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# Cystic pancreatic neuroendocrine tumors: A distinctive subgroup with indolent biological behavior? A systematic review and meta-analysis

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ABSTRACT

*Background/objectives:* The clinicopathological features and biological behaviors of cystic pancreatic neuroendocrine tumors (pNETs) are unclear and controversial. Here we performed a systematic review and meta-analysis to investigate the unique characteristics of cystic pNETs, to determine whether they represent a distinct clinical entity.

*Methods:* We selected comparative studies published since January 2000 that explore the differences between clinicopathological features of cystic and solid pNETs. Demographic information, pathological characteristics, and survival information were analyzed.

*Result:* The 12 selected studies comprised 355 and 1530 patients diagnosed with cystic and solid pNETs, respectively. Compared with solid pNETs, cystic pNETs were less likely to be functional (odds ratio, OR = 0.31, 95% confidence interval (CI) 0.19–0.50, $p < 0.00001$), more likely to affect males (OR = 1.56, 95% CI 1.22–2.00, $p = 0.0005$), and significantly associated with multiple endocrine neoplasia type 1 (OR = 2.71). Cystic pNETs were more likely to present with G1 and G2 rather than G3 (OR = 1.66). Cystic pNETs were associated with less frequent distant organs and lymph node metastasis, microvascular invasion, perineural invasion, and a low Ki-67 index and mitotic count. There were no significant differences between 5- and 10-year overall survival. However, the 5-year disease-free survival (DFS) and 10-year DFS rate of patients with cystic pNETs was significantly higher compared with those with solid pNETs (94.6% *vs* 83.5%, OR = 3.00; 92.7% *vs* 63.6%, OR = 5.92, respectively).

*Conclusions:* Cystic pNETs represent a distinct subgroup of pNETs that present with an indolent biological behavior, and patients experience better DFS. Observation and surveillance should be considered in some selected cases.



## Introduction

Pancreatic neuroendocrine tumors (pNETs) arise from the islets of Langerhans and exhibit heterogeneous phenotypes. The estimated incidence of pNETs is 4–5 individuals per 100,000 annually in the United States, comprising approximately 1%–5% of pancreatic neoplasms [1–3]. Due to the development and wide application of cross-sectional and endoscopic imaging, as well as increased awareness of physicians, more cases are detected incidentally recent years, and have led to increases in the prevalence of PNETs [3–5]. Patients' clinicopathological characteristics and the biological behaviors of pNETs vary significantly because of different functional states and histologic grades [2,3].

Most pNETs are solid and infrequently present as cystic lesions, termed cystic pNETs. Cystic pNETs were first described by Thigpen in 1940, and few small case series or case reports were published before 2000 [6]. More recent studies investigate the demographics and clinicopathological characteristics of patients with cystic pNETs [6,7]. These cystic subgroups account for 6.5%–36.1% of all resected PNETs [7–10]. The initial hypothesis to explain its pathogenesis maintains that cystic pNETs are secondary to solid-tumor necrosis

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1424-3903/

or hemorrhage and subsequent cystic degeneration [6,11,12]. They shared clinicopathological features of solid PNETs, and were thought to be similar entity with their solid counterparts [7,13]. However, conflicting reports show that cystic pNETs are distinctive, more likely associated with MEN-1, and present with well differentiated and less aggressive behavior compared with solid pNETs [6,8,14]. Notably, the degree of the cystic component may predict biological behavior and prognosis [15]. The etiology, clinicopathological features, and prognosis of cystic pNETs are controversial, and it is uncertain whether they represent a distinct subgroup of NETs or just the cystic degeneration of their solid counterparts.

Here we performed a systematic review and meta-analysis of studies that explored the clinical and histopathologic characteristics of cystic pNETs, and we conducted a detailed comparison of the differences between cystic and solid pNETs. We aimed to provide a panoramic view of cystic pNETs to illuminate their clinical and pathological features as well as patients' long-term prognosis. Our ultimate goal was to identify the unique characteristics of cystic pNETs to establish if these tumors represent a distinct clinical entity.

## Material and methods

### *Search strategy and study selection*

We conducted a comprehensive search of PubMed, Web of Science, EMBASE, the Cochrane Database, and CNKI (published in Chinese). The study protocol was developed and previously registered on PROSPERO (registration number: CRD42019121923). The last search was conducted on February 10, 2019. Relevant studies beginning in January 2000, were included for further analysis. The search strategy included the search terms as follows: "pancreatic neuroendocrine/endocrine/islet tumors/neoplasms/cancer," and "cystic/cyst". We further reviewed the reference sections of relevant publications and those of previously published meta-analyses to avoid omission of relevant studies. J. K. Zhu, D. Wu, and H. X. Zhan independently reviewed and crosschecked the publications. The titles and abstracts of articles were initially screened, and full-text articles of eligible publications were further reviewed according to the criteria as follows: Inclusion criteria: (1) studies aimed to compare clinical and histopathological features between cystic pNETs and solid pNETs; (2) key data of outcomes included; (3) for studies published from same institution, only articles with a larger sample size and those most recently published were included. Exclusion criteria: (1) publications including only an abstract; (2) reviews, meta-analyses, case reports; (3) missing key data for outcomes; (4) duplicate publication; (5) studies investigating the diagnostic value of endoscopic ultrasound (EUS), EUS-guided fine needle aspiration (EUS-FNA) of cystic pNETs, or both; (6) studies that focused on imaging and immunohistochemical analysis missing key pathological and clinical features.

### *Data extraction and quality assessment*

A qualitative assessment of the selected studies was performed according to the Newcastle Ottawa Scale [16]. J. K. Zhu, D. Wu, and H. X. Zhan independently assessed each study for inclusion. The relevant data from full-text articles were extracted and entered into standardized data collection forms. Discrepancies in study selection and data collection were resolved through discussions that reached a consensus.

### *Outcomes of interest and definitions*

All included pNETs were confirmed by pathological analysis. Cystic pNETs were diagnosed according to the cystic lesion on preoperative imaging, as well as final confirmation of the pathological features of NETs with macroscopic or microscopic cystic components. Variables associated with cystic pNETs and solid pNETs included for statistical analysis were as follows: demographics, functional status, multiple endocrine neoplasia type 1 (MEN-1), tumor size, tumor location, extent of cystic component, detailed pathological characteristics, and survival. One study divided pNETs into 4 different subgroups: purely cystic, mostly cystic (cystic component $\geq$50% of tumor diameter), mostly solid (cystic component < 50% of tumor diameter) and purely solid tumors [15]. We assigned patients with most solid lesions to cystic pNETs group because of the presence of cystic lesions. For studies that 2010 WHO grading system for pNETs were not available, we compared the mentioned WHO 2000 classification (benign + uncertain behavior *vs* carcinoma) between cystic pNETs and solid pNETs patients.

### *Statistical analysis*

Statistical analysis was conducted according to the recommendations of the Cochrane Collaboration [17]. Review Manager, version 5.3 (Cochrane collaboration, http://www.cochrane.org) was used for statistical analysis. Heterogeneity was evaluated using the Cochran's Q test, and the $I^2$ index was used to evaluate the extent of true heterogeneity [18]. A fixed effect model using Mantel–Haenszel method was used to calculate the outcome. If the $I^2$ >50%, a considerable heterogeneity was defined, and random-effect model was applied. If standard deviations (SDs) of patients age and tumor size were unavailable in some selected studies, the average of SDs from other included studies was assigned [19]. Funnel plots were applied to assess possible publication bias when $\geq$10 studies were included in the corresponding analysis. P values are 2-sided, and $P < 0.05$ indicates a significant difference.

## Results

We initially identified 442 publications. After screening the abstracts, 381 studies were excluded, and 61 full-text articles were collected for further evaluation. We excluded case reports (n = 20), review articles (n = 5, one paper published in Spanish), papers missing key data (n = 1), not relevant (n = 1), and those focused on diagnosis using EUS (n = 16), CT (n = 7), and IHC (n = 1). Another 2 studies were included from reference sections or previous meta-analysis. Ultimately, a total of 12 studies were included in this systematic review and meta-analysis [6,7,9,10,13–15,20–24] (Fig. 1).

