EUS-Guided FNA for Diagnosis of Pancreatic Cystic Lesions: a Meta-Analysis

Qi-Xian Wang a Jun Xiao a Matthew Orange b Hu Zhang a You-Qing Zhu a

aDepartment of Gastroenterology and Hubei Provincial Center of Clinical Study for Digestive Diseases; Zhongnan Hospital; Wuhan University School of Medicine; Wuhan, Hubei, China
bDepartment of Physical Education and Human Performance, Central Connecticut State University, New Britain, CT (USA)

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Abstract
Background: Preoperative diagnosis of pancreatic cystic lesions (PCLs) must be reliable as the current standard treatment, major or total pancreatectomy, dramatically affects quality of life. Additionally, early diagnosis of malignancy is essential to an improved prognosis. The diagnostic accuracy of fluid analysis using endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) has been demonstrated in pancreatic solid lesions. The utility of this technique in the diagnosis of PCLs is still unknown. Methods: A comprehensive search was performed in multiple databases. Studies differentiating benign and malignant PCLs via EUS-FNA were included in this meta-analysis. The quality of diagnostic accuracy studies (QUADAS) was adopted to evaluate the selected studies. Pooled sensitivity, specificity, likelihood ratio, diagnostic odds ratio, and summary receiver operating characteristic (sROC) curve analyses were conducted. Two main classification types of malignancy were characterized and analyzed. We also generated a subgroup analysis of available clinical factors. Publication bias was evaluated by Begg's and Egger's tests. Results: Sixteen studies containing 1024 subjects have been published. The pooled sensitivity for malignant cytology according to classification 1 was 0.51 (95% CI, 0.45-0.58), and pooled specificity was 0.94 (95% CI, 0.92-0.96). When the detected PCLs were identified as classification 2, suspicious malignancy or potential malignancy, sensitivity and specificity were similar, 0.52 (95% CI, 0.46-0.57) and 0.97 (95% CI, 0.95-0.98) respectively. Conclusion: This meta-analysis demonstrates that EUS-FNA is a reliable clinical tool for the diagnosis of PCLs. However, a more accurate algorithm is needed to reduce various biases and to improve the sensitivity of EUS-FNA in the detection of malignant PCLs.
Introduction

Pancreatic cystic lesions (PCLs) comprise a diverse group of histopathologic bodies possessing varying degrees of malignancy. The majority of PCLs (80%-90%) are pseudocysts (PC), the remainder are mucinous neoplasms (MCNs, including mucinous cystadenomas (MCyA) and mucinous cystadenocarcinomas (MCyA-CA)), intraductal papillary mucinous neoplasms (IPMN), or serous cystadenomas (SCyA) [1-3]. In the premalignant stage, the five-year survival rate for patients with MCNs and IPMNs is nearly 100%. With the development of an invasive carcinoma, the survival rate drops significantly, down to 37.5%-57.5% [4]. Most PCLs, save for SCyA, are recommended for resection due to their tendency to be malignant. However, a dilemma arises with patients at an increased risk for postsurgical complications. For this reason, it will be beneficial to determine malignancy of PCLs before operations.

As a minimally invasive diagnostic tool, endoscopic ultrasonography-fine needle aspiration (EUS-FNA) provides investigators with cyst fluid for chemical and cytological analyses [5]. As the cytology may assist diagnosis of PCLs, thus providing surgeons with critical information, EUS-FNA has recently attracted more attention, particularly to those interested in researching pancreatic cystic neoplasms.

The international consensus guidelines for management of IPMN and MCN have proposed to include examination by way of EUS-FNA [6]. However, as PCLs, as a category, contain more lesions of the PC and MCyA types than IPMN/MCN, misdiagnoses by various image modalities, including EUS-FNA, occur. As a result, despite published literature evaluating EUS-FNA on pancreatic mucinous neoplasm, and meta-analysis suggesting that it achieved low sensitivity and high specificity [7], it is still necessary to conduct a meta-analysis evaluating the use of EUS-FNA in detecting malignancy of PCLs.

