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Comparing accuracy of high-risk features for detecting advanced neoplasia in pancreatic cystic lesions: a systematic review and meta-analysis

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Abstract

Background The American Gastroenterological Association recommends endoscopic ultrasound (EUS) for evaluating pancreatic cystic lesions (PCL) with ≥2 high-risk features (HRF), whereas the American College of Gastroenterology recommends EUS for ≥1 HRF. This systematic review and meta-analysis compared the diagnostic accuracy of using ≥1 vs. ≥2 HRF for assessing the risk of advanced neoplasia (AN) and performing EUS in PCL.

Methods An electronic database search was performed for eligible studies. AN was defined as pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm or mucinous cystadenoma with high-grade dysplasia, pancreatic intraepithelial neoplasia and pancreatic neuroendocrine tumors. HRF included cyst size ≥3 cm, solid component, and dilated pancreatic duct ≥5 mm. The primary outcome was the sensitivity and specificity of using ≥1 vs. ≥2 HRF as an indication for EUS to detect AN in PCL.

Results Of 38 studies initially screened, 8 were included in the final analysis. Seven studies assessed the accuracy of ≥2 HRF and 4 studies assessed ≥1 HRF. The pooled sensitivity, specificity, positive and negative predictive values of EUS for detecting AN were 41.7% (95% confidence interval 19.5-67.8%), 90.8% (81.9-95.5%), 30.4% (19.4-44.2%) and 94.3% (89.6-97.0%) with ≥2HRFs, and 77.1% (66.1-85.3%), 72.7% (50.4-87.5%), 17.95% (10.3-29.4%), 98.1% (90.8-99.6%), respectively, with ≥1 HRF.

Conclusion Performing EUS for PCL with ≥1 HRF could offer greater sensitivity in detecting AN compared to ≥2 HRF, with a similar negative predictive value.

Keywords Pancreatic cystic lesions, pancreatic cancer, endoscopic ultrasound, meta-analysis

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Introduction

Pancreatic cystic lesions (PCL) are often detected incidentally in asymptomatic patients who undergo cross-sectional imaging. The prevalence of PCL ranges from 13-45% in patients who undergo contrast-enhanced computed tomography and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography [1-3]. PCL display a wide variety, most of which are benign [4]. Some cysts, such as solid pseudopapillary neoplasms, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms, have malignant potential and can evolve into pancreatic cancer. Pancreatic cancer has a high mortality and typically presents with lymphadenopathy or metastasis when curative interventions are not feasible [5]. This makes early identification of high-risk PCL imperative.

Endoscopic ultrasound (EUS) is an excellent modality for evaluating PCL and defining cyst features, including size, mural

nodularity, internal features, relation of the cyst with pancreatic duct, and location within the gland [6]. It also facilitates the aspiration of cyst fluid for analysis for carcinoembryonic antigen, amylase, and cytology. These features make EUS a useful diagnostic tool in risk stratification for PCL [7].

The current literature suggests that specific high-risk features (HRF) on cross-sectional imaging are associated with a cyst's progression to malignancy [8-10]. These HRF include: (a) dilated pancreatic duct (≥5 mm); b) presence of a solid component or mural nodule; and c) cyst size ≥3 cm. The American Gastroenterological Association (AGA) in 2015 recommended further evaluation with an EUS if 2 or more HRF are identified [11]. The subsequently published American College of Gastroenterology (ACG) guideline, however, recommends EUS for 1 or more HRF [12]. This discrepancy in the recommendations for EUS in PCL can lead to confusion in risk-stratifying patients and raise questions about which guideline should be used in clinical practice [13]. Several studies have assessed the diagnostic accuracy of these guidelines, with variable results. We performed a systematic review and meta-analysis to compare the diagnostic accuracy of using ≥1 or ≥2 HRF for assessing the risk of advanced neoplasia (AN) and performing EUS in PCL.

