

The Effect of Linked Color Imaging for Adenoma Detection. A Meta-analysis of Randomized Controlled Studies

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ABSTRACT

Background & Aims: The effect of linked color imaging (LCI) compared with white light imaging (WLI) is conflicting. The aim of this meta-analysis is to compare the efficacy of LCI versus WLI for the adenoma detection.

Methods: PubMed, Embase, Google Scholar and Cochrane Library were searched up to the end of Aug 18, 2021. All randomized controlled trials (RCTs) comparing LCI with WLI were included. Dichotomous data were pooled to obtain the relative risk (RR) with a 95% confidence interval (CI), whereas continuous data were pooled using a mean difference (MD) with 95%CI.

Results: A total of 10 RCTs involving 5,510 patients were included. The use of LCI was associated with a statistically significant improvement in adenoma detection rate (ADR), polyp detection rate (PDR), mean adenomas per patient (MAP) and mean polyp per patient (MPP) when compared to WLI (ADR: RR=1.15, 95%CI: 1.07-1.23, p=0.0001, PDR: RR=1.15, 95%CI: 1.08-1.22, p<0.0001; MAP: MD=0.18, 95%CI: 0.09-0.28, p=0.0002; MPP: MD=0.13, 95%CI: 0.01, 0.25, p=0.03). When stratified by size, LCI group had a higher detection rate of small adenomas (<10 mm) than the WLI group. Besides, LCI showed a significant decrease in adenoma miss rate (AMR) when compared to WLI. There were no statistically significant differences between the two groups in advanced ADR (AADR), sessile serrated lesion detection rate (SDR), cecal intubation rate, insertion time, and withdrawal time.

Conclusions: The pooled evidence suggests that LCI can significantly improve the detection of ADR, especially for small adenomas (<10 mm). Moreover, the AMR were significantly lower using LCI compared with WLI.

Key words: colonoscopy – linked color imaging – adenoma detection – meta-analysis.

Abbreviations: AADR: advanced adenoma detection rate; ADR: adenoma detection rate; AMR: adenoma miss rate; CI: confidence interval; CRC: colorectal cancer; IEE: image-enhanced endoscopy; LCI: linked color imaging; MAP: mean adenomas per patient; MD: mean difference; MPP: mean polyp per patient; PDR: polyp detection rate; RCT: randomized controlled trial; RR: relative risk; SDR: sessile serrated lesion detection rate; SMR: sessile serrated lesion miss rate; WLI: white light imaging.

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INTRODUCTION

Screening colonoscopy has been shown to reduce incidence of and mortality from colorectal cancer (CRC) [1, 2]. Adenoma detection rate (ADR) is now the main quality indicator of colonoscopy because of its inverse correlation with interval cancer rate. Every 1% increase ADR is associated with a 3% reduction of interval CRC and 5% reduction of fatal interval CRC [3, 4].

Image-enhanced endoscopy (IEE) has been used frequently in clinical practice for polyp detection and characterization. Linked color imaging (LCI) is a new mode of IEE, produced by Fujifilm (Tokyo, Japan), with a different mode of wavelength optimization using all 3 primary colors (red, blue, and green). It is designed to detect subtle color differences in the red gastrointestinal mucosa, enhancing the contrast of hemoglobin for detection of the mucosal vascular pattern. Further signal processing enhances the red color and makes the white color whiter [5, 6].

In the last years, several randomized controlled trials (RCTs) have explored the efficacy of LCI as compared with white light imaging (WLI), providing conflicting results [7-10]. Aside individual studies, a recent meta-analysis [11] including 6 RCTs and 1 parallel study concluded that LCI has

significantly greater polyp detection rate (PDR) and ADR of previously missed polyps compared with WLI. After that, six RCTs comparing LCI and WLI have recently been published [12-17]. Therefore, we conducted a meta-analysis of published data in order to evaluate the efficacy of LCI.

METHODS

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18].

