Efficacy of digital single-operator cholangioscopy in the visual interpretation of indeterminate biliary strictures: a systematic review and meta-analysis

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REVIEW ARTICLE

Efficacy of digital single-operator cholangioscopy in the visual interpretation of indeterminate biliary strictures: a systematic review and meta-analysis

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Abstract

Objective Indeterminate biliary strictures remain a significant diagnostic challenge. Digital single-operator cholangioscopy (D-SOC) incorporates digital imaging which enables higher resolution for better visualization and diagnosis of biliary pathology. We aimed to conduct a systematic review and meta-analysis of available literature in an attempt to determine the efficacy of D-SOC in the visual interpretation of indeterminate biliary strictures.

Material and methods Electronic searches were performed using Medline (PubMed), EMBASE, and Cochrane Library. All D-SOC studies that reported the diagnostic performance in visual interpretation of indeterminate biliary strictures and biliary malignancies were included. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 was used to evaluate the quality of the included studies. All data were extracted and pooled to construct a 2 × 2 table. The visual interpretation of D-SOC was compared to resected surgical specimens or clinical follow-up in the included patients. Pooled sensitivity, specificity, positive predictive value, negative predictive value, prevalence, positive likelihood ratio (+LR), negative likelihood ratio (−LR), and diagnostic odds ratio (OR) were calculated. The summarized receiver operating characteristic (SROC) curve corresponding with the area under the curve (AUC) was also analyzed.

Results The search yielded 465 citations. Of these, only six studies with a total of 283 procedures met inclusion criteria and were included in the meta-analysis. The overall pooled sensitivity and specificity of D-SOC in the visual interpretation of biliary malignancies was 94% (95% CI 89–97) and 95% (95%CI 90–98), respectively, while +LR, −LR, diagnostic OR, and AUC were 15.20 (95%CI 5.21–44.33), 0.08 (95%CI 0.04–0.14), 308.83 (95%CI 106.46–872.82), and 0.983, respectively. The heterogeneity among 6 included studies was moderate for specificity ($I^2 = 0.51$) and low for sensitivity ($I^2 = 0.17$) and diagnostic OR ($I^2 = 0.00$).

Conclusion D-SOC is associated with high sensitivity and specificity in the visual interpretation of indeterminate biliary strictures and malignancies. D-SOC should be considered routinely in the diagnostic workup of indeterminate biliary lesions.

Keywords Cholangioscopy · Spyglass · Biliary malignancies · Indeterminate strictures · Diagnosis · Meta-analysis

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Cholangioscopy was first described in 1976 to evaluate the biliary tract under direct visualization [1]; however, due to technical limitations, its efficacy in imaging the biliary tree was limited by cumbersome and fragile equipment, the need for two expert endoscopists and unsatisfactory image quality [2]. It was not until several decades later that cholangioscopy rose as a promising tool to aid in diagnosis and management of various biliary diseases.

The SpyGlass® direct cholangioscopy system (Boston Scientific, Marlborough, Massachusetts) was introduced in 2007 and is designed for single-operator examination. Encompassing a reusable optical probe coupled with a disposable catheter, this four-way deflection device could be inserted through the working channel of a duodenoscope and advanced into the papilla. Despite significant advances in usability and improved imaging, this system, then referred as SpyGlass Legacy, still had several limitations including suboptimal image quality and probe durability.

In 2015, the new SpyGlass DS® was released, which was completely digital and the first Digital Single-Operator Cholangioscopy (D-SOC) system available. This provided higher resolution, brighter images, improved maneuverability, and versatility of operator accessories, rectifying the shortcomings of the previous generation. Addressing many of the limitations of its predecessor, this new system consisted of a completely disposable scope with improved setup, steering, ergonomics, and remarkably improved image quality [3–6].

Biliary strictures are considered indeterminate when initial imaging and ERCP do not yield a definitive diagnosis. These strictures can be benign or malignant, and can originate anywhere in the biliary tree. Per-oral cholangiopancreatoscopy, including D-SOC, can be employed for both diagnostic and therapeutic purposes, and aid endoscopic retrograde cholangiopancreaticography for the diagnosis and management of various biliary pathology. As a diagnostic tool, cholangioscopy can provide reasonably accurate visual identification of indeterminate biliary strictures, as well as direct biopsies of these lesions. Well established therapeutic uses of the system include difficult to treat biliary stones, selective guidewire placement for difficult cannulation in cholangiography cases, and foreign body removal [7–19].

