—Original Article—

Efficacy of EUS-guided needle-based confocal laser endomicroscopy in the diagnosis of pancreatic lesions: A systematic review and meta-analysis

Syed Mohsin Saghir[1], Banreet Singh Dhindsa[1], Sarav Gunjit Singh Daid[2], Harmeet S. Mashiana[3], Amaninder Dhaliwal[3], Chad Cross[4], Shailender Singh[3], Ishfaq Bhat[3], Gordon V. Ohning[5], Douglas G. Adler[6]

[1]Department of Internal Medicine, University of Nevada Las Vegas School of Medicine, Las Vegas, NV, USA; [2]Department of Internal Medicine, Roger Williams Medical Center, Providence, RI, USA; [3]Division of Gastroenterology and Hepatology, University of Nebraska Medical Center, Omaha, NE, USA; [4]Department of Biostatistics and Epidemiology, University of Nevada, Las Vegas, NV, USA; [5]Department of Gastroenterology and Hepatology, University of Nevada Las Vegas School of Medicine, Las Vegas, NV, USA; [6]Huntsman Cancer Center, University of Utah School of Medicine, Salt Lake City, UT, USA

ABSTRACT

Background and Objectives: Needle-based confocal laser endomicroscopy (nCLE) is a procedure in which an AQ-Flex nCLE mini-probe is passed through an EUS-FNA needle into a pancreatic lesion to enable subsurface *in vivo* tissue analysis. In this study, we conducted a systematic review and meta-analysis of nCLE for the diagnosis of pancreatic lesions. **Materials and Methods:** We conducted a comprehensive search of several databases and conference proceedings, including PubMed, EMBASE, Google-Scholar, MEDLINE, SCOPUS, and Web of Science databases (earliest inception to March 2020). The primary outcomes assessed the pooled rate of diagnostic accuracy for nCLE and the secondary outcomes assessed the pooled rate of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and adverse events (AE) of nCLE to diagnose premalignant/malignant pancreatic lesions. **Results:** Eleven studies on 443 patients were included in our analysis. The pooled rate of diagnostic accuracy of EUS nCLE was 83% (95 confidence interval [CI] = 79–87; $I^2 = 0$). The pooled rate of sensitivity, specificity, PPV and NPV of EUS nCLE was 85.29% (95% CI = 76.9–93.68; $I^2 = 85\%$), 90.49% (95% CI = 82.24–98.74; $I^2 = 64\%$), 94.15% (95% CI = 88.55–99.76; $I^2 = 68\%$), and 73.44% (95% CI = 60.16–86.72; $I^2 = 93\%$), respectively. The total AE rate was 5.41% (±5.92) with postprocedure pancreatitis being the most common AE at 2.28% (±3.73). **Conclusion:** In summary, this study highlights the rate of diagnostic accuracy, sensitivity, specificity, and PPV for distinguishing premalignant/malignant lesions. Pancreatic lesions need to be further defined with more validation studies to characterize CLE diagnosis criteria and to evaluate its use as an adjunct to EUS-FNA.

Key words: lesions, meta-analysis, needle-based confocal laser endomicroscopy, pancreatic

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Address for correspondence

Dr. Douglas G. Adler, Huntsman Cancer Center, University of Utah School of Medicine, 30 N 1900 E, Room 4R118, Salt Lake City, UT 84132, USA.

E-mail: douglas.adler@hsc.utah.edu

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INTRODUCTION

Pancreatic lesions comprise a broad spectrum of benign and malignant processes.[1] These lesions can further be characterized as cystic, solid, or mixed.[1-3] Pancreatic cystic lesions (PCLs) include, but are not limited to, intraductal papillary mucinous neoplasms (IPMN), serous cystic neoplasms (SCN), mucinous cystic neoplasms (MCN), and pancreatic fluid collections.[1-3] Most solid lesions are pancreatic ductal adenocarcinomas (PDAC), although chronic pancreatitis can sometimes mimic this.[1-3] Pancreatic neuroendocrine tumors (PNET) or solid pseudopapillary neoplasms (SPN) can be solid, cystic, or mixed.[1-3] PCLs have an estimated prevalence of 2.4%–13.5% in asymptomatic individuals.[4] The prevalence of solid pancreatic lesions is less well-defined.[5] Compared to solid lesions, the ability of conventional imaging techniques to differentiate between benign and malignant cystic lesions is limited.[6]