Search Strategy

A literature search was conducted using PubMed, Embase, Google Scholar and Cochrane Library up to Aug 18, 2021 without language restrictions. Relevant studies were identified using the following terms: “linked color imaging”, “adenoma detection”. The search was restricted to human subjects. Additional studies were identified using a hand search of references of original or review articles and international conferences on this topic, primarily including United European Gastroenterology Week (UEGW) and Digestive Disease Week (DDW).

Two investigators (J.W., C.Y.) independently assessed the eligibility of the citations using the title and abstract, and full texts of potentially eligible studies were used to judge the final eligibility. Any disagreement between reviewers was resolved by discussion with a senior author (S.F.).

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: 1) RCTs that compared LCI and WLI, 2) presenting the detailed outcomes of LCI and WLI or including such data for calculation in the article text. Non-randomized prospective, retrospective, feasibility or pilot studies, meta-analysis, editorials, reviews, case reports/series, studies not reporting on ADR and duplicate publications were excluded.

Data Extraction

Two investigators (J.W., C.Y.) independently extracted the data and reached a consensus for all items. If the investigators generated different results, they checked the data again and had a discussion to reach an agreement. If they were unable to reach an agreement, an expert was invited to join the discussion. Data extracted from the selected articles included the first author's name, year of publication, country of origin, study period, indications for colonoscopy, baseline characteristic of the patients, and primary outcomes.

Bias Assessment

The risk of bias in individual studies was assessed using the Cochrane Collaboration tool [19]. This particular tool evaluates different domains of potential source of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The biases were evaluated by one investigator (J.W.) and double checked by another investigator (C.Y.). Any disagreement was resolved by discussion with the senior investigator (K.W.). The analysis results were defined as low, high or unclear bias (bias-related information is not clear or

bias cannot be determined). Publication bias was assessed using subjective judgement based on funnel plots as well quantitatively using Egger's regression analysis. A p-value <0.05 was indicative of substantial publication bias.

Outcome Measures

The primary outcome of this study was to calculate a pooled ADR. The secondary outcomes were PDR, advanced ADR (AADR), sessile serrated lesion detection rate (SDR), mean adenomas per patient (MAP), mean polyp per patient (MPP), adenoma miss rate (AMR), sessile serrated lesion miss rate (SMR), cecal intubation rate, insertion time and withdrawal time.

Statistical Analysis

A meta-analysis was performed using the Cochrane Collaboration RevMan 5.4 and STATA package version 12.0. Relative risk (RR) with 95% confidence interval (CI) for each binary outcome was calculated. Mean difference (MD) with 95% CI was calculated for continuous variables. The analyses were performed using the Mantel-Haenszel random effect model, because strong diversity among studies were expected. The χ^2 -test-based Q statistic test and I^2 test were performed to assess the between-study heterogeneity. An analysis of sensitivity was performed to evaluate the stability of the results. Additionally, we conducted subgroup analysis by location (left-side, right-side) and adenoma size (< 10 mm, \geq 10 mm). A p-value of < 0.05 was regarded as being statistically significant.

RESULTS

Study Characteristics

Following the searching strategy, a total of 607 citations were identified. Screening and evaluation excluded 596 studies. According to the inclusion criteria, 11 studies [7-10, 12-17, 20] were selected and subjected to further examination. We excluded one study because it was not RCT [20]. Therefore, 10 RCTs with 5,510 patients were included in the meta-analysis [7-10, 12-17] (Fig. 1). The characteristics of the selected studies are summarized in Table I. Of the ten eligible studies, four studies were from Japan, two from Italy, and one each from Thailand, Brazil, China, Hungary; Three studies were multi-center and seven were single-center experiences. All studies were published in English and in full text format from 2017 to 2021.

Risk of bias assessment using Cochrane Collaboration tool is provided in Supplementary File (Fig 1). The shape of the funnel plots did not reveal any evidence of asymmetry (Supplementary File. Fig. S2). Egger's test also showed no statistical significance in evaluation of publication bias ($p=0.077$).

Quantitative Data Synthesis

Primary Outcome

ADR

Nine studies with 5,466 patients reported ADR in the LCI and WLI groups. The pooled ADR was 51.3% (95%CI: 43-59.6) for LCI and 43.8% (95%CI: 34.5-53.1) for WLI. The pooled RR was 1.15 (95%CI: 1.07-1.23, $p=0.0001$) (Fig. 2, Table II).

