancer,⁵⁻⁷ little is known about the symptom experience of patients living with APC. Emphasis has been placed on developing or evaluating treatment methods rather than symptom management.

There is a lack of comprehensive and systematic approaches to understanding symptoms and their impact in patients with APC. This knowledge gap not only contributes to poor symptom management but also ignores how symptoms interfere with patients’ survival duration, HRQOL, psychological health, communication, decision making, and preparing for death.^{4, 8}

Furthermore, because of the quick disease progression, APC is an ideal prototype to understand symptom changes and care needs in patients who face rapid transition from healthy status to terminal illness.^{9, 10} Therefore, the purpose of this integrative review was to synthesize current evidence regarding APC patients' symptom experiences. Findings from this review will inform future research directions and help health care providers design comfort measures that support patients as they manage and cope with symptoms.

Methods

This integrative review was designed to fully examine the symptoms experienced by patients with APC and used the methodological strategies proposed by Whittemore and Knafl (2005).¹¹ An integrative review was selected because it allowed us to include heterogeneous resources such as different research methods and varying data collection instruments. The steps of the review included 1) problem identification, 2) literature search, 3) data evaluation, 4) data analysis, and 5) presentation of findings.

Literature Search

Literature describing the symptom experience of patients with APC was identified by searching in four databases: Pubmed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, and PsychINFO. We used two medical subject heading searches to find citations in Pubmed: 1) "pancreatic neoplasms" AND "symptom assessment" OR "quality of life" and 2) "pancreatic neoplasms," "signs and symptoms," AND "terminal care." The CINAHL headings of "pancreatic neoplasms" AND "symptoms" OR "quality of life" were used to search in the CINAHL, and the Emtree terms of "pancreas cancer," "terminally ill patients," AND

“symptoms” OR “quality of life” were used to search in Embase. Emtree terms are hierarchically structured terminologies which are used to index the Embase content. For PsychINFO, subject terms of "neoplasms," "pancreas," AND "symptoms” OR “quality of life" were used. In addition to subject terms, we also used key words (i.e., “pancreatic cancer” AND “stage three” OR “stage four” OR terminal OR palliative) AND (symptoms OR signs OR “quality of life”)) to search aforementioned databases. Search limitations were English language, human sample, and year published (2005-2015) since treatment protocols for APC advance quickly. Each journal article’s reference list was also carefully searched by hand to identify additional pertinent articles. The search results were imported into EndNote X7.5 and duplicates were removed. We then reviewed the titles, abstracts, and full text of the articles based on the inclusion and exclusion criteria to determine their eligibility.

Inclusion and exclusion criteria. Based on the theoretical definition of symptom experience in Armstrong’s concept analysis and Lenz’s Theory of Unpleasant Symptoms, only the patient can report on the symptom experience, including its four dimensions: intensity, timing, quality, and distress.^{4, 12} Therefore, manuscripts included in this review include quantitative, qualitative, and mixed-methods studies focusing on physical or psychological symptoms experienced and reported by patients with APC. APC patients were defined as patients diagnosed with locally advanced or distant pancreatic cancer that was not eligible for curative surgery at diagnosis. We also included studies with heterogeneous cancer patient populations only if the results for those with APC were analyzed separately.

We excluded manuscripts that: (1) did not report on empirical studies, including opinions, case reports, or editorials; (2) were review articles; (3) did not include patient “self-report” of

symptoms; or (4) only addressed symptoms related to a specific drug or procedure because the foci of these articles were on drug toxicity or safety/effectiveness of the procedure versus overall symptom experiences. Moreover, studies focused only on specific drug- or procedure-related symptoms often set inclusion criteria of particular symptom intensity (e.g., patients with moderate pain).

Data Extraction

We used an author-developed data coding sheet to conduct the two steps of data extraction. First, we extracted information regarding authors, year of publication, setting characteristics, participant characteristics, and study design. Second, we extracted information with regard to symptom-related variables based on the aforementioned concept analysis and theoretical framework. Second, the symptom-related variables, including type of symptom, measurement instruments, symptom profile (symptom intensity, timing, quality, and distress), and associated factors were identified. The four dimensions of symptom profile were defined based on the Theory of Unpleasant Symptoms.⁴ Specifically, symptom quality is related to characteristics of symptoms (e.g., “burning” pain). Symptom intensity quantifies the degree, strength, or severity of symptoms. Timing is related to the occurring time, duration, and frequency. The distress dimension refers to the affective aspect or meaning of symptoms.⁴ After reading the articles, two of the authors (C. T. & D. V.) highlighted relevant information and organized information using the coding sheet. We further created several tables to contrast and compare variables. Tables are presented along with findings in the next paragraph.

Findings

Nine hundred and sixteen articles were initially identified. After removing duplicates ($n=90$), the remaining 826 articles were screened by titles, which resulted in a total of 337 articles remaining. After screening the 337 abstracts using the established criteria, 293 articles were excluded. Among the 293 articles, 44% ($n=128$) did not report results specific to an APC population; 36 % ($n=106$) were non-empirical, non-peer-reviewed, or review articles; 16% ($n=47$) did not include patient-reported symptoms; and 4% ($n=12$) only addressed symptoms related to a specific drug or procedure. Among the 44 articles that were retained for full-text review, 29 were excluded because they (1) did not include patient-reported symptoms ($n=11$), (2) only addressed symptoms related to a specific drug or procedure ($n=11$), (3) did not report results specific to an APC population ($n=6$); and/or (4) were not written in English ($n=1$). A hand search of each manuscript's reference list resulted in adding one more article. Thus, a total of 16 studies was included in the analysis (Figure 1).