While the use of D-SOC has increased with time, data remain scarce on its direct impact and efficacy in visual interpretation of biliary disease, particularly biliary indeterminate biliary strictures. This study is aimed to comprehensively evaluate the diagnostic ability of D-SOC in elucidating indeterminate biliary strictures, differentiating malignant and non-malignant lesions based on visual findings.

Materials and methods

Protocol and registration

The study design was written in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [20] and recent recommendations for diagnostic test accuracy reviews [21]. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. Following the commencement of the study, there were no amendments and no deviations from the protocol. The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine Hospital das Clínicas and written consent was not required as this was a systematic review project.

Data collection and extraction

A literature search was performed for studies published from 2009 to June 2019. Titles and abstracts were screened for relevance, full texts were reviewed and inclusion, and exclusion criteria were applied to select the records.

The search was performed among the databases MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE. The string used for search was (((Biliary Tract OR common bile duct OR biliary tree OR Biliary OR periampullary) AND (Neoplasm* OR Cancer OR Malignanc*)) OR cholangiocarcinoma OR Klatskin) AND (POC OR cholangioscopy OR spyglass OR spybite OR cholangiopancreatoscopy OR DSOC), which contemplates biliary tract malignancies and digital single-operator cholangioscopy.

The titles and abstracts of potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed for additional articles by cross checking bibliographies. Two reviewers (PVAGO and IBR) independently screened the titles and abstracts of all the articles according to the inclusion and exclusion criteria. Any differences were resolved by mutual agreement with the third reviewer (DTM).

Data extracted from the records included characteristics of records (author, publication year, study period), the reference standard, research type, number of patients and cases, and data regarding the true positive (TP), false positive (FP), false negative (FN), true negative (TN) values.

Inclusion criteria

Studies were included if they met the following criteria:

(1) Adults aged 18 years and above.
(2) Studies which included all patients that were subjected to D-SOC evaluation for indeterminate biliary strictures during the defined period of time.
(3) The study utilized a control arm (reference standard) on all subjects which includes clinical follow-up and reported histology.
(4) Studies with true-negative, true-positive, false negative, and false-positive values which were extracted to construct a 2×2 table.

Both prospective and retrospective data collection were included. For studies which the older analog system was used on some patients, only the data referring to the cases with SpyGlass DS® were considered. Only full text manuscripts published in the English language were assessed.

Exclusion criteria

Studies were excluded if:

(1) The study was a case report, editorial, review, systematic review, commentary or non-sequential case series.
(2) Studies without a comparative standard or arm or studies with insufficient follow-up (defined as less than twelve months).
(3) Studies with incomplete data reported and with non-extractable diagnostic values.
(4) Data referring to the D-SOC could not be extracted from prior cholangioscopy system (legacy systems).

Risk of bias assessment and quality of evidence.

The quality of the included literature and the risk of bias were assessed according to the QUADAS-2 tool recommended by the Cochrane collaboration web [22]. Quality of studies were independently evaluated by two authors (PVAGO and AMPN), and disagreement was resolved by consensus in consultation with the third author (DTHM).

Analysis

The primary outcome analyzed was the presence or absence of malignancy based on visual interpretation of indeterminate biliary strictures using D-SOC system. The reference standard, which served as control arm to compare D-SOC visual interpretation, was either histology on surgical specimen (on patients who eventually underwent surgical resection) or clinical follow-up for up to 12 months. With these data, a definition of true malignant and non-malignant cases was obtained.

Meta-analysis for the accuracy of D-SOC in diagnosing malignant versus benign biliary stricture was carried out by calculating pooled sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (OR). A summarized receiver operating characteristic (SROC) curve was drawn and the area under the curve (AUC) was calculated.

This meta-analysis was performed by calculating pooled outcomes using the fixed effects model. The confidence intervals (CIs) were calculated using the F distribution method. Forest plots were made to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the forest plots indicated the assigned weight for that study. For 0 values, 0.5 was added, as described by Cox and Snell [23]. The heterogeneity of likelihood ratios and diagnostic odds ratios were tested using Cochran-Q test on the basis of inverse variance weights. The heterogeneity of the sensitivities and specificities was tested using the likelihood ratio test. Heterogeneity among studies was also tested using summary receiver operating characteristic (SROC) curves. Heterogeneity was assessed and data were analyzed using Meta-DiSc (Clinical Biostatistics HRC, Madrid, Spain) [24].