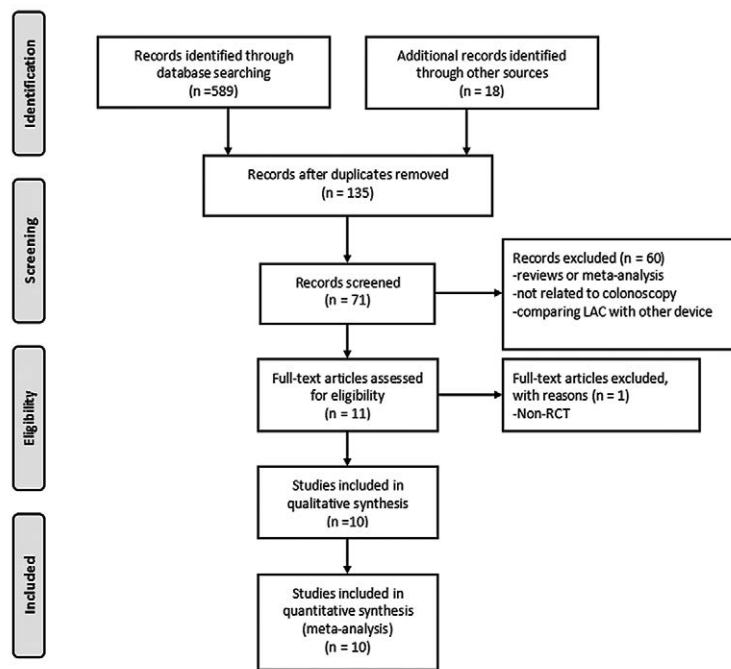


Fig. 1. Flow chart showing study selection procedure

Table I. Characteristics of the included studies.

Study, reference	Country	Year	Study period	Indications	Center	Number patients		Age, years		Gender (men %)		Primary outcome
						LCI	WLI	LCI	WLI	LCI	WLI	
Aniwan et al., [12]	Thailand	2021	2019-2020	Screening	1	250	250	61.7	61.1	37.2	33.2	ADR
dos Santos et al., [8]	Brazil	2019	2018-2019	Symptoms such as altered bowel habits, abdominal pain or discomfort, abdominal distension, and rectal bleeding; Screening or surveillance	1	151	150	NA	NA	35.4	35.2	ADR
Fujimoto et al., [7]	Japan	2018	2013.2-2013.8	Patients with SSA/P and those with a history of SSA/P that had been endoscopically removed	1	22	22	65.9	61.1	57	38	the additional SSA/P detection rate
Hasegawa et al., [13]	Japan	2021	2017-2020	Screening, surveillance, and diagnostic workup of colonic symptoms	1	349	351	66.5	65.8	62.5	63.2	ADR
Kuto et al., [14]	Japan	2021	2017-2018	Screening	1	152	150	63.2	62.5	53	49	the number of flat-type polyps per patient
Lovasz et al., [15]	Hungary	2020	2016-2018	Screening	1	552	726	51.95	51.96	49.5	49.2	ADR, PDR, MPP, MAP
Min et al., [10]	China	2017	2016.5-2016.9	Screening, surveillance, symptoms	3	71	70	45.69	47.99	52.11	54.29	the difference in sensitivity between LCI and WLI endoscopy for the detection of colorectal polyps during colonoscopy
Miyaguchi et al., [16]	Japan	2021	2018-2019	Screening, surveillance, symptoms, FIT	3	494	501	65.5	65	63.3	61.3	MAP
Paggi et al., [9]	Italy	2018	2017.7-2017.12	Screening, positive FIT, surveillance, diagnostic assessment	1	300	300	63.7	63.7	56.7	58	AMR in the right colon
Paggi et al., [17]	Italy	2020	2018-2019	Screening, FIT positivity	7	326	323	60.6	61.1	49.7	49.5	ADR

ADR: adenoma detection rate; AMR: adenoma miss rate; FIT: fecal immunochemical testing; LCI: linked color imaging; MAP: mean adenomas per patient; MPP: mean polyp per patient; NA, not available; PDR: polyp detection rate; WLI: white light imaging.

