**Title:** A Systematic Review of Economic Evaluation in Pancreatic Cystic Neoplasms

**Abstract**

**Background:** High-resolution imaging techniques and procedures have been recommended for the screening and surveillance of pancreatic cystic neoplasms (PCNs). Considering relatively high cost of imaging modalities, low incidence, and high mortality of pancreatic cancer in PCN patients, this study aimed to systematically review current evidence on the economic aspect on PCN management.

**Methods:** Original studies were obtained from PubMed, Embase, and Cochrane databases from inception to June 2022 that performed economic evaluations or modeled the natural history of pancreatic diseases. The quality of reporting was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline of 28 items. Data on cost and effectiveness of strategies and parameters of models were extracted.

**Results:** A total of 29 studies were eligible for this review. Of 21 economic evaluation studies, 11 studies scored at least 70% according to the CHEERS checklist. Compared to the no screening or surveillance strategy, the International Association of Pancreatology (IAP) 2006 but not the IAP 2017 recommendation was cost-effective, with incremental cost-effectiveness ratios of $20,096 and $171,143 per quality-adjusted life year, respectively. Using imaging modalities (computed tomography, magnetic resonance imaging, and endoscopic ultrasound) was more cost-effective than the full-watching strategy in populations of high-risk pancreatic cancer (e.g., 3-year pancreatic ductal adenocarcinoma (PDAC) risk of at least 1%, familial or hereditary diseases, or new onset diabetes). In contrast, immediate resection-based strategies were not cost-effective at the level of willingness-to-pay of $100,000. Of 24 model-based studies, only three studies considered histopathological features of PDAC, and four studies included different stages of pancreatic cancer.

**Conclusion:** There was lack of evidence for the cost-effectiveness of the current IAP recommendation and imaging modalities in entire population. Heterogeneity among management strategies, model parameters, and natural history of disease limited the derivation of robust findings. Further recommendations for PCN surveillance should consider the economic aspect in populations at different risk profiles.

**Keywords:** pancreatic cystic neoplasm; intraductal papillary mucinous neoplasm; cost-effectiveness analysis; Markov model; systematic review

**Introduction**

Pancreatic cystic neoplasms (PCNs) are the most common cysts identified in the pancreas, and they comprise intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystic neoplasm (SCN), solid pseudopapillary neoplasm (SPN), and cystic neuroendocrine tumor (cNET) as common types [1, 2]. The risk of developing malignancies varies considerably according to types of PCNs, with the probabilities of nearly 0% (SCN), 10% (cNET), 10%-15% (SPN), 10%-39% (MCN), 11%-30% (branch duct IPMN), and 36%-100% (main duct or mixed type IPMN) [3].

Incidental PCNs are known risk factors of pancreatic adenocarcinoma, and thus progress to pancreatic cancer, which is expected to increase as the second cause of cancer mortality in 2030 [4, 5]. Given the increased uptake of high-resolution imaging techniques (CT and MRI) and procedures (EUS-FNA), incidence of PCN in the general population is reported as 2.6% - 15% [6-8]. In contrast, up to 50% PCNs were defined in autopsy studies of the elderly population [9, 10]. Since the strategy for early-detection of PCNs can be helpful in reducing the overall mortality due to pancreatic adenocarcinoma, international guidelines have been established to provide recommendations on the management of PCNs, such as the American Gastroenterological Association (AGA) in 2015, the revised International Association of Pancreatology (IAP) in 2017, and the revised European Study Group on Cystic Tumours of the Pancreas (European) in 2018 [11-13]. Besides differences regarding imaging and clinical features, surveillance modalities, time intervals, and surgical indications, these guidelines showed different levels of performance [14]. Compared to the AGA 2015 guideline, the IAP 2017 guideline had higher sensitivity (IAP 2017: 98% vs. AGA 2015: 7%-62%) due to lower threshold of surgical recommendation, less missed cancers, lower PCN-related deaths, but higher medical costs and more surgeries, imaging studies, and surgical mortalities, whereas the European 2018 guideline showed lower specificity (European 2018: 28% vs. AGA 2015: 79%-95%) with a more conservative approach to stratify surgical risks [14].