The 12 studies were nonrandomized and retrospective design, published in academic journals from 2002 to 2019, with data acquisition dates ranging from 1977 to 2017. Based on the Newcastle Ottawa Scale, study quality scores ranged from 6 to 9, with an average of 7.58. For the funding support, 3 studies were supported by grants from government or academic society. No funding supported in 3 studies, and funding information not mentioned in other 6 studies. These studies included 355 cystic and 1530 solid pNETs, respectively, and the median number of cystic pNETs cases per study was 25.5 (range, 4–91). The number of patients with cystic pNETs was >20 in 75.0% (8/12) of the studies, which included 7 conducted at medical centers in the United States, two in Italy, and one each in Japan, and Brazil. Only non-functional pNETs patients were included in two study [22,24], both functional and non-functional pNETs were selected in other studies. Follow-up information was available in 6 studies [14,15,21–24]. The percentage of cystic pNETs ranged from 6.5% to 36.1%. The details of selected studies were summarized in Table 1.

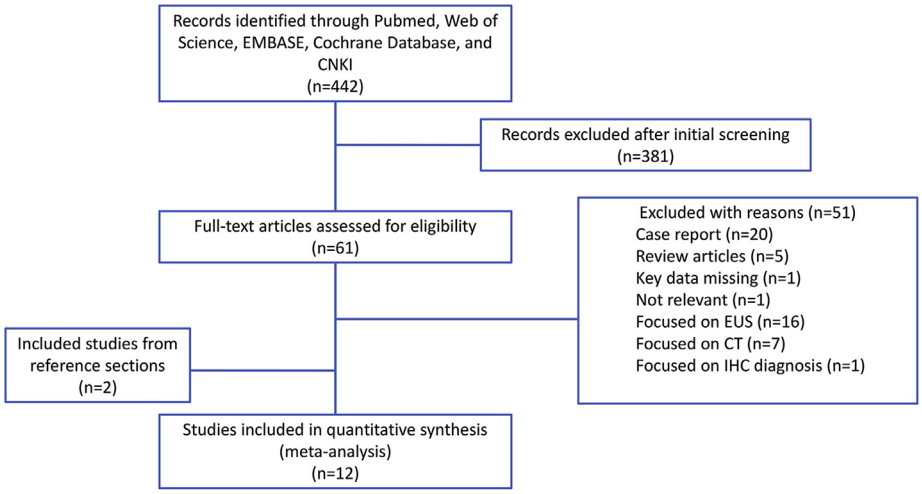



**Fig. 1.** Flowchart of study selection.

**Table 1**
Characteristics of the studies and patients included in the study.

| Researchers & published year | Period of data acquisition | Journals | Country | Cystic pNET,n | Solid pNET,n | Cystic percentage (%) | Funding | Study quality |
|---|---|---|---|---|---|---|---|---|
| Ahrendt et al., 2002 [10] | 1990–2000 | J Gastrointest Surg | USA | 4 | 34 | 6.5 | Not mentioned | 6 |
| Boninsegna et al., 2010 [23] | 1990–2008 | Neuroendocrinology | Italy | 21 | 161 | 11.5 | Not mentioned | 9 |
| Bordeianou et al., 2008 [14] | 1977–2006 | J Am Coll Surg | USA | 29 | 141 | 17.1 | Not mentioned | 7 |
| Carr et al., 2019 [19] | 1988–2016 | Pancreatology | USA | 91 | 239 | 27.6 | No funding supported | 8 |
| Cloyd et al., 2016 [15] | 1999–2014 | Surgery | USA | 30 | 184 | 14.0 | Not mentioned | 8 |
| Figueiredo et al., 2009 [13] | 1999–2008 | Pancreas | Brazil | 8 | 78 | 9.3 | Not mentioned | 6 |
| Gaujoux et al., 2012 [22] | 1995–2010 | Surgery | USA | 31 | 31 (matched) | 12.2(31/255) | European Society of Surgical Oncology | 9 |
| Goh et al., 2006 [7] | 1990–2004 | EJSO | Singapore | 6 | 32 | 15.8 | Not mentioned | 6 |
| Nakashima et al., 2019 [21] | 1999–2017 | Pancreatology | Japan | 14 | 61 | 18.7 | Japan Society for the Promotion of Sciences for Scientific Research | 8 |
| Paiella et al., 2018 [20] | 1988–2015 | Neuroendocrinology | Italy | 46 | 92 (matched) | 7.8 (46/587) | Italian Cancer Genome Project Italian Ministry of Health | 9 |
| Singhi et al., 2012 [6] | 1984–2012 | Am J Surg Pathol | USA | 53 | 438 | 10.8 | No funding supported | 8 |
| Yano et al., 2017 [9] | 2006–2013 | Pancreatology | USA | 22 | 39 | 36.1 | No funding supported | 7 |

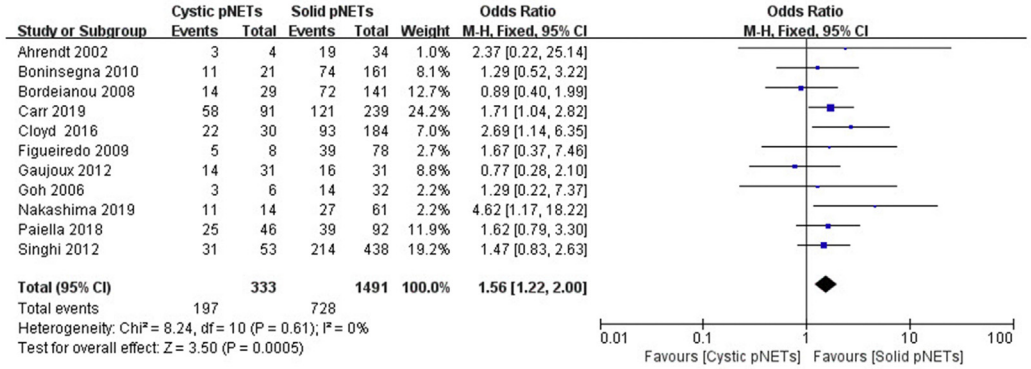
*Patients' demographics*

Information about sex was available from 11 studies that included 333 patients with cystic pNETs. Men accounted for 59.2% (197/333) of patients, and more men had cystic pNETs compared with solid pNETs (odds ratio, OR = 1.56, 95% confidence interval (CI) 1.22–2.00, p = 0.0005, $I^2 = 0\%$). There was no significant difference in age distributions between patients with cystic or solid pNETs.

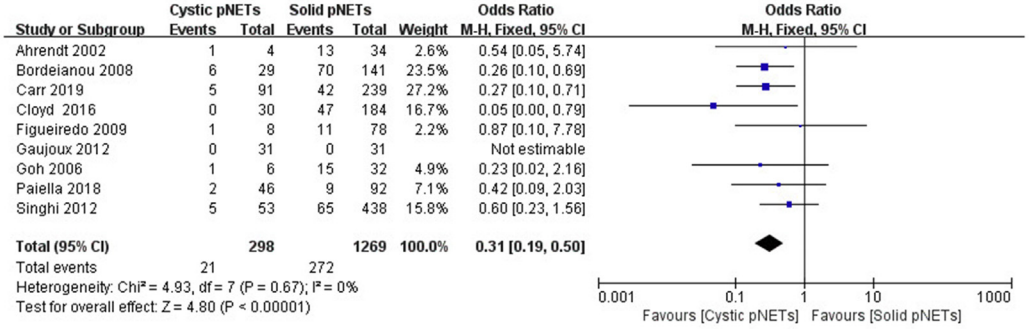
Insulinomas were most commonly reported, and cystic pNETs were functional less commonly than solid neoplasms (OR = 0.31, 95% CI 0.19–0.50, p < 0.00001, $I^2 = 0\%$). The frequency of symptoms upon diagnosed was not significantly different between these two groups. Moreover, details of associated MEN-1 status were described in 7 studies, and we found that cystic pNETs were also more likely to be associated with MEN-1 than their solid counterparts (OR = 2.71, 95% CI 1.55–4.73, p = 0.005, $I^2 = 0\%$) (Fig. 2, Table 2).