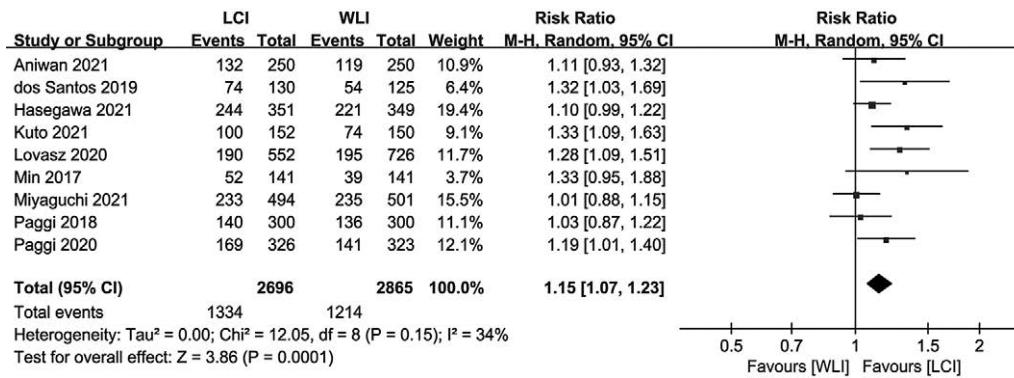


Fig. 2. Forest plots comparing linked color imaging (LCI) and white light imaging (WLI) in terms of adenoma detection rate (ADR)

In subgroup analyses based on adenomas size, the detection rate of small adenomas (<10 mm) was significantly higher in the LCI arm compared with the WLI arm (RR=1.14; 95%CI: 1.01-1.30; p=0.04), whereas the detection rate of ≥10mm adenomas was similar in the 2 groups (RR=1.12; 95%CI: 0.83-1.50; p=0.45) (Fig. 3, Table II). Regarding to location, no difference was observed between the 2 arms (right-side: RR=1.08; 95%CI: 0.92-1.27; p=0.33; left-side: RR=1.08; 95%CI: 0.91-1.28; p=0.37) (Table II).

Second Outcome

PDR

Six studies with 3,325 patients reported PDR. The pooled PDR in the LCI group was 67.1% (95%CI: 59.3-74.9) and in the WLI group was 57.8% (95%CI: 49.1-66.5). The pooled RR was 1.15 (95%CI: 1.08-1.22, p<0.0001) (Fig. 4A, Table II).

AMR and SMR

Three studies reported AMR. The pooled AMR was 12.2% (95%CI: 1.4-23) for LCI and 24.4% (95%CI: 12.6-36.1) for WLI. The pooled RR was 0.55 (95%CI: 0.37-0.82, p=0.004) (Fig. 4B, Table II).

Two studies reported SMR. The pooled SMR was 12.3% (95%CI: 0-39.3) for LCI and 32.9% (95%CI: 5.7-60.2) for WLI. The pooled RR was 0.38 (95%CI: 0.08-1.76, p=0.22) (Table II).

MAP and MPP

Five studies reported the available data between LCI and WLI and the pooled MD was 0.18 (95%CI: 0.09-0.28, p=0.0002) for MAP, 0.13 (95%CI: 0.01-0.25, p=0.03) for MPP (Fig. 4C, D, Table II). The results above indicate significant difference between the two groups.