Despite the relatively high diagnostic accuracy of detecting PCNs, prospective cohort studies revealed the overall low risk of malignancy progression [15-18]. Out of 1,077 German participants with a PCN prevalence of 49.1% and an incidence of 12.9% after 5 years of follow-up, only 6% of cysts were detected with a size of more than 1 mm and thus considered as clinically meaningful [18]. In a recent cohort of 7,211 veterans with PCNs in the United States, after a median follow-up of 4.4 years, the incidence and mortality of pancreatic cancer was 1.1% and 0.9%, respectively [17]. Besides, the relatively high cost of imaging modalities and procedures makes the need of considering the most cost-effective prevention strategy of pancreatic cancer. So far, one narrative review on the health economic aspects of pancreatic cancer treatments has been published in 2013 [19]. Other systematic reviews on the economic evaluation of and pancreatic cancer screening strategies [20] and pancreatic ductal adenocarcinoma [21] were also reported. However, these reviews limited to familial high-risk populations [20] and focused on main findings or checklist of parameters [19, 21] in individual studies. Since then, several studies on the cost-effectiveness of different strategies in the management of PCNs have been published, however, these studies are much diverse depending on several assumptions. The lack of thorough review and the diverse methodology used in current literature on the economic evaluation of pancreatic cystic neoplasms and pancreatic cancer screening highlight the need for further research in this area. The present systematic review is designed to summarize current knowledge about the economic evaluation of PCN management strategies, and therefore to suggest the future research topics in this area. Our goal is to address the lack of economic evaluation in this field by filling in the evidence gap and examining the current status of the diverse methodology used in published literature on pancreatic cystic neoplasms and pancreatic cancer screening.

**Materials and methods**

*Search strategy*

We conducted a systematic literature search using the PubMed, Embase, and Cochrane databases. Two reviewers (co-first authors) independently examined relevance articles using the Covidence software. The search was filtered for articles published from inception until June 19th, 2022. We used search terms related to pancreatic diseases and PCNs, economic evaluation (including simulation modelling), and surveillance and screening. The search strategy is presented in detail in **Supplementary material 1**.

*Inclusion and exclusion criteria*

After a preliminary search and discussion among the team members, the following inclusion and exclusion criteria were agreed upon, which is summarized in **Table 1**. We did not impose any language restrictions during the search. The study population was composed of adults, with a focus on the elderly as defined. The inclusion criteria for eligible studies were as follows: (1) all economic evaluation studies (cost-effectiveness analysis, cost-benefit analysis, cost-minimization analysis, and cost-utility analysis); (2) model-based studies that do not include cost estimates; (3) studies in which the primary outcome was unit cost of intervention, effectiveness measure, cost-effectiveness outcome, and cost-utility analysis outcome. Studies were excluded if (1) clinical/cohort studies that compared only clinical benefits of different strategies with clinical/epidemiological outcome that are not model based; (2) considered different types of surgery or therapy for the treatment of pancreatic cancer; (3) review articles or clinical guidelines.

*Data extraction*

The two co-first authors (TH, HP) developed a data extraction form that was consistent with the purpose of the systematic review (**Supplementary material 2**) [22, 23]. The information collected included authors, publication year, perspective, country, base year, currency, annual discount rate, availability of protocol, consideration of reporting guideline (e.g. CHEERS 2022), study design and objective, model structure, types of parameters with the data source (utilities, costs), and outcome assessment. The corresponding author (HS) compared the co-first authors’ results based on the inclusion and exclusion criteria and resolved any inconsistencies.

*Quality assessment*

The quality of reporting in individual studies was evaluated using the 2022 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [24]. This checklist contains 28 items, and each item was evaluated as fully reported, partially reported, not reported, and not applicable [24]. Each item on the checklist was given equal weight of 1 point, and the percentage score for each study was calculated by dividing the total score by the maximum score of 28 points.

*Presentation of the results*

**Figure 1** displays the main contents of the review. First, we summarized the PICO question on study population, management strategies, outcomes, and main finding (e.g. the most cost-effective strategy) of individual studies. Of these, we divided into studies considering and not considering costs. Economic evaluation studies were further classified as cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), and cost minimization analysis (CMA) research based on their corresponding types of outcomes.