Results

Search results and characteristics of included studies

A total of 591 studies were originally extracted based on our search methodology. Among those, 126 studies were removed due to the duplicate records while 446 studies were excluded for not meeting criteria after title and abstract screen. The 18 remaining studies were evaluated using the pre-specified inclusion and exclusion criteria. This resulted in a total of 6 studies including 283 patients undergoing D-SOC evaluation (Fig. 1). The characteristics of the selected studies are shown in Table 1. The reference standards from each study and the aggregate result of the individual data are shown in Table 2 [25–30].

Risk of bias and quality

The quality of the included studies was evaluated according to the QUADAS-2. Risk of bias and applicability concerns of the 6 studies is shown in Fig. 2. The quality of the included studies was considered to be high. Regarding the index test domain, one study was considered to have unclear risk, as the visual findings were not described. Regarding

Fig. 1 Flow diagram showing study selection process for meta-analysis

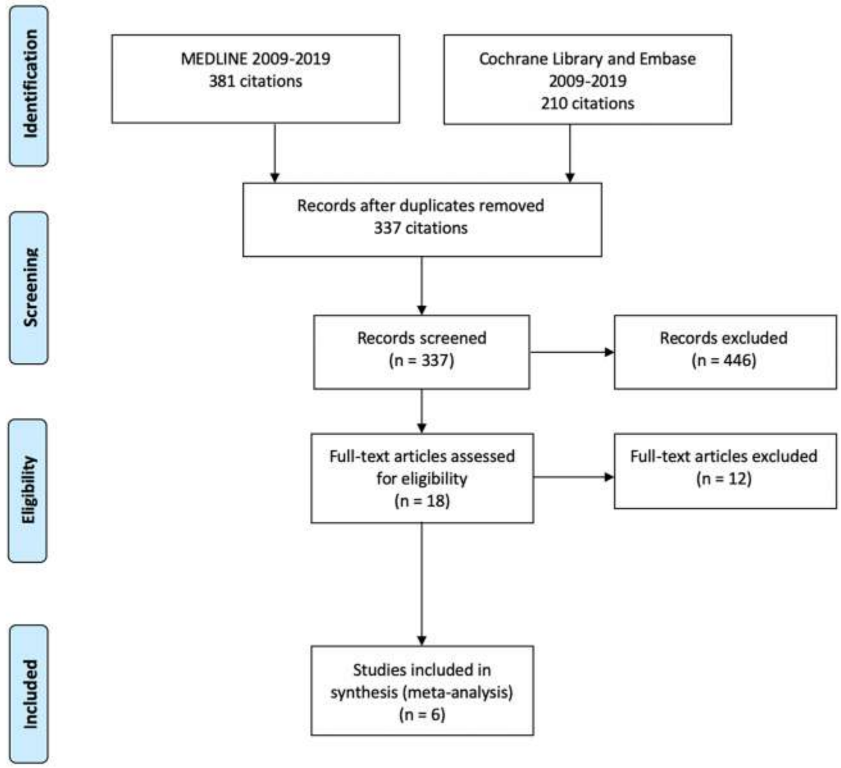


Table 1 Characteristics of included studies

References	Study period	Country	Research type	No. of patients		Raw data			
				SpyGlass DS	SpyBite biopsies	TP	FP	FN	TN
Shah et al. [25]	2015.02–2015–04	USA	Retrospective study	74	49	28	1	3	42
Ang et al. [26]	2013.01–2016.11	Singapore	Retrospective study	17	13	11	0	0	7
Urban et al. [27]	2016.01–2017.05	Czech Republic	Prospective study	30	0	13	4	0	13
Lenze et al. [28]	2015.08–2017–07	Germany	Retrospective study	41	29	24	1	3	39
Turowski et al. [29]	2015.11–2017.01	Germany	Retrospective study	99	41	42	3	2	52
Yan et al. [30]	2015.06–2018.05	USA	Retrospective study	22	15	10	0	0	12

TP true positive, *FP* false positive, *FN* false negative, *TN* true negative

Table 2 Individual results of included studies

Study	Index test	No. of patients		Reference standard	Final diagnosis	
		D-SOC(+)	D-SOC(−)		Malignant	Non-Malignant
Shah et al. [25]	D-SOC evaluation	31	43	Histology on surgical specimen or Clinical Follow-up	29	45
Ang et al. [26]	D-SOC evaluation	11	7	Histology on surgical specimen or Clinical Follow-up	11	7
Urban et al. [27]	D-SOC evaluation	17	13	Histology on surgical specimen or Clinical Follow-up	13	17
Lenze et al. [28]	D-SOC evaluation	25	42	Histology on surgical specimen or Clinical Follow-up	27	40
Turowski et al. [29]	D-SOC evaluation	45	54	Histology on surgical specimen or Clinical Follow-up	44	55
Yan et al. [30]	D-SOC evaluation	10	12	Histology on surgical specimen or Clinical Follow-up	10	12

D-SOC+ Visual impression suggestive of malignancy, *D-SOC*− visual impression suggestive of non-malignant

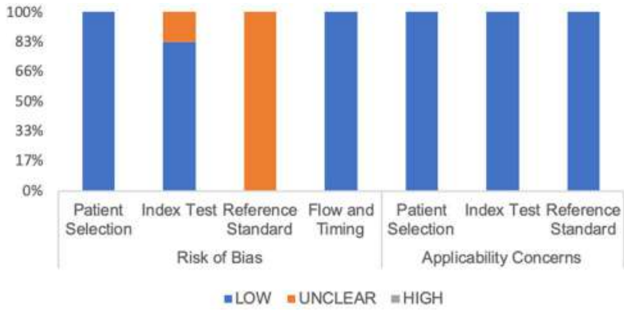


Fig. 2 Grouped bar charts showing risk of bias and applicability concerns of 6 included record using QUADAS-2

Table 3 Calculated diagnostic values for D-SOC

Diagnostic measure	Calculated values
Sensitivity	0.94 (95% CI: 0.89–0.97)
Specificity	0.95 (95% CI: 0.90–0.98)
Positive likelihood ratio	15.20 (95% CI: 5.21–44.33)
Negative likelihood ratio	0.08 (95% CI: 0.04–0.14)
Accuracy	0.94 (95% CI: 0.90–0.98)
Diagnostic Odds-ratio	308.83 (95% CI: 106.46–872.82)
Positive predictive value	0.926 (95% CI: 0.85–0.99)
Negative predictive value	0.978 (95% CI: 0.95–1.00)

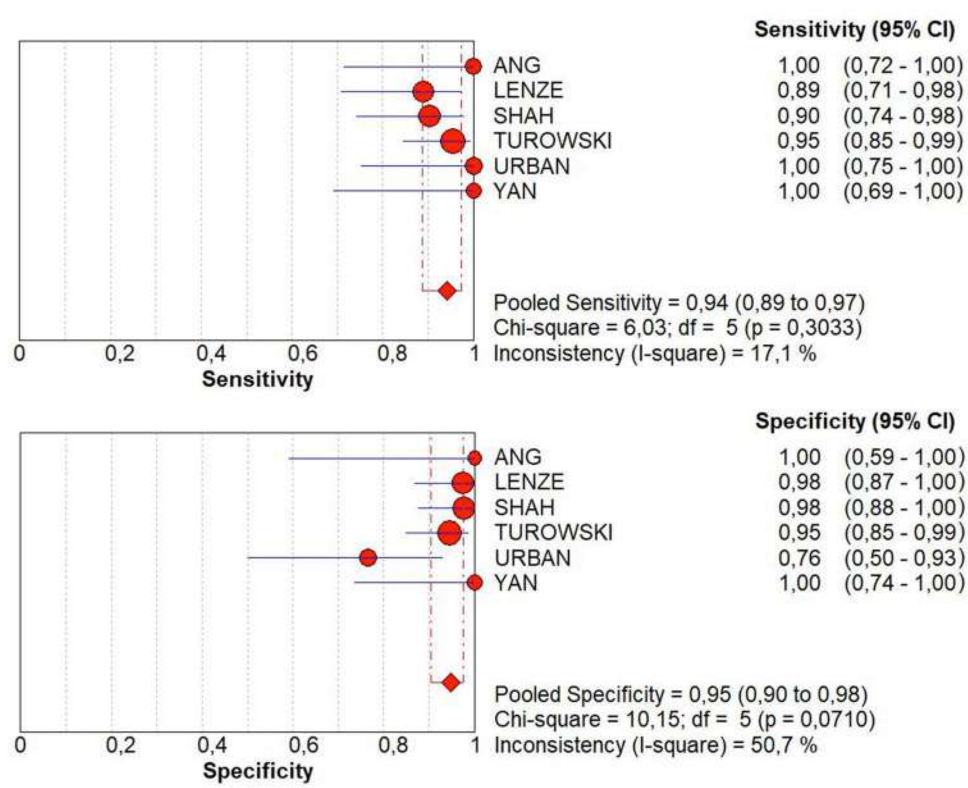
the reference standard domain, all studies had unclear risk of bias as each was composed of multiple variables with no possibility of blinding. Regarding flow and timing domain, the included studies had low risk of bias, with consecutive cases and no unjustified exclusions. There was low concern for applicability with regard to the first three QUADAS-2 domains for all 6 included studies.

Meta-analysis

The result of this meta-analysis is shown in Fig. 3 and Table 3. With regard to the diagnosis of malignancy within indeterminate biliary strictures based on D-SOC visual interpretation, compared to standard reference of pathology on surgical resection or disease course at 12 months, the pooled sensitivity was 0.94 (95% CI: 0.89–0.97), pooled specificity 0.95 (95% CI: 0.90–0.98), pooled+LR = 15.20 (95% CI: 5.21–44.33), pooled−LR = 0.08 (95% CI: 0.04–0.14), pooled diagnostic OR = 308.83 (95% CI: 106.46–872.82), and accuracy = 0.94 (95% CI: 0.90–0.98). We also calculated pooled prevalence, positive predictive value and negative predictive value, summarized in Table 3.

With regard to the diagnosis of malignancy within indeterminate biliary strictures based on cholangioscopic visual impression, heterogeneity for specificity was moderate

Fig. 3 Forest plots of pooled sensitivity and specificity



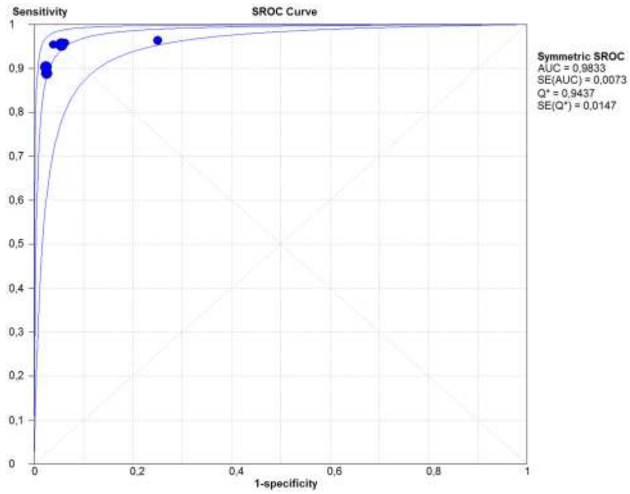


Fig. 4 Forest plots of pooled SROC curve

($I^2 = 50.7\%$), and minimal for sensitivity ($I^2 = 17.1\%$) and odds ratio ($I^2 = 0.0\%$).

The pooled SROC is shown in Fig. 4. The pooled Area-under-curve (AUC) = 0.98.

Discussion

Digital single-operator cholangioscopy was introduced in 2015, superseding the earlier system which had been available since 2007 and faced many limitations. The newer digital system present nowadays has proven to be advantageous with higher resolution, brighter images, improved maneuverability, and versatility of operator accessories. Its introduction has revolutionized the diagnostic and therapeutic approach to various biliary pathologies.

Biliary strictures are considered indeterminate when initial imaging and ERCP do not yield a definitive diagnosis. These strictures can be benign or malignant, and can originate anywhere in the biliary tree. Accurate and timely diagnosis avoids unnecessary surgical interventions, and provides optimal planning for patient care [3, 7]. Cholangioscopy has had a hand in the diagnosis and management of indeterminate biliary strictures. However, there is no universally accepted standardized classification system for image findings seen in cholangioscopy. Tortuous and dilated vessels, infiltrative strictures, polypoid masses, and the presence of fish-egg lesions tend to be associated with malignancy but only suggestive of it. Conversely, benign strictures are associated with smooth mucosa and no abnormal vessels [2, 31, 32]. Robles-Medranda et al. [33] proposed a classification system based on neoplastic and non-neoplastic findings on cholangioscopy. Findings of abnormal vessels, irregularities, and ulceration were associated with neoplastic processes, and were of adequate diagnostic value.

This review and meta-analysis included cross-sectional studies from which basic diagnostic data, including true positive, false positive, true negative, and false negative numbers, could be extracted. These studies compared the image findings of cholangioscopy examinations against a control standard, defined as follow-up or surgical specimens on resection. Patients that underwent D-SOC with no surgery afterwards would be followed for a certain amount of time (12–18 months) before being deemed malignant or non-malignant, and the ones which eventually underwent surgery had the histology of the surgical specimen to confirm or deny malignancy. This approach allowed the allowed the comparison of D-SOC image findings with the ultimate diagnosis.

The assessment of the quality of included studies is fundamental for systematic reviews of diagnostic accuracy studies. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was developed with an evidence-based process, and offers the ability to not only estimate risk of bias, but also to distinguish between bias and applicability. The studies included in the analysis were generally regarded as of adequate quality, with low risk of bias and high applicability. It should be noted that assessing the quality of diagnostic tests for which there are no single-step universal standard is challenging, as the control test needs to be specifically designed, often being complex and subject to limitations of other types of studies, such as loss to follow-up. Even so, the included records managed to provide control test information for every patient.

The results of this meta-analysis are consistent with previous studies, revealing very high diagnostic yield for cholangioscopy. Earlier studies, which considered both legacy and digital systems, had lower sensitivity and similar specificity [34]. As this is the first meta-analysis limited to the more novel and vastly superior digital system, it is expected that the diagnostic yield is higher [35]. We showcase high sensitivity and specificity, with excellent positive and negative likelihood ratios and predictive values with this new generation of cholangioscopy. We need to consider that the actual diagnostic value in real world applications greatly depends on the studied population prevalence of malignancy. In this study, the pooled prevalence, which can be interpreted as the pre-test chance of malignancy, was 0.46 (95% CI: 0.40–0.52). The pooled positive predictive value, which is the actual post-test chance of malignancy, was calculated to be 0.92 (95% CI: 0.85–0.99). These results calculate a 2.2 (95% CI: 1.8–2.5) fold increase in diagnostic certainty, confirming high applicability of cholangioscopy on the differential diagnosis of indeterminate biliary strictures.

Compared to other diagnostic methods, such as endoscopic ultrasonography and fine-needle aspiration tissue sampling, the visual interpretation of D-SOC provides higher sensitivity and similar accuracy, although it should be noted that cholangioscopy is limited to ductal lesions [36, 37].

This is the first meta-analysis to assess the diagnostic value of visual interpretation in D-SOC separately. Previous systematic reviews did not differentiate cases which employed the older analog system from cases which utilized the newer digital variant [34]. When compared to the legacy analog single-operator cholangioscopy system, D-SOC provides considerably higher sensitivity and specificity, which is to be expected considering the significant improvement in image quality. The visual impression using the analog system provides sensitivity and specificity of 84.5% (95% CI: 79.2–88.9) and 82.6% (95% CI: 77.1–87.3), respectively [38]. Such reviews, while still generally favorable to cholangioscopy as a diagnostic tool, might underestimate the real diagnostic value of the newer system. The inclusion of cases using solely the digital system was made possible because the number of published reports has increased in the last few years.

It is important to recognize that this analysis is limited on basis of the types of studies available at the present moment, which were cross-sectional studies. The lack of randomized controlled trials which could evaluate change in medical procedures or effects on survival limits the interpretation. Furthermore, advances in image processing, machine learning, and artificial intelligence could enhance the diagnostic value to a higher degree. Randomized trials are due to assist in determining improvement in outcomes when cholangioscopy is used for the diagnosis of indeterminate biliary strictures.

Conclusion

Digital single-operator cholangioscopy provides high diagnostic performance for the diagnosis of biliary malignancies based on visual impression in patients with indeterminate biliary strictures, with consistent results across all studies.

Author contributions PVAGO: acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval; DTHDM: acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval; IBR: analysis and interpretation of data, revising the article; ANDB: analysis and interpretation of data, revising the article; TPF: analysis and interpretation of data, drafting the article, final approval; MELDS: analysis and interpretation of data, drafting the article, final approval; WMB: analysis and interpretation of data, drafting the article, final approval; EGHDM analysis and interpretation of data, drafting the article, revising the article, final approval;

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Compliance with ethical standards

Disclosures Drs. Tomazo Antonio Prince Franzin and Marcos Eduardo Lera dos Santos reports personal fees from BOSTON SCIENTIFIC, outside the submitted work; Dr. Eduardo Guimarães Hourneaux de Moura reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work. Drs. Pedro Victor Aniz Gomes de Oliveira, Diogo Turiani Hourneaux de Moura, Igor Braga Ribeiro, Ahmad Najdat Bazarbashi, and Wanderley Marques Bernardo have nothing to disclose.

Ethical approval The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine Hospital das Clínicas and written consent was not required as this was a systematic review project.

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