Table II. Outcomes of meta-analysis comparing LCI and WLI

Outcomes	No.	LCI, %	WLI, %	RR (95% CI)	p	I ² , %
ADR	9	51.3 (43-59.6)	43.8 (34.5-53.1)	1.15 (1.07-1.23)	0.0001	34
Size						
≥10mm	2	13.4 (4.4-22.4)	12.1 (4.7-19.4)	1.12 (0.83,1.50)	0.45	0
< 10mm	2	48.8 (44.7-52.9)	42.5 (38.4-46.5)	1.14 (1.01,1.30)	0.04	0
Location						
RDR	3	29.8 (22.4-37.1)	27.4 (24.4-30.4)	1.08 (0.92-1.27)	0.33	14
LDR	2	33 (29.1-36.8)	30.5 (26.7-34.3)	1.08 (0.91-1.28)	0.37	0
PDR	6	67.1 (59.3-74.9)	57.8 (49.1-66.5)	1.15 (1.08-1.22)	<0.0001	23
AADR	4	15.7 (11.3-20.1)	15.3 (11.4-19.2)	1.03 (0.86-1.24)	0.74	0
SDR	3	4 (0.1-7.9)	3.4 (0.2-6.6)	1.21 (0.77-1.90)	0.41	0
AMR	3	12.2 (1.4-23)	24.4 (12.6-36.1)	0.55 (0.37,0.82)	0.004	39
SMR	2	12.3 (0-39.3)	32.9 (5.7-60.2)	0.38 (0.08,1.76)	0.22	43
Cecal intubation rate	3	96.3 (89.9-1)	95.6 (88-1)	1.23 (0.71-2.13)	0.47	0
				MD (95% CI)	p	I ²
MAP	5	-	-	0.18 (0.09-0.28)	0.0002	0
MPP	5	-	-	0.13 (0.01-0.25)	0.03	0
Withdrawal time	9	-	-	0.03 (-0.39,0.45)	0.88	98
Insertion time	5	-	-	-0.24 (-0.55,0.07)	0.12	0

AADR: advanced ADR; ADR: adenoma detection rate; AMR: adenoma miss rate; CI: confidence interval; LCI: linked color imaging; LDR: left-side lesion detection rate; MAP: mean adenomas per patient; MD: mean difference; MPP: mean polyp per patient; PDR: polyp detection rate; RDR: right-side lesion detection rate; RR: relative risk; SDR: sessile serrated lesion detection rate; SMR: sessile serrated lesion miss rate, WLI: white light imaging.

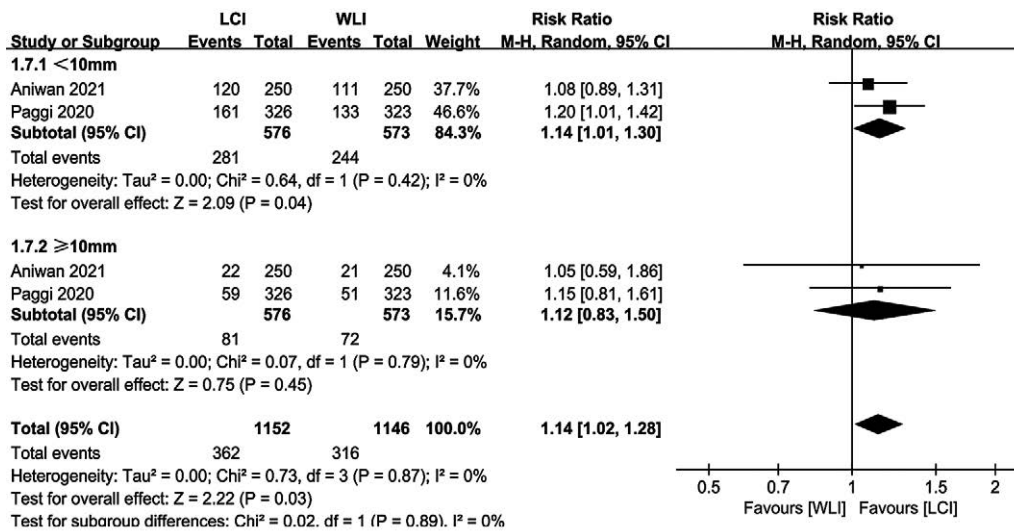


Fig. 3. Forest plots comparing linked color imaging (LCI) and white light imaging (WLI) in terms of adenomas size

Other Outcomes

For additional secondary outcomes, including AADR, SDDR, cecal intubation rate, insertion time, and withdrawal time, there was no significant difference between the two groups (Table II).

