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ORIGINAL ARTICLE

Endoscopic Ultrasound Guided Fine-Needle Aspiration for Solid Lesions in Chronic Pancreatitis: A Systematic Review and Meta-Analysis

Mohamed A. Abdallah[1] · Khalid Ahmed[2] · Wesam Taha[3] · Abdullahi Musa[4] · Erin E. Reardon[1] · Abubaker O. Abdalla[5] · Guru Trikudanathan[1]

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Abstract

Background Patients with chronic pancreatitis (CP) are at a higher risk of developing pancreatic adenocarcinoma compared the general population with an estimated 5% risk of developing pancreatic cancer in 20 years. Endoscopic ultrasound fine needle aspiration (EUS-FNA) of solid pancreatic lesions (SPL) has an excellent sensitivity (85–90%) and specificity (98–100%) for diagnosing pancreatic malignancy. However, data on the performance characteristics of EUS-FNA in CP are mixed.

Aims In this systematic review and meta-analysis, we aim to examine data from published studies on the diagnostic performance of EUS-FNA in detecting pancreatic malignancy in CP.

Methods We conducted a comprehensive search of MEDLINE, Cochrane, EMBASE, Scopus databases for studies published in English language that reported performance characteristics of EUS-FNA for SPL up to November 2020. Two reviewers independently conducted screening, full text review and data extraction according to the PRISMA guidelines. Quality of included studies was assessed using the risk of bias in non-randomized studies of interventions (ROBINS-I) tool. The parameters of interest were sensitivity, specificity, negative, and positive likelihood ratios. Cochran Q test and I statistics were used to determine the between-study heterogeneity. Funnel plots were used to describe publication bias.

Results A total of 6753 studies were identified on initial search. Studies that reported EUS-FNA of cystic pancreas lesions were excluded. Eight studies met the inclusion criteria. Seven studies were retrospective, and one was prospective. A total of 593 patients with CP underwent EUS-FNA for SPL. The pooled sensitivity of EUS-FNA was 65% (95% CI 52.6–75.6%, $I^2 = 44\%$), specificity was 96.8% (75–99.7%, $I^2 = 89\%$), negative likelihood ratio (NLR) 41.4 (11.1–149.6, $I^2 = 70\%$), positive likelihood ratio (PLR) 24.1 (2.8–208, $I^2 = 90\%$). The pooled data from seven studies that compared 901 non-CP vs. 127 CP showed that the sensitivity of EUS-FNA in diagnosing pancreatic malignancy was 91.5 vs. 65.3% [OR (95% CI) 5.5 (2.9–10.2), I^2: 31.8%]. The specificity pooled from six studies [333 non-CP vs. 357 CP] was 95.9% vs. 82.4%, [OR (95% CI) 1.3 (0.2–9.8), $I^2 = 73\%$]. The risk of bias was serious in one study, low in four studies and moderate in three studies.

Conclusion This pooled meta-analysis shows a low sensitivity of EUS-FNA in diagnosing malignancy in CP patients with SPL in comparison to patients without CP. Modalities such as EUS-fine needle biopsy have high sensitivity and specificity for diagnosing pancreatic cancer and should be considered in patients with CP and suspected pancreatic malignancy.

Keywords Chronic pancreatitis · Eendoscopic ultrasound guided fine needle aspiration · Pancreatic adenocarcinoma · Solid pancreatic lesion

Introduction

Patients with chronic pancreatitis (CP) have an increased risk of developing pancreatic adenocarcinoma estimated to be 2.3–18.5 folds higher than the general population, and also 5% risk of developing pancreatic cancer in 20 years [1–3]. In addition, symptoms of CP can resemble pancreatic malignancy including jaundice, malabsorption, and unexplained

✉ Mohamed A. Abdallah
abdal088@umn.edu

Extended author information available on the last page of the article

weight loss. Endoscopic ultrasound guided-fine needle aspiration (EUS-FNA) is a reliable procedure to obtain tissue diagnosis for solid pancreatic masses (SPL) in patients with suspected pancreatic malignancy [4]. EUS-FNA is a well-tolerated procedure with very low overall complication rate of < 2%, and a rate of major complications such as gastrointestinal (GI) perforation of only 1:2500 [5]. Many retrospective and prospective studies have demonstrated an excellent diagnostic performance of EUS-FNA in diagnosing SPL. In a meta-analysis of 33 studies including 4984 patients by Hewitt et al., the pooled sensitivity of EUS-FNA for malignant cytology was 0.85 (95% confidence interval [CI], 0.84–0.86), and the pooled specificity was 0.98 (95% CI 0.97–0.99) [4]. In another meta-analysis by Banafea et al. of 20 studies involving a total of 2761 patients, the pooled sensitivity and specificity of EUS-FNA in the diagnosis of solid pancreatic lesions were 90.8% [95% CI 89.4–92%] and 96.5% (95% CI 94.8–97.7%), respectively. The positive and negative likelihood ratios were 14.8 (95% CI 8.0–27.3) and 0.12 (95% CI 0.09–0.16), respectively. The overall diagnostic accuracy of EUS-FNA for pancreatic cancer in patients with SPL was 91.0% [6].

