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ORIGINAL ARTICLE – PANCREATIC TUMORS

Accuracy of Fukuoka and American Gastroenterological Association Guidelines for Predicting Advanced Neoplasia in Pancreatic Cyst Neoplasm: A Meta-Analysis

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ABSTRACT

Background. A differential diagnosis of advanced pancreatic cystic neoplasms (PCNs) is critical to determine optimal treatment. The Fukuoka and American Gastroenterological Association (AGA) guidelines are the most widely accepted criteria for the management of PCNs.

Objective. This study aimed to evaluate the diagnostic value of these guidelines in predicting advanced neoplasia (AN).

Methods. A comprehensive electronic search of the PubMed, EMBASE, Web of Science, Cochrane Library, and Scopus databases was conducted to identify all relevant studies evaluating the Fukuoka and AGA guidelines in surgically resected and histologically confirmed PCNs. Pooled sensitivity, specificity, and diagnostic odds ratios (DORs) were calculated as compound measures of diagnostic accuracy using the random-effects model. Summary of receiver operating characteristic (SROC) curves and the area under the curve (AUC) were also performed.

Results. A total of 21 studies with 3723 patients were included in this meta-analysis. Of these studies, 15, 4, and 2 evaluated the Fukuoka guidelines, the AGA guidelines, and both guidelines, respectively. For AN prediction, the Fukuoka guidelines had a pooled sensitivity of 0.67 (95% confidence interval [CI] 0.64–0.70), pooled specificity of 0.64 (95% CI 0.62–0.66), and pooled DOR of 6.28 (95% CI 4.38–9.01), with an AUC of the SROC of 0.78. AGA guidelines showed a pooled sensitivity of 0.59 (95% CI 0.52–0.65), pooled specificity of 0.77 (95% CI 0.74–0.80), and pooled DOR of 5.84 (95% CI 2.60–13.15), with an AUC of 0.79 (95% CI 0.70–0.88).

Conclusion. When used alone, the Fukuoka and AGA guidelines showed similar but unsatisfactory diagnostic accuracy in the risk stratification of malignant potential of PCN. Thus, we recommend that they be applied only as a broad framework in clinical practice.

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Pancreatic cystic neoplasms (PCNs) are a rare subset of pancreatic tumors that not only exhibit vast histological and imaging appearances but also differ in clinical presentation, biological behavior, and malignant potential.[1] PCN diagnosis is increasing due to the aging population and wide use of high-resolution cross-sectional imaging techniques.[2,3] An increased risk of pancreatic malignancy has been found among patients with PCNs compared with the general population.[4] Once detected, patients and their physicians are challenged by the complex management of these cysts. Timely surgical removal of these potentially malignant cysts provides a unique opportunity to achieve the ever-elusive goal of preventing and improving the prognosis of pancreatic cancer. The precise diagnosis of non-malignant cysts will ease patients' anxiety and save resource by limiting long-term imaging surveillance. Thus, precise lesion characterization and accurate diagnosis, particularly the distinction between potentially and non-potentially malignant PCNs, are essential for PCN management.

As the understanding of the natural history of PCNs has improved, clinicians now know that not all cysts are premalignant and therefore not all of them require surgery.[5] Mucinous cysts, especially intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), are considered precursors of invasive pancreatic malignances, while mostly serous cystic lesions, such as serous cystic neoplasm, are generally regarded as benign.[6] At present, the main controversy regarding PCN management is the inability to precisely determine the histopathologic type of PCN before surgery. Even with the improvement of detective methodology, the initial diagnostic accuracy for PCNs remains limited; for example, the accuracies of imaging and cytology are less than 80% and 50%, respectively.[7,8] Several studies have demonstrated that the correlation between preoperative and pathological diagnosis is less than 50%, and up to 20% of all resections performed due to concerns on the malignant potential of these neoplasms have been found to show benign performance on final pathology.[9] Therefore, developing a reasonable approach to improve the classification of the malignant risk of individual patients and judgment for surgical indication is an important and difficult clinical task.

In the last two decades, several guidelines have been drafted for PCNs, to avoid the indiscriminate use of high-risk (HR) surgical procedures and to provide recommendations for non-operative management with follow-up strategies.[10,11] In 2006, the first international guidelines for IPMN and MCN management, commonly known as the Sendai Consensus Guidelines (SCG), were published by a panel of experts from the International Association of Pancreatology (IAP).[12] The SCG are highly sensitive for correctly identifying malignant lesions but limited by their low specificity, resulting in the unnecessary resections of numerous benign lesions.[13] The updated version of the SCG, also called the Fukuoka guidelines, was published in 2012 to increase specificity and preserve sensitivity for predicting advanced neoplasia (AN).[14] In 2015, the American Gastroenterological Association (AGA) proposed guidelines for PCN treatment.[15] At present, the Fukuoka and AGA guidelines are the most widely accepted standards for PCN management, and the utility of these two guidelines in clinical practice has been extensively reported. However, an extreme difference has been found among the existing results, causing inconsistencies in the real value of these guidelines in clinical applications. In this study, we performed a meta-analysis of the published data to evaluate the accuracy of the Fukuoka and AGA guidelines to detect AN in PCNs.

METHODS

Literature Search Strategy

A comprehensive electronic search of the PubMed, EMBASE, Web of Science, Cochrane Library, and Scopus databases was conducted for all studies evaluating the utility of the Fukuoka and AGA guidelines for PCNs, from 1 January 2012 to 15 May 2019 (the Fukuoka guidelines were published in 2012). No language limitation was indicated. The search terms included ('Fukuoka' or 'Sendai 2012' or 'AGA' or 'American Gastroenterological Association') and ('pancreatic cyst neoplasm' or 'pancreatic cyst' or 'pancreatic cystic lesion' or 'pancreas'). The reference lists of the identified studies or reviews were also screened to retrieve relevant papers. This meta-analysis was reported following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement.[16]

Inclusion and Exclusion Criteria

Two researchers, namely Jiayuan Wu and Yufeng Wang, independently conducted the literature search and selection. Any discrepancies were addressed by discussion. The titles and abstracts of each study were checked to determine potential eligibility. The full text was then examined for further determination. Studies were included if (1) they attempted to evaluate the accuracy of Fukuoka or AGA guidelines for the identification of AN in PCNs; (2) sufficient data were provided to construct the 2×2 contingency tables of true positive, false positive, false negative, and true negative; (3) surgical pathology data were used as the reference standard for the final diagnosis; and (4) they were published as full-text articles. The exclusion criteria were (1) abstracts, reviews, editorials, case reports, letter to editors, comments, expert opinions, or technical notes; (2) studies that did not classify PCNs in accordance with the Fukuoka or AGA criteria; (3) studies with insufficient information to establish 2×2 crosstabs; and (4) studies with overlapping cohorts of patients based on assessment of the study centers and recruitment period.