DISCUSSION

In this study, we included 10 RCTs involving 5,510 patients to assess the efficacy of the LCI. The results showed that LCI can significantly improve the detection of ADR, PDR, MAP, MPP.

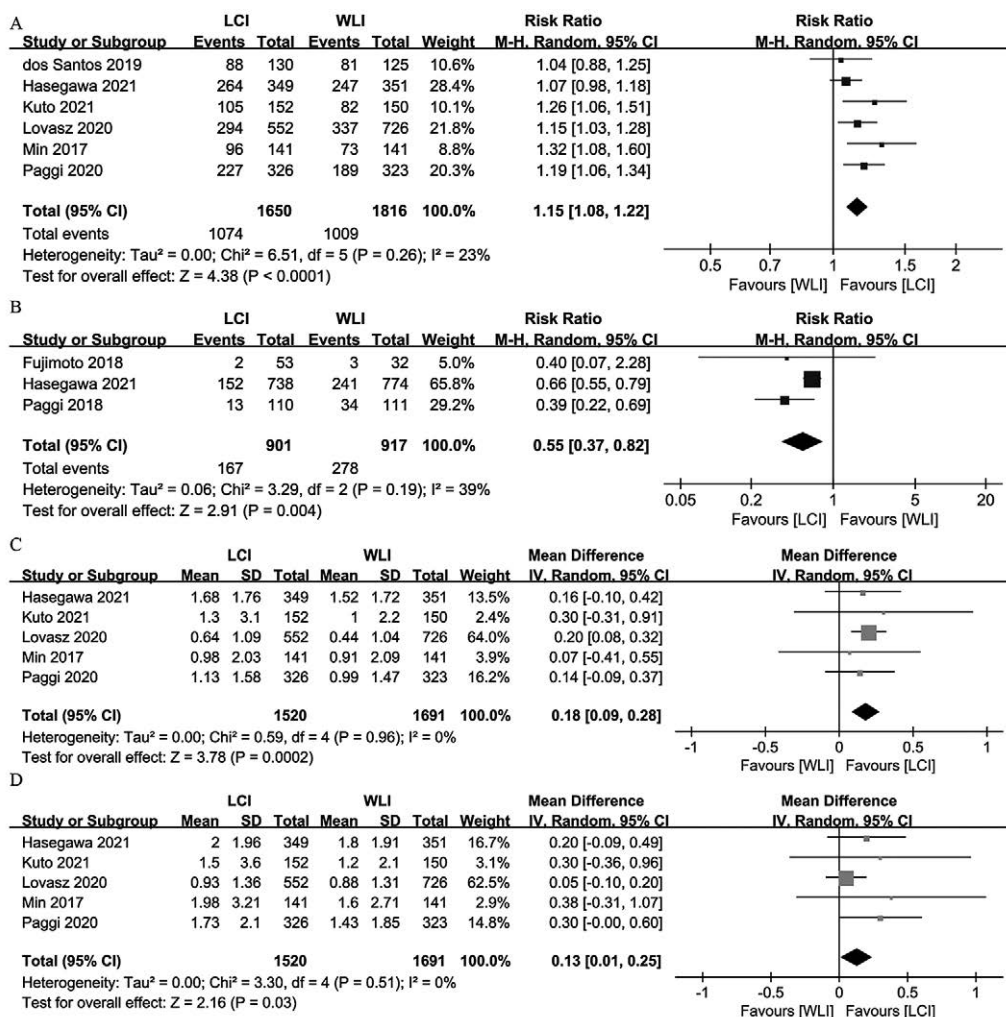


Fig. 4. Forest plots comparing linked color imaging (LCI) and white light imaging (WLI) in terms of second outcomes. A: polyp detection rate (PDR); B: adenoma miss rate (AMR); C: mean adenomas per patient (MAP); D: mean polyp per patient (MPP)

LCI showed a significant decrease in AMR when compared to WLI. No significant difference was found in AADR, SADR, SMR, cecal intubation rate, insertion time, and withdrawal time between LCI and WLI.