However, the performance characteristics of EUS-FNA have been reported to be low in the setting of CP [7]. EUS-FNA for diagnosing SLP in the setting of CP is influenced by the impaired visibility of pancreatic structures secondary to the presence of acoustic shadowing from a calcified stone or extensive vascularization, and the need for more needle passes to reach a definitive diagnosis [8]. Specifically, EUS-FNA in the setting of CP was characterized by low negative predictive value (NPV) and high false-negative (FN) rate [8–11]. In addition, a few retrospective and prospective case series studying EUS-FNA of solid pancreatic lesions in patients with chronic pancreatitis have been published. These studies report a significant variability in the reported sensitivity (40–87.8%), specificity (20–100%), and accuracy (80–94%) [9, 11–13]. The aim of our study is to perform a systematic review and meta-analysis of the available literature on the diagnostic performance of EUS-FNA for solid lesions of the pancreas in patients with CP.

Methods

Search Strategy and Study Selection for Analysis

A comprehensive literature search was conducted in MEDLINE via Ovid, EMBASE via Ovid, Scopus, ClinicalTrials.gov, and the Cochrane registry through November 2020 for the diagnostic performance of EUS-FNA in patients suspected to have pancreatic malignancy (Supplementary Document 1). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to identify full-length articles in English reporting [14]**.** In this PRISMA-compliant meta-analysis, all types of studies including case–control, cross-sectional, or cohort studies published in English language were screened. Reviews, case reports, and letters were excluded from the database results before screening using Scottish Intercollegiate Guidelines Network (SIGN) filters. The title/abstract screening was performed independently by three investigators (K.A, H.A, W.T) using inclusion criteria: (a) EUS-FNA for pancreatic cancer; (b) included adult subjects; (c) published in English language; and (d) reported as full papers. The studies were excluded if: (1) studied cystic pancreatic lesions; (2) did not provide data on diagnostic performance data for EUS-FNA in CP; and (3) reported the role of fine needle biopsy (FNB). References of selected retrieved articles were manually reviewed for additional potentially relevant articles. In the case of duplicate studies from the same institution/database, the latest study with largest number of patients was included to avoid duplication. Any discrepancy among investigators was resolved by consensus among all the investigators.

Study Quality Assessment and Risk of Bias Assessment

Two reviewers (M.A and K.A) independently assessed the methodological quality of studies using the risk of bias in non-randomized studies of interventions (ROBINS-I) tool [15]. Assessment was based on the following parameters: sequence generation for the randomization of subjects, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, attrition bias, selective reporting, and other sources of bias. Trials with high or unclear risk for bias for any of the first three components were considered to have a high risk of bias.

Study Outcomes

The primary outcome of this study was to examine the diagnostic performance of EUS-FNA in detecting pancreatic malignancy in CP. The secondary outcome of this study was to compare diagnostic performance of EUS-FNA for detecting pancreatic malignancy in patients with CP vs. patients with no CP.

Definitions

CP was diagnosed either based on clinical history of CP, evidence of CP on imaging, or based on the Rosemont criteria and endosonographic impression, categorized as "consistent with," "suggestive of," or "indeterminate for" CP [16]. Pancreatic malignancies included: pancreatic adenocarcinoma, pancreatic neuroendocrine tumor, cystadenocarcinoma,

malignant lymphoma, solid pseudopapillary tumor, and metastasis to the pancreas (Table 1).

Data Extraction

Data from studies selected for analysis were extracted independently by three authors (K.A, H.A, W.T) on: (a) characteristics (sample size, study population); (b) definition of CP; (c) basis on suspicion for pancreas malignancy; (d) histologic type of pancreatic malignancy; (e) sensitivity, specificity, and accuracy of EUS-FNA in diagnosing of pancreatic malignancy; and (f) diagnostic performance of EUS-FNA in diagnosing pancreatic malignancy in patients with no CP.

Statistical Analysis

Data analysis was performed using Open Meta analyst software (CEBM, Brown University, Providence, RI, USA) [17] and Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). Data for sensitivity and specificity for studies that reported outcomes for patients with chronic pancreatitis were pooled. In the studies that reported continuous variables as means, mean difference (MD) was calculated. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Der Simonian and Laird method (random effects model). The I^2 statistic was used to determine the heterogeneity between the studies, with significant heterogeneity defined with value above 50% or P value < 0.1. Sensitivity analysis was conducting in the case of substantial heterogeneity by excluding one study from the overall analysis at a time "leave-one-out method" to explore the potential source of substantial heterogeneity. Publication bias was assessed by inspection of funnel plots, the largest studies on the funnel plot are near the average, while small studies are spread on both sides of the average of the funnel plot.

Results

The PRISMA flow diagram and results based on the search strategies and selection criteria described above are outlined in (Fig. 1). Of 6753 articles on the initial search, 2896 were duplicates. Title and abstract screening of the remaining 3857 was conducted, and 15 full text studies were assessed for eligibility. Of 15 studies of interest, eight were selected for the final meta-analysis. Seven studies were retrospective, and one study was prospective.

Chronic pancreatitis was diagnosed based on EUS criteria in six studies, clinical history, and imaging in one study, and a combination of clinical, imaging, and EUS criteria in one study. The suspicion for pancreatic malignancy was based on clinical history and abnormal imaging in four studies, abnormal imaging, and abnormal endoscopic retrograde cholangiopancreatography (ERCP) in one study and was not reported in three studies.