Materials and Methods

Study selection and subgroup categories

Prior to conducting a literature search, we agreed to include only those studies that met all of the following criteria: (1) analyzed cytology from EUS-FNA on subjects for diagnosis of pancreatic cystic lesions (or separately reported PCLs from others); (2) published in English; (3) utilized, as a gold standard, surgical histology or clinical follow-up of at least 6 months to confirm EUS-FNA findings [8, 9]; (4) included at least 15 patients with cystic neoplasm; (5) presented sufficient data for the calculation of sensitivity and specificity.

We excluded studies that met any of the following criteria: (1) review articles, case reports, letters to the editor, brief communications, or rapid communications; (2) studies that used specimens from CT guided or abdominal ultrasound or from percutaneous puncture; (3) studies that used conclusions from EUS-FNA as the gold standard without final confirmation by histology or clinical follow-up; (4) studies with insufficient data; (5) studies that did not analyze cytology results, but instead based conclusions solely on EUS-FNA cyst fluid analysis; (6) studies in which “Y” of QUADAS analysis was less than 8 of 14.

Ambiguity regarding definite malignancy of cytology diagnoses occurred because, while some articles reported PCLs as malignant, others reported cytology diagnoses as non-diagnostic, benign, atypical, suspicious, potential, or malignant. To avoid divergence of positive results and to reduce any intrinsic heterogeneity (showed in Table 1), we predefined two classifications similar to those of Hewitt [8]. Classification 1—a highly stringent analysis based only on malignant cytology results; classification 2—a cautious evaluation method aiming to recognize a larger number of malignant results, that is, classify atypical and suspicious cytology results as malignant results. The histopathological determination of malignancy also referred to this classification. Additional information from each article was collected, including publication year, location, number of medical centers, patients and clinical experts, study design and time interval from EUS-FNA to pathological diagnosis, needle size, average number of needles for each case, successful aspiration rate, age, ratio of male: female patients, and the presence of an onsite cytopathologist. Subsequently, subgroup analysis was performed based on the obtained information.
Table 1. Unified standard of malignancy classification of FNA cytology (applied to clinical terminal diagnosis as well)

| Classification 1 | Classification 2 |
|------------------|------------------|
| **Negative**     | simple cyst, pseudocyst, atypical, serous cystadenoma, low/moderate dysplasia, non-diagnostic |
| pseudocyst, serous cystadenoma, non-diagnostic, low-grade/moderate dysplasia, mucinous cystadenoma or borderline neoplasm, atypical or suspicious for malignancy, all unclear described and premalignant IPMN/MCN | non-diagnostic, low/moderate dysplasia, non-diagnostic |
| **Positive**     | high-grade dysplasia, carcinoma in situ, invasive carcinoma | high-grade dysplasia, invasive carcinoma, suspicious for malignancy, described as potential malignant (mucinous cystadenoma, intraductal papillary mucinous tumor, cystic islet cell tumor, cystic adenocarcinoma), solid pseudopapillary tumor |

**Literature search**

A comprehensive search of literature published through May of 2014 was performed in multiple databases, including PubMed, Medline, Scopus, Web of Science, EMBase and the Cochrane Library. Search terms used were “‘endoscopic ultrasound-guided fine needle aspiration’ OR ‘(eus’ AND ‘fna’) OR ‘eus fna’” AND “(pancreas’ OR ‘pancreatic’) AND cystic”. In order to expand our search, we also inspected and included relevant articles mentioned by the studies originally identified by our parameters. Articles from the same research institutions and same authors were cautiously investigated to avoid data duplication.

Two investigators (Xiao J and Wang XQ) independently searched the literature, screened studies that met our criteria, and discussed their findings in order to reach an agreement. The aforementioned investigators and a third (Zhang H), each independently extracted data from these studies. Any disagreements during this procedure were resolved by an arbiter (Zhu IQ).

**Quality of studies**

The quality of diagnostic accuracy studies (QUADAS) tool [10] was adopted in order to evaluate the selected studies. In this assessment, 14 items were evaluated and each was either valued as “yes,” when positive or “no,” when unsupported or “unclear” due to unavailable and/or insufficient information.