*Oncological and histological characteristics*

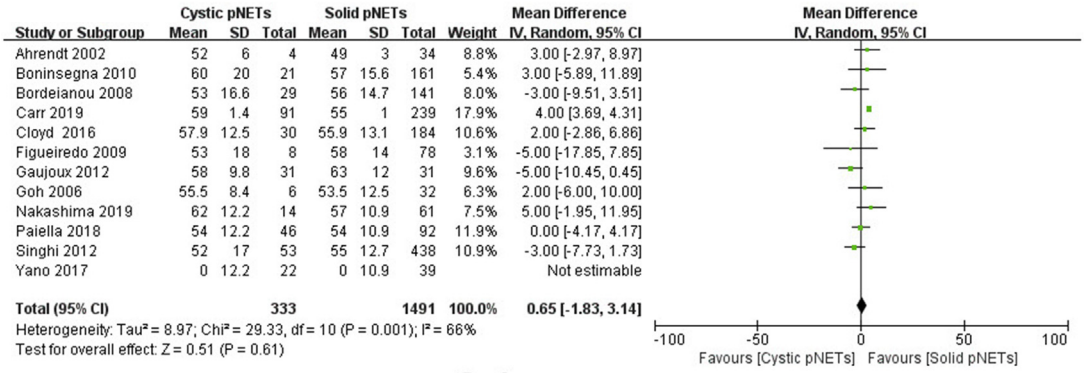
We paid particular attention to investigating the oncological and pathological features of cystic pNETs to identify its distinct existence. First, we analyzed tumor sizes and locations. Preoperative radiological or pathological tumor sizes available from the 12 studies did not reveal a difference between cystic pNETs and solid pNETs (p = 0.25). We extracted the raw data for tumor locations from 11 studies and divided them into a head and uncinate process group and a body and tail group. We found that cystic pNETs were significantly less frequent in the pancreatic head or uncinate process (OR = 0.40, 95% CI 0.30–0.54, p < 0.00001, $I^2 = 0\%$), but the likelihood of single lesion when surgical resected in patients with cystic pNETs was not different from likelihood of solid neoplasms (OR = 0.63, 95% CI 0.24–1.68, p = 0.36), with considerable heterogeneity among included studies ($I^2 = 61\%$). Tumor necrosis information was available from three studies, which included 89 patients with cystic pNETs. Their combined incidence of necrosis was 8.99% (8/89) compared with 14.52% (95/654) in the solid pNETs group (OR = 1.29, 95% CI 0.18–9.18, p = 0.80, $I^2 = 76\%$) (Fig. 3, Tables 2 and 3). Degree of cystic component information was reported in 4 studies, which including 112 cystic pNETs patients. 41.1% (46/112) patients presented with total cystic, mostly cystic (>50%) in 16 patients, partly cystic (<50%) in 31 patients, extent of cystic component (mostly or partly cystic) not mentioned in 19 patients.



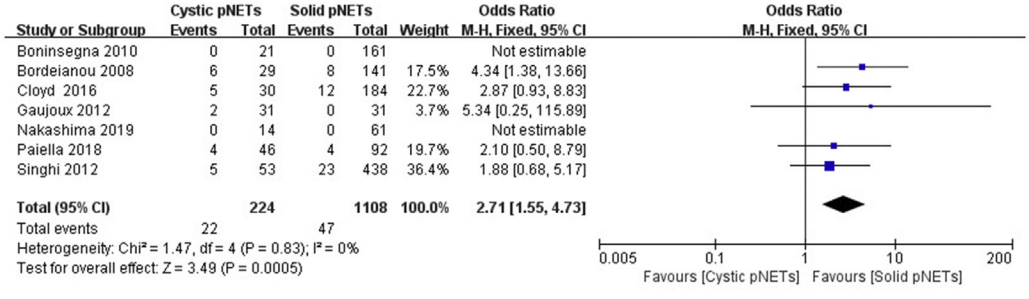

A. Gender




B. Functional status




C. Age




D. MEN-1

**Fig. 2.** Forest plots showing a meta-analysis of sex distribution (A), functional status (B), age (C), and associated MEN-1 status (D) associated with cystic pNETs vs solid pNETs.

**Table 2**
Clinical features comparison between cystic and solid pNETs.

| Clinical features | Included studies | Patients | Cystic pNETs n (%) | Solid pNETs n (%) | OR or WMD (95% CI) | P value |
|---|---|---|---|---|---|---|
| Gender | 11 | 1824 | Male: 197 (197/333, 59.2%)<br>Female: 136 (136/333, 40.8%) | Male: 728 (728/1491, 48.8%)<br>Female: 763 (763/1491, 51.2%) | 1.56 (1.22–2.00) | 0.0005 |
| Age | 11 | 1824 | Estimate mean = 56.4 ± 12.6 y | Estimate mean = 55.6 ± 12.1 y | 0.65 (−1.83–3.14) | 0.61 |
| Functional status | 9 | 1567 | Functional: 21 (21/298, 7.0%)<br>Non-functional: 277 (277/298, 93.0%) | Functional: 272 (272/1269, 21.4%)<br>Non-functional: 997 (997/1269, 78.6%) | 0.31 (0.19–0.50) | <0.00001 |
| Associated MEN-1 | 7 | 1332 | Yes: 22 (22/224, 9.8%)<br>No: 202 (202/224, 90.2%) | Yes: 47 (47/1108, 4.2%)<br>No: 1061 (1061/1108, 95.8%) | 2.71 (1.55–4.73) | 0.0005 |
| Unifocal | 8 | 1494 | Unifocal: 252 (252/273, 92.3%)<br>Multifocal: 21 (21/273, 7.7%) | Unifocal: 1151 (1151/1221, 94.3%)<br>Multifocal: 70 (70/1221, 5.7%) | 0.63 (0.24–1.68) | 0.36 |
| Symptoms | 6 | 920 | Presence: 114 (114/224, 50.9%)<br>Absence: 110 (110/224, 49.1%) | Presence: 401 (401/696, 57.6%)<br>Absence: 295 (295/696, 42.4%) | 0.80 (0.46–1.40) | 0.43 |
| Tumor location | 11 | 1824 | Head: 77 (77/333, 23.1%)<br>Body & tail: 256 (256/333, 76.9%) | Head: 647 (647/1491, 43.4%)<br>Body & tail: 844 (844/1491, 56.6%) | 0.40 (0.30–0.54) | <0.00001 |
| Tumor size | 12 | 1885 | Estimate mean = 31.8 ± 24.4 mm | Estimate mean = 32.4 ± 31.5 mm | 2.62 (−1.84–7.08) | 0.25 |

Eight studies described synchronous distant metastasis. The frequency of synchronous distant metastasis was significantly lower in cystic pNETs compared with that of solid pNETs (OR = 0.48, 95% CI 0.30–0.78, p = 0.003, $I^2$ = 7%). There was a significant differences between cystic pNETs and solid pNETs associated with regional lymph node metastasis (OR = 0.54), microvascular invasion (OR = 0.38), and perineural invasion (OR = 0.27) (p < 0.0001). Cystic pNETs were generally associated with a moderate and indolent phenotype (Fig. 4, Table 3).

*Prognostic features*

According to the WHO 2010 grading system, cystic pNETs were more likely to present with G1+G2 phenotype when compared with solid pNETs (OR = 1.66, 95% CI 1.09–2.52, p = 0.02, $I^2$ = 0%). WHO 2000 classification was reported in 3 studies, OR value for cystic pNETs to present benign or uncertain behavior rather than carcinoma was 3.03 (95% CI 1.20–7.68, p = 0.02, $I^2$ = 0%). Four studies found that 138/211 (65.4%) cystic pNETs had a Ki-67 proliferation index <2%, which was significantly higher compared with that of solid pNETs (49.4%, 459/930), whereas cystic pNETs were more likely associated with a low Ki-67 index (OR = 2.52, 95% CI 1.77–3.60, p < 0.00001, $I^2$ = 33%). Cystic pNETs were more likely to have <2 mitoses/10 HPFs compared with those of solid pNETs (OR = 2.75, 95% CI 1.09–6.93, p = 0.03), with considerable heterogeneity among included studies ($I^2$ = 58%) (Fig. 5 and Table 3). TNM staging information was included in four studies of 173 cystic pNETs and 916 solid pNETs. Our results revealed that cystic pNETs were more likely associated with stages I and II upon diagnosis compared with their solid counterparts (OR = 2.32, 95% CI 1.36–3.95, p = 0.002).