The histopathological type of pancreatic malignancy was heterogenous among studies. Three studies reported only pancreatic adenocarcinoma, and five studies reported a mix of different histopathological types: pancreatic adenocarcinoma, metastasis to the pancreas, neuroendocrine tumor, cystadenocarcinoma, malignant lymphoma, and solid pseudopapillary tumor.

Five studies had an onsite cytologist at the time of EUS-FNA exam, two studies did not have an onsite cytologist, and one study did not report it. In regard to EUS-FNA needles; three studies used 22-gauge needles, one study used 19-gauge needles, two studies used a mix of 19-, 22-, and 25- gauge needles, and two studies did not report the gauge size.

Sensitivity, Specificity, Positive and Negative Likelihood Ratios of EUS-FNA in CP

In 593 patients with CP underwent EUS-FNA for SPL, the pooled sensitivity of EUS-FNA was 65% (95% CI: 52.6–75.6%, $I^2 = 44\%$).The specificity was 96.8% (75–99.7%, $I^2 = 89\%$), negative likelihood ratio (NLR) was 41.4 (11.1–149.6, $I^2 = 70\%$), and the positive likelihood ratio (PLR) was 24.1 (2.8–208, $I^2 = 90\%$) (Fig. 2).

Comparison of EUS-FNA in no CP vs. CP

In patients with no CP vs. CP, the pooled data from seven studies [901 non-CP vs. 127 CP] showed that the sensitivity of EUS-FNA in diagnosing pancreatic malignancy was 91.5 vs. 65.3% [OR (95% CI) 5.5 (2.9–10.2), I^2: 31.8%]. The specificity pooled from six studies [333 non-CP vs. 357 CP] was 95.9% vs. 82.4%, [OR (95% CI) 1.3 (0.2–9.8), $I^2 = 73\%$] (Fig. 3a, b).

Sensitivity Analysis

The dataset of CP had high heterogeneity in specificity ($I^2 = 89\%$), NLR ($I^2 = 70\%$), and PLR ($I^2 = 90\%$). A sensitivity analysis was conducted by excluding one study from the overall analysis at a time to explore the potential source of high heterogeneity "Leave-one-out method" (Fig. 4). For sensitivity, specificity and PLR, all studies were associated with a statistically significant change in pooled outcomes. However, for NLR, the study by Vitali et al. [13], was the only study with a statically significant change in pooled NLR.

After exclusion of Vitali et al., the pooled sensitivity 0.69 (0.60–0.77), specificity 0.98 (0.96–0.99), NLR 0.25 (0.10–0.63), and PLR 43.9 (17.5–110.6). Exclusion of this

Table 1 Baseline characteristics of studies included in the analysis

Author / Year	Study period/ Type	Number of patients	Method for diagnosis CP	Basis for suspicion of pancreatic malignancy	Type of pancreatic malignancy	Status of onsite cytologist	Type of needle gauge	Sensitivity of EUS-FNA (%95 CI)	Specificity of EUS-FNA (%95 CI)
Fritscher-Ravens/ 2002	1998–2000 / retrospective	No CP: 133 CP: 74	Clinical history, imaging and EUS criteria	Clinical suspicion and abnormal imaging	Pancreatic adenocarcinoma, metastasis to the pancreas, neuroendocrine tumor, cystadenocarcinoma	No onsite cytologist	22-gauge needles for All EUS-FNA	No CP: 89.3% (81.7–94.6) CP: 53.5% (25.1–80.8)	No CP: 100% (87.2–100) CP: 100% (93.7–100)
Varadarajulu/ 2005	2000–2003 / prospective	No CP: 225 CP:75	EUS (no specified criteria)	Clinical suspicion and abnormal imaging	Pancreatic adenocarcinoma	An onsite cytologist attended all EUS-FNA	Not reported	No CP: 91.3% (89.7–91.7) CP: 73.9% (63.0–73.9)	No CP: 93.8% (73.8–98.9) CP: 100.0% (94.8, 100)
Ardengh/ 2007	1997–2006	CP: 69	Clinical history of CP/Imaging evidence of CP	N/A	Pancreatic adenocarcinoma	No onsite cytologist	22-gauge needles for All EUS-FNA	72.7% (46.4–99)	100% (100–100)
Sreenarasimhaiah/ 2008	2004–2005/ retrospective	No CP: 64 CP: 41	EUS parenchymal and ductal criteria	N/A	Pancreatic adenocarcinoma	An onsite cytologist attended all EUS-FNA	22-gauge needles for All EUS-FNA	87.8%	100%
Krishna/ 2009	2002–2006 / retrospective	No CP: 477 CP: 147	EUS (no specified criteria)	Clinical suspicion and abnormal imaging	Pancreatic adenocarcinoma, metastasis to the pancreas, neuroendocrine tumor, cystadenocarcinoma, malignant lymphoma, solid pseudopapillary tumor	An onsite cytologist attended all EUS-FNA	Not reported	No CP: 95.7% (93.3–98.0) CP: 62.0% (41.1–82.7)	No CP: 97.8% (95.6–100.0) CP: 99.2% (97.7–100.0)
Vitali/2018	2007–2015 / retrospective	No CP: 121 CP: 97	EUS Rosemont criteria	Clinical suspicion and abnormal imaging	Pancreatic adenocarcinoma, metastasis to the pancreas, neuroendocrine tumor, cystadenocarcinoma, malignant lymphoma, solid pseudopapillary tumor	Not reported	19-gauge needles for All EUS-FNA	No CP: 70% CP: 40%	No CP: 80% CP: 20%