The current management for most solid pancreatic lesions (SPL) is surgical resection, whereas management of PCLs typically incorporates the utilization of EUS-FNA or imaging for surveillance depending on the characteristics of the cyst.[3,7-9] Differentiating the type of PCL is imperative when the diagnosis is unclear as misdiagnosis may adversely impact the quality of life.[3,10] The sensitivity and specificity of EUS FNA for diagnosing a PCL are variable, ranging from 63%–88% to 88%–92%, respectively.[3,11-14] Nonetheless, a significant proportion of premalignant PCLs remain undiagnosed, indicating that further investigations are warranted.[15,16]

A needle-based confocal laser endomicroscopy (nCLE) procedure has been developed for the evaluation of pancreatic lesions. In this procedure, an AQ-Flex nCLE mini-probe (Cellvizio; Mauna Kea Technologies, Paris, France) is passed through a 19-G EUS-FNA needle into a pancreatic lesion to enable subsurface imaging of the mucosa for *in vivo* tissue analysis.[17,18] The technique was first described in 2011 by Konda *et al.*[20] Several trials have been conducted thereafter with encouraging results.[19-21]

The current data regarding nCLE are limited and has varying results. We performed a systematic review and meta-analysis on the diagnostic accuracy of nCLE and its sensitivity and specificity on detecting premalignant/malignant lesions.

METHODS

Search strategy

A comprehensive search from multiple databases and conference proceedings was conducted, including PubMed, EMBASE, MEDLINE, SCOPUS, Cochrane, Web of Science, and Google Scholar from earliest inception to April 2020. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to identify studies utilizing nCLE for pancreatic lesions[22] [Supplementary Figure 1].

Literature search keywords consisted of a combination of "needle-based," "confocal," "laser," "endomicroscopy," "nCLE," "pancreatic," "cysts," "lesions," "masses," "Cellvizio," "endoscopic" and "ultrasound." The literature search was isolated to studies on human subjects from peer-reviewed journals. Titles and abstracts from each study were reviewed by two authors (SS, BD) independently and excluded them if our research question was not fulfilled, per prespecified inclusion and exclusion criteria. Further review of the studies was conducted to ascertain relevant information. A third author (SD) reviewed any study that may have had any discrepancies for resolution.

We reviewed the bibliographic sections from the articles of interest for any additional studies.

Study selection

We included studies that evaluated nCLE for pancreatic lesions in our meta-analysis. We included studies regardless of their geographical location, inpatient/outpatient setting, or abstract/manuscript status as long there was relevant information that could be extracted for analysis.

The exclusion criteria included: (1) ages <18 years,(2) sample size <10, and (3) studies published in languages

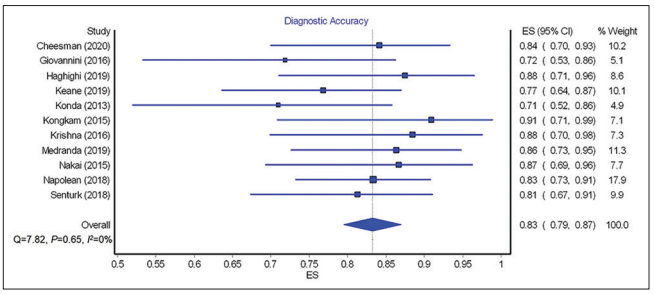

Figure 1. Forest plots showing diagnostic accuracy of EUS needle-based confocal laser endomicroscopy

other than English, (4) probe-based confocal laser endomicroscopy (pCLE), (5) pregnant women, and (6) prisoners

In the setting where publications contained either the same or overlapping cohort, data from the most comprehensive or recent study were included in our analysis.

Data abstraction and quality assessment

Information regarding study-related outcomes from each study was abstracted onto a standardized form by three authors (SS, BD, AD) and quality scoring was reported by two authors (SS, BD) independently.

To assess the quality of our studies, we utilized the quality assessment of diagnostic accuracy studies tool (QUADAS-2)[23] [Supplementary Table 1].

Outcomes assessed

Primary outcome

1. Pooled rate of diagnostic accuracy for nCLE.

Secondary outcomes

1. Pooled rate of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of nCLE to diagnose premalignant/malignant pancreatic lesions
2. Pooled rate of adverse events (AEs) for nCLE
3. Pooled rate of adverse event subtypes: pancreatitis, intracystic bleeding, abdominal pain, and infection.