**Statistical methods**

First, we performed this meta-analysis by calculating pooled sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratio (DOR). Heterogeneity among various studies was assessed using $\chi^2$ statistics [11, 12]. $I^2$>50% was considered significant heterogeneity, while research in which $I^2$<50% was considered statistically homogeneous. The “DerSimonian-Laird” method was used as a random-effect model whenever there was found to be significant heterogeneity. To the contrary, when there was no significant heterogeneity, the “Mantel-Haenszel” pooling method, a fixed-effect model, was applied [13]. Secondly, a summary receiver operating characteristic (sROC) curve was drawn. A value for the area under the curve (AUC) close to 1 would indicate that EUS-FNA is a well-validated tool for diagnosis of PCLs. Next, meta-regression analysis was performed to explore potential causes of heterogeneity according to the characteristics of the study. The Spearman coefficient, reflecting the correlation between log(sensitivity) and log (1-specificity), was performed to test the threshold effect. Finally, subgroup analyses [14] and analysis of sensitivity were performed. Each of these described statistical procedures was performed using Meta-DiSc freeware software version 1.4 (Ramony Cajal Hospital, Madrid, Spain).

Publication bias analysis was performed using the Begg’s [15] and Egger’s [16] tests with Stata software version 11.0 (Stata Corporation, College Station, Texas). When a count of zero occurred in the dataset, a continuity correction of 0.5 was applied to all values in order to permit subsequent calculations [7]. A continuity corrected P<0.05 indicated the presence of publication bias.

**Results**

**Systematic review**

The original search, using the previously defined search terms, yielded 247 studies, among which, 126 were thoroughly reviewed. We retrieved 18 articles published between
Fig. 1. Flowchart demonstrating the algorithm for identifying papers suitable for inclusion.

Table 2. Characteristics of included studies and the derived 2x2 table. NA: not available; m: month; y: year; * data for classification 2; # data from studies that combine cytology with cystic fluid analysis

| Studies          | Classification | Location | Center | Experts participated EUS-FNA | Design       | Duration | Cytopathologist | Needle |
|------------------|---------------|----------|--------|-------------------------------|--------------|----------|-----------------|--------|
| Maker AV[20]     | 1             | USA      | 2      | NA                           | Retrospective| 91 m     | NA              | 22     |
| Maker AV[28]*    | 2             |          |        |                               |              |          |                 |        |
| Zhan XB[20]      | 1             | China    | 1      | 2                            | Retrospective| 53 m     | YES             | 19,22  |
| Zhan XB[20]* #   | 1             |          |        |                               |              |          |                 |        |
| Ozmen D[27]*     | 1 or 2        | Turkey   | 1      | 2                            | Retrospective| 57 m     | NA              | 22     |
| Zhai H[19]       | 1             | USA      | 1      | 2                            | Retrospective| 17 y     | NA              | NA     |
| Linder [D17]* #  | 1             | USA      | 1      | 1                            | Retrospective| 53 m     | NA              | 19,22  |
| Linder [D17]* #  | 2             |          |        |                               |              |          |                 |        |
| Cagno L[29]*     | 1 or 2        | USA      | 1      | NA                           | Prospective  | >9 y     | NO              | 19,22  |
| Sawhney MS[25]   | 1             | USA      | 1      | 1                            | Retrospective| 1 y      | NA              | 22,25  |
| Brandwein SL[26] | 1             | USA      | 1      | 1                            | Retrospective| 3 y      | partly           | 22     |
| Zhang S[50]      | 1             | USA      | 1      | 2                            | Retrospective| 63 m     | YES             | NA     |
| Zhang S[50]*     | 2             |          |        |                               |              |          |                 |        |
| Pang [CI23]      | 1             | USA      | 1      | 1                            | Retrospective| 14 y     | partly           | NA     |
| Pang [CI23]* #   | 2             |          |        |                               |              |          |                 |        |
| Pittman MB[24]*  | 1 or 2        | USA      | NA     | Retrospective                | NA           | NA       | NA              | NA     |
| Attarasanaya S[22] | 1 or 2 | USA   | 1      | 7                            | Retrospective| 100 m    | YES             | 22     |
| Maire F[21]*     | 1             | France   | 1      | 1                            | Retrospective| 12 y     | NA              | 22     |
| Maire F[21]*     | 1             |          |        |                               |              |          |                 |        |
| Pais SA [18]     | 1             | USA      | 1      | 6                            | Retrospective| 112 m    | YES             | 22     |
| Quan H[31]*      | 2             | USA      | 1      | NA                           | Retrospective| 77 m     | NA              | 22     |
| Sedlack R[32]*   | 2             | USA      | 1      | NA                           | Retrospective| 98 m     | NA              | 22     |
| Frossard LI[33]  | 2             | France   | 1      | NA                           | Retrospective| 48 m     | NA              | 22     |
| Woolf KM[34]*    | 2             | England  | 1      | 3                            | Retrospective| 6 y      | NA              | NA     |