Table 1 (continued)

Author / Year	Study period/ Type	Number of patients	Method for diagnosis CP	Basis for suspicion of pancreatic malignancy	Type of pancreatic malignancy	Status of onsite cytologist	Type of needle gauge	Sensitivity of EUS-FNA (%95 CI)	Specificity of EUS-FNA (%95 CI)
Kurita/ 2019	2012–2017 / retrospective	No CP: 71 CP: 46	EUS Rosemont criteria	N/A	Pancreatic adenocarcinoma, metastasis to the pancreas, neuroendocrine tumor	Not reported	22-gauge needles in 64 25-gauge needles in 33	No CP: 96.7% CP: 57.1%	No CP: 100% CP: 100%
Xie/2020	2011–2017 / retrospective	No CP: 190 CP: 44	EUS Rosemont criteria	Biliary stricture on ERCP and abnormal Imaging	Pancreatic adenocarcinoma, metastasis to the pancreas, neuroendocrine tumor, malignant lymphoma	205 (88%) had an onsite cytologist	19-gauge needle in 2 22-gauge needles in 14 25-gague needles in 216	No CP: 94.8% (90.3, 97.6) CP: 80.0% (59.3, 93.2)	No CP: 100.0% (79.4, 100.0) CP: 94.7% (74.0, 99.9)

CP Chronic pancreatitis, *ERCP* Endoscopic retrograde cholangiopancreatography, *EUS-FNA* Endoscopic ultrasound-guided fine needle aspiration

study decreased heterogeneity among studies I^2 to 0 for sensitivity, specificity, PLR, and NLR (Fig. 5).

For the comparison between patients with CP vs. No CP, leave-one-out method did not identify a single study that contributed to high heterogeneity (Fig. 6).

Risk of Bias Within Studies

Of eight studies, the risk of confounding bias was low in six studies, one studies did not provide information, and in one study the risk of bias was high. Selection bias, bias in classification of intervention, and bias due to deviation from intended intervention were low in seven studies. Bias due to missing data was apparent in four studies. Risk of bias in the measurement of outcomes was low in all studies, while bias in selection of the reported results was suspected in one study. The overall risk of bias was estimated to be low in three studies, moderate in four studies and high in one study (Supplementary Fig. 1) and (Supplementary Fig. 2).

Evaluation for Publication Bias

Funnel plots were used to evaluate publication bias (Fig. 3a, b). The graphs were asymmetric and, thus, suggest that publication bias in favor of positive studies might have been present.

Discussion

The main finding of this meta-analysis with pooled data from multiple studies is that sensitivity of EUS-FNA for suspected solid pancreatic lesion is estimated at 65% in patients with CP, and the odds of diagnosing pancreatic malignancies using EUS-FNA are higher in non- CP vs. CP (OR 5.5 (2.9–10.2)).The low sensitivity of EUS-FNA persisted despite performing a sensitivity analysis (69%). The specificity of EUS-FNA was calculated at 96.8% in CP, which was comparable to patients with no CP (OR 1.3 (0.2–9.8)).

The lower sensitivity of EUS-FNA in CP can be explained by the fact that 10% of patients with CP can develop inflammatory lesions (pseudotumors) which can mimic pancreatic head malignancy [8, 9]. The lobulations produced by the chronic inflammation, acoustic shadowing of calcified stones that may undermine the visibility of a neoplasm, and the difficult process of obtaining FNA due to the coexistence of collateral vasculature seen in patients with severe CP have been postulated to results in low sensitivity of EUS-FNA [8]. Other limitations, such as the experience of endoscopist and the number of passes needed to reach the diagnosis of pancreatic malignancies has been implicated as many studies have shown that patients with CP vs. no CP required more