Materials and methods

Search strategy

A comprehensive electronic database search was conducted in PubMed/Medline, Cochrane library, Embase and Google Scholar to identify eligible studies/articles evaluating HRF in assessing the risk of neoplasia in PCL. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used in performing and reporting this systematic review and meta-analysis [14,15]. The literature search and data extraction were performed by 2 individual authors (AD and HB). The following Medical Subject Heading/Entrée terms (MeSH) and non-MeSH text words were used in our search strategy: "pancreatic cystic lesions", "endoscopic ultrasound", "endoscopic ultrasonography", "ultrasound", "IPMN", "EUS", "pancreatic cysts", "American Gastroenterological Association", "AGA", "American College of Gastroenterology", "ACG". The references from the full texts of selected articles were reviewed for any additional articles.

Eligibility criteria

The articles retrieved from the literature search were reviewed based on the following eligibility criteria. Inclusion criteria were as follows: 1) studies reporting HRF for assessment of PCL, as suggested by AGA or ACG; and 2) studies using EUS for risk stratification of PCL. The exclusion criteria were as follows: 1) studies not reporting number of individual HRF; and 2) case reports, case series, review articles and only abstract form. All articles were assessed for eligibility by 2 independent reviewers (AD and HB) and any disagreement was resolved by consensus with the senior author (DK).

Data extraction

Data extraction from the selected studies was performed by one author (HB) and verified for accuracy by another author (AD). The following data were extracted from each study: first author, year of publication, PubMed ID, type of study, single- or multicenter, country of study, number of patients in each group, mean age, presence of symptoms, location of the cyst, number of HRF in the cyst, cysts with concerning diagnosis of advanced neoplasia, use of EUS and criteria for diagnosis of neoplasia.

Definitions and outcomes

AN was defined as the presence of pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm with high-grade dysplasia, mucinous cystadenoma with high-grade dysplasia, pancreatic intraepithelial neoplasia, or pancreatic neuroendocrine tumors. Missed AN was defined as the number of patients with AN who would have been missed if EUS was restricted to patients with 1 or 2 HRF.

The primary outcome was the sensitivity and specificity of using ≥2 HRF (as suggested by the AGA) and ≥1 HRF (as suggested by the ACG) while performing EUS for the detection of AN in patients with PCL. Secondary outcomes were the number of EUS procedures needed for detecting cysts with AN, based on ≥2 HRF or ≥1 HRF, and the missed AN rate.

Quality assessment

The Newcastle-Ottawa scale, a validated tool designed for meta-analysis, was used to assess the quality of each non-randomized study included in the study [16]. A score ≥7 was considered high quality. The examined domains were selection, comparability and outcome. Selection domains examined included representativeness of population, ascertainment of exposure and demonstration that the outcome was not present at the start of the study. Each study was assessed for comparability of groups on the basis of design or analysis when eligible. Finally, outcome was evaluated on the basis of how the outcome assessment was done, whether follow up was complete and long enough for the outcome to occur. Studies were assigned a "star" score for each feature and 2 "star" scores for comparability if adjusted or matched comparison of 2 groups were performed.

Statistical analysis

The meta-analysis was performed according to the PRISMA statement, and a complete checklist has been provided in

Supplementary Table 1 [14,17]. Diagnostic test accuracy measures were presented in the form of sensitivity, specificity, positive and negative predictive values. These parameters were either used as absolute values (effect size) yielded by individual studies, or calculated based on event/non-event rates in exposed/non-exposed totals. Each effect size taken from an individual study was used to calculate the pooled event rates and pooled total rates with proportions (percentages) in the meta-analysis model. Pooled rates of missed AN were calculated in a similar manner from individual studies and used to calculate final summary estimates. All the pooled rates were calculated with 95% confidence intervals (CI), and a P-value <0.05 was considered statistically significant. Heterogeneity among studies was calculated using I^2 statistics with ranges of 0-30%, 30-50%, 50-75% and 75-100% representing low, moderate, substantial and high heterogeneity, respectively. All statistical analyses were performed using Comprehensive meta-analysis version 3 (BioStat, Englewood, NJ).

Results

The initial literature search resulted in 38 articles. After a review of the abstracts and full texts to exclude redundant and duplicate studies, 20 articles were screened and 8 studies were included in the final analysis, based on the selection criteria above (Fig. 1). All the 8 studies were retrospective cohort studies; they included 2 multicenter studies and 6 single-center studies. Seven studies were from the United States and one study was from Japan [18-25]. The quality of the studies was assessed using the Newcastle-Ottawa scale and is reported in Supplementary Table 2.