*Long-term outcomes*

Long-term survival data were included in six studies. The 5-year overall survival (OS) rates for patients with cystic and solid pNETs were not significantly different (93.7% [104/111] and 88.2% [510/578], respectively, OR = 1.82, 95% CI 0.82–4.03, p = 0.14, $I^2$ = 0%) (Fig. 6). Our analysis of three studies, which include 82 cystic pNETs and 437 solid pNETs found no significant difference in the 10-year OS between groups (79.3% [65/82] vs 82.4% [360/437], OR = 2.12, 95% CI 0.12–37.33, p = 0.61, $I^2$ = 81%, respectively). In contrast, the 5-year disease-free survival (DFS) rates were much higher in cystic pNETs group than that of solid pNETs (94.6% *vs* 83.5%, OR = 3.00, 95% CI 1.28–7.04, p = 0.01, $I^2$ = 0%). Further, the 10-year DFS of patients with cystic pNETs (92.7% [76/82]) was significantly higher compared with that of solid pNETs (63.6% [278/437]). The estimated OR was 5.92 (95% CI 1.17–29.94, p = 0.03, $I^2$ = 55%) (Table 4).

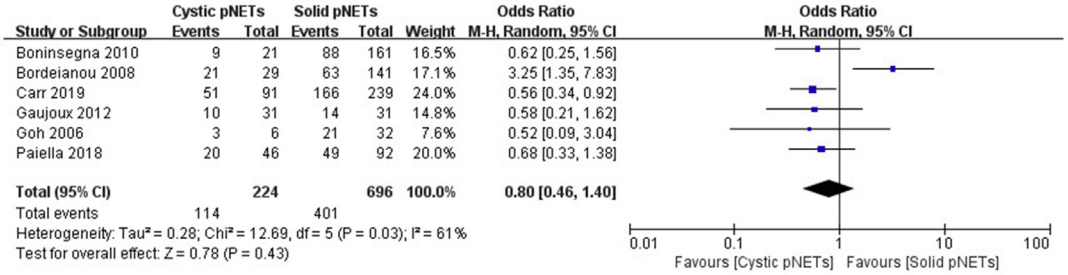
As shown in Fig. 7, visual inspection of the funnel plots demonstrated that the included studies distributed symmetrically on each sides of the horizontal line, which indicating no obvious publication bias among these studies. According to Oxford CEBM Levels of Evidence criteria, the level of evidence of this systematic review and meta-analysis was 3A.

## Discussion

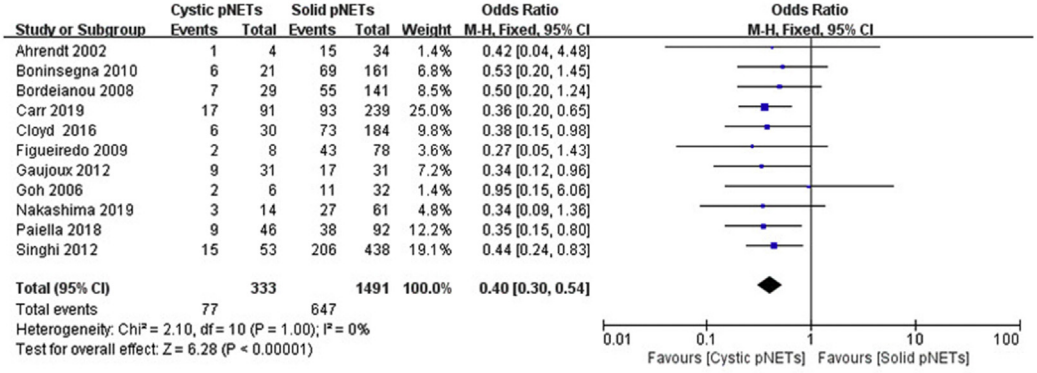
Biological behavior as well as the morphology of pNETs are highly heterogeneous, which has been increasingly recognized. Cystic pNETs were once considered rare, and only case reports or case series (<10 patients) were published before 2000. As true for other pancreatic cystic neoplasms, more cystic pNETs are now reported because of the ubiquitous use of cross-sectional imaging, and the largest patient population among these studies is 91[19]. Whether cystic pNETs represent morphological variants of the same entity or a distinct subgroup of pNETs is a contentious subject.

Here we reviewed studies that investigated the clinicopathological characteristics of cystic pNETs, and we compared these features with those of solid PNETs. Compared with an analysis published in 2014 [8], here we included more studies with more patients (12 vs 7 studies; 355 vs 152 cystic patients with pNETs). Moreover, we selected more recently published studies with larger sample sizes (46–91 patients) conducted at high-volume academic centers, which may help strengthen statistical validity. Our results revealed that cystic pNETs presented as a distinct entity with more favorable pathological features, they have indolent biological behaviors and may have better long-term prognosis than solid pNETs.

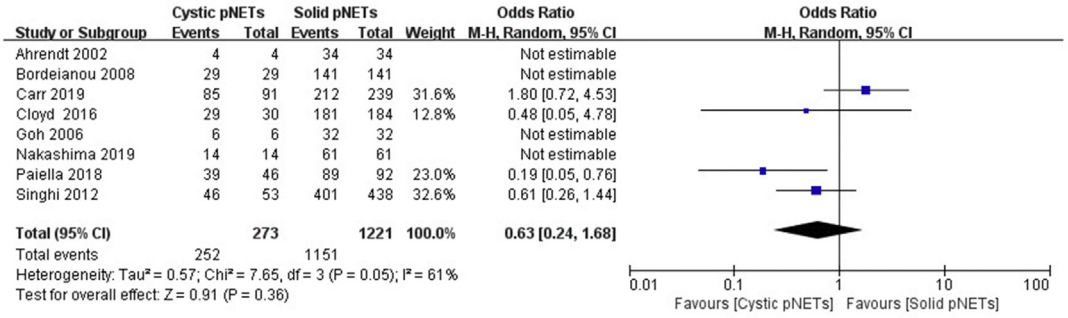
The proportion of cystic pNETs among all patients with pNETs varies significantly among the studies (6.5%–36.1%), and we observed an increasing ratio of cystic to solid pNETs in more recent studies. For example, studies published in 2017 [9] report 36.1% patients with cystic pNETs vs 6.5% in 2002[10], which may be explained by the development and wide use of cross-sectional imaging in clinical practice. Asymptomatic, incidental pancreatic cystic lesions are increasingly detected and surgically resected because of worrisome features revealed by imaging or those that are confirmed by biopsy cytology. Moreover, these studies were conducted at high-volume academic centers specializing in pancreatic disease, which may introduce selection bias. Another important reason for this variation is the definition of “cystic”. Most studies confirmed the diagnosis according to the presence of cystic lesions detected by preoperative imaging, whereas other studies identified cystic components according to pathology. Microscopic



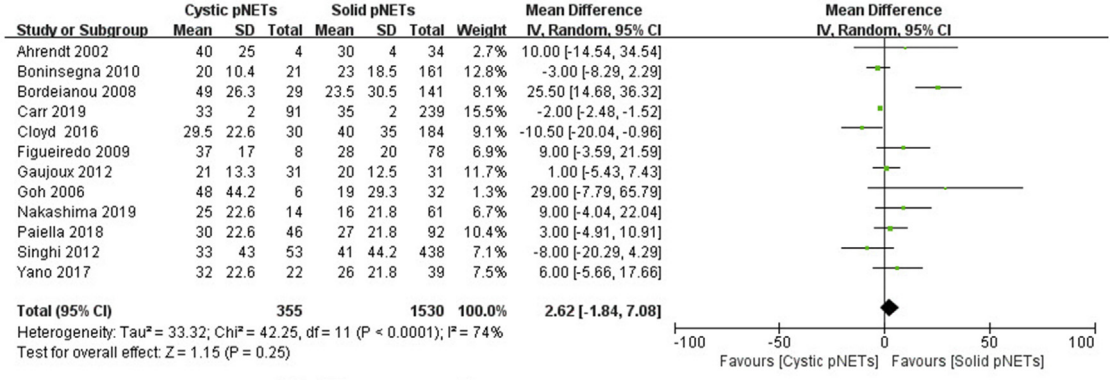

A. Presence of symptoms




B. Tumor location




C. Single lesion




D. Tumor size

**Fig. 3.** Forest plots showing a meta-analysis of the presence of symptoms (A), tumor locations (B), percentages of single lesions (C), and tumor sizes (D) of cystic pNETs vs solid pNETs.