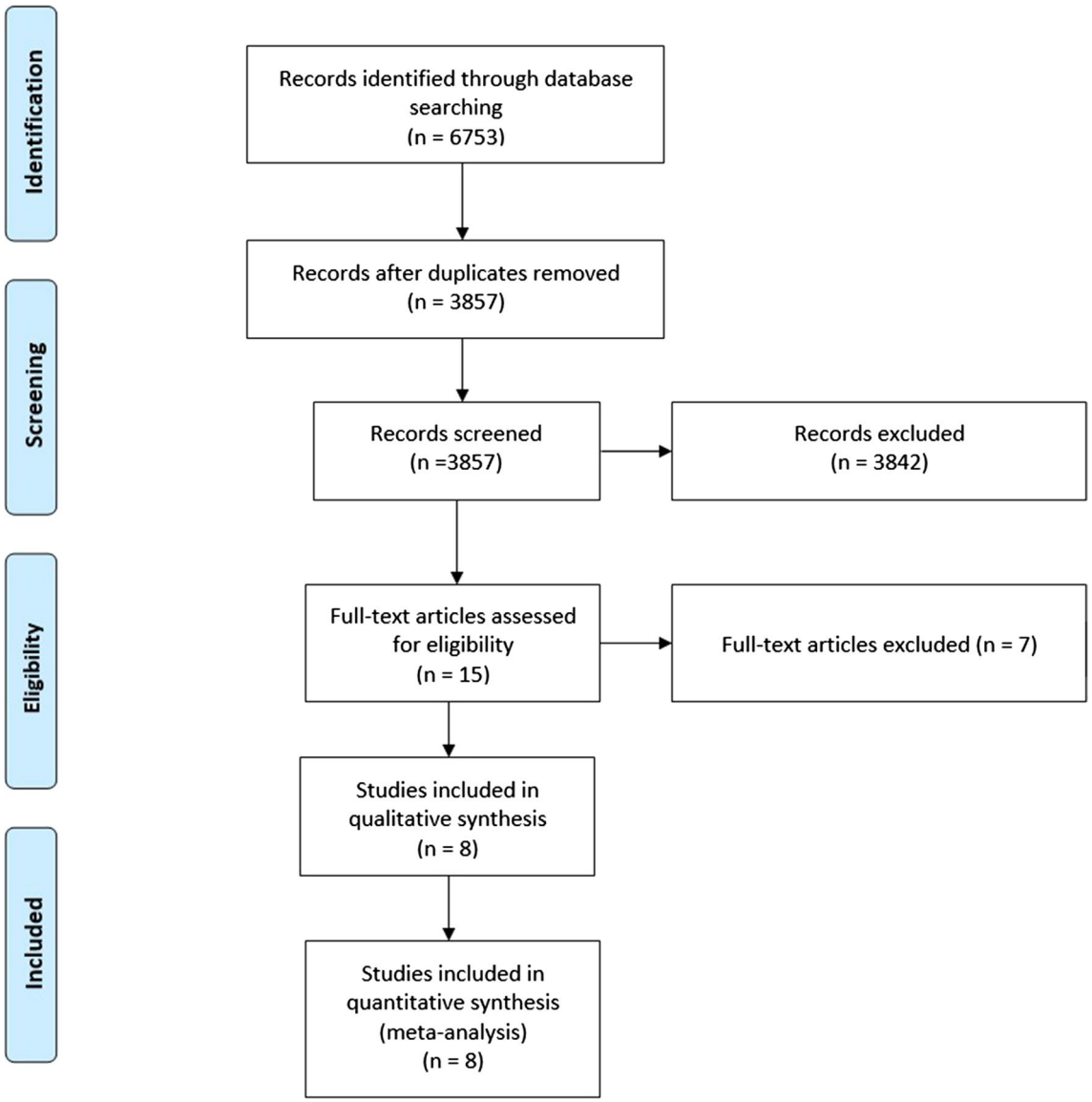

Fig. 1 Literature review process using PRISMA flow diagram for studies included in the analysis

FNA passes to establish a diagnosis of pancreatic cancer (5 vs. 2, $P < 0.001$) [10].

Fine needle biopsy (FNB) has emerged as an accurate and reliable tool for diagnosing pancreatic malignancy and has replaced EUS-FNA in many institutions. In a meta-analysis of eight randomized controlled trials (RCTs) of 921 cases, Wang et al. demonstrated that FNB is comparable to FNA in terms of diagnostic accuracy, adverse events, and technical success. In addition, FNB provided higher specimen adequacy than that of FNA, despite performance of fewer needle passes [18]. Grassia et al. compared EUS-FNA vs. EUS-FNB in diagnosing malignancy in patients with pancreatic masses and clinico-radiological-endosonographic features of CP [12]. In EUS-FNA group ($N = 110$) vs. EUS-FNB (N$N = 100$), the diagnostic accuracy was 83.6 vs. 93%, sensitivity 69.5 vs. 86.6%, specificity 100 vs. 100%, PPV100 vs.100%, and negative predictive value [NPV] 73.9 vs. 87% ($P = 0.03$). On multivariate regression analysis, FNB use (OR 2.5; $P < 0.01$) was independently associated with correct diagnosis of parenchymal pancreatic masses.

EUS-FNB with the use of end-cutting needles "e.g., fork-tip" may enhance the diagnostic yield of EUS-FNB in CP by procuring larger samples with preserved tissue architecture [19]. In a randomized controlled trial (RCT), Crinò et al. compared fork-tip vs. side-fenestrated 22-G or 25-G needles in 192 patients and demonstrated that fork-tip needles produced better quality histologic samples and fewer needle passes to reach a diagnosis in SPL [20]. In another RCT (N = 108), Oppong et al. showed that FNB with fork-tip needle was more sensitive than the FNA needle (82% vs. 71%,