2001 and 2014 for final analysis (see Fig. 1 for a detailed screening flow chart). A total of 1024 patients, with a median number of 57 (range 20-198) per study, were included in...
our meta-analysis. Time interval for the selected studies ranged from 1 to 17 years. Of the 18 articles, 17 were retrospective studies, 12 covered almost all types of PCLs, 3 studies excluded IPMN [17-19], and 3 [18, 20, 21] specifically studied IPMN. As obtaining cytological samples from EUS-FNA may not have been the original intention of many of these studies, the ratio of qualified aspiration varies; some reached 100% [18, 20, 22-26], but, even at its lowest, it was within 66% [27]. Detailed information from each article is summarized in Table 2. There were no reports of severe complications during any of the procedures in the included articles.

**Quality of studies**

detailed information regarding quality of the selected studies is listed in Table 3. Items 2, 3, 7, and 12 are those most commonly valued "yes;" items 4 and 11 are those most often valued "unclear;" the remaining items are those most frequently valued "no." Overall, each selected study scored "yes" on 8-13 items, suggesting good quality of data collection.

**Meta-analysis**

Cytology classification 1. Forest plots of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, DOR, and the sROC curve of EUS-FNA-based cytology, or cytology combined with cystic fluid analysis, are shown in Fig. 2. Here, we classified high-grade dysplasia and carcinoma in situ, or invasive carcinoma, as the determinant of a positive result. As shown in Fig. 2, pooled sensitivity and specificity are 51% (95% CI, 0.45-0.58) (Fig. 2a) and 94% (95% CI, 0.92-0.96) (Fig. 2b) respectively. If both sensitivity (74.6%) and specificity (80.1%) is >50%. As such, we conducted a more cautious analysis using a random-effect model. The asymmetrical sROC curve (Fig. 2e), displaying a "shoulder arm" distribution pattern, suggested to us the presence of threshold effect. Further analysis enhanced this judgment. For instance, Spearman’s rank coefficient is 0.514 with a significant P value of 0.042. The AUC for classification 1 is 0.90 (standard error = 0.0276), indicating that EUS-FNA has a great value for diagnosing malignant PCLs. For this classification, the pooled positive LR is 7.62 (4.58-12.67), the pooled negative LR is 0.50 (0.39-0.64), and the DOR is 23.91 (14.09-40.59).
Table 3. Quality of studies using the QUADAS tool. Y, Yes; N, no; U, unclear. Item 1. Was the spectrum of patients representative of the patients who will receive the test in practice? Item 2. Were selection criteria clearly described? Item 3. Is the reference standard likely to correctly classify the target condition? Item 4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? Item 5. Did the whole sample or a random selection of the sample receive verification by using a reference standard of diagnosis? Item 6. Did patients receive the same reference standard regardless of the index test result? Item 7. Was the reference standard independent of the index test? Item 8. Was the execution of the index test described in sufficient detail to permit replication of the test? Item 9. Was the execution of the reference standard described in sufficient detail to permit its replication? Item 10. Were the index test results interpreted without knowledge of the results of the reference standard? Item 11. Were the reference standard results interpreted without knowledge of the results of the index test? Item 12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? Item 13. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? Item 14. Were withdrawals from the study explained?