Definitions

Definition of outcomes

The pooled rate of diagnostic accuracy of nCLE was defined as the total number of lesions diagnosed by nCLE out of the total number of lesions sampled from the final diagnosis cohort.[20,21,24-30] Final diagnosis was taken under consideration by the agreement of a multidisciplinary team through a combination of histology from surgical specimens, cross-sectional imaging, observation for 6–12 months, cytology from EUS FNA, and cyst fluid analysis (CEA, amylase).

Premalignant/malignant included MCN, IPMN, PDAC, PNET, SPN, and cystic lymphoma.

Benign lesions included chronic pancreatitis, SCN, PC, retention cyst, epidermoid cyst, lymphoepithelial cyst, and congenital pancreatic cyst.

AEs were defined as complications which were directly related to the nCLE procedure.

Statistical analysis

We utilized the random-effects model, which is a meta-analysis technique suggested by DerSimonian and Laird to assess the pooled outcomes of interest.[31] As adverse event values of zero occurred in our data and we wished to provide an accurate representation of mean events that included zeroes, we constructed syntax to calculate the weighted mean to avoid introducing positive bias to the analysis. The Cochran Q statistical test and I^2 statistics were utilized to assess heterogeneity between study-specific estimates.[32,33] In addition to the traditional 95% confidence intervals (CIs) calculated based on the random-effects model, we also provided prediction intervals (PIs) for the estimated total effects as suggested by Riley *et al.*[34] Heterogeneity was described as low, moderate, substantial, and considerable according to the values of <30%, 30%–60%, 61%–75%, and >75%, respectively.[35] Publication bias was qualitatively assessed visually with a funnel plot and quantitatively via the Luis Furuya-Kanamori (LFK) index and Doi plot.[36] We assessed potential bias after the removal of studies leading to LFK asymmetry and then conducted a sensitivity analysis by recalculating the statistics. The study would be removed from our analysis if the sensitivity analysis impacted the outcomes. All meta-analyses were performed using MetaXL software (v 3.5; EpiGear International Pty Ltd.; Queensland, Australia), and the exact 95% CIs for study accuracy were estimated using the Clopper–Pearson exact method implemented in the <PropCIs> package in R (v 3.6.1; Vienna, Austria).

Author disclosures

Conflicts of interest were disclosed by several authors reporting on nCLE.[20,21,27,28,37] Nakai *et al.* disclosed competing interests with Mauna Kea Technologies, Cook Medical, and Novartis. Cheesman *et al.* disclosed competing interests with Olympus, Boston Scientific, Medtronic, Apollo Endosurgery, Gyrus Acmi, Cook Medical, Endogastric Solutions, and US Endoscopy. Giovannini *et al.*, Konda *et al.,* and Napoleon *et al.* disclosed competing interests with Mauna Kea Technologies.

RESULTS

Search results and population characteristics

From an initial pool of 423 studies, 11 studies reported

the use of EUS nCLE. Multiple studies with overlapping cohorts were found in our research, and the most appropriate ones were included in the final analysis.

Our study included 170 males (48%) and 186 females (52%) based on data available from 9 studies. The mean age was 62.86 years, based on data available from six studies. Table 1 describes the characteristics of the included studies.

Characteristics and quality of included studies

The meta-analysis included 11 independent cohort studies with a total of 443 patients with 443 lesions. Nine studies had patients with single lesions and two studies had patients with multiple lesions in which the largest one was sampled. The majority of the procedures were performed via a transgastric approach. The mean cyst size, as described in 7 studies, was 50.02 mm.

None of the studies were population-based. Four studies were multicenter, and 7 studies were single center. Two studies had more than 50 patients, 7 studies had more than 30 patients, and 2 studies had more than 20 patients. Nine studies were published in manuscript form and 2 were published in abstract form. All of the included studies had clear information reporting on the diagnostic accuracy of EUS nCLE for the diagnosis of pancreatic lesions. Seven out of eleven studies reported outcomes for sensitivity, specificity, NPV, and PPV of EUS nCLE in diagnosing premalignant/malignant lesions. AEs were reported in eight studies.

Meta-analysis outcomes

Primary outcomes

The pooled rate of diagnostic accuracy of EUS nCLE for pancreatic lesions was 83% (95% CI = 79–87; I^2 = 0). Figure 1 shows the forest plots for the diagnostic accuracy of nCLE.