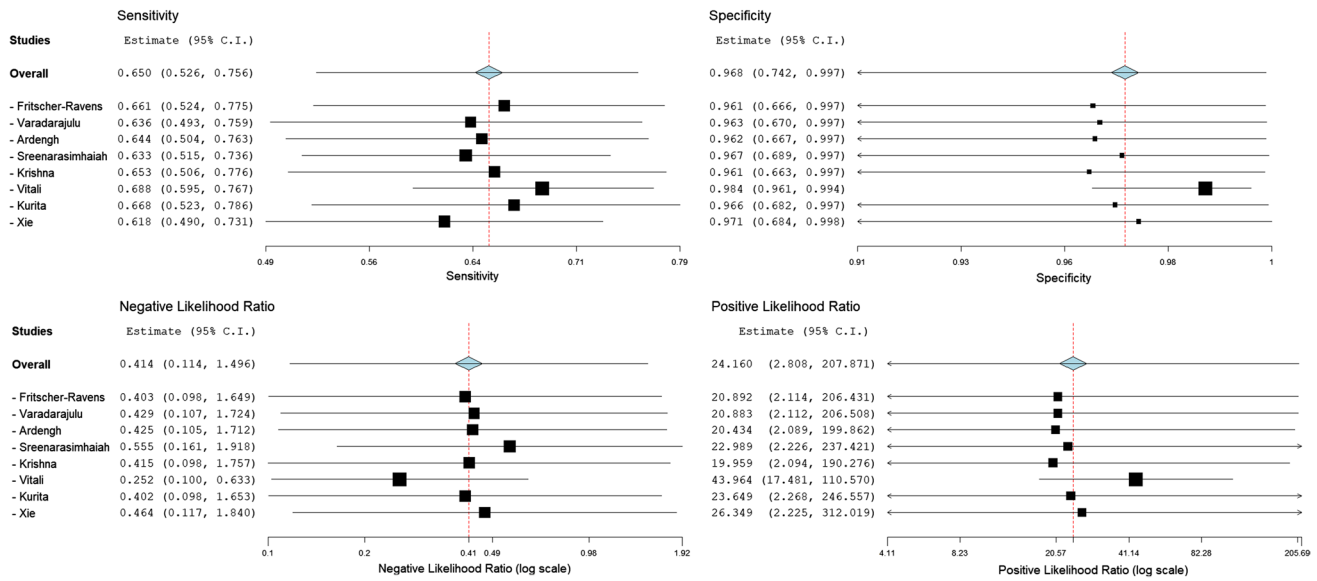

Fig. 2 Forest plots for sensitivity, specificity, negative likelihood ratio (NLR), and positive likelihood ratio (PLR) of endoscopic ultrasound fine needle aspiration (EUS-FNA) for solid pancreatic lesions (SPL) in chronic pancreatitis

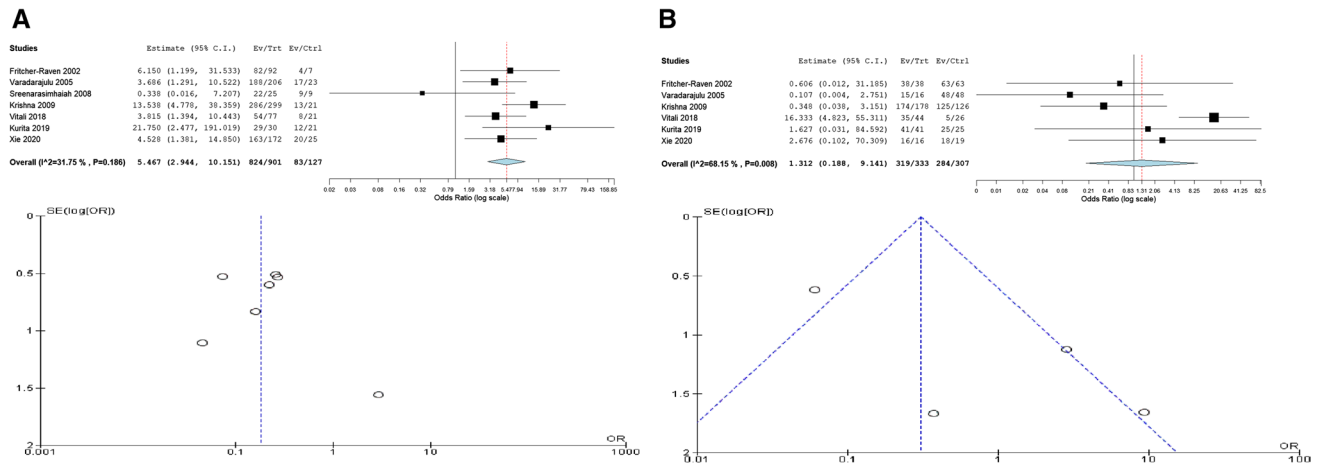

Fig. 3 Forest plots and funnel plots of studies that compared **a** sensitivity and **b** specificity of endoscopic ultrasound fine needle aspiration (EUS-FNA) for solid pancreatic lesions (SPL) in patients with no chronic pancreatitis vs. chronic pancreatitis

$p < 0.001$) for diagnosing SPL, with shorter sampling and pathology viewing times besides greater ease of diagnosis by cytopathologists [21]. Despite the multiple studies favoring FNB to FNA for diagnosing SPL, EUS-FNA is still used by many community and tertiary care centers due to wide availability and lower cost.

High degree of heterogeneity was noted in our meta-analysis. The sensitivity analysis that was performed to address high heterogeneity showed that all included studies contributed to this heterogeneity. However, the study by Vitali et al. [13] had a more profound effect than other studies. This is likely due to the low sensitivity (40%) and specificity (20%) of EUS-FNA reported in that study.