All 16 studies were quantitative, with five descriptive studies,¹³⁻¹⁷ four correlational studies,¹⁸⁻²¹ and seven quasi-experimental studies.²²⁻²⁸ Six of the 16 studies (37.5%) explored overall symptom experiences or the relationship among symptoms in patients with APC,^{15, 17-21} and two studies (12.5%) compared symptom experiences across different pancreatic cancer stages.^{13, 16} Five studies (31.25%) focused on pain or pain management strategies for patients with APC,^{14, 22, 23, 27, 28} and the remaining three studies (18.75%) focused on interventions other than pain management.²⁴⁻²⁶ Only 2 of the 16 studies explicitly described a guiding theory or framework. The theoretical frameworks utilized were systematic inflammation¹⁷ and descriptions of nociceptive and neuropathic pain.¹⁴ The number of study participants ranged from 20 to 654, and the APC patients' median survival duration for those articles that reported on this variable ($n=8$) was about 6.36 months (range from 3.5 to 8.9 months). About half ($n=8$) of the studies

were conducted in Europe^{15, 17, 18, 21-24, 26} and the other half in North America ($n=7$).^{13, 14, 16, 19, 20, 25, 27} One study was conducted in Asia.²⁸ Table 1 displays study aims, designs, population, and symptom-related results. From our review, we organized the studies by symptom types and instruments, symptoms identified, symptom profiles, and factors associated with symptoms.

Instruments

All studies used instruments to evaluate pre-determined symptoms. The 9 instruments used in the 16 studies were in two categories: one focused on evaluating cancer patients' multiple symptoms and HRQOL and the other focused solely on pain. Six instruments that focus on multiple symptoms are the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) with or without the pancreatic special module (EORTC QLQ-PAN26), the Edmonton Symptom Assessment Scale (ESAS), the European Quality of Life-5 Dimensions (EQ-5D), the Functional Assessment of Cancer Therapy general module (FACT-G) with or without the hepatobiliary module (FACT-HEP), the Linear Analog Scale Assessment (LASA), and the M.D. Anderson Symptom Inventory (MDASI). Table 2 displays the symptom inventory captured by these six instruments. Three instruments focused solely on pain are the McGill Melzack Pain Questionnaire,¹⁴ the Brief Pain Inventory (BPI),²² and a single item for rating pain intensity and frequency.²⁴ Overall, the EORTC QLQ-C30 and/or EORTC QLQ-PAN26 were the most frequently used measurement tools ($n=8$),^{13, 15, 17, 18, 20, 23, 26, 27} followed by the FACT-G ($n=2$).^{16, 22} Though investigators used a variety of different instruments to measure symptoms, some symptoms are included in instruments more often than others. Specifically, almost all symptom evaluation instruments measured pain and depression symptoms. However, taste

change, numbness, and most psychological symptoms were addressed by only one or two instruments.

Symptoms Identified

All studies identified physical symptoms, and nine of the 16 (56.25%) studies^{13, 15, 17-19, 21-23, 25} also covered psychological symptoms. Table 3 shows authors, the symptoms reviewed, and measurement instruments. Importantly, Table 3 also displays the problematic symptoms identified by each study and the corresponding operational definitions of problematic symptoms. The physical symptoms identified in the APC samples were pain, fatigue/lack of energy, loss of appetite, dry mouth, taste change, digestive problems (e.g., nausea, vomiting, altered bowel habits, indigestion, and flatulence), respiratory problems (e.g., dyspnea), and poor sleep. The psychological symptoms were related to sense of well-being, anxiety, depression/sadness, emotional distress/mood disturbance, life enjoyment, and fear. Congruent with our previous observation that all instruments measured pain, pain was the most prevalent symptom discussed in all studies, followed by fatigue ($n=11$, 68.75%), digestive symptoms ($n=9$, 56.25%), and loss of appetite ($n=7$, 43.75%). However, although depression was also included in most instruments used, it was only discussed in six (37.5%) of the studies.

Symptom Profile: Intensity, Timing, Quality, and Distress

In this section, we report APC patients' symptom profiles using the Theory of Unpleasant Symptoms' four dimensions: intensity, timing, quality, and distress. The majority of the studies found that patients with APC had substantial physical and psychological symptoms, especially as related to the intensity dimension.^{13, 15-28} Compared to the healthy population and early stage

pancreatic cancer population, patients with APC reported more total symptoms and more intense symptoms such as fatigue, appetite loss, pain, digestive symptoms (e.g., indigestion), anxiety, and depression.^{13, 15, 16, 25} Although the researchers used various instruments with different operational definitions to determine the level of intensity of symptoms, they reported that a considerable number (more than 25%) of patients experienced moderate to severe intensity of symptoms that included fatigue,^{15, 18-20, 26-28} loss of appetite,^{15, 18-20, 26-28} pain,^{13, 15, 19, 20, 24-27} insomnia,^{20, 26-28} digestive symptoms,^{13, 26-28} impaired sense of well-being,^{15, 18} anxiety and depression,²⁵ and fear.¹³ Fatigue, loss of appetite, and pain were the top three severe symptoms reported.