| Items                          | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | ¥% |
|-------------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|
| Maker AV                      | Y | Y | Y | U | Y | Y | Y | Y | N | U | U | Y | Y | Y | 71 |
| Zhang S                       | Y | Y | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 93 |
| Zhang XB                      | N | Y | Y | Y | Y | Y | Y | U | U | Y | Y | Y | Y | Y | 79 |
| Zhai J                        | Y | Y | Y | Y | Y | Y | Y | Y | U | U | Y | Y | Y | 86 |
| Pais SA                       | N | Y | Y | Y | Y | Y | Y | Y | Y | U | U | Y | Y | Y | 93 |
| Oguz D                        | Y | Y | Y | U | Y | N | Y | N | Y | Y | Y | Y | Y | Y | 71 |
| Sawhney MS                    | Y | Y | Y | Y | Y | Y | Y | Y | Y | U | U | Y | Y | Y | 99 |
| Lindor JD                     | Y | Y | Y | U | N | Y | Y | Y | N | Y | Y | Y | Y | Y | 79 |
| Eliginer S                    | Y | Y | Y | Y | Y | Y | Y | N | N | Y | Y | Y | Y | Y | 79 |
| Brandwein SL                  | Y | Y | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 93 |
| Attasaranay S                 | Y | Y | Y | U | Y | Y | Y | Y | N | U | U | N | Y | Y | 64 |
| Maire F                       | N | Y | Y | U | Y | Y | Y | N | Y | N | U | N | N | N | 57 |
| Frossard JL                   | Y | Y | Y | Y | N | N | Y | Y | N | Y | Y | Y | Y | Y | 71 |
| Pang JC                       | Y | Y | Y | Y | N | N | Y | N | U | U | Y | Y | Y | Y | 64 |
| Woof KM                      | Y | Y | Y | U | U | U | U | Y | N | Y | Y | Y | Y | Y | 99 |
| Pitman MB                     | Y | Y | Y | U | U | Y | Y | Y | Y | Y | Y | Y | Y | Y | 93 |
| Sadelack R                    | Y | Y | Y | U | U | Y | U | Y | U | U | N | Y | Y | Y | 64 |
| Qian X                        | Y | Y | Y | Y | N | Y | Y | N | U | U | Y | Y | Y | Y | 64 |

**Cytology classification 2.** Forest plots of sensitivity and other indices were also generated for classification 2. In this classification, we defined PCLs suspicious for malignancy, and those identified as potentially malignant (mucinous cystadenoma, cystic adenocarcinoma, intraductal papillary mucinous tumor, cystic islet cell tumor, solid pseudopapillary tumor), as positive results. There were 12 suitable studies for this analysis. We found that the pooled sensitivity and specificity increased to 52% (95% CI, 0.46-0.57) (Fig 3a) and 0.97 (95% CI, 0.95-0.98) (Fig 3b), that12 is 92.1%, and that specificity is 71.1%. Mannel-Haenszel and DerSimonian-Laird methods were selected for pooling. The sROC curve (Fig 3e) does not show a “shoulder arm” distribution pattern, and Spearman’s correlation coefficient is 0.238 (P=0.457). As a result, we conclude that there is no threshold effect. The AUC is 0.9482 (standard error = 0.0152), the pooled positive LR is 8.83 (5.53-14.08), the pooled negative LR is 0.64 (0.51-0.80), and the DOR is 22.35 (8.74-57.13) for classification 2.

**Subgroup analyses and meta-regression**

We pre-identified several potential sources of heterogeneity: sample size; location of study; single versus multiple medical centers; study design (prospective versus retrospective); number of performers; time interval; EUS-FNA needle size; whether or not cytopathologists were onsite; average age of patient; ratio of male to female patients; Y of QUADAS; successful aspiration rate.
According to classification 2, where atypical and suspiciously malignant PCLs, in addition to high-grade dysplasia and carcinoma were considered positive results, no threshold effect is present. In order to explore the potential sources of heterogeneity, meta-regression analysis of these subgroups was performed (see Table 4).

We analyzed each of the subgroups classified by the 13 potential factors listed above, and, as RDOR for male to female patients is 4.78 (95% CI, 1.14, 20.00) (P=0.035), concluded that gender may be one of the factors that caused heterogeneity. Our analysis indicates that the gender ratio of patients may cause a difference to diagnostic accuracy of up to 4.78 fold. Four studies with a ratio of male to female patients below 1, have a lower pooled sensitivity (0.38) than studies in which the ratio is above 1 (0.62) or is unknown (0.57). Specificity, however, does not vary significantly (below 1=0.97, above 1=0.98, unknown=0.96). The DOR is 15.41 for studies in which the male to female ratio is below 1, 228.05 in studies above 1, and 15.84 when the gender ratio is unknown.

Other factors, described below, can also reduce heterogeneity to within an acceptable range, but our meta-regression analysis did not reveal significant P values. For studies of
Table 4. Predefined subgroup analysis of indices (with 95% confidence intervals) and subsequent meta-regression on DOR (for classification 2)

| Subgroup                          | No. of studies | Pooled sensitivity | P% | Pooled specificity | P% | Pooled DOR | P% | RDOR | P value |
|-----------------------------------|---------------|--------------------|-----|--------------------|-----|------------|-----|------|---------|
| Classification 1                  | 18            | 51(45.58)          | 74.6| 94(92.96)          | 80.1| 23.90(14.09,40.59)| 0   |      |         |
| Classification 2                  | 12            | 52(46.57)          | 92.1| 97(95.98)          | 17.1| 2.28(0.74,57.13) | 48.9|      |         |
| Sample size ≥50                   | 8             | 55(49.61)          | 94.6| 96(94.98)          | 31.0| 29.61(8.70,100.79)| 62.9| 1.00(0.99,1.02)| 0.617 |
| <40                               | 4             | 39(27.52)          | 40.9| 100(92.10)         | 0   | 12.29(2.89,64.09)| 0   |      |         |
| Location                           |               |                    |     |                    |     |            |     |      |         |
| USA                               | 9             | 45(37.49)          | 88.6| 97(94.98)          | 27  | 14.51(8.33,35.52)| 37.3| 3.37(2.72,4.10)| 0.304 |
| other countries                   | 3             | 83(73.91)          | 93.3| 98(90.10)          | 0   | 115.55(62.12,189.3)| 46.9|      |         |
| Centers                            |               |                    |     |                    |     |            |     |      |         |
| Single                             | 11            | 54(48.69)          | 92.5| 97(95.98)          | 23  | 25.61(9.55,68.65)| 51.5|      |         |
| Multiple                           | 1             | 28(12.49)          | NA  | 100(100.10)        | NA  | 3.64(1.76,4.76) | NA  |      |         |
| Design                             |               |                    |     |                    |     |            |     |      |         |
| Retrospective                     | 11            | 56(50.62)          | 92.4| 97(95.98)          | 23.2| 26.02(8.26,81.93)| 53.6|      |         |
| Prospective                        | 1             | 38(26.50)          | NA  | 96(91.99)          | NA  | 15.42(5.27,16.01)| NA  |      |         |
| Length of studies                  |               |                    |     |                    |     |            |     |      |         |
| <100 months                        | 9             | 58(52.65)          | 92.5| 97(94.99)          | 36.7| 34.33(8.21,14.52)| 58.0| 0.39(0.36,1.02)| 0.267 |
| ≥160 months                       | 3             | 35(25.45)          | 92.5| 96(91.98)          | 0   | 12.37(5.57,8.94) | 0   |      |         |
| Needle type                        |               |                    |     |                    |     |            |     |      |         |
| 22                                 | 6             | 61 (52.69)         | 92.6| 98(94.10)          | 0   | 30.99(6.50,157.90)| 40.6|      |         |
| Unknown                            | 4             | 33 (24.43)         | 97 | 97(93.99)          | 66.7| 8.57(3.36,21.86) | 85.3|      |         |
| 19 or 22                           | 2             | 58 (48.67)         | 98  | 96(91.98)          | 0   | 95.06(4.80,61.74)| 4.78(1.14,26.0) | 0.035 |
| Ratio of male to female            | ≥1             | 2                | 62 (50.73) | 98.1 | 98 (94.10) | 77.8 | 220.05(14.41,317.16) | 43.4 |
| Unknown                            | <1             | 4                | 38 (29.48) | 92.9 | 97 (94.99) | 1.5  | 15.94(5.34,14.19) | 52.7 |
| Successful aspiration rate         | ≥0.9, <1      | 5                | 36 (24.10) | 98.0 | 95 (94.99) | 19.9 | 15.52(3.39,333.32) | 0   |
| 0–0.9                             | 4              | 48 (38.76)        | 94.3 | 95 (98.99)        | 46.6 | 44.88(3.91,51.23) | 72.3 |
| Unknown                            | 3              | 49 (42.55)        | 91.6 | 97 (94.99)        | 33.6 | 17.17(3.57,54.85) | 44.5 |
| Whether cytopathologist onsite or not | Yes | 3 | 33 (26.94) | 95 (94.98) | 30.6 | 0.95 (25.7,18.77) | 0 |
| Unknown                            | 8              | 61 (54.67)        | 94.1 | 98 (95.10)        | 4   | 49.99(11.67,241.16) | 45.7 |
| Net                               | 1              | 37 (28.50)        | NA  | 96 (91.99)        | NA  | 14.52(5.23,16.01) | NA  |
| Average age of patients in each study | Available | 6 | 48 (41.55) | 92.5 | 97 (95.99) | 29  | 34.35(6.2,116.52) | 45.9 |
| Unknown                            | 6              | 57 (49.66)        | 92.9 | 96 (91.98)        | 1.5  | 15.84(5.34,6.18) | 53.7 |
| QIADAS of included studies        | ≥10            | 5                | 48 (41.56) | 93.5 | 96 (95.96) | 57.6 | 24.87(5.8,108.61) | 62.8 |
| ≤10                               | 7              | 56 (48.64)        | 92.1 | 97 (94.99)        | 0   | 22.07(5.53,88.08) | 44.2 |
| Experts participated to performing EUS-FNA | ≥2 | 4 | 46 (32.61) | 96 (90.00) | 46.8 | 10.56(3.73,33.08) | 1.3 |
| 1                                 | 2              | 75 (61.86)        | 97.5 | 98 (92.98)        | 0   | 73.64(40.12,1299) | 89.1 |
| Unknown                            | 6              | 48 (41.55)        | 94  | 98 (91.98)        | 20.7 | 24.51(6.13,97.07) | 45.3 |

Sensitivity analysis

We performed sensitivity analysis by identifying the studies that produced edge values as shown in Figure 2 and Figure 3. After excluding the studies of Zhang [30], Linder [17].
heterogeneity remains. This indicates that the pooled diagnostic value of the included studies is stable and reliable.

After exclusion of the studies by Linder [17] and Frossard [33] in classification 2, the remaining studies are homogeneous. However, the sensitivity declines to 0.36, with I² of 0, and specificity is 0.97, with I² of 28.3%. The DOR is 11.76, with I² of 0. Combining subgroup and meta-regression analyses indicates that factors such as gender, sample size, interval time, and others may affect the ability of EUS-FNA to evaluate pre-malignancy and malignancy of PCLs.