Colonoscopy is imperfect as 22% of polyps and up to 26% of adenomas remain undetected, particularly in the proximal colon [21–22]. Missed adenomas are considered to give rise to interval CRC; thus, reducing miss rates of precancerous lesions might be a key element in reducing CRC related mortality [23]. ADR, defined as the percentage of colonoscopies with at least one adenoma identified, has been recognized as a key performance measure for quality colonoscopy [24]. A LASER endoscopic system (LASEREO: Fujifilm Co., Tokyo, Japan) was developed in 2012. It allows blue laser imaging (BLI), BLI-bright, and linked color imaging (LCI) as narrow band light observation [25]. These modes have been reported to be useful for tumor detection and characterization [26–28]. Desai et al. [29] performed a systematic review and meta-analysis to examine the AMR of white-light endoscopy compared with electronic chromoendoscopy and they discovered that the use of electronic chromoendoscopy does not decrease AMR when compared with WLE [29]. More recently, a network meta-analysis by Azizi et al. [30] was performed to compare all the available endoscopic interventions (including LCI) for improving serrated adenoma detection rate (SADR) and the results showed that add-on devices, narrow band imaging, water-based techniques and chromoendoscopy were comparable to each other and improved SADR compared to high-definition colonoscopy. In our study, we focused on LCI and added several additional studies, which allowed for a larger number of subjects and a more precise risk estimation. The pooled results showed that LCI appears as a promising and reliable technology able to significantly decrease the number of adenomas missed.

Up to 15.5% of small adenomas and up to 3.4% of diminutive adenomas contain high-grade dysplasia, the omission of those adenomas may contribute to the occurrence of interval cancers diagnosed between surveillance colonoscopies [31]. In this study, we also conducted subgroup analysis based on adenomas size. The results showed that LCI can increase the detection rate of small polyps (< 10mm), but had no significant difference in the detection rate of large polyps (≥10mm). With regard to location, no significant difference was found.

Serrated lesions are difficult to detect owing to their location and appearance in colon. Given the proportion of CRC caused by serrated lesions (20–30%), there is certainly a need to enhance the current endoscopic technique to improve the serrated lesions detection. In our study, we failed to detect a difference between LCI and WLI, which was in accordance with a recent meta-analysis [32]. However, because only few studies were included in the above analysis, the result should be interpreted with caution, and more studies are required.

Withdrawal time is defined as the length of time the colonoscopist spends withdrawing the colonoscope from the cecal pole to the anus. A withdrawal time ≥ 6 minutes has been associated with increased detection of both adenomas and advanced adenomas in several studies [33–34]. In our study, the withdrawal time between LCI and WLI did not have statistically significant differences.

There are certain limitations to our study that merit further discussion. First, the endoscopists in both groups were not blinded, which is common to most endoscopic studies designed for assessment of external attachments. This brings into play performance and detection biases. Secondly, the number of included trials was relatively few and some relevant subgroup analyses could not be performed owing to the lack of data. Thirdly, study heterogeneity, differences in population undergoing colonoscopy, study indication (i.e., screening, surveillance, and/or diagnostic) and geographical distribution can lead to misinterpretation of our results. Moreover, three studies reported industry funding for the RCT, making it difficult to eliminate funding bias [7, 8, 17]. Finally, the quality of bowel preparation was incompletely reported using different scoring criteria in the included studies, whereas intestinal cleanliness had a great impact on the detection of lesions.

CONCLUSION

This meta-analysis showed that LCI could increase ADR and decrease AMR when compared to WLI. However, LCI does not seem to determine higher AADR and SDR than WLI. Further studies are needed to confirm the value of LCI in improving the AADR and SDR.

Conflicts of interest: None to declare.

Authors' contribution: S.F. generated the idea for the study. C.Y. and J.W. analyzed and interpreted the data. J.W. prepared the original draft. K.W. and S.F. critically revised the paper. All authors read and approved the final version of the manuscript submitted for publication.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointest Liver Dis* at <http://dx.doi.org/10.15403/jgld-4027>.

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