Next, we focused on main findings of the most cost-effective strategy in different scenarios. Data on cost and effectiveness for each management strategy and the incremental cost-effectiveness ratio (ICER) of the guideline-based strategy, use of diagnostic modalities (including CT, MRI, and EUS), and resection comparing to the no screening and surveillance strategy were summarized.

Finally, we reviewed the model structure for the natural history of disease in both studies with or without economic evaluations. We listed how the parameters of costs, utilities, and transition probabilities were selected into the model. Cost parameterization was identified as screening cost, surgical and postoperative cost, cancer non-surgical treatment cost, palliative care cost, and patient cost. Regarding input parameters other than costs, we summarized information on diagnostic performance, cut-off proportion, transition probability, quality of life and/or utility, time horizon, and cycle length of the model.

**Results**

*Selection of studies*

Overall, a total of 905 studies were identified through searching the databases. After removing duplicates, 601 studies remained for title and abstract screening according to inclusion and exclusion criteria. 556 articles were excluded during the title and abstract screening due to irrelevance. The full texts of 45 articles were assessed for eligibility, upon which 16 studies were excluded. Finally, 29 articles were eligible for this systematic review (**Figure 2**) [25-53].

*Main characteristics*

The main characteristics of studies, including types of modelling, study population, management strategies, main outcomes, and findings of the dominant strategy, are presented in **Table 2**. Of 29 included studies, most studies (72.4%, n=21) evaluated economic aspects, whereas remaining studies (27.6%, n=8) only modelled the natural history of PCNs or compared the effect of different management strategies without considering costs. Among economic evaluation studies, the majority (76.2%, n=16) of studies were CEA and one CBA. Other four studies were CMA studies, which compared costs of strategies without calculating incremental cost per unit of utility/ effectiveness/ benefit. Economic evaluation research was reported in the perspective of third-party payer (n=5), society (n=4), and healthcare sector (n=3), using US dollar (n=16) and euro currency (n=5), with the annual discount rate of 3% (n=14) and 4% (n=1).

Most of the studies (82.8%, n=24) were model-based, of which 12 used Markov models [25, 28, 29, 35, 36, 42, 44-46, 48, 51, 52], 4 used decision analytical models [32, 33, 40, 49], 5 used both Markov and decision analytical models [26, 30, 31, 39, 50], 2 used nomograms [34, 53], and 1 used microsimulation [38].

Of all 29 studies, the majority of studies (69.0%, n=20) used a hypothetical cohort, and nine studies [27, 29, 33, 34, 37, 40, 41, 43, 47] used individual data. Research targeted asymptomatic PCN population (n=7 [30, 31, 41, 43, 47, 51, 53]), IPMN (n=6 [25, 26, 32, 34-36]), pancreatic intraepithelial neoplasia (n=1 [46]), familial or inherited individuals (n=9 [27, 28, 37-40, 45, 48, 49]), pancreatic cancer patients (n=2 [29, 33]), new-onset diabetes individuals (n=2 [50, 52]), and entire elderly population aged more than 50 years (n=2 [42, 44]).

*Reporting quality assessment*

We compared the quality of reporting in 21 studies using the 28 items in CHEERS 2022 checklist (**Figures 3A-3B**). Detailed scores for each study are shown in **Table S1**. **Figure 3A** illustrates that a significant number of papers have not provided sufficient descriptions of key elements of their health economic analysis plan (item 4), setting and location (item 6), characterization of heterogeneity (item 18), characterization of distributional effects (item 19), approach to engagement with patients and others affected by the study (item 21), and the effect of engagement with patients and others affected by the study (item 25). **Figure 3B** presents the individual scores of 21 studies on economic evaluation, which had an average score of 70% due to the equal weight given to each item.

*Main findings of economic evaluating studies*

*Guideline part (Sharib, Huang, Lobo): by Pf. Sohn & Dr. Han*

ICERs and cost differences of management strategies in economic evaluation studies are listed in **Table 3** and **Table S4**. Five studies have mentioned MRI as a screening modality [27, 28, 39, 43, 52]. In Wang et al., ICER decreased as the 3-year risk of pancreatic ductal adenocarcinoma increased [52]. MRI-based screening was found to be cost-effective compared to no screening or surveillance in two studies, with an ICER ranging from $7,847/QALY to $47,948/QALY [28, 52]. When compared to single abdominal ultrasound, the ICER for single MRI screening was $214,488/QALY in Kowada et al [43].