Overall, the 8 studies included 1882 patients (40.4% male; mean age 64.5 years; Table 1). Among these, Kohli *et al* [20], Sighinolfi *et al* [23] and Imbe *et al* [19] reported the location of the cyst, most commonly in the head of the pancreas (39.5%). The diagnosis of advanced neoplasia was made based on a histological evaluation of resected pancreas [18,21,23], cytological analysis of cells aspirated from pancreatic cysts [20,24], or a combination of the two [22]. Singhi *et al* also performed molecular testing on aspirated pancreatic cyst fluid to assess mutations in *KRAS*, *GNAS*, *VHL*, *TP53*, *PIK3CA,* and *PTEN* genes [24]. Imbe *et al* did not provide details of how pancreas cancer was defined [19].

Diagnostic accuracy of recommendations for EUS for detecting advanced neoplasia

EUS for ≥2 HRF

The AGA recommends performing EUS only for PCL with ≥2 HRF [11]. Seven studies provided information regarding the presence of ≥2 HRF in the PCL, seen in 234 patients [18,20-25]. The sensitivity and specificity of ≥2 HRF in detecting advanced neoplasia were 41.7% (95%CI 19.5-67.8%) and 90.8% (95%CI 81.9-95.5%), respectively. The corresponding positive and negative predictive values were 30.4% (95%CI 19.4-44.2%) and 94.3% (95%CI 89.6-97.0%), respectively (Table 2).

EUS for ≥1 HRF

The ACG recommends performing EUS in the presence of 1 or more HRF seen on cross-sectional imaging [12]. Four studies provided information regarding the presence of ≥1 HRF in the PCL, seen in 329 patients [18-20,22]. The sensitivity and specificity of ≥1 HRF in detecting advanced neoplasia were 77.1% (95%CI 66.1-85.3%) and 72.7% (95%CI 50.4-87.5%), respectively. The corresponding positive and negative predictive values were 17.9% (95%CI 10.3-29.4%) and 98.1% (95%CI 90.8-99.6%), respectively (Table 2).

Missed rates for AN

Different investigators have provided varying amounts of information regarding AN in relation to HRFs. Seven studies [18,20-25] provided cytological or histological assessment to confirm the presence of AN. In the pooled analysis of these studies, 173 patients demonstrated AN. Of these, 77 had at least 2 HRF (44.5%), meeting the threshold for EUS using the AGA criteria. However, 96 (55.5%) patients with definite AN had <2 HRF and hence would not undergo EUS per the AGA recommendations.

Table 1 Demographic information from individual studies

Author [Ref.]	Journal	Year	Sample size	Age (years; mean ± SD)	Male	Female
Sahar *et al* [22]	Surgical Endoscopy	2018	125	66	43	82
Kohli *et al* [20]	Pancreatology	2016	210	58±13.6	108	102
Ge *et al* [18]	Endoscopy International Open	2017	300	62.6±13.8	113	187
Lee *et al* [21]	Endoscopy International Open	2017	152	65	43	100
Singhi *et al* [24]	Gastrointestinal Endoscopy	2016	225	64.7	98	127
Sighinolfi *et al* [23]	Digestive Diseases and Sciences	2017	209	62.18±12.04	93	116
Xu *et al* [25]	Medicine (Baltimore)	2017	269	67±12.4	78	191
Imbe *et al* [19]	European Radiology	2018	392	70.5	185	207