Secondary outcomes

The calculated pooled rate of sensitivity, specificity, PPV, and NPV of EUS nCLE in diagnosing premalignant/malignant lesions was 85.29% (95% CI = 76.9–93.68; I^2 = 85%), 90.49% (95% CI = 82.24–98.74; I^2 = 64%), 94.15% (95% CI = 88.55–99.76; I^2 = 68%), and 73.44% (95% CI = 60.16–86.72; I^2 = 93%), respectively. Figures 2-5 show pooled rate of sensitivity, specificity, PPV, and NPV of EUS nCLE in diagnosing premalignant/malignant lesions. The total adverse event rate was 5.41% (±5.92) with post procedure pancreatitis being the most common adverse event at 2.28% (±3.73). Severity of pancreatitis was only reported in two studies with one case as mild, one case as moderate, and one case as severe.[20,26] AE of EUS nCLE are shown in Table 2.

Validation of meta-analysis results

Sensitivity analysis

We excluded one study at a time to analyze its effect on the main estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

Heterogeneity

Based on Q statistics, and I^2 analysis for heterogeneity,

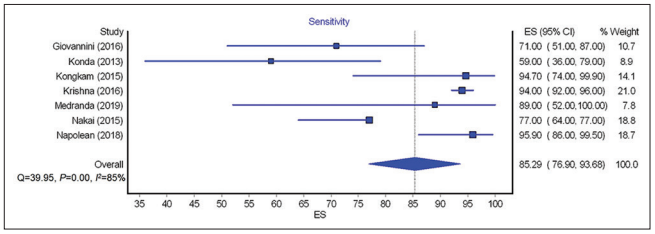

Figure 2. Forest plots showing the sensitivity of EUS needle-based confocal laser endomicroscopy for premalignant/malignant lesions

Table 1. Demographics of studies included for EUS needle-based confocal laser endomicroscopy

Study name	Country	Type of study	Single/multi center	Manuscript/abstract	Mean age	Males	Females
Keane *et al.*[24]	UK	Prospective	Multi	Manuscript	-	35	21
Konda *et al.* (2013)[20]	USA/EU	Prospective	Multi	Manuscript	63.1	36	30
Kongkam *et al.* (2015)[25]	Thailand	Prospective	Single	Manuscript	62.7	14	8
Nakai *et al.* (2015)[21]	USA	Prospective	Single	Manuscript	-	9	21
Krishna *et al.* (2016)[26]	USA	Retrospective	Single	Manuscript	54.8	10	16
Napoleon *et al.* (2018)[27]	France	Prospective	Multi	Manuscript	-	-	-
Cheesman *et al.* (2020)[28]	USA	Retrospective	Single	Manuscript	66	16	28
Haghighi *et al.* (2019)[38]	USA	Retrospective	Single	Manuscript	65.6	12	20
Giovannini *et al.* (2016)[37]	France	Prospective	Multi	Manuscript	65	18	14
Robles-Medranda *et al.* (2019)[30]	Ecuador	Prospective	Single	Abstract	-	-	-
Senturk *et al.* (2018)[29]	Turkey	Prospective	Single	Abstract	-	20	28

Table 2. Adverse events of EUS needle-based confocal laser endomicroscopy

Name of study	Total adverse events	Pancreatitis	Abdominal pain	Intracystic bleeding	Infection	Other
Cheesman *et al.* (2020)[28]	4	0	2	1	1	0
Giovannini *et al.* (2016)[37]	0	0	0	0	0	0
Haghighi *et al.* (2019)[38]	0	0	0	0	0	0
Keane *et al.*[24]	2	0	0	0	1	1
Konda *et al.* (2013)[20]	6	2	1	3	0	0
Kongkam *et al.* (2015)[25]	1	0	0	0	0	1
Krishna *et al.* (2016)[26]	3	3	0	0	0	0
Nakai *et al.* (2015)[21]	2	2	0	0	0	0

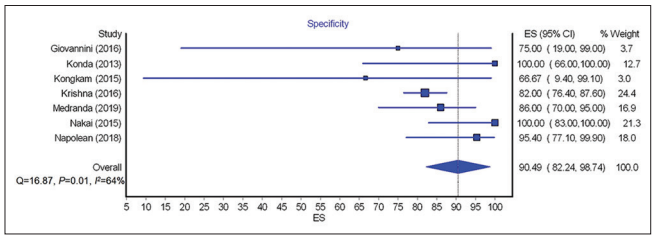

Figure 3. Forest plots showing the specificity of EUS needle-based confocal laser endomicroscopy for premalignant/malignant lesions