**Table 3**
Pathological characteristics comparison between cystic and solid pNETs.

| Pathological characteristics | Included studies | Patients | Cystic pNETs (%) | Solid pNETs n (%) | OR (95% CI) | P value |
|---|---|---|---|---|---|---|
| Synchronous distant metastasis | 8 | 1566 | Yes: 22 (22/302, 7.3%)<br>No: 280 (280/302, 92.7%) | Yes: 211 (211/1264, 16.7%)<br>No: 1053 (1053/1264, 83.3%) | 0.48 (0.30–0.78) | 0.003 |
| Lymph node metastasis | 8 | 1654 | Yes: 51 (51/313, 16.3%)<br>No: 262 (262/313, 83.7%) | Yes: 383 (383/1341, 28.6%)<br>No: 958 (958/1341, 71.4%) | 0.54 (0.39–0.75) | 0.0003 |
| Vascular invasion | 7 | 1332 | Yes: 30 (30/224, 13.4%)<br>No: 194 (194/224, 86.6%) | Yes: 342 (342/1108, 30.9%)<br>No: 766 (766/1108, 69.1%) | 0.38 (0.19–0.77) | 0.007 |
| Perineural invasion | 4 | 918 | Yes: 12 (12/143, 8.4%)<br>No: 131 (131/143, 91.6%) | Yes: 204 (204/775, 26.3%)<br>No: 571 (571/775, 73.7.2%) | 0.27 (0.15–0.51) | <0.0001 |
| Tumor grading | 8 | 1484 | G1&G2: 252 (252/308, 81.8%)<br>G3: 56 (56/308, 18.2%) | G1&G2: 941 (941/1176, 80.0%)<br>G3: 235 (235/1176, 20.0%) | 1.66 (1.09–2.52) | 0.02 |
| Tumor necrosis | 3 | 743 | Yes: 8 (8/89, 9.0%)<br>No: 81 (81/89, 91.0%) | Yes: 95 (95/654, 14.5%)<br>No: 559 (559/654, 85.5%) | 1.29 (0.18–9.18) | 0.80 |
| TNM stage | 4 | 1089 | I&II: 154 (154/173, 89.0%)<br>III&IV: 19 (19/173, 11.0%) | I&II: 703 (703/916, 76.7%)<br>III&IV: 213 (213/916, 23.3%) | 2.32 (1.36–3.95) | 0.002 |
| Ki-67 index | 4 | 1141 | <2%: 138 (138/211, 65.4%)<br>>2%: 73 (73/211, 34.6%) | <2%: 459 (459/930, 49.4%)<br>>2%: 471 (471/930, 50.6%) | 2.52 (1.77–3.60) | <0.00001 |
| Mitotic count | 4 | 1065 | <2%: 140 (140/196, 71.4%)<br>>2%: 56 (56/196, 28.6%) | <2%: 537 (537/869, 61.8%)<br>>2%: 332 (332/869, 38.2%) | 2.75 (1.09–6.93) | 0.03 |

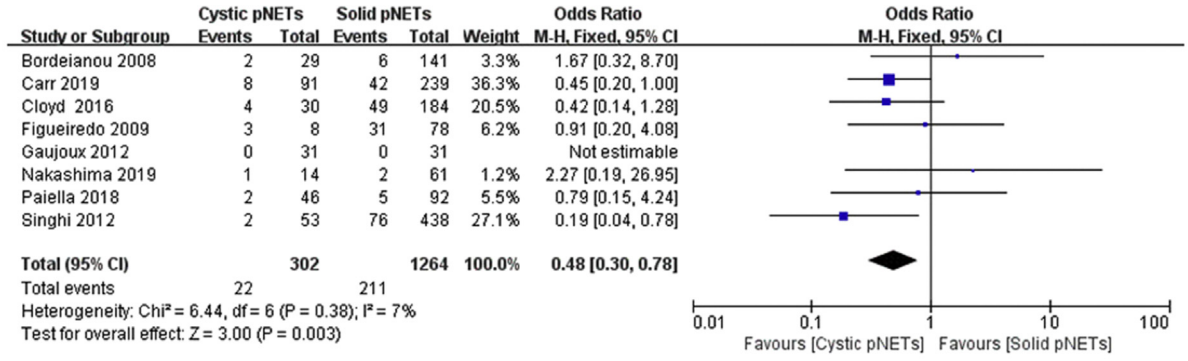
cystic components detected by pathology may present as solid lesions on CT scans, which may contribute to the inconsistency of reported rates of cystic disease. For example, Yano et al. [9] conducted a CT and pathology correlation analysis of cystic pNETs and found that imaging detects 36.1% (22/61) of pNETs with cystic components, while pathological examinations detect 58.3% (35/60) of tumors with cystic components. Further, 33.3% and 25.0% are microscopically cystic or macroscopically cystic, respectively. Accurate definition and the degree of classification criteria employed in preoperative imaging and pathology may help determine the true incidence of cystic pNETs.

Three of 12 studies analyzed here found a moderate male predominance of cystic pNETs, which was confirmed by our present meta-analysis. The entire population of pNETs shows a slight preponderance of men [25]. In Cloyd's study [15], the proportion of men with cystic pNETs was significantly higher compared with those with solid pNETs (73.3% vs 50.5%), which increases proportionately with the degree of cystic components (87.5% in male patients with purely cystic lesions). Few mechanisms have been suggested to explain these findings. Male sex hormones may contribute to carcinogenesis and cystic degeneration of pNETs [22]. A recent published study with 92 cystic pNETs patients found that age was older in cystic than solid pNETs. However, no significant difference was found in the present meta-analysis. Tumor size is considered as a pivotal factor for evaluating biological behavior and risk of recurrence of pNETs [26–28], and tumors >2.0 cm are associated with more aggressive behavior [27]. The comparisons of tumor sizes between cystic and solid pNETs vary among the selected studies. Some studies confirmed larger tumor size in cystic pNETs, however, the grading stage, lymph node metastasis, microvascular invasion and prognosis had no difference with solid pNETs [14,22]. In contrast, Cloyd et al. [15] observed smaller tumors in purely or mainly cystic pNETs, which are associated with more favorable clinicopathological features and long-term prognosis. This inconsistency may be explained by selection bias. All these included tumors were surgical resected. Pancreatic cystic neoplasms are less likely to be malignant, and surgeons therefore prefer to remove smaller solid rather than cystic lesions. Asymptomatic patients or those without worrisome imaging features with cystic lesions <3 cm are generally recommended to undergo close surveillance. Further, much smaller incidental cystic lesion are diagnosed and resected because of the use of advanced imaging techniques, which may explain the conflict with the conclusions of earlier studies. Thus, tumor size and degree of cystic components should be both considered when evaluating biological behavior [22].

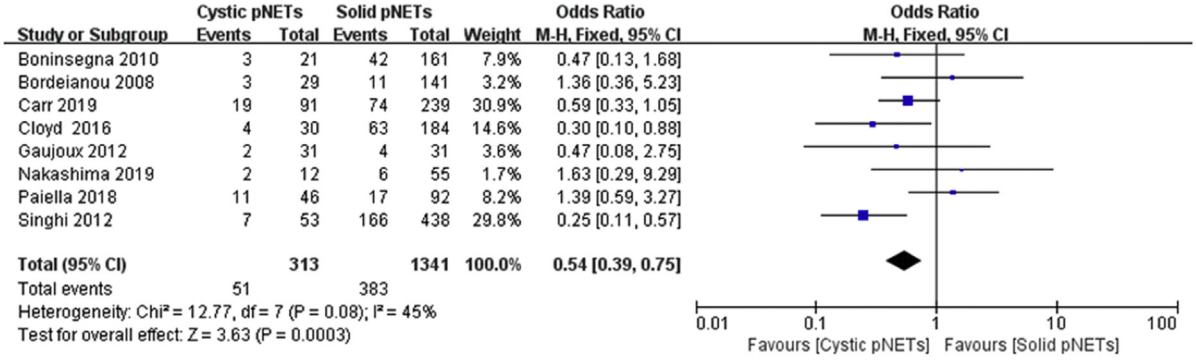
Our study shows that cystic pNETs were more likely to be nonfunctional, while the frequency of reported symptoms upon diagnosis was not significantly different between the two groups. Compared with functional pNETs, nonfunctional pNETs usually present as a larger tumor with aggressive behavior [5]. Asymptomatic patients with cystic pNETs are usually diagnosed incidentally, and nonspecific symptoms may be apparent only when patients harbor large tumors that may subsequently compress adjacent tissues. In the present study, we analyzed papers published from 1977 to 2017, during which time the strategy for treating pancreatic cystic lesions was significantly modified. Asymptomatic patients with solid pNETs are usually recommended to undergo resection, while surgical resection is only recommend for symptomatic patients with cystic lesions or those with high-risk features revealed by CT or MRI. These selection and confounding biases should be considered. Another important finding of our study was the strong association between cystic pNETs and MEN-1, which was not established in a previous meta-analysis [8]. More studies and patients were included here (7 vs 4 studies, 224 vs 113 patients), which we believe improved the validity of the statistical analyses. The association of cystic pNETs with MEN-1 was first reported by Blandine Ligneau et al., in 2001 [29] and was subsequently confirmed [14,23], although other studies did not find this association [6,21–23]. The underlying mechanism is unknown, and further molecular investigations should be conducted to establish this association.