Definition

The pathological diagnosis of PCN was carried out based on the most aggressive histological changes according to the World Health Organization (WHO) classification systems.[17,18] AN was defined as the histological presence of high-grade dysplasia or invasive carcinoma. These neoplasms were considered 'positive' if they satisfied the criteria for surgical resection based on the Fukuoka or AGA guidelines, and 'negative' otherwise.

Data Extraction and Quality Assessment

Data extractions were performed by two independent reviewers, namely Yufeng Wang and Zitao Li, using a standardized form. Any disagreements were resolved by an arbiter (Huilai Miao). Data obtained from the original papers included study characteristics, such as first author, publication year, country of origin, study design, and recruitment time; patient features, such as sample size, age, sex, cyst size, and study cohort; and clinical outcomes, such as definition of 'positive' and final pathology.

The included studies were assessed for methodological quality using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, which consists of four key domains, namely patient selection, index test, reference standard, and flow and timing.[19]

Statistical Analysis

Based on the results from the 2 × 2 tables, data syntheses for pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were performed via the random-effects model (DerSimonian–Laird methodology); forest plots of each study and pooled estimates were also conducted. When empty cells occurred in the 2 × 2 table, 0.5 was added to these cells for continuity correction. Summary of receiver operating characteristic (SROC) curves were constructed to show the relationship between the sensitivity and proportion of false positives (1-specificity), which could solve the inconsistency of various results. The area under the curve (AUC) of the SROC curve was also calculated to obtain the probability of correctly recognizing diseased and non-diseased cases by a diagnostic test. In this study, we considered the guidelines to show good precision and poor performance when the AUC of the SROC is close to 1 and 0.5, respectively.[20]

Heterogeneity in the meta-analysis of diagnostic tests is generally caused by threshold or non-threshold effects. In this study, heterogeneity from the threshold effect was assessed by the appearance of the SROC curves, which present a 'shoulder arm' distribution, indicating the existence of a threshold effect, and by calculation of the Spearman correlation coefficient (ρ) between log(sensitivity) and log(1-specificity). The extent of heterogeneity induced by the non-threshold effect was qualitatively assessed by applying the Chi-square test for sensitivity and specificity, and Cochran's Q test for PLR, NLR, and DOR, and quantitatively determined by I^2 statistics.[21] Statistically significant heterogeneity was considered to be present if $p < 0.05$ or $I^2 > 50\%$. Subgroup and meta-regression analyses were applied to identify potential sources of heterogeneity. The above analyses were performed using the statistical software Meta-DiSc version 1.4 (Clinical Biostatistics Unit, Ramóny Cajal Hospital, Madrid, Spain).

Deek's funnel plot asymmetry test was applied to evaluate publication bias by investigating log(DOR) against the effective sample size.[22] In this study, calculations were completed by STATA version 14.0 (STATA Corporation, College Station, TX, USA). Quality assessment of the included studies was performed through the QUADAS-2 tool using Revman version 5.2 software.

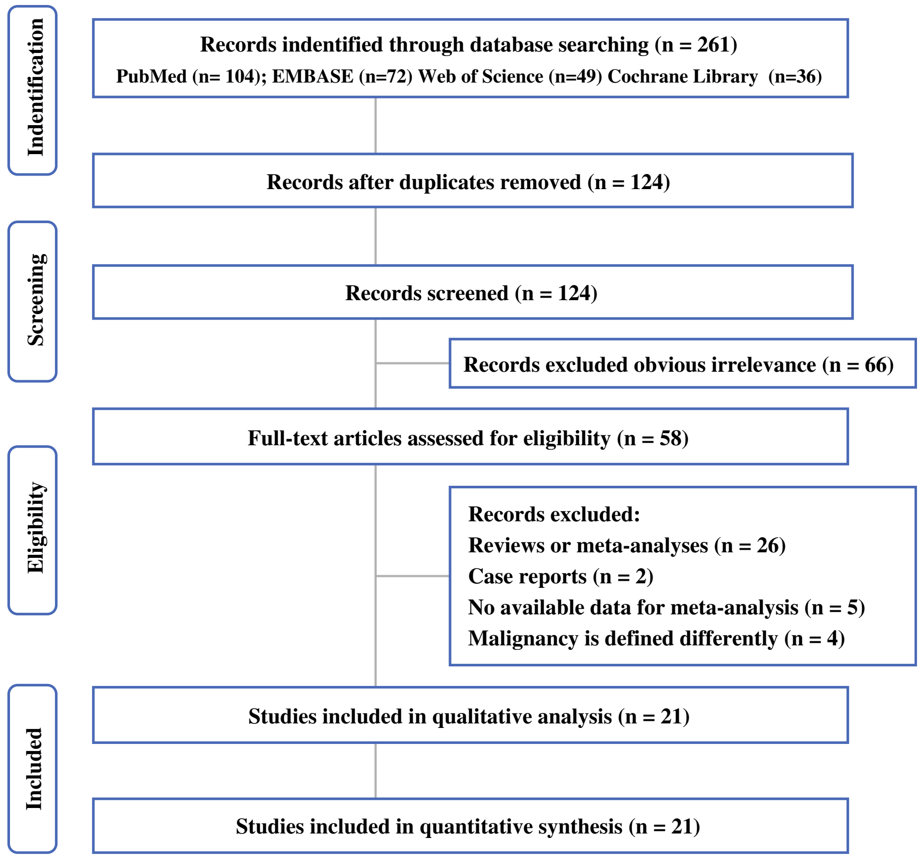
RESULTS

Study Characteristics and Quality Assessment

The flow diagram shown in Fig. 1 describes the details of the study selection process. From the 124 papers that initially qualified for detailed analysis, 21 studies comprising a total of 3723 patients were finally included.[1–21] All of these studies were retrospectively designed. The number of enrolled patients ranged from 41 to 350, with a mean/median age of 57–69 years; 45.9% (1707/3723) of the patients were males. The studies principally originated from the US,[3–5,7–9,14,17,20,21] China,[1,11] The Netherlands,[2] Germany,[16] France,[10] Korea,[12,15] Japan,[6,13,18] and Singapore.[19] In summary, 15 studies reported solely on the Fukuoka guidelines,[1,6,9–21] two studies reported on the AGA guidelines,[3,7] and four studies reported on both guidelines.[2,4,5,8] Six studies employed patients with all types of PCNs, including IPMN, MCN, SCA, and others, as study objects[1,3,4,7,8,14]; 13 studies employed IPMN cases[2,6,9–13,15–18,20,21]; and two studies enrolled patients with IPMN and MCN.[5,19] A summary of the study characteristics is outlined in Table 1, and the clinical features of each study are shown in Table 2.

The quality evaluation of the included studies is presented in Fig. 2. Thirteen studies presented an unclear risk of selection bias because of insufficient information to assess whether a case–control design or inappropriate exclusion was avoided. The majority of the studies did not report the 'blinding' of the assessors in the results of the reference standard, resulting in an unclear assessment of the index test domain. Similarly, interpretation of the reference standard without knowledge of the index test was poorly documented, leading to an unclear risk of reference standard bias in 14 studies. Moreover, 15 studies failed to report the time interval between the collection of the index test and reference standard, leading to an unclear assessment of disease progression bias. These possible biases may lead to overestimation of pooled outcomes. In general, the applicability of the patient selection, index test, and reference standard domains was good.