EUS was investigated in comparisons with no screening or surveillance [28, 40, 48, 49], abdominal ultrasound [39], and surveillance guidelines [32]. Comparing to no screening or surveillance, single EUS-based modality was found to be dominant of more life-year gained with lower costs in Rulyak et al [49]. When considering QALYs as measurement of effectiveness, single EUS was found to be cost-effective at the willingness-to-pay of $100,000 (ICER: 83,699 $/QALY) in Kumar et al [40]. In contrast, the cost-effectiveness of annual EUS-based modality appeared to be heterogenous according to population risks, which was more cost-effective in individuals of high-risk pancreatic cancer (dominant when RR(relative risk) >20 and ICER was 13,200 $/QALY when RR=5-20) [28], but less cost-effective in individuals of first-degree relative pancreatic cancer [49]. Besides, annual contrast-based EUS was shown to be dominant comparing to the IAP 2017, Italian consensus, ACG and European guidelines in PCN patients at different cyst sizes in Faccioli et al [32]. Furthermore, EUS-based surveillance every 3 years appeared to be cost-effective at the willingness-to-pay of 100,000$ (ICER=84,020 $/QALY) in Corral et al [28].

*Key model parameters*

We classified cost parameters into screening costs (including costs of biomarkers and imaging modalities), surgical and postoperative costs (including costs of resection, surgical complication, and postoperative care), cancer non-surgical treatment cost, palliative care, and patient costs (appointment medical doctor, dying from surgery-related or cancer-related events) (**Table S2**). Most of the studies (n=15 [25-28, 30, 31, 36, 37, 39, 40, 48-52]) separated the costs of cancer surveillance and treatment during the surveillance states. Of remaining studies, costs of only modalities were included in CMA studies (n=3 [27, 41, 43]) and in studies comparing management guidelines (n=2 [32, 42]). Study by Ghatnekar et al. targeting on pancreatic cancer patients, thus included treatment costs only [33]. Other sources of costs were included in only some studies, such as costs related to palliative care [25, 28, 31, 36, 50-52], disease recurrence [26], appointment follow-up visit [25, 36, 47], and terminal pancreatic cancer or surgery [28, 36, 51].

Parameterization of other parameters than costs are summarized in **Table S3**. Ghatnekar et al.’s study [33] reported both the disease diagnostic accuracy and the performance of surveillance strategies, while studies by Schwartz et al. and Aronsson et al. [25, 50] included the accuracy of (pancreatic cancer and BD-IPMN) disease diagnosis only. The sensitivity and specificity of screening tests, imaging modalities, and guidelines were reported in both economic evaluation and model-based studies (n=15 [26, 28, 30-32, 36, 38-40, 44, 45, 48, 49, 52, 53]). The range of average values was reported for CT (sensitivity 0.57-0.90, specificity 0.63-0.99), MRI (sensitivity 0.56-0.93, specificity 0.76-1.00), and EUS (sensitivity 0.54-0.91, specificity 0.60-1.00). Regarding outcome parameters, 15 studies referred to utility of different health states [25, 28, 30, 31, 33, 35, 36, 39, 40, 42, 48, 50-53], while two studies included quality of life [26, 32]. Other parameters of proportions of health states as well as probability of transitioning among health states were also included in model-based studies using hypothetical cohorts.

*Simulation process*

**Figure S1** displays the model structures implemented to simulate the natural history of PCNs. In most studies, asymptomatic or high-risk individuals (PCN, inherited mutation, history of pancreatitis, and new-onset diabetes) transited among different states of PDAC (pancreatic ductal adenocarcinoma), pancreatic cancer, postoperation, and death. Histopathological features of PDAC (including low-grade and high-grade dysplasia) were assessed in three studies [28, 38, 44], and four studies considered pancreatic cancer of different stages [28, 38, 44, 46].

The time horizon and cycle length of the model varied in individual studies (**Table S3**). While most studies modeled a lifetime horizon [28-31, 33, 36, 38-40, 44-46, 48, 49, 51, 52], some studies considered a horizon of 10 years [32], 15 years [42], 20 years [35, 53], and 35 years [25]. Annual cycle length was mostly used [25, 26, 30, 31, 38, 39, 44, 45, 48, 51, 53], whereas some studies considered shorter lengths of one month [46, 50], three months [35, 52], six months [36], and imaging-based intervals [28].

**Discussion**

Several studies evaluated the economic evaluation of guidelines, imaging modalities, and resection approach in the screening and surveillance of PCNs. However, there was still high heterogeneity in the results for the cost-effectiveness of different management strategies due to population’s risk profile and differences in input parameters and model assumptions.

In the present review, economic evaluation studies reported third-party payer, societal, or health care sector perspectives. However, of all four studies reporting societal perspective, none of them included costs related to time of patients and caregivers, transportation, or non-health care sectors. Adapting the recommendation from the second panel on cost-effectiveness in health and medicine [54], we identified current studies were limited to health care sector perspective, which included medical and care giving costs reimbursed by third-party payers and/or paid out-of-pocket by patients.

To date, numerous guidelines are available for the management of PCNs [55, 56]. The recommendations of imaging modalities and surveillance intervals vary by PCN size and clinical features [55, 56]. Although the accuracy and its corresponding range of management strategies were parameterized in the model and adjusted in the sensitivity analysis, the criteria of selecting literatures to identify the modality performance values remained unclear. In a recent study, the overall diagnostic accuracy in discriminating high-grade dysplasia or malignancy with low- or moderate-grade dysplasia in BD-IPMN differed according to imaging features, such as cyst size, thickened/ enhancing cyst walls, multiplicity, mural nodule, solid component, main pancreatic duct dilation, abrupt change in main pancreatic duct caliber with distal pancreatic atrophy, and lymphadenopathy [57]. However, the accuracy of specific types of imaging modalities were not accessed due to the lack of individual studies [57]. Nevertheless, the diagnostic accuracy used in the model of individual studies in the current review was somewhat in line with pooled estimates from previous meta-analysis for CT (sensitivity 0.72 and specificity 0.74), MRI (sensitivity 0.76 and specificity 0.80), and EUS (sensitivity 0.75 and specificity 0.75) [16].

Among all types of PCNs, IPMN was known to most likely to progress malignancy [3]. Of four studies investigating the cost-effectiveness or cost-benefit of BD-IPMN management strategies [25, 26, 32, 36], surveillance of either initial 6-month EUS then annual MRI or the IAP 2006 guideline was more cost-effective than the watchful waiting strategy, with the ICER of 31,682 €/QALY and 20,096 $/QALY, respectively [25, 36]. Although immediate resection strategy improved the QALY comparing to the nothing strategy even in Hu et al.’s non-economic evaluation study [35], it did not appear to be cost-effective the willingness-to-pay of 50,000$ [25, 36]. The results supported the importance of imaging modalities in the surveillance of BD-IPMN in decision making. However, the cost-effectiveness according to types and time intervals of imaging modality in individuals of different risk profiles and cyst sizes require further investigations.

This study remained some limitations. First of all, we observed that the methodology used in current literature is varied regarding economic evaluation on the pancreatic cystic neoplasms. Due to the limited number of studies available, it was not possible to conduct a systematic review in this field. Instead, we performed a subgroup analysis to identify factors shared among the studies on same modalities or guidelines. Another limitation of our study is that we assigned equal weight to all items for the CHEERS scoring. However, to address this, we also separately evaluated the importance of certain items. Also, the wide range of diseases encompassed by pancreatic cystic neoplasms made it challenging to make a comprehensive comparison according to each disease type. Consequently, we were unable to compare the detailed model parameters among the studies.

Many of the studies on the economic evaluation of pancreatic cystic neoplasms are model-based, and we have noted differences in model parameters, structure, and interpretation among these studies, which can lead to different conclusions and potentially cause confusion in decision making. Additionally, a small number of studies have focused on the patient perspective. In light of these issues, we suggest that there should be more trial-based studies on economic evaluation in this area, and this could be expanded to other areas as well. Future studies may comprehensively identify populations of different risk profiles for pancreatic cancer and develop the cost-effectiveness research comparing different management strategies accordingly.

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