Cystic pNETs are more likely to be located in the pancreatic body or tail, which may be attributed to selection bias. Morbidity and mortality associated with resection of the pancreatic head or enucleation of tumors in the proximal pancreas are much higher compared with those involving the distal pancreas. Surgeons therefore prefer to observe cystic lesions in the head of pancreas rather than performing a resection, which accounts for the predominant proportion of cystic pNETs resected in the pancreatic body or tail.

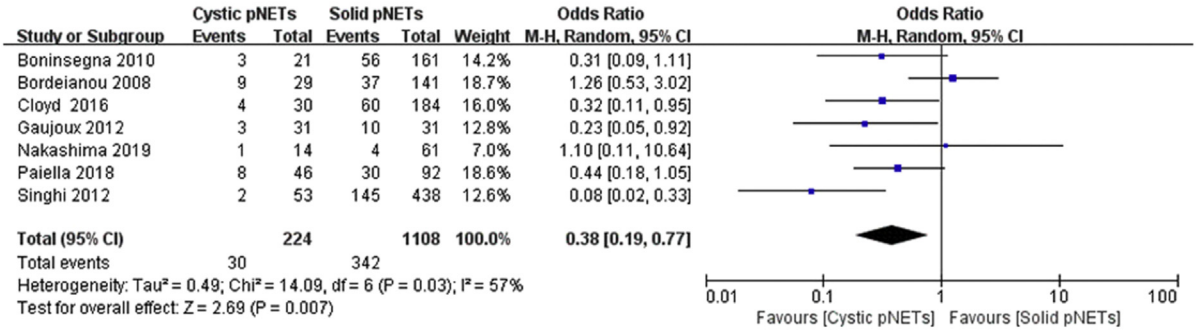
We show here that cystic pNETs are distinct entities with a less aggressive biological behavior compared with solid pNETs. Cystic pNETs are less likely to represent synchronous distant metastasis, lymph node involvement, microvascular invasion, or perineural invasion, which is consistent with the findings of a previous meta-analysis [8]. A low Ki-67 index and low mitotic counts are more commonly associated with cystic pNETs. These results are



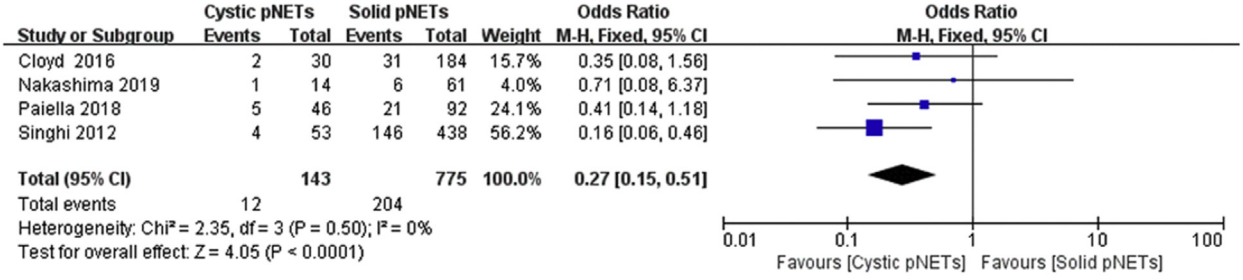

A. Synchronous distant metastasis




B. Lymph node metastasis

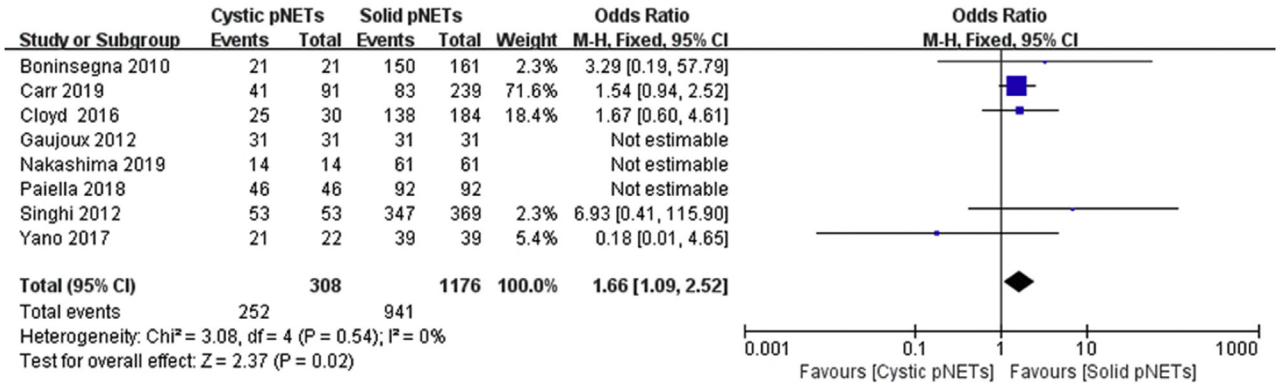



C. Vascular invasion

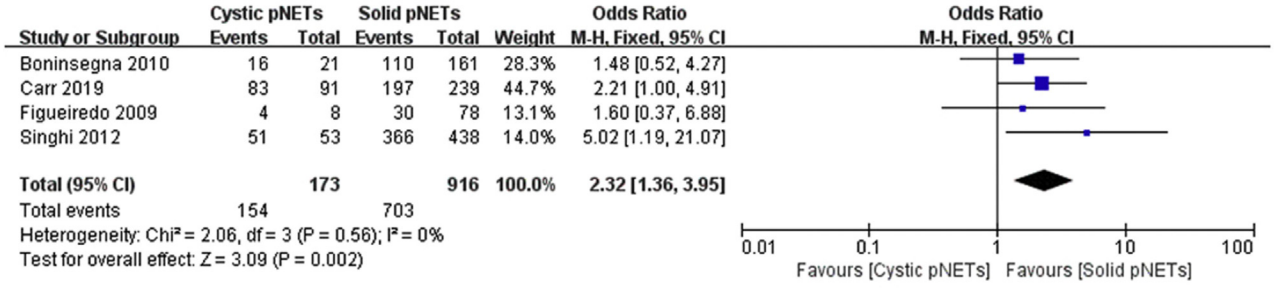



D. Perineural invasion

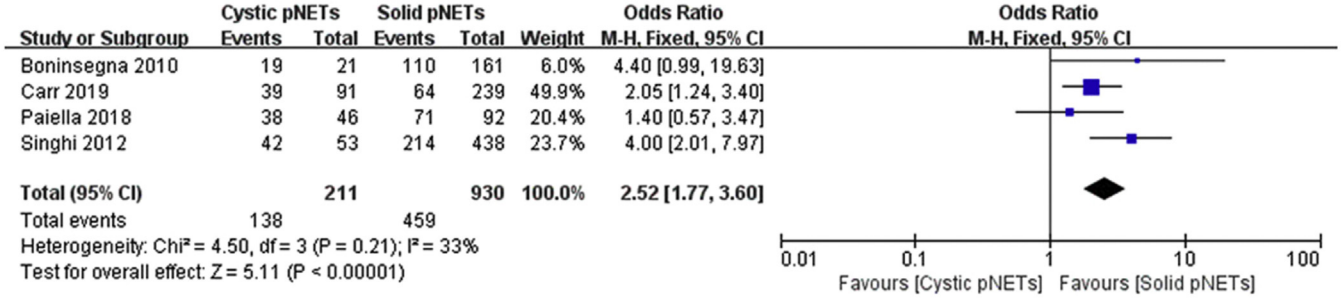
**Fig. 4.** Forest plots illustrating the results of a meta-analysis of distant metastasis (A), lymph node metastasis (B), vascular invasion (C) and perineural invasion (D) of cystic vs solid pNETs.



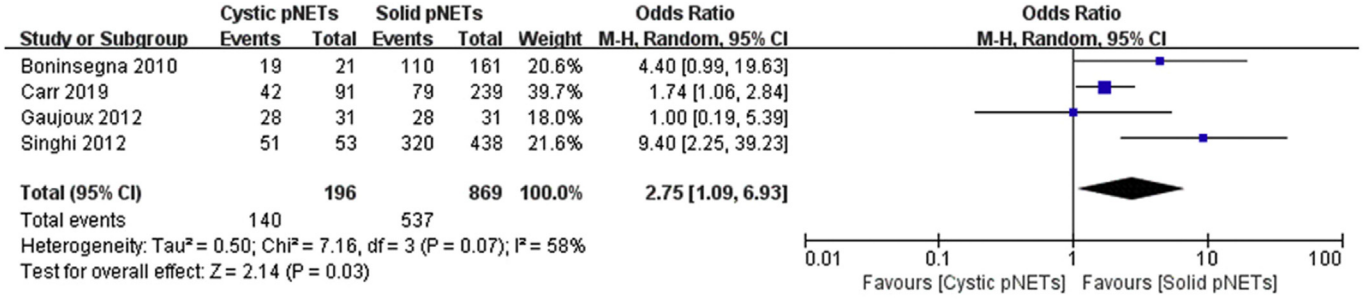

A. G1&G2




B. TNM I & II

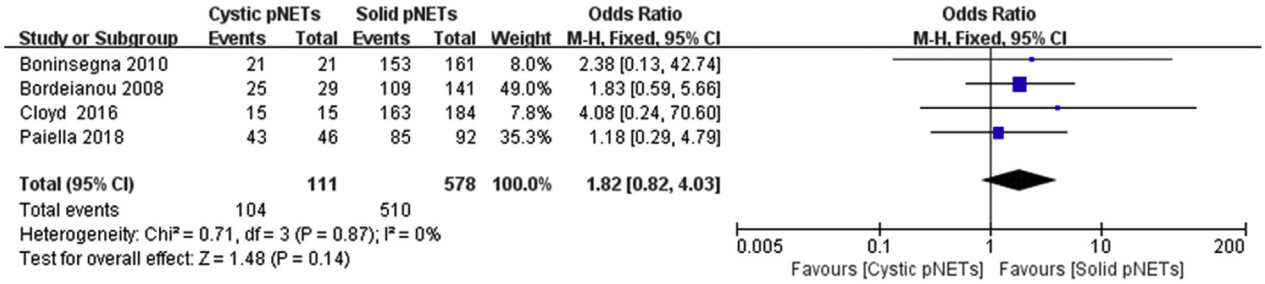



C. Ki-67< 2%

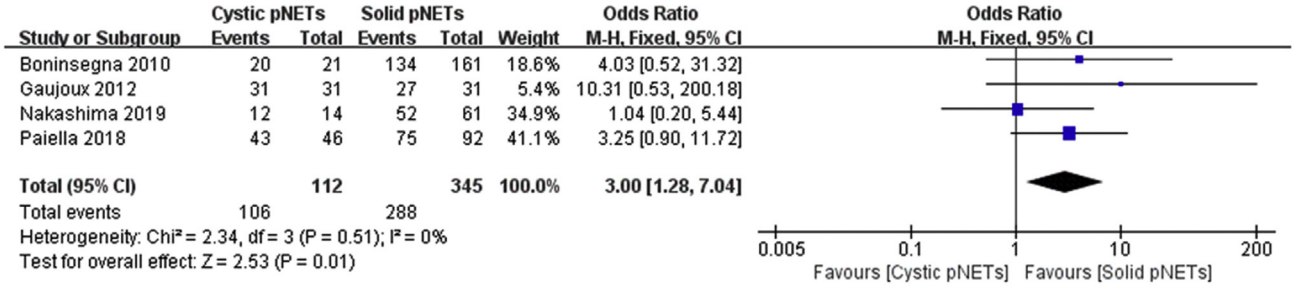



D. Mitotic count < 2 mitoses/ 10 HPF

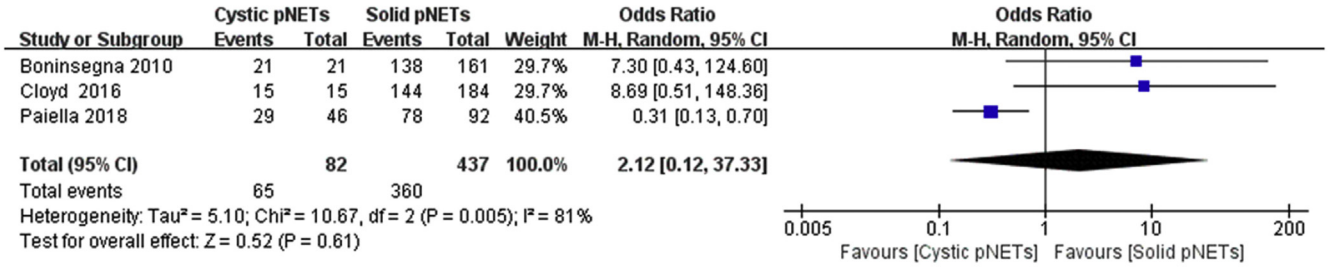
**Fig. 5.** Forest plots showing a meta-analysis of tumor grading (A), TNM stages (B), Ki-67 indexes (C), and mitotic counts (D) of cystic pNETs vs solid pNETs.



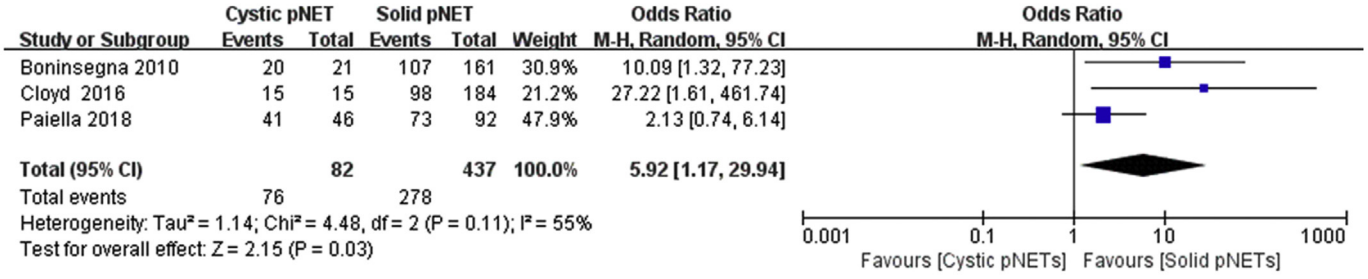

A. 5-year OS




B. 5-year DFS




C. 10-year OS




D. 10-year DFS

**Fig. 6.** Forest plots showing a meta-analysis of long-term survival of cystic pNETs vs solid pNETs. A. 5-year OS, B. 5-year DFS, C. 10-year OS, and D. 10-year DFS.

significant, because they provide strong evidence to resolve the controversy of whether cystic pNETs represent a distinct subgroup of pNETs. Because of their indolent behavior, different treatment strategies are recommended for treating cystic pNETs [20,21]. Instead of surgical resection, some selected patients, particularly those with purely cystic pNETs, can be safely managed with only surveillance [15,20,21]. Considering the low rate of lymph node metastasis and perineural invasion, organ and function-preserving surgical procedures such as tumor enucleation and spleen-preserving distal pancreatectomy can be performed to reduce adverse outcomes, which will ensure the quality of life of selected patients with cystic pNETs.

Risk stratification according to malignant potential should be considered in the management of patients with cystic pNETs,

**Table 4**
Long-term survival comparison between cystic and solid pNETs.

| Long-term outcome | Included studies | Patients | Cystic pNETs n (%) | Solid pNETs n (%) | OR(95% CI) | P value |
|---|---|---|---|---|---|---|
| 5-year OS | 4 | 689 | Alive: 104 (104/111, 93.7%)<br>Died: 7 (7/111, 6.3%) | Alive: 510 (510/578, 88.2%)<br>Died: 68 (68/578, 11.8%) | 1.82 (0.82–4.03) | 0.14 |
| 5-year DFS | 4 | 457 | No recurrence: 106 (106/112, 94.6%)<br>Recurrence: 6 (6/112, 5.4%) | No recurrence: 288 (288/345, 83.5%)<br>Recurrence: 57 (57/345, 16.5%) | 3.00 (1.28–7.04) | 0.01 |
| 10-year OS | 3 | 519 | Alive: 65 (65/82, 79.3%)<br>Died: 17 (17/82, 20.7%) | Alive: 360 (360/437, 82.4%)<br>Died: 77 (77/437, 17.6%) | 2.12 (0.12–37.33) | 0.61 |
| 10-year DFS | 3 | 519 | No recurrence: 76 (76/82, 92.7%)<br>Recurrence: 6 (6/82, 7.3%) | No recurrence: 278 (278/437, 63.6%)<br>Recurrence: 159 (159/437, 36.4%) | 5.92 (1.17–29.94) | 0.03 |

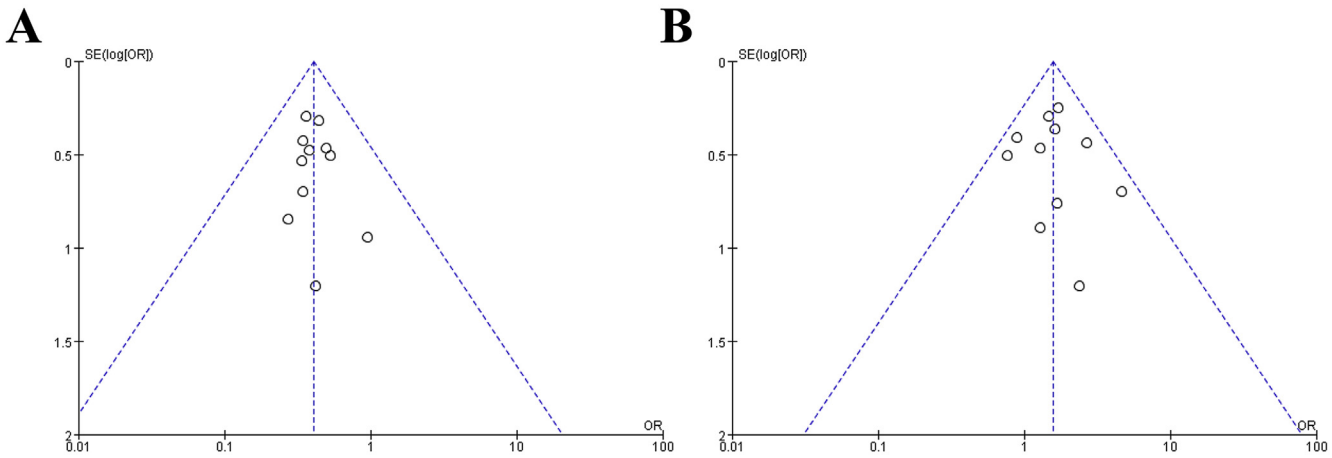



**Fig. 7.** Assessment of publication bias using funnel plots of included studies reporting on tumor location (A) and gender distribution (B).

similar to those with other pancreatic cystic lesions. However, preoperative diagnosis of this disease is nevertheless challenging [30,31]. Nearly 50% of patients are misdiagnosed before surgery, even when they are treated in high-volume centers specializing in pancreatic tumors [6,21]. Rare functional, incidentally diagnosed, and nonspecific symptoms make it difficult to distinguish cystic pNETs from other common pancreatic cystic lesions. EUS and EUS-FNA accurately diagnose pNETs. For example, the cumulative sensitivity of EUS for diagnosing pNETs is 87.2% with a specificity of 98.0% [32]. EUS imaging and cytology are the most accurate diagnostic methods, achieving a specific diagnosis of cystic pNETs of 71% of biopsies compared with 38% of patients examined using only EUS [33]. Subsequent studies confirm the significant role of EUS and EUS-fine needle aspiration (FNA) in differentially diagnosing cystic pNETs [34,35]. EUS-FNA is technically challenging, and the diagnostic accuracy of EUS and EUS-FNA depends on the experience of the operators. Appropriate training is required, and communication with the pathologist is recommended to optimize analyses [36–38].

The long-term prognosis of cystic pNETs was believed to be similar to that of solid pNETs [8,21]. We show here that despite our findings that there were no significant differences in 5-year OS and 10-year OS, the 5-year DFS and 10-year DFS of patients with cystic pNETs was significantly longer. Favorable, less aggressive biology may explain the low recurrence rate after surgical resection. However, survival data were available in only 6 studies, and therefore the small sample size may not reflect actual long-term outcomes of patients with cystic pNETs. Multicenter studies of more patients may more accurately determine the long-term prognosis of such patients.

Two main hypotheses may explain the pathogenesis of cystic pNETs. Kamisawa et al. [11] suggest a mechanism involving tumor infraction and subsequent necrosis caused by an insufficient blood supply and the fibrous capsule. However, tumor necrosis is rare [6,15], and there is no significant difference between necrosis of cystic and solid pNETs, even higher in patients with solid pNETs (8.99% vs 14.52%) as shown here. In addition, previous study revealed that cystic components may associate with increasing tumor size [39], but tumor size of cystic pNETs was reported to be comparable or even smaller than that of solid pNETs [6,8,15,20]. Instead of necrotic debris, the cavity of cystic pNETs was filled with clean fluids [40]. These findings did not support this hypothesis. The second hypothesis maintains that intratumor hemorrhage follows cystic degeneration [12]. Data for hemorrhage were not available in the studies analyzed here, which obviously precludes concluding that hemorrhage causes, or is the consequence, of cyst development [6]. Malignant degeneration of pancreatic pseudocysts or combination of the above mechanisms were also hypothesized to explain the incidence of cystic pNETs [7]. Validating either hypothesis requires identification of the molecular mechanism underlying the pathogenesis of cystic pNETs.

The major strength of this study is its detailed comparisons of studies that explore the differences in clinicopathological features between cystic and solid pNETs. To our knowledge, the present study analyzed the largest sample size of any study identified by our initial literature search. Moreover, we meticulously matched the design of our analytical techniques to minimize reduce inconsistencies. Thus, we believe that our findings are more convincing than those of descriptive studies [9,19,20]. Further, we analyzed the long-term survival of patients with cystic pNETs and found, for the first time to our knowledge, that their 5-year and 10-year DFS was much better in cystic pNETs than their solid counterparts. This finding contributes strong evidence supporting the conclusion that the biological behavior of cystic pNETs is less

aggressive compared with that of solid pNETs.

Due to the retrospective design, heterogeneity existed between these 12 studies. The selection of studies conducted from 1977 through 2017, during which time the treatment strategies greatly improved, which may have biased the results. Further, only patients who underwent surgical resection were evaluated, introducing intrinsic selection bias, which may account for some of the observed differences, for example, in tumor location and size. Finally, the included studies had different study purpose and design, data of key outcomes was not available in every study. Meanwhile, variation of patient selection and raw data collection may also have important influence on the statistical results. For instance, only 3 studies among these 12 studies reported the 10-year DFS information, high heterogeneity was observed ($I^2 = 55\%$), the statistical result may not reflect the real survival condition of cystic pNETs. These conclusions should be read discerningly. It is important that future studies of larger numbers of patients include detailed follow-up information to further evaluate the biological behavior and long-term prognosis of cystic pNETs.

In conclusion, our comprehensive investigation of the clinical and histopathological characteristics of cystic pNETs establish that cystic pNETs represent a distinct subgroup of pNETs, which presents with indolent biological behavior and longer DFS. These unique features indicate that observation and surveillance should be considered as an alternative to surgery for selected patients, for example, those with purely cystic features and tumors <2 cm. The atypical clinical manifestations of cystic pNETs pose a preoperative diagnostic dilemma, requiring experienced operators to perform EUS-FNA to unambiguously distinguish this disease from other pancreatic cystic lesions. Moreover, identification of the molecular mechanisms may help understand the pathogenesis of cystic pNETs, which will facilitate management of patients with this tumor that is no longer rare.

## Conflicts of interest

The authors declare no conflicts of interest.

## Acknowledgments

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