SD, standard deviation

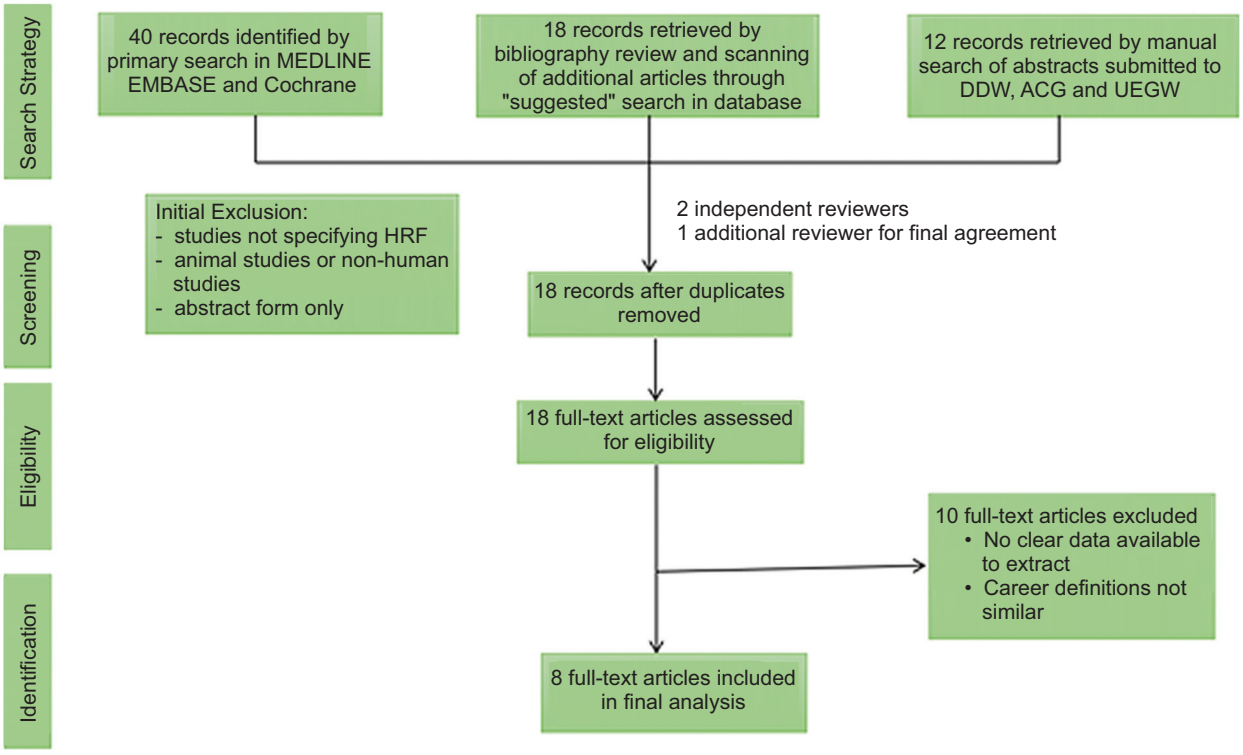

Figure 1 Study flow diagram depicting search strategy, screening, and identification of studies for final analysis
HRF, high-risk features; DDW, digestive disease week; ACG, American College of Gastroenterology; UEGW, United European Gastroenterology Week

Table 2 Performance characteristics of number of high-risk features in predicting advanced neoplasia in pancreatic cystic lesions

Measure	≥2 high-risk features (95%CI)	≥1 high-risk features (95%CI)
Sensitivity	41.7% (19.5-67.8%)	77.1% (66.1-85.3%)
Specificity	90.8% (81.9-95.5%)	72.7% (50.4-87.5%)
Positive predictive value	30.4% (19.4-44.2%)	17.9% (10.3-29.4%)
Negative predictive value	94.3% (89.6-97.0%)	98.1% (90.8-99.6%)

CI, confidence interval

Five studies [18,20-22,24] provided the number of total HRFs in the study population. In the pooled analysis of these 5 studies, 88 patients were reported to have AN. Of these 88 patients, 20 had no HRF (22.72%), 33 had 1 HRF (37.5%), and 35 had 2 HRFs (39.7%).

Three studies [18,20,22] described individual HRFs in the PCLs. Among the 201 patients with 1 HRF reported in the studies, 26 harbored AN, with a pooled incidence of 12.93%.

Using pooled data from all studies reporting relevant data, the rate for missed AN was calculated. The missed AN rate when using 2 HRF was 4.7% (95%CI 2.4-8.8; I^2=87%) in all patients with PCL and 58.3% (95%CI 32.3-80.5; I^2=85%) in patients with confirmed neoplasia. The missed AN rate with 1 HRF was 1.8% (95%CI 0.8-4.2; I^2=58%) in all patients with PCL and 23.6% (95%CI 15.8-33.6; I^2=0) in patients with confirmed neoplasia (Fig. 2-5). Overall, there was significant heterogeneity among the studies, with an I^2 value of 96.47%.