FIG. 1 PRISMA flowchart describing the selection process for study inclusion. *PRISMA* Preferred Reporting Items for Systematic Review and Meta-Analyses



Meta-Analysis of Fukuoka Guideline

A total of 19 studies with 3382 patients reported the diagnostic performances of the Fukuoka guidelines (Table 3). Overall, the pooled sensitivity of the Fukuoka guidelines in predicting AN was 0.67 (95% confidence interval [CI] 0.64–0.70) (Fig. 3a), their pooled specificity was 0.64 (95% CI 0.62–0.66) (Fig. 3b), their pooled PLR was 2.16 (95% CI 1.75–2.66) (Fig. 3c), their pooled NLR was 0.45 (95% CI 0.34–0.59) (Fig. 3d), and their pooled DOR was 6.28 (95% CI 4.38–9.01) (Fig. 3e). Furthermore, the pooled AUC of the SROC curve was 0.78 (95% CI 0.73–0.83) and the Q* index was 0.72 (95% CI 0.68–0.76) (Fig. 3f).

No significant threshold effect was observed among individual studies on the Fukuoka guidelines according to the appearance of the SROC curve (Fig. 3f]. The Spearman correlation coefficient ($\rho = 0.377$) with an insignificant p value of 0.231 further confirmed this assessment. When the non-threshold effect was analyzed, extreme heterogeneity was found in the overall sensitivity ($I^2 = 93.7\%$, $p < 0.001$), pooled specificity ($I^2 = 97.4\%$, $p < 0.001$), PLR ($I^2 = 92.0\%$, $p < 0.001$), NLR ($I^2 = 90.6\%$, $p < 0.001$), and DOR ($I^2 = 61.0\%$, $p < 0.001$). Therefore, the heterogeneity of the results of the Fukuoka guidelines arises from the non-threshold effect.

We performed subgroup analyses to explore the difference in diagnostic accuracy and explain the heterogeneity observed (Table 3). The Asian population (pooled DOR 9.23, 95% CI 5.92–14.40) exhibited higher diagnostic accuracy than the Caucasian population (pooled DOR 4.36, 95% CI 2.75–6.91). The PCN cohort showed an increased specificity of 0.80, but the IPMN/MCN and IPMN cohorts exhibited elevated sensitivities of 0.74 and 0.72, respectively. Overall, the PCN cohort (pooled DOR 10.28, 95% CI 3.73–28.24) showed better diagnostic accuracy compared with the IPMN/MCN (pooled DOR 3.75, 95% CI 1.37–10.26) and IPMN (pooled DOR 6.08, 95% CI 4.10–9.00) cohorts. When both HR stigmata and worrisome (WR) features were involved in the definition of 'positive', increased sensitivity (pooled sensitivity 0.79, 95% CI 0.74–0.84) and diagnostic accuracy (pooled DOR 8.58, 95% CI 2.65–27.78) were found, but reduced specificity (pooled specificity 0.56, 95% CI 0.52–0.59) was observed. When HR stigmata was involved in the definition of 'positive', the pooled calculations of sensitivity, specificity, and DOR were 0.62 (95% CI 0.59–0.66), 0.67 (95% CI 0.65–0.70), and 5.98 (95% CI 4.03–8.89), respectively.

TABLE 1 Characteristics of the included studies

References	Region	Study design	Recruitment time	*N*	Age, years	Male [*n* (%)]	Cyst size, mm (range)	Guidelines
Zhou et al.[23]	China	Retrospective	2008–2015	197	Median 57	78 (29.9)	Median 30 (22–48)	Fukuoka
Lekkerkerker et al.[24]	Netherlands	Retrospective	2006–2015	75	Mean 60	32 (42.6)	Median 40 (30–61)	Fukuoka, AGA
Ge et al.[25]	USA	Retrospective	2004–2014	300	Mean 62.6	113 (37.7)	NR	AGA
Sighinolfi et al.[26]	USA	Retrospective	2007–2016	209	Mean 62.18	93 (44.5)	Mean 39.16 ± 31.17	Fukuoka, AGA
Xu et al.[27]	USA	Retrospective	2008–2013	269	Mean 67.0	78 (23.9)	Mean 28.5 ± 17.0	Fukuoka, AGA
Kimura et al.[28]	Japan	Retrospective	1994–2015	98	Mean 68.3	54 (55.1)	Mean 29.4 ± 17.5	Fukuoka
Singhi et al.[29]	USA	Retrospective	2014–2015	41	Median 62	20 (48.8)	Median 35 (23–49)	AGA
Ma et al.[30]	USA	Retrospective	2000–2014	239	Median 65	78 (36.8)	Median 27 (17–39)	Fukuoka, AGA
Ridtitid et al.[31]	USA	Retrospective	2001–2013	135	Mean 65.2	71 (52.6)	Mean 26 ± 16	Fukuoka
Robles et al.[32]	France	Retrospective	2006–2014	120	Mean 57.9	65 (54.2)	Mean 22 ± 11	Fukuoka
Hsiao et al.[33]	Taiwan	Retrospective	2000–2015	138	Median 64	67 (48.6)	NR	Fukuoka
Han et al.[34]	Korea	Retrospective	1996–2011	230	Median 63	153 (66.5)	Mean 36	Fukuoka
Watanabe et al.[35]	Japan	Retrospective	2006–2014	49	Median 73	29 (59.2)	NR	Fukuoka
Kaimakliotis et al.[36]	USA	Retrospective	2000–2008	194	Median 58	74 (38.1)	Median 33 (2–204)	Fukuoka
Jang et al.[37]	Korea	Retrospective	1995–2012	350	Mean 63.4	216 (61.7)	Mean 32.1 ± 15.0	Fukuoka
Fritz et al.[38]	Germany	Retrospective	2004–2012	233	Median 65	93 (39.9)	NR	Fukuoka
Roch et al.[39]	USA	Retrospective	1992–2012	340	Mean 68.2	165 (48.5)	NR	Fukuoka
Aso et al.[40]	Japan	Retrospective	2006–2013	100	Median 67	70 (70.0)	NR	Fukuoka
Goh et al.[41]	Singapore	Retrospective	1991–2012	114	Median 59	40 (35.1)	NR	Fukuoka
Nguyen et al.[42]	USA	Retrospective	1996–2012	66	Median 69	24 (36.4)	Median 24 (13–30)	Fukuoka
Sahora et al.[43]	USA	Retrospective	1995–2012	226	Median 65	94 (39.2)	Mean 24 ± 12	Fukuoka

NR none reported, *AGA* American Gastroenterological Association

To further determine the sources of heterogeneity with respect to the Fukuoka guidelines, we performed meta-regression analysis with several pre-identified potential factors (Table 3). The overall outcome revealed that the study population ($p = 0.126$), cohort ($p = 0.147$), and definition of 'positive' ($p = 0.833$) did not contribute to the observed heterogeneity.

Meta-Analysis of American Gastroenterological Association Guidelines

As shown in Table 3, according to the data synthesis of six papers with 1133 cases, the pooled sensitivity, specificity, PLR, NLR, and DOR of the AGA criteria in AN prediction were 0.59 (95% CI 0.52–0.65) (Fig. 4a), 0.77 (95% CI 0.74–0.80) (Fig. 4b), 2.34 (95% CI 1.68–3.27) (Fig. 4c), 0.42 (95% CI 0.20–0.88) (Fig. 4d), and 5.84 (95% CI 2.60–13.15) (Fig. 4e), respectively. In addition, the AUC under the SROC curve was 0.79 (95% CI 0.70–0.88) and the Q* index was 0.73 (95% CI 0.65–0.80) (Fig. 4f).

From the shape of the SROC curve (Fig. 4f) and estimation of the Spearman correlation coefficient ($\rho = 0.443$, $p = 0.115$), no threshold effect appears to exist. When the non-threshold effect was investigated, conspicuous heterogeneity was observed in the overall sensitivity ($I^2 = 95.7\%$, $p < 0.01$), pooled specificity ($I^2 = 95.0\%$, $p < 0.01$), PLR ($I^2 = 76.1\%$, $p = 0.001$), NLR ($I^2 = 97.2\%$, $p < 0.001$), and DOR ($I^2 = 73.2\%$, $p = 0.002$).

Upon subgroup analysis, the PCN cohort exhibited a much higher diagnostic accuracy (pooled DOR 9.93, 95% CI 6.28–15.69) than the IPMN with/without MCN cohort (pooled DOR 1.91, 95% CI 0.19–19.20). The subgroup using positive cytology with two HR features to define 'positive' (pooled DOR 5.71) showed a diagnostic accuracy similar to that of the subgroup applying positive cytology with one HR feature (pooled DOR 6.18).

According to the results of the meta-regression analysis, the heterogeneity of the AGA guidelines could not be explained by the variables of cohort ($p = 0.091$) and definition of 'positive' ($p = 0.149$) (Table 3).

Publication Bias

The publication bias of the included studies was assessed using Deek's funnel plot, as shown in Fig. 5. The regression analyses of funnel plots were statistically insignificant (Fukuoka guidelines, $p = 0.99$; AGA guidelines, $p = 0.84$), thus suggesting that publication bias is not

TABLE 2 Summary of studies evaluating the utility of the Fukuoka and AGA guidelines

References	Cohort	Definition of 'Fukuoka positive'	TP	FP	FN	TN
Fukuoka guideline						
Zhou et al.[23]	98 IPMNs, 55 MCNs, 34 SCAs, 10 others	At least one HR stigmata[a]	22	6	33	136
Lekkerkerker et al.[24]	75 IPMNs	At least one HR stigmata or two WR features[b]	36	31	0	8
Sighinolfi et al.[26]	89 IPMNs, 24 MCNs, 18 SCAs, 78 others	At least one HR stigmata or positive cytology with one WR feature	43	69	1	96
Xu et al.[27]	183 IPMNs, 86 MCNs	At least one HR stigmata or positive cytology	30	124	11	104
Kimura et al.[28]	98 IPMNs	At least one HR stigmata	30	11	10	57
Ma et al.[30]	163 IPMNs, 28 MCNs, 35 SCAs, 13 others	At least one HR stigmata	20	7	51	161
Ridtitid et al.[31]	135 IPMNs	At least one HR stigmata or WR features	1	5	17	112
Robles et al.[32]	120 IPMNs	At least one HR stigmata	34	55	2	29
Hsiao et al.[33]	138 IPMNs	At least one HR stigmata	39	12	7	41
Han et al. [34]	230 IPMNs	At least one HR stigmata or WR features	42	34	35	119
Watanabe et al.[35]	49 IPMNs	At least one HR stigmata	16	11	2	19
Kaimakliotis et al. [36]	43 IPMNs, 76 MCNs, 22 SCAs, 53 others	At least one HR stigmata	20	42	16	116
Jang et al.[37]	350 IPMNs	At least one HR stigmata or WR features	94	182	3	71
Fritz et al.[38]	233 IPMNs	At least one HR features	30	62	26	115
Roch et al.[39]	340 IPMNs	At least one HR stigmata	48	37	52	203
Aso et al.[40]	100 IPMNs	At least one HR stigmata	29	10	19	42
Goh et al.[41]	67 IPMNs, 47 MCNs	At least one HR stigmata	35	21	12	46
Nguyen et al.[42]	66 IPMNs	At least one HR features	10	23	5	28
Sahora et al.[43]	226 IPMNs	At least one HR stigmata	49	131	3	43
Study (year)	Cohort	Definition of 'AGA positive'	TP	FP	FN	TN
AGA guideline						
Lekkerkerker et al.[24]	75 IPMNs	At least one HR feature[c] or positive cytology	32	22	4	17
Ge et al.[25]	198 IPMNs, 63 MCNs, 39 SCAs	At least two HR features or positive cytology	45	76	9	170
Sighinolfi et al.[26]	89 IPMNs, 24 MCNs, 18 SCAs, 78 others	At least two HR features or positive cytology	39	62	5	103
Xu et al.[27]	183 IPMNs, 86 MCNs	At least two HR features or positive cytology	3	27	38	201
Singhi et al.[29]	41 suspected PCNs	At least two HR features or positive cytology	8	6	5	22
Ma et al.[30]	163 IPMNs, 28 MCNs, 35 SCAs, 13 others	At least two HR features or positive cytology	25	10	46	158

AGA American Gastroenterological Association, *HR* high-risk, *WR* worrisome, *IPMNs* intraductal papillary mucinous neoplasms, *MCNs* mucinous cystic neoplasms, *SCAs* serous cystadenomas, *PCNs* pancreatic cystic neoplasms, *TP* true positive, *FP* false positive, *FN* false negative, *TN* true negative

[a]HR stigmata for the Fukuoka guideline: obstructive jaundice, enhancing solid component, dilated main pancreatic duct ≥ 10 mm

[b]WR features for the Fukuoka guideline: pancreatitis, cyst size ≥ 3 cm,; thickened cyst wall, main pancreatic duct 5–9 mm, non-enhancing mural nodule, abrupt change in pancreatic duct caliber and distal atrophy, lymphadenopathy

[c]HR stigmata for the AGA guideline: cyst size ≥ 3 cm, dilated pancreatic duct with a solid component, mural nodule or abnormal cytology confirmed on endoscopic ultrasound and fine needle aspiration

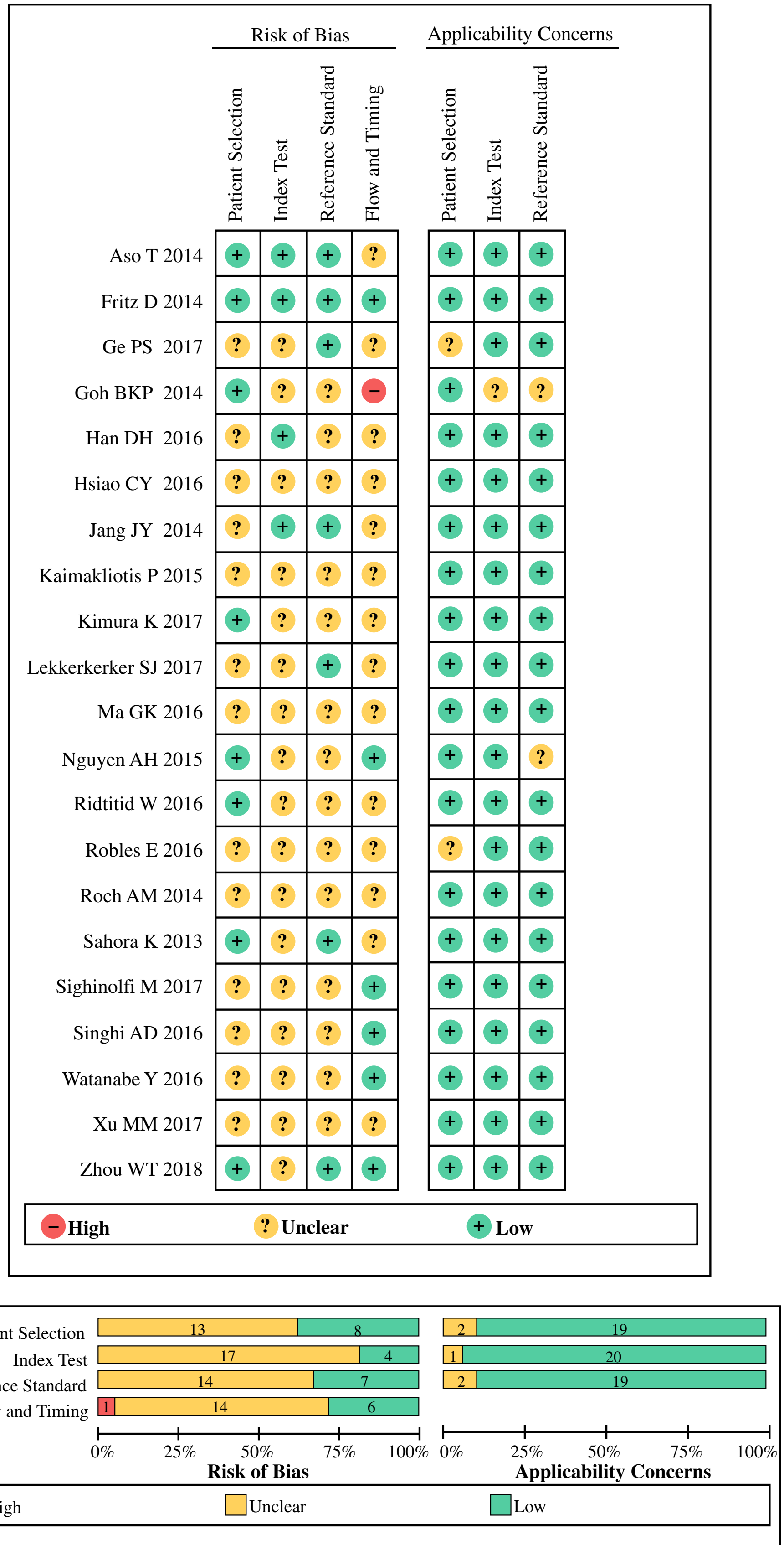


FIG. 2 Risk of bias of each included study using the QUADAS-2 Quality assessment tools. *QUADAS-2* Quality Assessment of Diagnostic Accuracy Studies-2

TABLE 3 Pooled and subgroup analyses of the meta-analysis

Category	No. of studies (cases)	Sensitivity (95% CI)	I^2 (%)	Specificity (95% CI)	I^2 (%)	DOR (95% CI)	I^2 (%)	P_m
Fukuoka guideline (all studies)	19 (3382)	0.67 (0.64–0.70)	93.7	0.64 (0.62–0.66)	97.4	6.28 (4.38–9.01)	61.0	
Study population								0.126
Asian	8 (1276)	0.72 (0.67–0.76)	92.1	0.65 (0.62–0.68)	97.3	9.23 (5.92–14.40)	42.7	
Caucasian	11 (2106)	0.64 (0.59–0.68)	94.7	0.63 (0.61–0.66)	97.7	4.36 (2.75–6.91)	55.2	
Cohort								0.147
PCN	4 (839)	0.51 (0.44–0.58)	95.6	0.80 (0.77–0.83)	97.3	10.28 (3.74–28.24)	73.3	
IPMN and/or MCN	2 (383)	0.74 (0.63–0.83)	0.0	0.51 (0.45–0.57)	91.1	3.75 (1.37–10.26)	69.4	
IPMN	13 (2160)	0.72 (0.68–0.75)	93.0	0.60 (0.57–0.62)	97.1	6.08 (4.10–9.00)	53.7	
Definition of 'positive'								0.833
HR stigmata involvement	14 (2383)	0.62 (0.59–0.66)	90.2	0.67 (0.65–0.70)	97.0	5.98 (4.03–8.89)	62.8	
HR stigmata and WR features involvement	5 (999)	0.79 (0.74–0.84)	96.8	0.56 (0.52–0.59)	98.3	8.58 (2.65–27.78)	67.4	
AGA guideline (all studies)	6 (1133)	0.59 (0.52–0.65)	95.7	0.77 (0.74–0.80)	95.0	5.84 (2.60–13.15)	73.2	
Cohort								0.091
PCN	4 (789)	0.64 (0.57–0.71)	93.7	0.75 (0.71–0.78)	95.0	9.93 (6.28–15.69)	0.0	
IPMN and/or MCN	2 (344)	0.45 (0.34–0.57)	98.3	0.82 (0.76–0.86)	97.2	1.91 (0.19–19.20)	85.8	
Definition of 'positive'								0.149
Positive cytology with one HR feature	1 (75)	0.89	NA	0.44	NA	6.18	NA	
Positive cytology with two HR features	5 (1058)	0.54 (0.47–0.60)	95.6	0.78 (0.75–0.81)	95.0	5.71 (2.18–14.96)	78.5	

P_m *p*-value for statistical outcome based on multivariate meta-regression analysis, *DOR* diagnostic odds ratio, *PCN* pancreatic cystic neoplasm, *IPMN* intraductal papillary mucinous neoplasm, *MCN* mucinous cystic neoplasm, *HR* high-risk, *WR* worrisome, *CI* confidence interval, *AGA* American Gastroenterological Association, *NA* not available

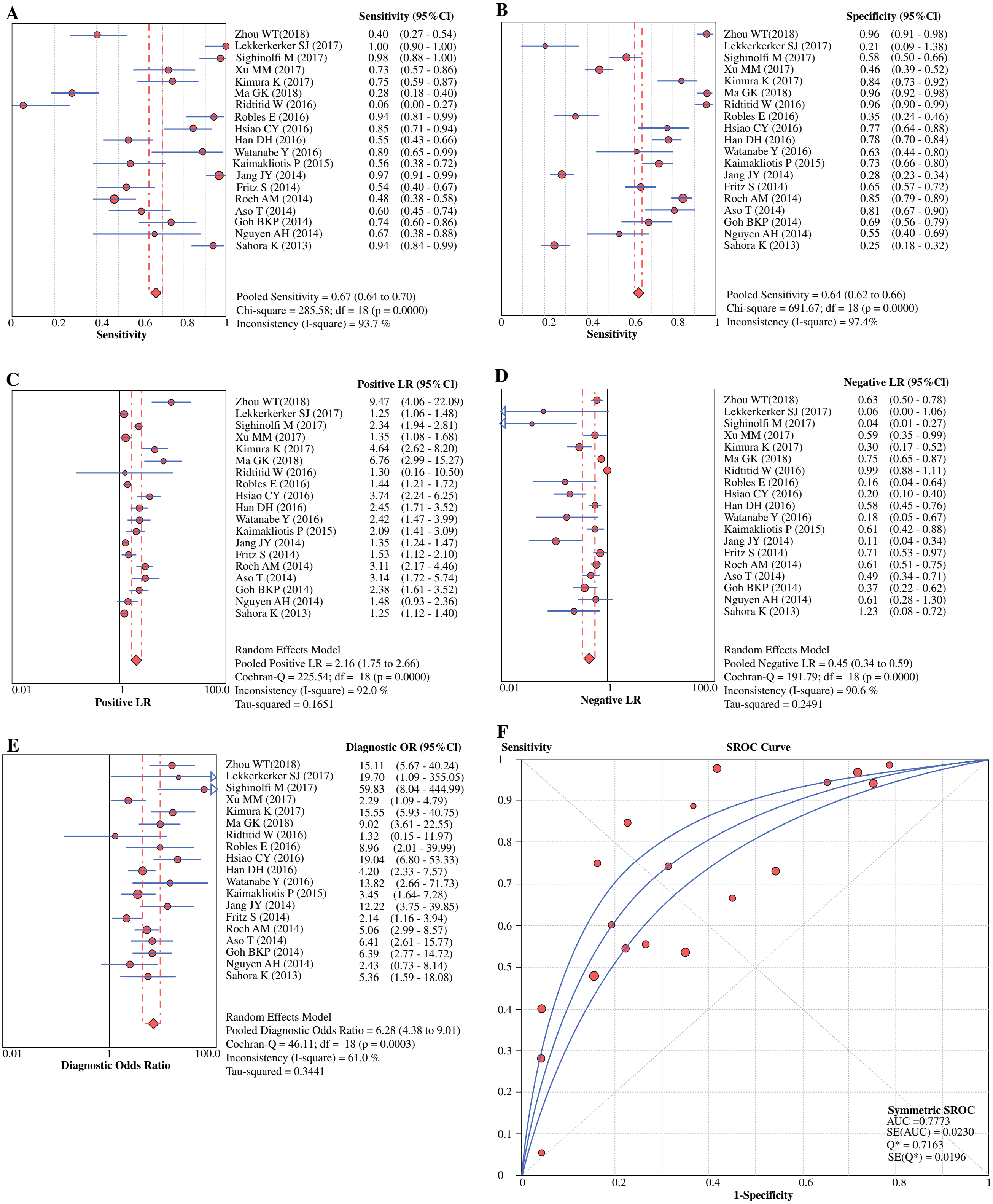


FIG. 3 Forest plots of diagnostic accuracy for the Fukuoka guideline in predicting pancreatic cystic neoplasms with malignant potential: **a** sensitivity; **b** specificity; **c** positive LR; **d** negative LR; **e** diagnostic odds ratio; and **f** summary of receiver operating characteristic curve. *AUC* area under the curve, *SE* standard error, *CI* confidence interval, *df* degrees of freedom, *LR* likelihood ratio, *OR* odds ratio, *SROC* summary of receiver operating characteristic curve

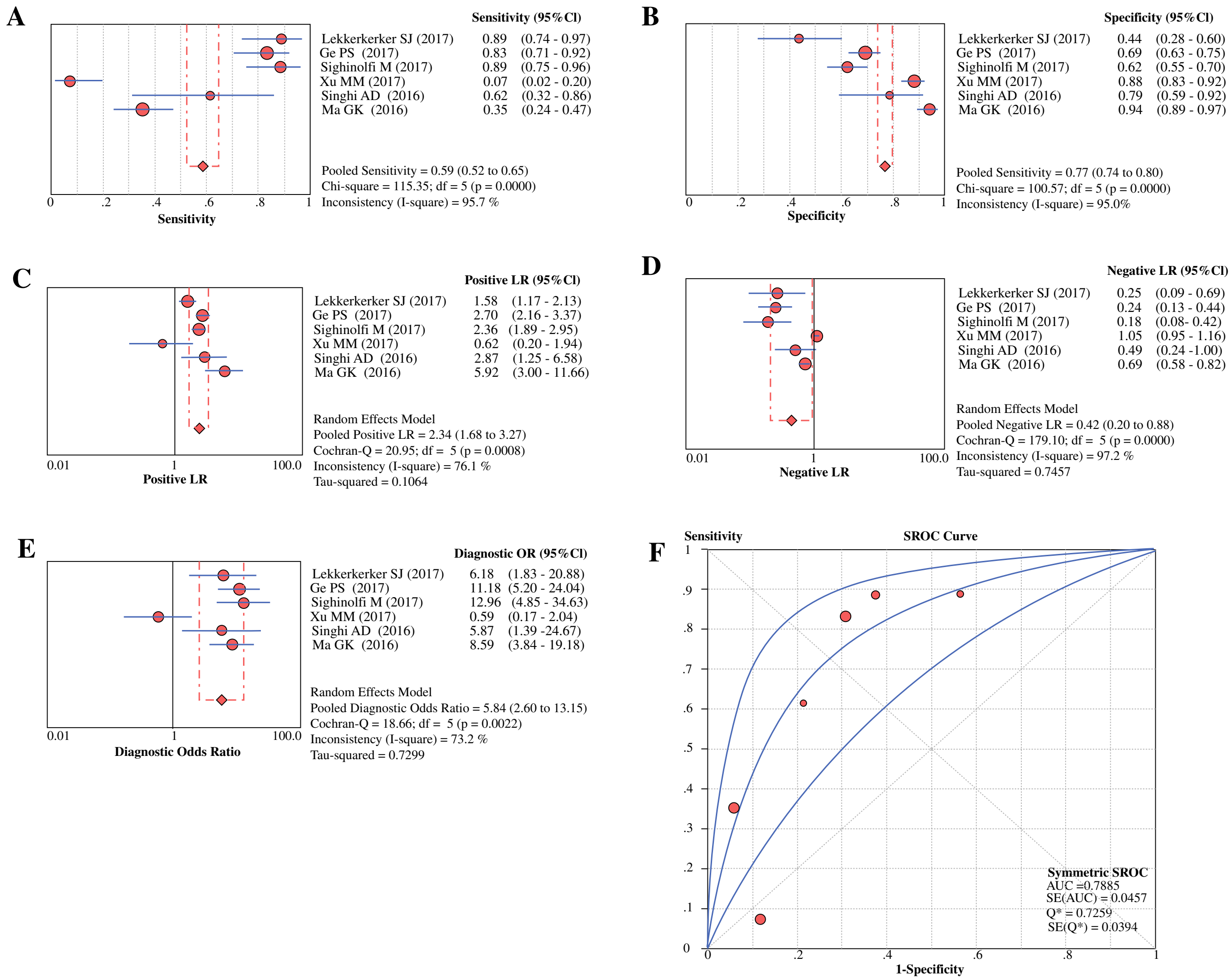


FIG. 4 Forest plots of diagnostic accuracy for the AGA guideline in predicting pancreatic cystic neoplasms with malignant potential: **a** sensitivity; **b** specificity; **c** positive LR; **d** negative LR; **e** diagnostic odds ratio; **f** summary of receiver operating characteristic curve. *AUC* area under curve, *SE* standard error, *AGA* American Gastroenterological Association, *CI* confidence interval, *df* degrees of freedom, *LR* likelihood ratio, *OR* odds ratio, *SROC* summary of receiver operating characteristic curve

a major determinant of pooled diagnostic accuracy in this meta-analysis.

DISCUSSION

The Fukuoka guidelines provide risk stratification by identifying three categories of PCN, namely those with HR stigmatas, those with WR features, and those without HR stigmatas or WR features (Table 4).[14] Patients with at least one HR stigmata were regarded as of high malignant potential and warranted immediate surgical resection. In the case of WF features, further evaluation with endoscopic ultrasound (EUS) was suggested to improve stratification of the risk of malignancy. The AGA guidelines provide two different categories of risk stratification, namely HR features and low-risk features (Table 4).[15] In the presence of two of the three HR features and positive cytology at EUS-fine needle aspiration (FNA), patients must undergo surgical evaluation. Key differences were observed between the Fukuoka and AGA guidelines. The former specifically targets suspected IPMNs and MCNs, whereas the latter is restricted to all incidentally found patients with asymptomatic PCNs.[44] Other key differences involve suggestions and the best-suited modality for surveillance. According to the Fukuoka guidelines, surveillance to be scheduled according to cyst size is recommended for patients without HR stigmata or WR features at initial diagnosis. For patients without surgical indication, the AGA guidelines suggest patient surveillance with MRI starting 1 year after diagnosis and then every 2 years. For the first time, the AGA guidelines boldly recommend discontinuation of follow-up for low risk cysts 5 years after diagnosis, thus

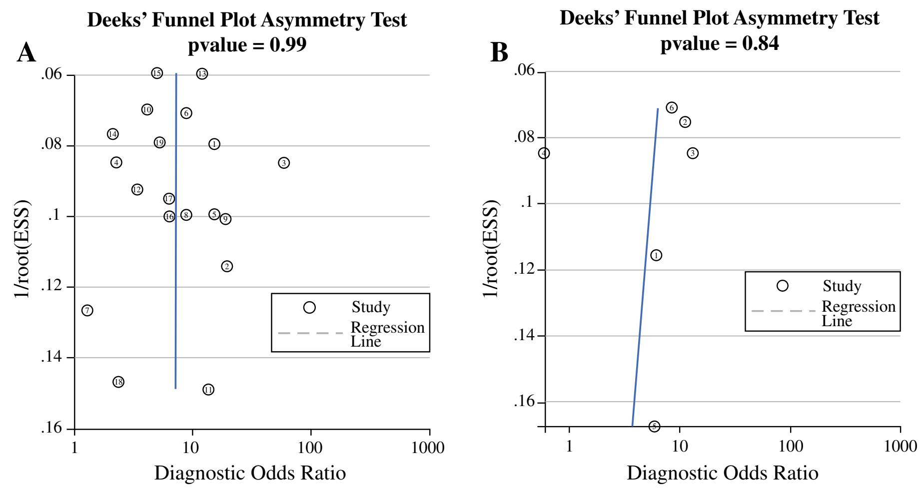


FIG. 5 Deek's funnel asymmetry plot test for evaluation of potential publication bias: **a** Fukuoka guideline; **b** American Gastroenterological Association guideline

TABLE 4 Fukuoka guidelines and AGA guidelines for the management of pancreatic cystic neoplasms

Guidelines	Year	Type of PCN	Absolute indications for surgery	Relative indications for surgery	Surveillance
Fukuoka	2012	IPMN, MCN	High-risk stigmata: Enhancing mural nodules ≥ 5 mm MPD measuring ≥ 10 mm Obstructive jaundice	Worrisome features: Episodes of acute pancreatitis Cyst size ≥ 30 mm Enhancing mural nodules < 5 mm Thickened/enhancing cysts walls MPD measuring 5–9 mm Lymphadenopathy Change in MPD caliber with distal atrophy Increased serum CA19-9 level Cyst growth rate ≥ 5 mm/2 years	Those without high-risk stigmata or worrisome features
AGA	2015	Asymptomatic PCNs	High-risk features: Cysts measuring ≥ 30 mm, A dilated MPD A solid component Cytology positive for malignancy	Not mentioned	Not mentioned

AGA American Gastroenterological Association, *PCN* pancreatic cyst neoplasm, *IPMN* intraductal papillary mucinous neoplasm, *MCN* mucinous cystic neoplasm, *MPD* main pancreatic duct, *CA* carbohydrate antigen

assuming that stable cysts exhibit a small risk of malignant progression, which may likely be offset by the cost of lifelong surveillance and the risk of surgery.[45]

In the current meta-analysis, equivalent pooled DOR demonstrated that both guidelines show similar diagnostic accuracy in recognizing AN. However, while the Fukuoka guidelines are more sensitive than the AGA guidelines, the specificity of the former is less than that of the latter.

The Fukuoka guidelines exhibited an overall sensitivity of 0.67 and specificity of 0.64 for predicting AN, thus suggesting that 33% of patients with AN would have been missed, while 36% of patients without AN would have been misdiagnosed. The Fukuoka guidelines sought to improve the specificity, but there seemed to be no significant improvement. These outcomes indicate that the Fukuoka guidelines are imperfect because experts' consensus, not evidence-based methods, were used to develop them. Clinical symptoms and imaging features make up the basis of the Fukuoka guidelines. Overall, symptomatic cysts exhibit a high risk of malignant progression, depending on the clinical circumstances, and either resection (if amelioration of symptoms is necessary) or further evaluation is warranted. Lesion-related obstructive jaundice, which has been addressed as the sole 'absolute' criterion for surgery by the Fukuoka guidelines, is a condition that highly suggests malignancy, but could also be seen in benign lesions, i.e. a large serous cystadenoma located in the pancreatic head.[46] According to a comprehensive data synthesis of published studies, the accuracy of single imaging modalities for identifying the specific type of PCNs is relatively low.[47] Therefore, the application of a single feature for predicting AN is inefficient, and a combined approach is needed.

As previously noted, the Fukuoka guidelines were developed for IPMN and MCN management. When subgroup analyses were conducted based on the cystic types, patients with IPMN and/or MCN, as well as with IPMN solely, exhibited higher sensitivity but lower specificity compared with patients with all types of PCNs (Table 3), similar to the results of a large meta-analysis by Heckler et al.[48]. For patients with suspicious IPMN and MCN, current clinical practices deem them at high risk of malignant transformation and recommend surgical resection for these patients. Thus, increased sensitivity was achieved in this subgroup. Several included studies enrolled all patients with a pancreatic cyst because the preoperative diagnosis of IPMNs and MCNs, especially BD-IPMNs, is currently not reliable.[49] Furthermore, when HR stigmatas or WR features were used as the definition of 'malignant', the pooled sensitivity considerably improved whereas the pooled specificity decreased, thus suggesting that some WR features may exhibit high predictive value for AN recognition. In fact, several issues have been suggested to improve the accuracy of the Fukuoka guidelines. Over half of the patients with a main pancreatic duct (MPD) measuring 5–9 mm harbor malignant cysts; thus, an MPD size of $\geq$ 5 mm must be regarded as an 'HR stigmata' instead of a 'WR feature'.[50] Diabetes mellitus in IPMN patients is associated with AN and therefore must be considered as an additional WR feature.[51]

The present work is the first meta-analysis to evaluate the diagnostic value of the AGA guidelines for AN. According to the pooled results, application of the AGA guidelines missed 41% of cases with AN, which could be attributed to the highly stringent criteria applied for pancreatic cyst resection. The high threshold of the AGA guidelines was set from the viewpoint of medical economics; thus, these guidelines generally favor surveillance over surgical resection. However, 23% of the patients selected by the AGA guidelines would have been misdiagnosed as AN. This poor accuracy of the AGA guidelines is not surprising and could be largely attributed to their inherent performance characteristics. The AGA guidelines were developed by an evidence-based approach using the GRADE framework, but most of the available evidence is of very low quality due to the retrospective nature of the cases studied. Given that cross-sectional imaging cannot reliably differentiate between advanced and non-advanced neoplasms, the AGA guidelines first require the HR features seen on cross-sectional imaging to be further verified by EUS and cytology. The morphological features of EUS alone exhibit poor diagnostic value for AN, but their predictive value is enhanced when combined with FNA and cytopathological evaluation.[52] Given highly variable definitions for 'concerning' cytology, the use of cytology in distinguishing malignant and benign PCNs remains problematic.[53] To solve the low sensitivity of AGA guidelines and cytology, we recommend combination of these procedures with cystic fluid analysis. While some novel biomarkers, including carcinoembryonic antigen,[54] carbohydrate antigen 19-9,[55] and mucin,[56] are quite promising, additional trials with larger populations are required.

In the subgroup analyses of the AGA guidelines, patients with IPMN or MCN showed an extremely low sensitivity of 0.45, possibly because the included studies comprised patients from as early as 2000, which is prior to the publication of the AGA guidelines, when less restrictive criteria were used to recommend resection. Some included studies enrolled both asymptomatic and symptomatic patients with PCNs, which is contradictory to the usable range of the AGA guidelines. In fact, seven of the nine studies cited by the AGA technical review documented symptomatic patients ranging from 46 to 74% in their study cohorts.[57–65] In clinical practice, it is challenging, even impossible, to determine whether symptoms are due to the pancreatic cyst or non-specific in nature, because the presenting symptom inducing further imaging examination is rarely related to the cyst.[27] Therefore, the statement that "AGA guidelines only pertain to asymptomatic PCNs" may be a flawed approach.

Although this meta-analysis provides a comprehensive assessment of the diagnostic performance of the Fukuoka and AGA guidelines for AN, several caveats should be taken into account when interpreting the results. First, an extreme degree of heterogeneity was found between the included studies. We detected substantial heterogeneity by meta-regression analysis, but none of the potential confounders contributed to the majority of heterogeneity found. Subgroup analyses revealed that the stratification of the confounding factors did not remove the heterogeneity for specificity. However, heterogeneity markedly differed in the subgroup analyses of study cohorts related to the sensitivity of the Fukuoka guidelines and the DOR of the AGA guidelines, which may be responsible for the differences in morphological characteristics and malignant potential among cystic types. In terms of the DOR of the Fukuoka guidelines, extreme heterogeneity was found in the Caucasian population, but not in the Asian population, which may be attributed to racial differences and variations in clinicians' experience. Second, the included studies only enrolled surgically resected cases to ensure the histopathology of the cysts. However, the results may possibly be skewed by the higher prevalence of malignancy compared with a surveillance-only population, because the true sensitivity and specificity could not be calculated with a shrinking 'denominator'. Third, most of the included studies could not satisfy all of the QUADAS-2 criteria for methodological weakness, and lacked reporting clarity to some degree. This phenomenon could be mainly explained by the retrospective case–control design of the included studies, which may be attributed to the rarity of PCNs in the general population. Thus, a study with an improved design and more homogenous population is required to address the abovementioned questions.

While this meta-analysis has immediate applicability to practitioners using these two clinical guidelines, it is no doubt without its limitations. First, despite a broad search strategy, we could only find six eligible studies describing the AGA guidelines; this number is extremely small. Second, the imaging features of the included studies were mainly extracted from radiological reports, and measurement bias from different radiologists could not be excluded. Third, because the recruitment time of the included studies ranged from 1991 to 2016, the morphological features of the imaging examinations may be adversely affected due to rapid developments in radiological technologies and scanning protocols over the past 20 years. Fourth, each study exhibited its own descriptions of malignancy, patient features, and imaging technologies, which may lead to extreme between-study divergence. Finally, given insufficient information, we could not conduct a comparison between these two guidelines.

CONCLUSIONS

When used alone, the Fukuoka and AGA guidelines exhibited unsatisfactory sensitivity and specificity for the risk stratification of malignant potential of PCN, making them partially unreliable in clinical practice. However, given that no better guidelines are yet available, these guidelines are still useful tools for PCN management. As no single cyst feature can independently predict malignancy, it is imperative to remember that these guidelines must only be used as a broad framework, and guideline selection must be tailored according to comprehensive considerations. The decision for the management of PCN, including resection or surveillance, depends on the patient's risk–benefit assessment, including the prevalence of malignant PCNs, the surgical type, complications, surgical fitness, and life expectancy. The additive effect of multiple criteria for predicting malignant pancreatic cysts requires further validation, and an alternative approach to increase the diagnostic accuracy of AN must be developed.

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