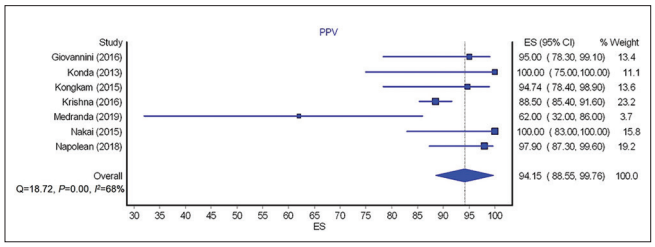

Figure 4. Forest plots showing the positive predictive value of EUS needle-based confocal laser endomicroscopy for premalignant/malignant lesions

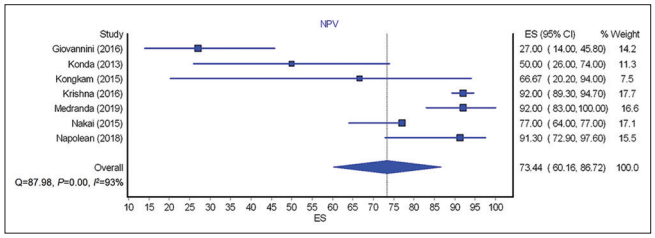

Figure 5. Forest plots showing the negative predictive value of EUS needle-based confocal laser endomicroscopy for premalignant/malignant lesion

no heterogeneity was noted in the analysis for diagnostic accuracy of EUS nCLE. Considerable heterogeneity was noted in analysis of sensitivity and NPV and substantial heterogeneity was noted in analysis of specificity and PPV.

Publication bias

Potential publication bias was evident based on the funnel plot, Doi Plot, and LFK index. Sensitivity analysis by removing asymmetric studies revealed the possibility of publication bias, but this did not lead to a statistical change in the calculated estimate or the conclusion of this meta-analysis. Although it should be noted that the ability to detect bias is limited.

DISCUSSION

In this meta-analysis, the pooled diagnostic accuracy rate of nCLE was 83%, which is comparable to EUS-FNA.[39-42] nCLE provides *in vivo* visualization of PCLs and acts as an adjunct to conventional diagnostic modalities such as EUS FNA. However, nCLE is limited by prolonged procedure time (the procedure records at 12 frames/s, so 2–5 min of video recording is needed to make certain the lesion undergoes appropriate evaluation) and limited visualization of a pancreatic lesion secondary to significantly restricted maneuverability through a 19G FNA needle, anatomical abnormalities such as duodenal stenosis, or the presence of a solid lesion impeding access to the target lesion.[20,21,24,25,27,28,37,43-45]

The pooled sensitivity, specificity, PPV, and NPV rate of nCLE in distinguishing premalignant/malignant versus benign pancreatic lesions were 85.29%, 90.49%, 94.15%, and 73.44%, respectively. There were two studies which evaluated SPLs,[25,37] whereas the other studies evaluated PCLs.[20,21,24,26-30,38] EUS FNA has had high rates of false-negative or inadequate specimens reported in some studies; nCLE can aid in improving sensitivity and specificity for the diagnosis of pancreatic lesions.[46-48] However, high cost, the necessity of physician training for nCLE interpretation and variable interobserver agreement limit the use of this technology.[25,37,44,45,49]

The total AE rate was 5.41% with post-procedure pancreatitis being the most common AE reported at 2.28%.[20,21,26] The cause of the pancreatitis was hypothesized to be secondary to extended duration of the nCLE procedure, scope-torque while attempting to

access other parts of the lesion, the FNA itself, or a combination of these factors.[20,21,26] The pooled rate of intracystic bleeding in our study was 1.14%, which was self-limited in all cases.[20,28]

There are several limitations in this study. Some studies were retrospective, which is a risk factor for selection bias. This technique may not be generalizable to an unexperienced endoscopist. The population of patients is small, including the number of surgical specimens available for criteria development for nCLE.