Impact on EUS procedures

Based on the pooled analysis from 3 studies [18,20,22], if ACG guidelines [1] were to be followed, and EUS performed for any HRF, 277 EUS procedures would be performed and would detect 52 AN. However, if AGA guidelines [1] were to be used, and EUS restricted to patients with at least 2 HRF, 76 EUS procedures would be performed and would detect 26 AN. Using ACG guidelines, 201 additional EUS procedures would be performed and approximately 8 EUS procedures would be needed to detect 1 patient with AN. In contrast, 3 EUS procedures would be needed to detect 1 AN using AGA guideline. Using AGA guidelines, the use of EUS would be reduced by 63% compared to ACG guidelines, but 50% of AN would be missed.

Discussion

Increasing use of high-resolution abdominal imaging has led to more frequent incidental detection of asymptomatic PCL. Two professional gastroenterology societies, the ACG and AGA, have published consensus guidelines on the

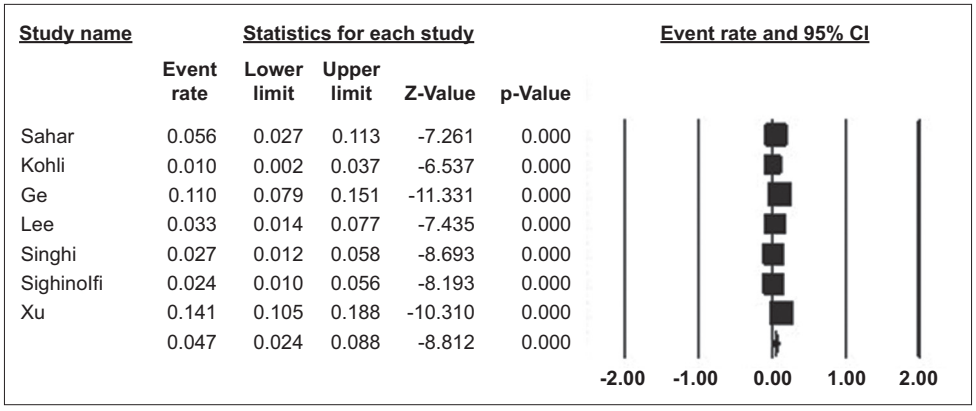

Figure 2 Absolute pooled missed advanced neoplasia rates using ≥2 high-risk features in all patients with pancreatic cysts
CI, confidence interval

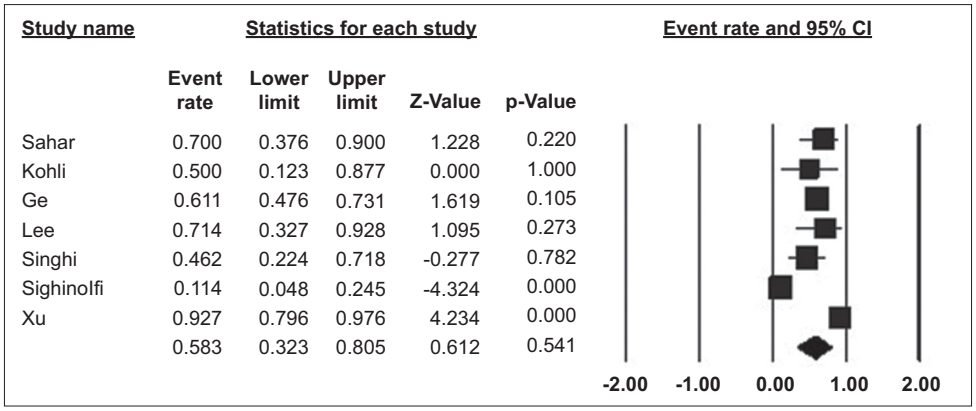

Figure 3 Missed advanced neoplasia rates using the ≥2 high-risk features criterion in patients with confirmed advanced neoplasia
CI, confidence interval