Our study has strength of meta-analysis approach with pooling data and increasing the sample size. However, the study is limited with most studies being observational retrospective studies with heterogeneous data, and drawing conclusions based on baseline characteristics and outcomes patients is restricted by this heterogeneity. Variability in the studied patient populations, criteria of diagnosing chronic pancreatitis and the histologic type of pancreatic malignancies may have contributed to the high heterogeneity of included studies and likely limit generalization of the findings of this study. EUS-FNB is a promising tool for diagnosing SPL, especially with the advent of newer needle technologies. Further research on its use in CP is needed.

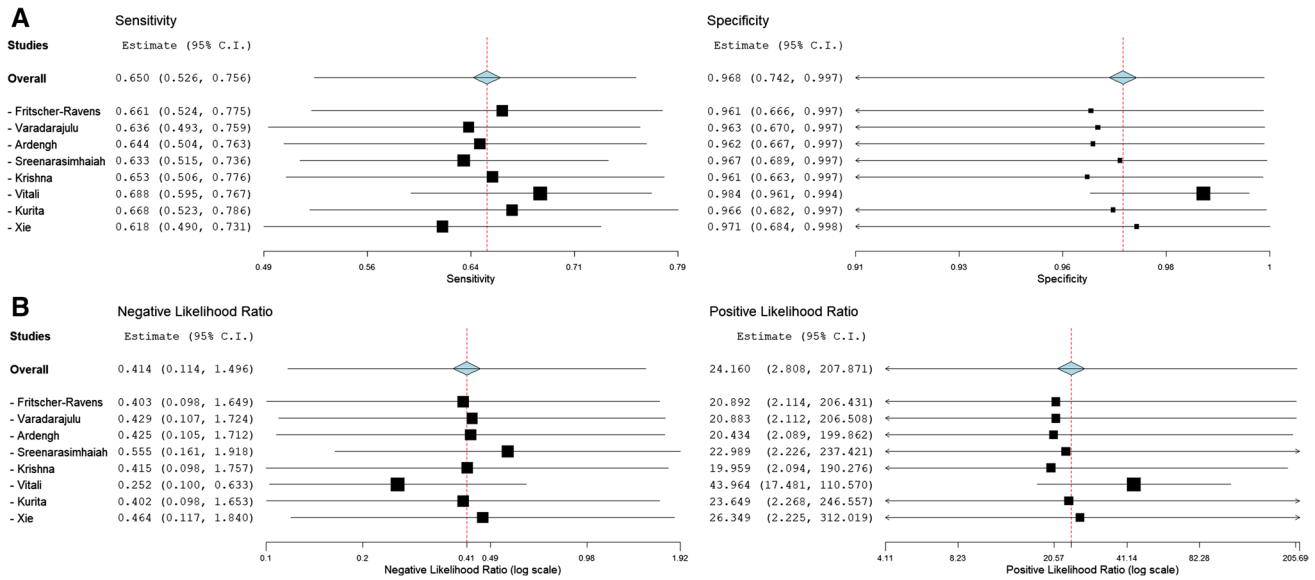

Fig. 4 Leave-one-out method for sensitivity analysis for studies that reported performance of endoscopic ultrasound fine needle aspiration (EUS-FNA) for solid pancreatic lesions (SPL) in chronic pancreatitis

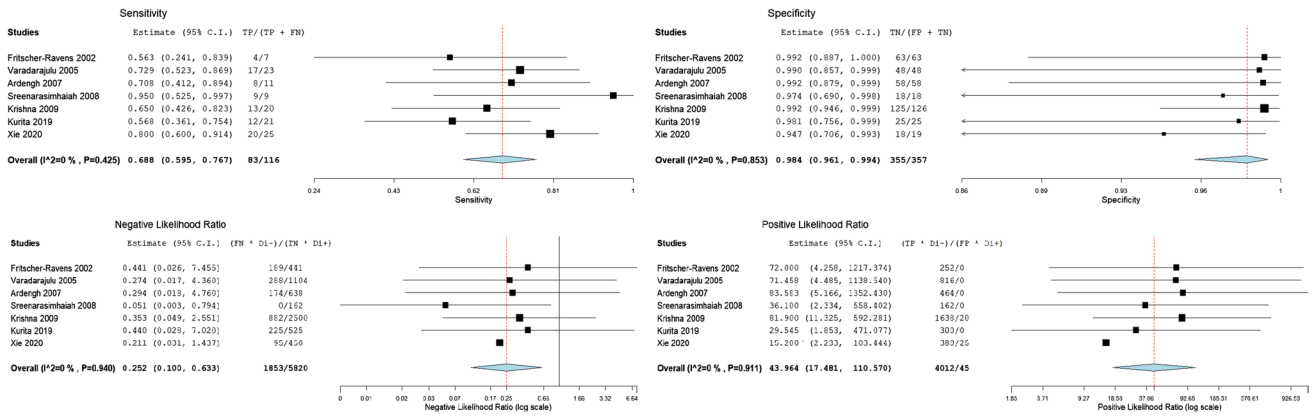

Fig. 5 Sensitivity analysis showing the sensitivity, specificity, negative likelihood ratio (NLR), and positive likelihood ratio (PLR) of endoscopic ultrasound fine needle aspiration (EUS-FNA) for solid pancreatic lesions (SPL) in chronic pancreatitis

Conclusion

This pooled meta-analysis shows a low sensitivity of EUS-FNA in diagnosing malignancy in CP patients with SPL in comparison to patients without CP. Research should be focused in evaluating modalities (e.g., EUS-FNB) that can enhance the diagnosis of pancreatic malignancy in CP. Future RCT on the utility of EUS-FNB in diagnosing SPL in patients with CP is warranted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-021-07066-3.