Analysis of diagnostic accuracy studies is an area of active research and utilizes many sophisticated models, which could not be accomplished in our study. A more robust sample size with raw data is needed to utilize these models. Our study provides summaries for sensitivity and specificity independently, which emphasizes that our findings are preliminary and hypothesis-generating for future studies.

CONCLUSION

In summary, this study highlights nCLEs high rate of diagnostic accuracy, sensitivity, specificity, and PPV for distinguishing premalignant/malignant lesions. The role of this technique in evaluating pancreatic lesions needs to be further defined. Larger validation studies are needed to further characterize CLE criteria. Future studies should evaluate nCLE as an adjunct with EUS FNA or some other modality such as through the needle microforceps biopsy or cystoscopy as a few studies have demonstrated with promising results.[21,28,30,38]

Supplementary Materials

Supplementary information is linked to the online version of the paper on the *Endoscopic Ultrasound* website.

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Conflicts of interest

There are no conflicts of interest.

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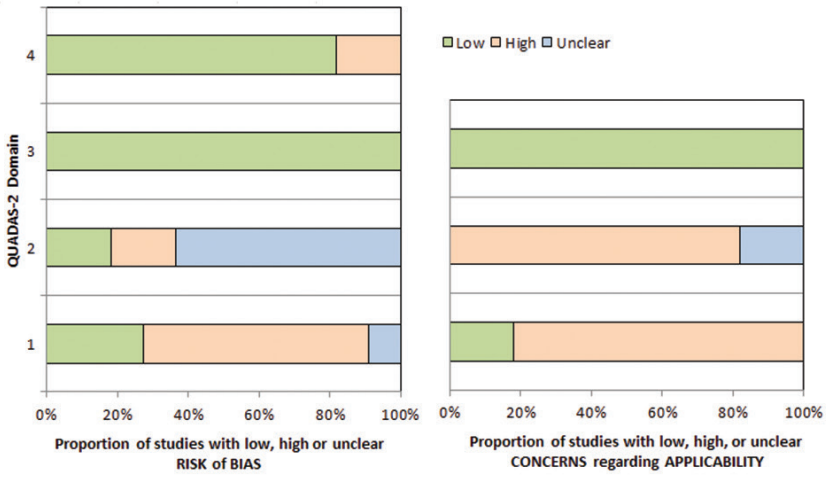
Supplementary Table 1. Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2)

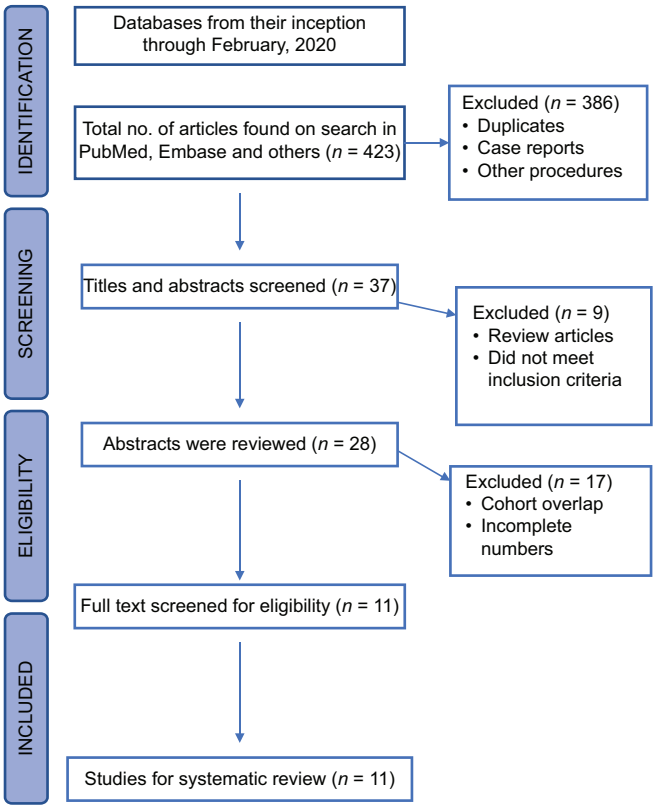
Risk of Bias Scoring

	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Low	3	2	11	9
High	7	2	0	2
Unclear	1	7	0	0

Applicability Scoring

	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Low	2	0	11
High	9	9	0
Unclear	0	2	0





Supplementary Figure 1. Study selection process in accordance with preferred reporting items for systematic reviews and meta-analysis statement