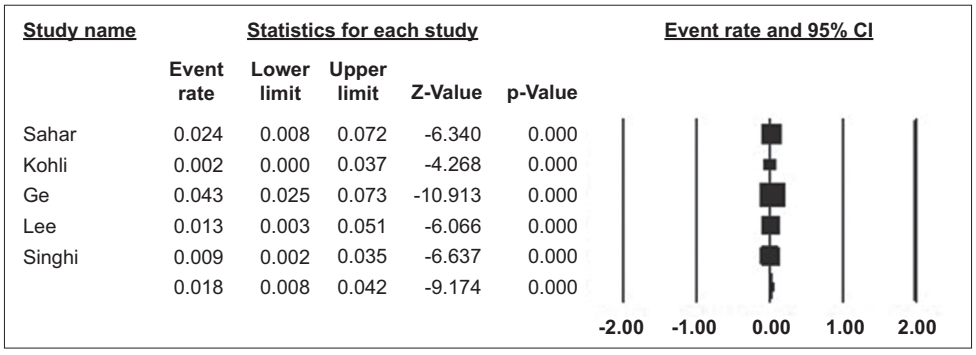

Figure 4 Absolute pooled missed advanced neoplasia rates using ≥1 high-risk features in all patients with pancreatic cysts
CI, confidence interval

suggested approach to these lesions [11,12]. Both guidelines have risk-stratified PCL based on their morphology on cross-sectional imaging. This approach is crucial in identifying the minority of PCL that harbor early invasive cancer or high-grade dysplasia. The 2015 AGA guideline recommended the performance of EUS only if 2 or more HRF are present [11]. This conditional recommendation is based on a poor quality of evidence and precludes performing an EUS in patients with 1 HRF, who may still be at higher risk for development of AN compared to patients with no HRF [20]. The ACG, however, recommends performing an EUS in the presence of any HRF [12].

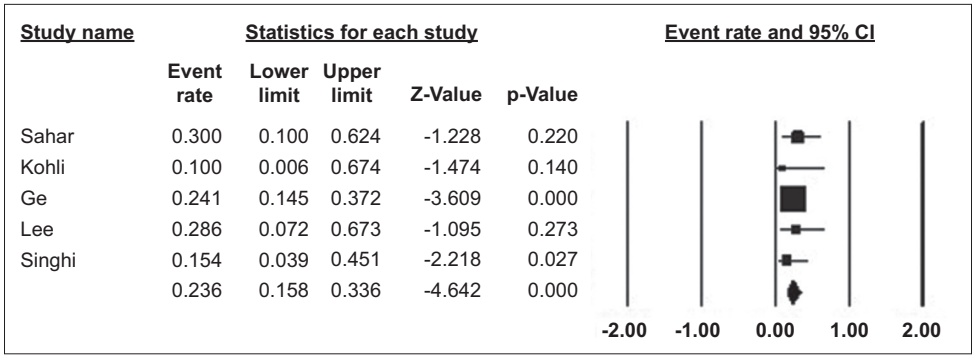

Figure 5 Missed advanced neoplasia rates using the ≥1 high-risk features criterion in patients with confirmed advanced neoplasia
CI, confidence interval

In this study, we demonstrated that performing EUS in patients with at least 1 HRF, as suggested by the ACG, had a sensitivity of 77.1% for diagnosing AN. Restricting EUS to patients with ≥2 HRF, reduced the sensitivity for AN to 41.7%. Indeed, this pooled analysis demonstrated that 37.5% of patients with AN had only 1 HRF.

Other investigators have similarly reported that following the AGA recommendations and performing EUS only in patients with at least 2 HRF reduces sensitivity for the detection of high-risk lesions. Kohli *et al* demonstrated that using the AGA guidelines reduced the sensitivity for detecting pancreatic malignancy to 50%, and suggested that performing EUS in patients with at least 1 HRF on imaging would increase the sensitivity to 100%. On the other hand, the number of EUS procedures performed would have been reduced by 91% if AGA guidelines were followed, compared to a 67% reduction for EUS procedures performed for 1 HRF [20]. Singhi *et al* similarly showed that AN was detected with a sensitivity and specificity of 62% and 75% by using AGA guidelines. Moreover, 45% of advanced neoplastic cysts were missed by the AGA guidelines. They proposed an alternative algorithm to manage PCL, which included molecular analysis of cyst fluid aspirate [24]. In a study by Sahar *et al*, abiding by the AGA guidelines and using 2 HRF as threshold for performing EUS, the diagnosis of malignant and high-risk premalignant lesions (including pancreatic adenocarcinoma, mucinous cystadenoma, neuroendocrine tumors, and intraductal papillary mucinous neoplasm with dysplasia) had a 40% sensitivity and 100% specificity. If EUS was used based on a threshold of 1 HRF on imaging, malignant and high-risk premalignant lesions would have been identified with 80% sensitivity and 95% specificity [22]. However, it is not known if an early diagnosis of AN within a pancreatic cyst necessarily prevents progression to cancer or has a mortality benefit.

It is also notable that the 3 individual HRF have a variable risk of progression to malignancy. The AGA technical review calculated that the risk of malignancy in a pancreatic cyst was the highest with mural nodularity (odds ratio [OR] 7.73, 95%CI 3.38-17.67), followed by a cyst size >3 cm (OR 2.97, 95%CI 1.82-4.85). A dilated pancreas duct did not increase the odds of malignancy (OR 2.38, 95%CI 0.71-8.0) [8]. Hence, a risk stratification algorithm that considers these 3 HRF to be equivalent may not be ideal.

Certain investigators have also questioned the rationale for performing EUS in the presence of ≥2 HRF on MRI since the interobserver agreement between EUS and MRI is poor and the misdiagnosis rate of cross-sectional imaging is high. In view of the limited accuracy of cross-sectional imaging, EUS can improve diagnostic yield with its higher resolution and can also provide aspirated fluid for chemical and cytological analysis [26].

An EUS can also help in the down-stratification of PCL, which can lead to avoiding unnecessary imaging procedures and a consequent reduction in healthcare costs [27,28]. In the study by Sahar *et al*, EUS was useful in classifying 14 cysts as pseudocysts and serous cystadenomas and consequently down-stratifying this group and removing them from a surveillance program [22]. It is notable that an EUS with cyst aspiration is a relatively safe endoscopic procedure with a low complication rate in the hands of an experienced operator [29].

Different scientific organizations have provided broadly similar recommendations for the management of PCL, but there are some significant variations among them. The European Society of Gastrointestinal Endoscopy recommends EUS as an adjunct to other imaging modalities, especially if the cystic lesion demonstrates clinical or radiological features of concern [4] and if a precise diagnosis changes patient management [30]. It also recommends against performing EUS for lesions ≤10 mm in diameter with no high-risk stigmata [30]. Notably, this guideline uses a cyst size of ≥4 cm as a cutoff, instead of the 3 cm recommended by the ACG and AGA guidelines. The revised Fukuoka guidelines recommend EUS for patients with worrisome features on imaging, including a cyst of ≥3 cm, enhancing mural nodule <5 mm, thickened enhanced cyst walls, main pancreas duct size of 5-9 mm, abrupt change in the duct caliber with distal pancreatic atrophy, lymphadenopathy, an elevated serum level of carbohydrate antigen 19-9 and a rapid rate of cyst growth >5 mm/2 years [9]. The revised guidelines are more aggressive than those in 2012 and the Sendai guidelines in 2006, with the recommendation for initial surveillance to occur at a shorter interval [10,31]. The American College of Radiology, however, stratifies risk based on age at presentation, interval increase in cyst size, and overall cyst size [32]. It recommends EUS even for cysts >1.5 cm in size, especially if main duct

communication is visualized or interval growth is detected on serial imaging [32]. It is notable that the ACG and AGA guidelines were authored by gastroenterologists, whereas the other guidelines were authored by an expert multidisciplinary panel consisting of gastroenterologists, surgeons, radiologists, and pathologists [31]. There is no single guideline that has sufficient accuracy to definitively guide clinical decision making [31].