Publication bias analysis

The Begg’s funnel plot is symmetric (Fig. 4a). Additionally, valuation of publication bias (Fig. 4b) by Begg’s (P=0.174) and Egger’s (P=0.078) tests indicates that publication bias did not affect the pooled diagnostic accuracy of this meta-analysis.
**Discussion**

Due to its malignancy or its potential to be malignant, patients with pancreatic mucinous neoplasm are recommended to undergo resection therapy [35]. However, for patients with high risk of postsurgical complications, the preoperative determination of malignancy is critical for management of these lesions. We can most benefit from modern medicine if malignant PCLs are removed or monitored and benign PCLs are not exposed to unwarranted surgery or surveillance. Therefore, we are in need of exploring a more accurate and less invasive diagnostic tool. After a comprehensive meta-analysis of diagnostic accuracy, we have demonstrated that EUS-FNA can accurately confirm the presence of malignancy, but does not perform well at excluding malignant or premalignant pancreatic lesions. In clinic
practice, the majority of patients diagnosed with benign lesions such as simple cyst by other convenient inspection before, they do not carry out EUS-FNA and will not undergo surgical resection. Statistically, this have in some degree led to lower sensitivity falsely unavoidably. Thus, EUS-FNA reasonably deserves a higher sensitivity than we have, here, concluded.

In this study, we first conservatively defined only high-grade dysplasia and carcinoma as positive results; we then cautiously classified premalignant and suspicious lesions as positive results. Between these two categories, the sensitivity (94% vs. 97%), specificity (51% vs. 52%), DOR (23.90 vs. 22.35), and AUC (0.9009 vs. 0.9482) varies little. Subgroup analysis reveals gender as a factor that causes heterogeneity between studies, as those with more female than male patients have a lower sensitivity (38% vs. 62%). Studies grouped by other factors (seen in Table 4) are partially heterogeneous. This suggests that pooling of data is appropriate, but that improvement by meta-regression was not always statistically significant. Given that there are an insufficient number of multicenter, randomized controlled trials, these subgroup factors may, in fact, be critical.

Although several large sample studies reported primary complications of 1-3.6% [36-39] for PCLs, higher than that of solid pancreatic lesions, none of included studies reported severe complications during EUS-FNA.

In order to interpret the results of this study, the following strengths and limitations must be considered: 1) each study has its own descriptions for malignancy, gold standard of diagnosis, study design, and localization of pancreas, allowing for divergence between the studies themselves; 2) some important factors (such as size of cyst) are not available in each study, making further analysis difficult; 3) cultivation of a qualified operator is a costly endeavor; and the experience of this operator has a great impact on the results [40]; 4) the obtained samples are often bloody and contaminated by the gastrointestinal tract [41]; 5) EUS-FNA based cytology, unlike CT and MRI, cannot detect distant metastatic disease.

To date, most studies have focused on either pancreatic solid lesions or mucinous pancreatic neoplasm. There are a limited number of studies that focus primarily on pancreatic cystic lesions. Thus, this is the first meta-analysis to evaluate the diagnostic accuracy of EUS-FNA in all types of pancreatic cystic lesions. Our results are similar to previous meta-analysis that evaluated the diagnostic accuracy of EUS-FNA in differentiation of mucinous from non-mucinous pancreatic neoplasms [7]. This study demonstrated a sensitivity and specificity of 0.54 and 0.93 because non-mucinous pancreatic neoplasms belong to the larger category of pancreatic cystic lesions and mostly develop into malignant bodies.

Advantages such as being minimally invasive, possessing higher accuracy than CT or MRI [42], and having a lower cost and lower specimen requirement (than EchoBrush) [43], may lead to increased use of EUS-FNA in diagnosis of cystic pancreatic lesions. In addition, pseudocysts and some benign cystic lesions can be treated by aspiration and drainage [44]. Furthermore, a combination of genetic markers, molecular analysis, and DNA analysis of affiliated samples obtained from EUS-FNA will enhance the accuracy of cytology.

In order to further investigate the validity of cytology from EUS-FNA for the early diagnosis and prediction of prognosis in PCLs, future studies will consider additional practical factors. We hope that a more reasonable algorithm of EUS-FNA will be developed to confirm the value of this promising tool in the management of pancreatic cystic lesions.

Disclosure Statement

The authors have declared that no competing interests exist.

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