Eleven studies explored fatigue, and most of these reported patients' average fatigue intensity was moderate to severe.^{15, 18-20, 26-28} In those articles that provided more specific information, 19% to 63% patients experienced moderate to severe fatigue.^{15, 17-19} Similarly, studies examining loss of appetite ($n=7$) reported the average intensity of appetite loss was moderate to severe,^{15, 18-20, 26-28} with about 24% to 63% of patients in those articles giving that information having loss of appetite that was moderate to severe.^{15, 18, 19} With regard to pain, patients experienced moderate to severe pain on average regardless of treatment types or disease progression.^{13, 15, 20, 26} Specifically, 15%-43% of patients with APC reported moderate to severe pain.^{17-19, 24} Symptom intensity changed along with treatment and disease progress. Though pain^{20, 27, 28} and insomnia^{20, 27, 28} improved significantly after treatments (e.g., celiac plexus block surgery), the intensity of several physical symptoms including fatigue,²⁸ digestive symptoms,^{15, 18, 26, 28} dyspnea¹⁵, and dry mouth¹⁵ worsened with general care, palliative resection, or celiac plexus block surgery. For loss of appetite, some studies found a significant improvement after

celiac plexus block surgery;^{27, 28} and other studies demonstrated that the symptom got worse with general care and palliative bypass surgery.^{20, 26}

Among the studies reporting psychological symptoms ($n=9$), the focus was on sense of well-being,^{15, 18, 23} depression,^{15, 17-19, 22, 25} and anxiety.^{15, 18, 29} Two studies found that patients with APC experienced moderate to severe impairment in their sense of well-being, which worsened as the disease progressed.^{15, 18} Studies presented contradictory findings regarding depression. Some showed that most patients experienced mild depression, with mean intensity scores of 2 to 3 out of 10,^{15, 19} whereas others showed that about 40% of patients experienced moderate to severe depression.^{17, 18} Similarly, Bye and colleagues (2013) found that 37-44% patients experienced moderate to severe intensity of anxiety, although the mean intensity score for anxiety reported by Labori et al. (2006) was at a mild level. Regardless of the intensity level, Romanus et al. (2012) reported that more than half of the patients experienced anxiety and depression. When the disease progressed, the intensity of anxiety and depression stayed the same or slightly increased.^{15, 18} Most studies used EORTC QLQ-C30 to measure anxiety and depression.^{15, 17, 18}

Three studies examined the timing dimension of the symptoms, including frequencies²⁴ and possible coexisting symptoms or symptom clusters.^{17, 19} Muller et al. (2008) reported that 51% of the patients with APC had daily pain. For the coexisting symptoms, Reyes-Gibby et al. (2007) reported all possible symptoms, but Laird and colleagues (2011) focused on the common symptom cluster of pain, fatigue, and depression in cancer patients. These two studies found that about 24% to 51% of the patients had two or more coexisting symptoms with moderate to severe levels of intensity. The proportion of patients with such symptoms tended to increase temporarily during chemoradiation.¹⁹ Specifically, researchers identified two possible symptom clusters.

Laird et al. reported more than double the number of patients who would have been expected to have had the symptom combination of pain, fatigue, and depression if the symptoms were to coexist by chance. Reyes-Gibby et al. (2007) reported a strong relationship between fatigue and loss of appetite. Only one study explored how patients described their symptom quality verbally.¹⁴ With a very small sample size, Dobratz (2008) could not distinguish pain patterns (e.g., nociceptive vs. neuropathic pain) based on APC patients' word choices. No study explored the distress dimension of the symptoms.

Factors Associated with Symptoms

A number of factors were noted to play into APC patients' symptom experiences. Researchers found that fatigue, loss of appetite, pain, and mood were significantly associated with other factors such as comorbidity, mortality, function or performance level, energy intake, psychological status, HRQOL, social relationships, and survival duration. Specifically, fatigue was negatively associated with energy intake and predicted the interference levels of walking, activity, work, enjoyment of life, and survival.^{18, 19, 21} Loss of appetite was not only linked to physical function such as energy intake, walking, and activity, but it also predicted psychological function including mood and enjoyment of life.^{18, 19} Pain was negatively related to performance, energy intake, and relationships with other people.^{18, 19, 21, 22} One study further indicated that pain intensity can predict survival in patients receiving chemotherapy. In this study, researchers also found that poor performance was associated with impaired mood.²¹ Low energy intake and complex comorbid medical conditions were linked to higher overall symptom intensity.^{18, 19}

Discussion

The purpose of this review was to synthesize current evidence regarding APC patients' symptom experiences. Based on the 16 reviewed studies, all using a quantitative approach with a pre-determined symptom inventory, our main findings were that patients with APC experienced multiple intense physical symptoms, especially fatigue, loss of appetite, and pain. With limited and inconsistent study results, APC patients' experiences regarding psychological symptoms remains unclear. Similarly, evidence of coexisting symptoms or symptom clusters in the APC population is limited. However, current evidence suggests that coexisting symptoms exist. Although there is no qualitative study met our inclusion criteria, qualitative evidence supported one of our main findings: patients with APC incur a number of complex symptoms that can become debilitating. Qualitative studies exploring terminal pancreatic cancer patients' concerns showed that patients and their caregivers experienced several symptoms and expressed their great concerns about both physical and psychological symptoms.^{30, 31} The following paragraphs further discuss findings in depth with several identified knowledge gaps.

First, the use of various symptom measurement instruments makes it difficult to compare identified symptoms and symptom intensity across studies. Instrument variation is especially problematic when interpreting psychological symptoms because every instrument uses different terms and definitions in relation to psychological symptoms (e.g., depression and sadness). Instruments such as LASA measure psychological symptoms using one general term (i.e., mood) to capture patients' experience with regard to depression, anxiety, and stress. Furthermore, all reviewed studies only focused on intensity dimension of predetermined symptoms because of forced-choice instruments and might ignore other symptoms and other symptom dimensions such as quality and distress. Another problem with regard to the instrument is that using the

instruments designed to measure HRQOL to evaluate symptoms, as most of our reviewed articles did, causes difficulties in understanding and managing nutrition-related symptoms.³²

Second, although our results show that fatigue, loss of appetite, and pain were prevalent and intense physical symptoms reported by the patients across studies, these symptoms received disproportionate attention. It is not surprising that pain has been the major focus of studies since pancreatic cancer is widely known to be one of the most painful malignancies.³³ All reviewed studies addressed pain and about half of them focused on pain management strategies. In contrast, only half or fewer of the studies mentioned other problematic physical symptoms (e.g., fatigue or loss of appetite) and their symptom management strategies. Our review found that fatigue is a prominent and severe problem in the APC population, which corresponds to existing assumptions in all cancer population.³⁴ On the other hand, there is a growing recognition that loss of appetite is one of the most distressing symptoms for APC and their caregivers, but is often overlooked by health care professionals.³⁵⁻³⁷ Although the etiology of loss of appetite is multifactorial and not fully understood, the experience and management of loss of appetite can be particularly complicated for patients with APC because it may be associated not only with treatment and physical deterioration but also with reduced pancreatic function (e.g., pancreatic exocrine insufficiency) and depression,^{18,37} which is a prevalent symptom in this context.³⁸ The disproportion emphasis of physical symptoms is not only obvious in research but also observable in the clinical practice. Two articles which reported the most significant problems faced by health care providers when caring patients with APC only discussed pain and anorexia-cachexia.^{39,40} Other studies showed that while pain management has been noted as the most frequent intervention provided in the hospice consultation for patients with APC, nutrition related evaluation and intervention was documented in less than 15% of the charts.^{41,42} This

ignorance of non-pain symptoms prohibits health care providers from understanding APC patients' symptom profile fully and addressing their needs. A qualitative study reported that pancreatic cancer patients expressed their lack of knowledge, confidence, resource access, and effective communication with health care providers when managing their digestive symptoms.³² Our limited understanding of these problematic symptoms may also partly explain why there are still no effective symptom management strategies for the majority of the symptoms, although APC patients experienced these intense symptoms until death. For example, whereas general treatments (e.g., chemotherapy) and pain management surgeries (e.g., nerve block) improved pain and insomnia, fatigue and digestive symptoms did not change or even worsened. Studies pointed out that the severe symptoms continuously contribute to APC patients' poor functional status and HRQOL with nutrition and digestion symptoms and fatigue being the most significant symptoms affecting HRQOL.^{32, 41, 43}

Third, psychological symptoms also have received insufficient attention. Only about half of the studies addressed psychological symptoms, and there was little in-depth exploration or discussion. Our findings showed different symptom profiles of psychological symptoms and, because of the limited number of studies looking at these symptoms, cannot either support nor reject the mounting evidence of strikingly high psychological distress rates in pancreatic cancer population compared to other types of cancer.^{38, 44, 45} For example, although two reviewed studies^{17, 18} found that depression was a severe problem, with approximately 33-50% of the pancreatic cancer patients experiencing depression,³⁸ other researchers^{15, 19} concluded that depression is mild in APC population. These different results may be because of different measurement methods (e.g., mean symptom score vs. the percent of patients with a high

symptom score). However, our results do support that psychological distress is elevated when disease progresses over time.⁴⁶

Despite the insufficient evidence, qualitative evidence suggested that psychological distress bothers APC patients and their caregivers. Researchers analyzing the types of questions asked by terminal pancreatic cancer patients and their caregivers online indicated that 11-23% of the questions were related to psychological concerns.^{30, 47} Interestingly, while maintaining hope is one of the main themes identified with regard to pancreatic cancer patients' experience,⁴⁸ only one instrument was used by our sample studies that evaluates hope. None of our sample studies addressed hope in their result or discussion. Although the evidence is not enough to determine the possible cause of psychological symptoms in pancreatic cancer,^{49, 50} it is clear that there is a complicated relationship among patients' physical symptoms, physical symptoms, and health related outcomes. A qualitative study demonstrated that nearly all patients expressed feelings of anger, frustration, and powerless related to the lack of knowledge of symptoms, unfamiliarity of symptom management strategies, and poor symptom control.³² Researchers suggested that the psychological distress is significantly related to poor QOL, fatigue, pain, and loss of appetite in pancreatic cancer population.⁴⁴

Fourth, with only three studies exploring pain frequencies and co-existing symptoms, we know little about the timing dimension of the symptoms. Although our findings suggest that symptom clusters may exist, more evidence is needed to determine if there is any unique symptom cluster that is associated with APC. Lastly, we have almost no clues regarding the quality and distress dimension of the symptoms since only one article discussed pain quality and no study explored symptom distress.

Conclusion

To our knowledge, this is the first integrative review to explore symptom experiences of patients living with APC. By synthesizing the important evidence and highlighting the knowledge gaps, this review has important implications for both clinical and research practice. For clinical practice, the review findings help to target problems for improved symptom management in APC patients. Furthermore, we have identified pressing needs to raise awareness of and design interventions for a number of poorly managed and severe symptoms. For future research, given that quantitative methodology has been the predominant approach to examine symptom experience of patients with APC to date, qualitative studies are needed to explore the multiple dimensions of symptoms. For both researchers and clinicians, it is imperative to focus on psychological symptoms, which are still underexplored yet were the main concerns mentioned by patients and caregivers during patient-health care provider discussions.⁴⁷ Studying psychological symptoms will facilitate a deeper understanding of the high psychological distress rate and the causes so that interventions to alleviate this distress can be developed.

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Table 1. Summary of the Reviewed Studies

First author (year of publish)	Study aim	Study design	Population (n=number of study participants)	Symptom related results [measurement tool]
Allen (2011)	To assess the efficacy of laparoscopic celiac plexus block.	Quantitative; quasi-experimental study	Unresectable pancreatic malignancy with significant pain (n=20)	Symptom intensity: a) Baseline: Mean pain score: 7.8/10 [BPI] and 65.8/100 [EORTC QLQ-C30]. b) Follow-up: pain, insomnia, and appetite loss improved significantly 4 weeks after procedure [EORTC QLQ-C30].
Bernhard (2010)	To investigate the prognostic value of QOL relative to tumor marker carbohydrate antigen in patients with APC receiving chemotherapy.	Quantitative; predictive correlational study	APC patient treated in an international phase III trial (n=295)	Symptom intensity: Baseline: Median pain score for patients with increased tumor marker concentration (n=247): 83/100 and for patients with normal tumor marker concentration (n=48): 88/100; median tiredness score for patients with increased tumor marker concentration: 62/100 and for patients with normal tumor marker concentration: 70/100; median physical well-being score for patients with increased tumor marker concentration: 71/100 and for patients with normal tumor marker concentration: 72/100; median mood score for patients with increased tumor marker concentration: 63/100 and for patients with normal tumor marker concentration: 59/100 [LASA] Associating factors: a) Poor performance associated with worse symptoms including mood, tiredness, and pain. b) Pain and tiredness can predict survival independently.
Bye (2012)	To assess energy intake, weight loss and symptoms during the disease course and investigate associations between symptoms and energy intake.	Quantitative, descriptive correlational study	APC (n=39)	Symptom intensity: a) Baseline: 37% to 63% patients had moderate to severe intensity of almost all symptoms [ESAS]. Flatulence, oral dryness and indigestion were the most frequent symptoms reported [QLQ-PAN26]. b) Follow-up: minor changes from baseline [ESAS & QLQ-PAN26] Associating factors: c) The correlations between energy intake and symptoms become stronger when disease progress: At 2-month follow-up, there is strong negative correlation between energy intake, appetite loss, oral dryness and fatigue. At 3-month follow-up, there is a strong negative correlation between energy intake and appetite loss, pain, dyspnea and flatulence.
Braun (2013)	To examine if baseline QoL and QoL changes	Quantitative; descriptive	Stage IV pancreatic cancer (n=186)	Symptom intensity:

	from baseline until 3 months after treatment could predict survival in patients with stage IV pancreatic cancer.	correlational study		<p>a) Baseline: In average, patients experienced fatigue (41.8/100), pain (37.6/100), insomnia (36.6/100), and appetite loss (33.3/100) at moderate level [EORTC QLQ-C30].</p> <p>b) Follow-up: fatigue and appetite loss worsen; pain and insomnia improved 3 months after treatment.</p> <p>Associating factors:</p> <p>c) Physical function, social function, fatigue, pain, dyspnea, and global health were predictive of survival.</p>
Crippa (2008)	Evaluate the QoL and survival in patients with different stages of pancreatic cancer	Quantitative; descriptive longitudinal study	Pancreatic cancer (n=92; n of APC: 64)	<p>Symptom intensity:</p> <p>APC patients tended to report more abdominal pain than patients had localized pancreatic cancer</p>
Dobratz (2009)	To determine if nociceptive/ neuropathic pain could be identified by word selections	Quantitative; descriptive study	Advanced cancer patients received home-based hospice services (n=76; n of APC: 4)	<p>Symptom quality:</p> <p>APC patients showed no distinct pain pattern (nociceptive or neuropathic) in their word choices while colon and liver cancer selected words that described 2 types of nociceptive (visceral, somatic) pain and prostate cancer patients noted somatic pain.</p>
Gao (2014)	To evaluate the effectiveness of standard pain medication with or without NCPB	Quantitative; quasi-experimental study	Unresectable pancreatic cancer with pain (n=100)	<p>Symptom intensity:</p> <p>a) Baseline: in average, patients experienced fatigue and constipation at moderate level; pain, insomnia, and appetite loss at severe level [EORTC QLQ-C30].</p> <p>b) Follow-up: pain, appetite loss, and insomnia improved significantly 3 month post-therapy.</p>
Labori (2006)	To describe prospectively the prevalence and severity of disease-related symptoms, QoL and need for palliative care in patients with APC	Quantitative, descriptive longitudinal study	APC (n=51)	<p>Symptom intensity:</p> <p>a) Baseline: fatigue and loss of appetite have highest mean score [ESAS & EORTC QLQ-C30]. Compared to general population, APC patients' fatigue, pain, and appetite loss were significantly impaired [EORTC QLQ-C30].</p> <p>b) Follow-up: increasing intensity of all symptoms the last 8 weeks before death, except for pain at rest and appetite [ESAS].</p>
Laird (2011)	To examined whether pain, depression, and fatigue exist as a symptom cluster in advanced cancer patients with cachexia and might be related to the presence of systematic inflammation	Quantitative; comparative descriptive study	Cachectic, advanced, unresectable cancer (n=654; n of APC: 181)	<p>Timing dimension of symptom:</p> <p>a) Pain, depression, and fatigue is an identifiable symptom cluster in a cohort of cachexic cancer patients. The prevalence of symptom cluster of pain, fatigue and depression is greater in lung and GI cancer than APC [EORTC QLQ-C30].</p> <p>Associating factors:</p> <p>b) For all patients, Pain, depression, and fatigue symptom cluster was associated with reduced physical functioning, but not related to CRP.</p>

Moningi (2015)	To evaluate how QoL change based on clinical stage at presentation to the JH Pancreas Multidisciplinary Clinic	Quantitative; descriptive study	Patients visited the Johns Hopkins Pancreas Multidisciplinary Clinic (n=77; n of APC: 39)	<p>Symptom intensity:</p> <p>a) APC patients had significantly worse indigestion, flatulence, and diet limitations than patients with non-advanced stage [EORTC QLQ-PAN26].</p> <p>Associating factors:</p> <p>b) Patients with lower performance status had significantly worse pancreatic pain and digestive symptoms.</p>
Muller (2008)	To evaluate a palliative surgical bypass procedure in patients with obstructive and intraoperative pancreatic cancer	Quantitative; quasi-experimental study	Non-resectable pancreatic cancer (n=136)	<p>Symptom intensity:</p> <p>a) Baseline: 26% patients had moderate- to severe- pain.</p> <p>Timing dimension of symptom:</p> <p>b) Baseline: 51% patients had daily pain</p> <p>Associating factors:</p> <p>c) Daily pain associated with significant poor survival after bypass surgery and was a significant independent indicator of poor survival.</p>
Reyes-Gibby (2007)	To assess symptoms of patients with locally advanced pancreatic cancer receiving chemoradiation to determine the prevalence, and co-occurrence, of symptoms and to identify the extent to which symptoms interfered with function	Quantitative, descriptive correlational study	Locally advanced pancreatic cancer (n=43)	<p>Symptom intensity:</p> <p>a) Baseline: 95% of patients reported at least one of the 13 symptoms. The most commonly reported symptoms of moderate to severe intensity were lack of appetite (24%), pain (19%), fatigue (19%), and sleep disturbance (10%) [MDASI].</p> <p>b) Follow-up: An increase in patients reporting moderate to severe fatigue, nausea, and sleep disturbance during chemoradiation. The proportion of patients reporting moderate to severe symptoms of pain, lack of appetite, fatigue and sleep disturbance significantly decreased after 94 days of chemoradiation.</p> <p>Associating factors:</p> <p>c) Presence of a comorbid medical condition was a significant factor for symptom intensity. Lack of appetite, fatigue, sleep, and pain were the symptoms that accounted for variation in walking, activity, mood and enjoyment of life.</p>
Romanus (2012)	To evaluate health-related QoL in patients with APC participating in a multicenter, double-blind, randomized trial	Quantitative; quasi-experimental study	Inoperable pancreatic cancer with ECOG status of 0-2 (n=186)	<p>Symptom intensity:</p> <p>a) Baseline: compared with the U.S. general population, a larger proportion of APC patients reported problems in pain/discomfort (78%) and anxiety/depression (53%) [EQ-5D].</p> <p>b) Follow-up: symptoms of anxiety/depression and pain/discomfort improved.</p>
Seicean (2013)	To evaluate the safety and efficacy of EUS-CPN in patients with painful unresectable pancreatic cancer	Quantitative; quasi-experimental study	Inoperable, chemo-naïve body-tail pancreatic cancer receiving opioid analgesia (n=32)	<p>Symptom intensity:</p> <p>a) Follow-up: pain improved significantly in 75% patients [BPI].</p> <p>Associating factors:</p> <p>b) After procedure, ratings of “pain interfering with general activity, walking, work, mood, enjoyment of life, relations with others, and</p>

				sleep” improved significantly. Physical, functional, and emotional well-being also improved significantly [FACT].
Stefaniak (2005)	To compare the effectiveness of two invasive pain treatments (NCPB & VSPL) to a control group concerning pain and QoL	Quantitative; quasi-experimental study	Inoperable pancreatic cancer with pain (n=59)	<p>Symptom intensity:</p> <p>(a) Follow-up: Both methods of invasive pain treatment resulted in significant reduction of pain and fatigue.</p> <p>Associating factors:</p> <p>(b) Physical, emotional and social well-being improved significantly only in NCPB group.</p>
Walter (2011)	To compare QoL of patients with APC who were given palliative resection or double loop bypass surgery	Quantitative; quasi-experimental study	APC (n=196)	<p>Symptom intensity:</p> <p>(a) Baseline: the average intensity level of appetite loss, insomnia, pain, fatigue, dyspnea, constipation, and diarrhea is moderate.</p> <p>(b) Follow-up: Palliative resection group had significantly increased dyspnea at discharge; increased nausea, dyspnea, constipation, and diarrhoea at 3 months after surgery. Appetite loss was more aggravated in double loop bypass group at 6 months after surgery.</p>

Abbreviations: APC, advanced pancreatic cancer; ECOG, Eastern Cooperative Oncology Group performance; ESAS, Edmonton Symptom Assessment Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer core module; EORTC QLQ-PAN26, European Organization for Research and Treatment of Cancer pancreatic cancer module; EQ-5D, European Quality of Life-5 Dimensions; FACT, Functional Assessment of Cancer Therapy; EUS-CPN; Endoscopic ultrasound-guided celiac plexus neurolysis; LASA, Linear Analog Scale Assessment; MDASI, M.D. Anderson Symptom Inventory; NCPB, neurolytic coeliac plexus block; JH, Johns Hopkins; VSPL, videothoroscopic splanchnicectomy; QoL, quality of life.

Table 2. Symptoms Measured by EORTC QLQ-30/Pan26, EQ-5D, ESAS, FACT-G/Hep, LASA, and MDASI

Instruments Symptoms	EORTC		ESAS	EQ-5D	FACT		LASA	MDASI
	Core module (QLQ-30)	Pancreatic cancer module (PAN26)			General module (G)	hepatobiliary module (Hep)		
Pain	X	X	X	X	X	X		X
Loss of appetite	X					X		X
Fatigue/ lack of energy	X		X		X	X	X	X
Sleep	X							X
Respiratory	X		X					X
Oral dryness		X				X		X
Test change		X				X		
Digestive ^a	X	X	X		X	X		X
Numbness								X
Senses of well-being			X		X			
Anxiety			X	X			X	
Depression/ sadness	X		X	X	X		X	X
Emotional distress/ mood disturbance								X
Stress							X	
Life enjoyment								X
Fear	X	X						
Worry	X				X			X
Drowsiness			X					X
Satisfaction	X				X			
Sense of meaning							X	
Relationship with God							X	
Hope					X			

Abbreviations: EORCT, European Organization for Research and Treatment of Cancer; ESAS, Edmonton Symptom Assessment Scale; EQ-5D, European Quality of Life-5 Dimensions; FACT, Functional Assessment of Cancer Therapy; LASA, Linear Analog Scale Assessment; MDASI, M.D. Anderson Symptom Inventory.

^aDigestive symptoms includes nausea and vomiting, flatulence, altered bowel movement and indigestion

Table 3. Symptoms and Problematic Symptoms Identified by Reviewed Studies and Corresponding Instruments^a

	Bye	Labori	Braun	Gao	Larid	Allen	Moningi	Walter	Stefaniak	Crippa	Seicean	Reyes-Gibby	Romanus	Dobratz	Muller	Bernhard	
Physical	Pain	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Loss of appetite	X	X	X	X	X						X					
	Fatigue/ lack of energy	X	X	X	X	X		X	X		X	X				X	
	Sleep			X	X	X					X	X					
	Respiratory			X	X	X						X					
	Oral dryness	X	X									X					
	Test change	X															
	Digestive ^b	X	X	X	X	X	X				X	X					
	Numbness											X					
	Psychological	Senses of well-being	X	X						X							
Anxiety		X	X										X			X	
Depression/ sadness		X	X					X			X	X	X			X	
Emotional distress/ mood disturbance												X					
Stress																X	
Life enjoyment											X						
Fear of future health problems							X										
Instruments		• EORTC QLQ-C30 & PAN26 • ESAS	EORTC QLQ-C30	EORTC QLQ-C30	• EORTC QLQ-C30 & PAN26 • BPI	EORTC QLQ-PAN26	EORTC QLQ-C30	• EORCT QLQ-C30 • FACT-G	• FACT-G • FACT-Hep	• FACT-G • BPI	MDASI	EQ-5D	McGill Melzack Pain Questionnaire	Single item of pain intensity and frequency	LASA		
Operational definition of intensity levels		[EORTC] M: ≥33.3; S: ≥66.7 [ESAS] M-S: ≥4	[EORTC] M: ≥33.3; S: ≥66.7				Pain, fatigue, and depression respectively: M: ≥ 50, ≥ 60, ≤70 S: ≥60, ≥70, ≤50				[BPI] M: 4-6; S: ≥7	M-S: ≥5					
Determination of the relatively		More than half	M intensity on	M intensity on EORTC								Top 3 highest	Symptoms reported by more				Compared to other

problematic symptoms	reported M-S intensity	ESAS or EORTC	mean score	than half of the patients	examined symptoms
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Abbreviations: BPI, Brief Pain Inventory; EORCT QLQ-C30, European Organization for Research and Treatment of Cancer core module; EORCT QLQ-PAN26, European Organization for Research and Treatment of Cancer pancreatic cancer module; EQ-5D, European Quality of Life-5 Dimensions; ESAS, Edmonton Symptom Assessment Scale; FACT-G, Functional Assessment of Cancer Therapy general module; FACT-HEP, Functional Assessment of Cancer Therapy hepatobiliary module; LASA, Linear Analog Scale Assessment; M, Moderate; MDASI, M.D. Anderson Symptom Inventory; S, severe.

^a Shading cells represent relatively problematic symptoms

^b Digestive symptoms includes nausea and vomiting, flatulence, altered bowel movement and indigestion

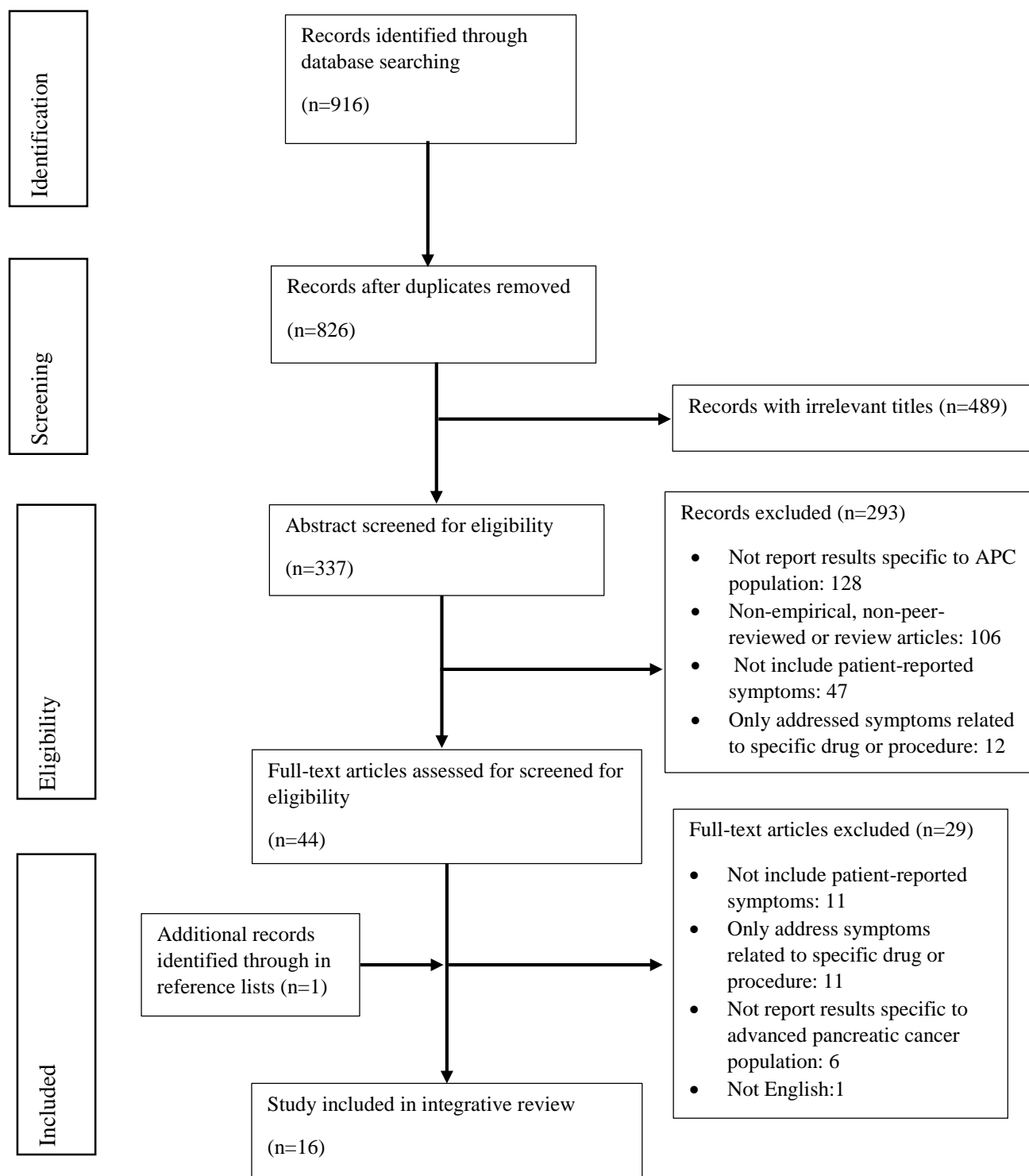


Figure 1. PRISMA Diagram of Search Results and Screening Process



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