Recently, Wu *et al* published a meta-analysis comparing the Fukuoka and AGA guidelines in risk-stratifying the malignant potential of pancreatic cysts. The study revealed that the diagnostic accuracy was similar and "unsatisfactory" with either guideline [33]. Our meta-analysis, in contrast, compared 2 American society guidelines and demonstrates that the sensitivity of the AGA guideline is lower, with a higher missed rate for advanced neoplasia compared to the ACG guideline. The ACG guideline, however, has a higher utilization of EUS for assessing PCL.

This systematic review and meta-analysis is the first study to perform a pooled analysis of multiple retrospective studies to assess the diagnostic accuracy of the AGA and the ACG guidelines, based on the number of HRF on cross-sectional imaging for EUS evaluation, and provides an objective assessment of each of these guidelines in risk-stratification. It also provides comparative objective data regarding the reduction in unnecessary EUS procedures based on 2 commonly used guidelines. Given the small number of populations in these retrospective studies, our results could have been underpowered. However, given the uncertain natural history of pancreatic cysts and their slow rate of progression to malignancy, prospective trials are challenging to perform.

This meta-analysis is heavily limited by the significant heterogeneity in the individual source studies. The presence or absence of advanced neoplasia was based on varying criteria, including a combination of cyst fluid analysis and cytology [20,22,24], histopathological review of resected specimens [18,23,25], imaging features [19], or a combination of the above [21]. Similarly, the follow up after EUS was not uniform, as some investigators performed resection of the cyst [18,21,23,25] whereas others opted for surveillance [19,20]. This lack of uniformity impedes a clear understanding of the natural history of the pancreatic cysts. Finally, some studies assessed the HRF and EUS findings as a method to select candidates for surgery, rather than solely to assess the indication for an EUS.

While these studies assessed the primary outcome differently, our aim was to compare the existing literature on diagnostic accuracy and prediction of AN while using either ≥1 or ≥2 HRF. Previous guidelines have also formulated their decision based on such available data [11,12]. In our review, carefully planned prospective randomized trials comparing the 2 strategies are lacking and no single study has conclusively answered the question of how many criteria should be used to refer a patient for EUS.

In conclusion, this systematic review and meta-analysis suggests that performing EUS for PCL with at least 1 HRF could offer a higher sensitivity in detecting advanced neoplasia compared to ≥2 HRF, with a high negative predictive value. Given the safety profile of EUS, it may be reasonable to consider using ≥1 HRF as the criterion for performing an EUS in select patients with PCL. However, prospective multicenter randomized studies are required to validate these findings.

Summary Box

What is already known:

- The American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) guidelines have recommended different thresholds of high-risk features (HRF) for performing endoscopic ultrasound for pancreatic cysts

What the new findings are:

- Restricting endoscopic ultrasound to ≥2 HRF, as recommended by the AGA, may lead to missing advanced neoplasia in pancreatic cysts
- Performing endoscopic ultrasound for pancreatic cysts with ≥1 HRF, as recommended by the ACG, offers higher sensitivity with comparable negative predictive value

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Supplementary material

Supplementary Table 1 PRISMA guidelines for meta-analysis

		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. Supplementary Table **2**	Page 8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 8,9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 8,9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
		RESULTS	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Pages 9,10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Pages 9,10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Pages 8,9,10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Pages 9,10, Fig. 3-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 10,11

(Contd...)

Supplementary Table 1 *(Continued)*

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
		DISCUSSION	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	Pages 12,13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 14
		FUNDING	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Supplementary Table 2 Newcastle-Ottawa scale for assessment of quality of studies

Study, year [Ref.]	Selection				Comparability	Outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough?	Adequacy of follow up of cohorts	
Kohli 2016 [20]	*	-	*	-	-	*	*	*	5
Ge 2017 [18]	-	-	*	-	-	*	*	*	4
Imbe 2017 [19]	*	-	*	*	-	*	*	*	6
Lee 2017 [21]	*	-	*	*	-	*	*	*	6
Sahar 2018 [22]	*	-	*	*	-	*	*	*	6
Sighinolfi 2017 [23]	-	-	*	-	-	*	*	*	4
Singhi 2016 [24]	*	-	*	*	-	*	*	*	6
Xu 2017 [25]	-	-	*	-	-	*	*	*	4