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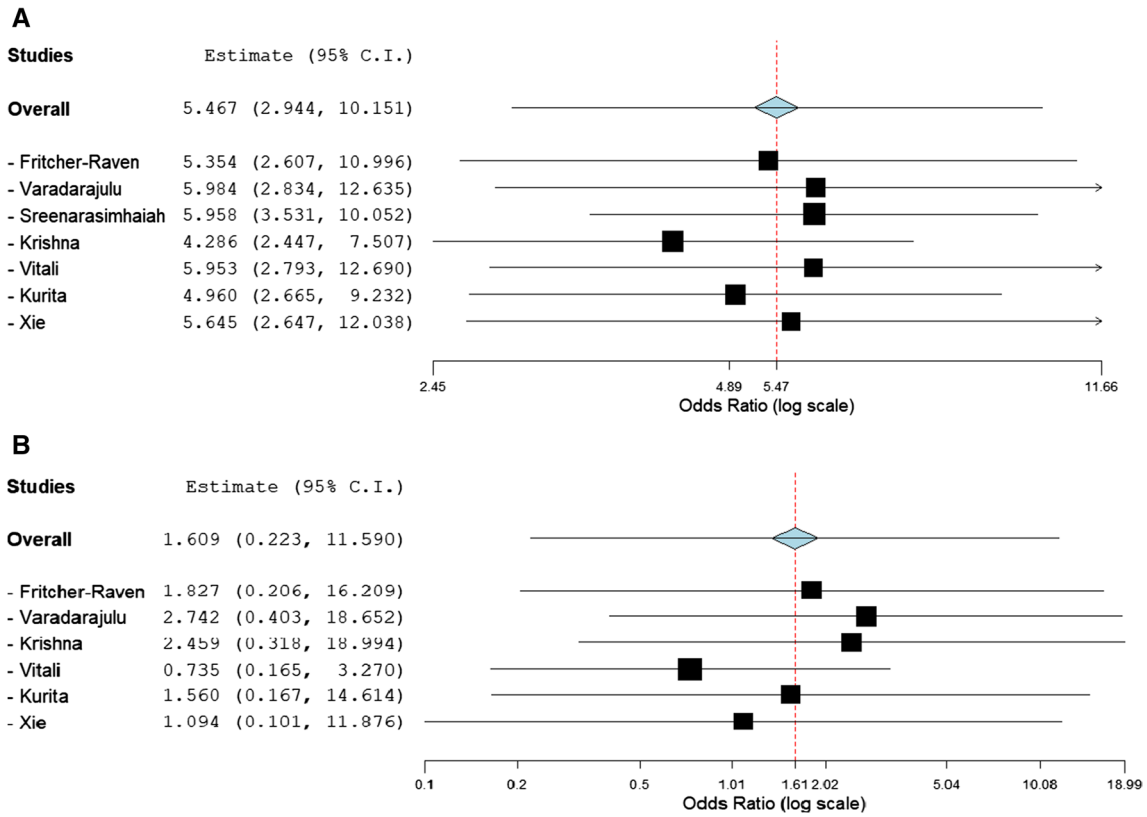

Fig. 6 Leave-one-out method for sensitivity analysis for studies that compared patients with no chronic pancreatitis vs. chronic pancreatitis

Declarations

Conflict of interest Guru Trikudanathan serves as a consultant for Boston Scientific. The other authors declare that they have no conflict of interest.

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Authors and Affiliations

Mohamed A. Abdallah[1] · Khalid Ahmed[2] · Wesam Taha[3] · Abdullahi Musa[4] · Erin E. Reardon[1] · Abubaker O. Abdalla[5] · Guru Trikudanathan[1]

Khalid Ahmed
khalidhashim00@gmail.com

Wesam Taha
wesamhassan800@gmail.com

Abdullahi Musa
abdoomusa@gmail.com

Erin E. Reardon
ereardon@umn.edu

Abubaker O. Abdalla
abubaker.o.abdalla@gmail.com

Guru Trikudanathan
triku001@umn.edu

[1] Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, MMC 36, 420 Delaware St SE, Minneapolis, MN 55455, USA

[2] Department of Internal Medicine, The Wright Center for Community Health, 01 S Washington Ave Suite 1000, Scranton, PA, USA

[3] Department of Internal Medicine, NewYork-Presbyterian Queens, 56-45 Main Street, Flushing, NY 11355, USA

[4] Division of Gastroenterology and Hepatology, Howard University, 2041 Georgia Ave NW, Washington, DC 20060, USA

[5] Department of Internal Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA