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Linked color imaging *versus* white light imaging in the diagnosis of colorectal lesions: a meta-analysis of randomized controlled trials

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Abstract

Background: Miss rate of colorectal neoplasia is associated with lesion histology, size, morphology, or location.

Objectives: We aim to compare the efficacy of Linked color imaging (LCI) *versus* white light imaging (WLI) for adenoma detection rate (ADR), the detection of sessile serrated lesions (SSLs), serrated lesions (SLs), advanced adenomas (AAs), diminutive lesions (DLs), and flat lesions (FLs) by using per-patient and per-lesion analysis based on randomized controlled trials (RCTs).

Design: Systematic review and meta-analysis.

Data sources and methods: PubMed, Embase, and Cochrane databases were searched through May 1st, 2023. We calculated risk ratio for dichotomous outcomes and mean difference for continuous outcomes, and performed sensitivity analyses and subgroup analyses.

Results: Overall, 17 RCTs (10,624 patients) were included. In per-patient analysis, ADR was higher in the LCI group *versus* the WLI group ($p < 0.00001$). This effect was consistent for SSL ($p = 0.005$), SLs ($p = 0.01$), AAs ($p = 0.04$), DLs ($p < 0.00001$), and FLs ($p < 0.0001$). In per-lesion analysis, LCI showed a significant superiority over WLI with regard to the mean number of adenomas per patient ($p < 0.00001$). This effect was in accordance with mean SSL ($p = 0.001$), mean SLs ($p < 0.00001$), and mean DLs ($p < 0.0001$) per patient. A subgroup analysis showed that the beneficial effect of the LCI group on the detection of AAs, SSL, and FLs was maintained only for studies when experts and trainees were included but not for experts only.

Conclusions: Meta-analyses of RCTs data support the use of LCI in clinical practice, especially for trainees.

Keywords: advanced adenomas, colonoscopy, linked color imaging, serrated lesions

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Introduction

Colorectal cancer (CRC) is the third most common cancer overall.[1] Colonoscopy with polypectomy has been shown to prevent the incidence and mortality of CRC, but such efficacy is strictly contingent upon the early detection of adenomas.[2,3]

Over the last decade, new techniques and technological equipment have been used to improve adenoma detection. Among them, image-enhanced endoscopy (IEE) systems that enhance mucosa architecture and/or vasculature visualization without the use of dye have been developed. Linked color imaging (LCI) is a newly developed IEE modality in 2014, produced by Fujifilm (Tokyo, Japan) and includes two systems: the laser endoscopic system (LASEREO) and the light-emitting diode endoscopic system (ELUXEO). It is designed

to detect subtle color differences in the red colon mucosa, enhancing the contrast of hemoglobin and thus detecting the mucosal vascular pattern. In addition, the post-processing could enhance the red color and make the white color whiter.[4,5]

The role of colonoscopy in CRC prevention is limited by the potential for missed neoplasia. Recently, serrated lesions (SLs) are believed to comprise most interval cancers with a trend toward higher cancer risk than conventional adenomas. Among them, sessile serrated lesion (SSL) is the most prevalent premalignant subtype, accounting for roughly 20% of all CRCs through the serrated adenoma pathway.[6] However, SSLs are difficult to detect using white light imaging (WLI) during colonoscopy because they typically occur in the proximal colon and are relatively flat in morphology.[7,8] A systematic review of six tandem colonoscopy studies reported that the miss rate was higher (26%) for diminutive polyps (<5 mm), as compared with small or large polyps.[9] Similar to diminutive adenomas, the detection of flat adenomas is more likely to harbor malignancy and has also been considered to be challenging.[10] In regard to the lesion location, a Canadian study found that the polyps are more commonly missed in the proximal colon, which progresses to CRC over time.[11] The failure to detect lesions with serrated histology, diminutive size, flat morphology, and proximal location has been considered to play a vital role in the development of interval CRCs.[12] Therefore, it is of critical importance to evaluate the detection efficacy of certain endoscopic techniques for the lesions discussed above, which is currently missing in the evaluation of LCI. Furthermore, a study that evaluated 2,664 colonoscopies showed that adenoma detection rate (ADR) among different endoscopists widely ranged from 7% to 44% in WLI during colonoscopy.[13] Considering that the variability among endoscopists' experience is another confounding factor in CRC prevention, it is also important to see whether LCI could overcome the limitation of WLI in that it may miss some polyps when using by trainees.

Regarding possible benefits, previous meta-analyses showed significantly greater ADR, polyp detection rate (PDR), and detection rate of missed polyps of LCI compared with WLI.[14,15] However, they failed to detect the beneficial effect of LCI on SSL and advanced adenomas (AAs). Consistent with this result, there is still uncertainty on whether the effort to increase ADR also results in increased detection of AAs.[16] Recently, seven randomized controlled trials (RCTs) with large sample sizes comparing LCI and WLI have been published,[17–23] showing divergent results in the detection of SSL, AAs, and so on. So, it is meaningful to re-evaluate the detection efficacy of LCI for SSL and AAs with all the RCTs included.

To the best of our knowledge, no previous study has compared the use of LCI with WLI in terms of the detection ability of SLs, SSL, AAs, DLs, flat lesions (FLs), proximal and distal adenomas by using per-patient and per-lesion analysis. To achieve the aims mentioned above, we conducted this systematic review with meta-analysis incorporating data exclusively from RCTs. In addition, we also did subgroup analyses based on the experience of endoscopists, the study cohort, and so on.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items Systematic Reviews and Meta-Analyses (PRISMA) statement. The PRISMA checklist was shown in the Supplemental Material.

Search strategy

This systematic review and meta-analysis were performed following the PRISMA guidelines. PubMed, Embase, and Cochrane Library databases were searched up to May 1st, 2023. The detailed search strategy was shown in Supplemental Table 1. Abstracts from the international congress including Digestive Disease Week (USA), United European Gastroenterology Week, and Asian Pacific Digestive Week were also searched.

Study selection

Titles and abstracts of all articles were independently reviewed by two authors (Y.N.S and X.H.L). Duplicate articles were excluded, and data were independently evaluated. In case of disagreement, the first and second authors discussed the matter with another co-author (X.Z) to reach a consensus.

Data extraction

The following baseline data were abstracted: first author, year of publication, country of origin, number of centers, study design, number of patients, gender, age, the experience of endoscopists, indication for colonoscopy, and endoscopic system. The following clinical data were collected in a separate table: ADR; adenoma miss rate (AMR); the number of patients with at least one SLs (sessile serrated or traditional serrated adenoma or hyperplastic polyp), SSL (or sessile serrated adenoma/polyp), AAs (adenoma $\geqslant$10 mm in size, with villous features, or with high-grade dysplasia), adenoma in the proximal and distal colon, DLs (diameter $\leqslant$5 mm), and FLs (flat-type morphology lesions); the number of lesions mentioned above per patient; PDR; procedure time. Two authors performed the data extraction (Y.N.S and X.H.L).

Quality assessment

We used the Cochrane Collaboration tool for assessing the risk of bias.[24] The risk of bias was judged as low, high, or unclear for individual elements. The quality assessment was independently performed by two authors (Y.N.S and X.Z), and eventual disagreements were discussed with a third author (J.W).

Statistical analysis

The risk ratio (RR) was used for dichotomous variables, and the mean differences (MD) were used between groups for continuous variables. All outcomes were reported with their 95% confidence intervals (CIs) and *p*-values. Heterogeneity among studies was evaluated with the chi-squared test and I^2 statistic; I^2 values of 0–25%, 25–50%, 50–75%, and more than 75% were roughly considered as no homogeneity, mild heterogeneity, moderate heterogeneity, and high heterogeneity, respectively. Publication bias was determined by the funnel plots, also assessed by the Begg–Mazumdar test and Harbord–Egger test. $p < 0.05$ was considered statistically significant. We used the Review Manager software (version 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata software (version 15.0, Stata Corporation, College Station, TX, USA) for all the data analysis.

Results

Study selection

A total of 359 studies were identified through both database and manual searching, and 132 duplicates were removed then. Screening and evaluation of titles and abstracts excluded a further 194 studies. The remaining 33 studies were assessed for full-text details, and 16 were excluded. Finally, 17 RCTs were included in this systematic review and meta-analysis (Figure 1).[17–23,25–34]

Characteristics of studies

Overall, 15 published studies[19–23,25–34] and 2 conference abstracts[17,18] were included; 5228 and 5396 patients underwent LCI and WLI, respectively. The years of publication or presentation are from 2017 to 2023. The included studies were mainly from Europe, Asia, and South America. In terms of design, two studies used a crossover design,[18,25] and three were tandem designs,[26–28] whereas the other eleven studies used a parallel design. In total, this quantitative analysis includes 10,624 patients with a median age of 59.2 (range 46.8–66.2 years). Slightly more female patients were enrolled (54.3% of all patients from 16 studies; Table 1).

Risk of bias assessment

For all included studies, the blinding of participants and personnel (performance bias) was judged as high risk because the use of LCI or WLI could not be blind to endoscopists. Two studies[17,18] did not report their methods of allocation concealment, therefore were judged as an unclear risk for selection bias. Four studies[17,18,25,34] did not report whether their outcome assessments were blinded or not, therefore were judged as an unclear risk for detection bias. Detailed risk assessment results can be seen in Supplemental Figure 1.

Primary endpoints

Adenoma detection rate. The ADR was provided from 15 studies (n=9986). LCI had a significant superiority over WLI (RR, 1.18; 95% CI, 1.11–1.25; $p < 0.00001$) with mild heterogeneity [I^2=45%; Figure 2(a)]. No statistical evidence of publication bias was found (Egger test: bias, −0.091; 95% CI, −1.801 to 1.618; p=0.910).

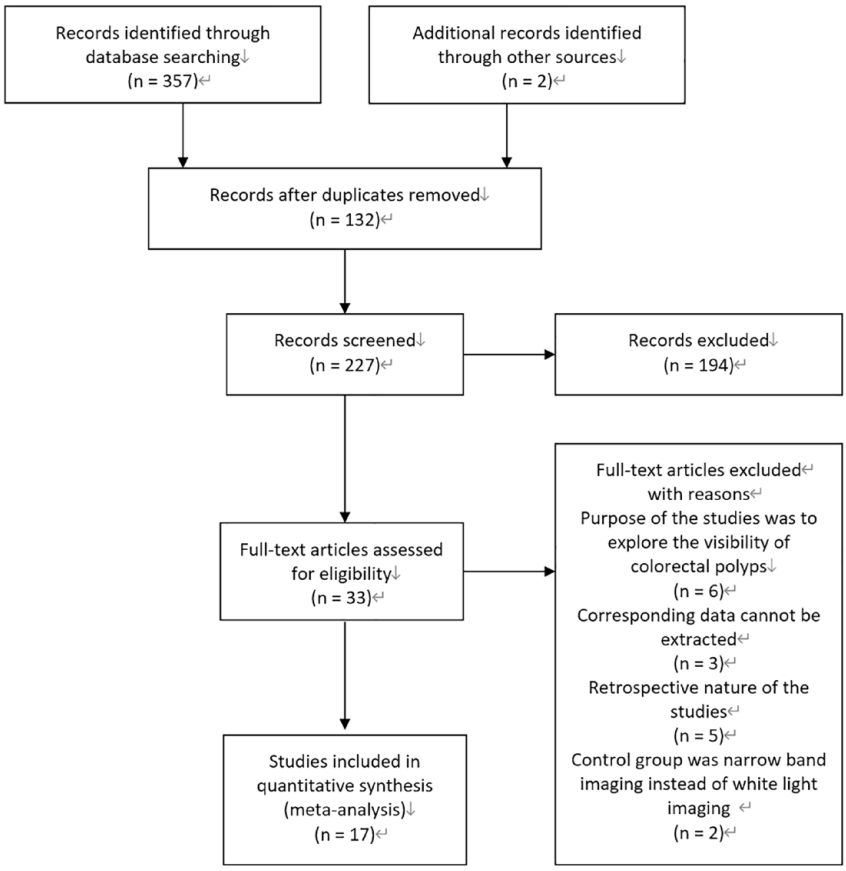

Figure 1. Flow diagram for assessment of studies.

Table 1. Characteristics of randomized controlled trials investigating LCI *versus* WLI colonoscopy for the detection of colorectal lesions.

Author	Year	Country	Center	Design	Patients (n)	Gender (M/F)	Mean Age (y)	Experience	Indication	System
Min *et al.*	2017	China	Multiple	Crossover	141	75/66	46.8	Experts	Sc+ Su + Di	LASEREO
Szalai *et al.*	2017	Hungary	Multiple	Parallel	247	NS	58.7	Experts	Sc	ELUXEO
Lim *et al.*	2018	Australia	Single	Crossover	149	65/84	60.0	Experts	Sc+ Su + Di	NS
Fujimoto *et al.*	2018	Japan	Single	Tandem	44	20/24	63.5	Experts + Trainees	Su	LASEREO
Paggi *et al.*	2018	Italy	Single	Tandem	600	344/256	63.7	Experts	Sc+ Su + Di	ELUXEO
Oliveira *et al.*	2019	Brazil	Single	Parallel	255	90/165	59.0	Experts	Sc+ Su + Di	LASEREO
Lovasz *et al.*	2020	Hungary	Multiple	Parallel	1278	630/648	52.0	Experts	Sc+ Su + Di	ELUXEO
Paggi *et al.*	2020	Italy	Multiple	Parallel	649	322/327	60.9	Experts	Sc	ELUXEO
Aniwan *et al.*	2021	Thailand	Single	Parallel	500	176/324	61.4	Experts + Trainees	Sc	ELUXEO
Hasegawa *et al.*	2021	Japan	Single	Tandem	700	440/260	66.2	Experts	Sc+ Su + Di	LASEREO

(Continued)

Table 1. (Continued)

Author	Year	Country	Center	Design	Patients (n)	Gender (M/F)	Mean Age (y)	Experience	Indication	System
Houwen *et al.*	2021	Multiple countries	Multiple	Parallel	332	141/191	48.4	Experts	Su	NS
Kudo *et al.*	2021	Japan	Single	Parallel	302	154/148	62.9	Experts	Sc	LASEREO
Miyaguchi *et al.*	2021	Japan	Multiple	Parallel	1000	620/380	65.3	Experts + Trainees	Sc + Su + Di	LASEREO
Dos Santos *et al.*	2021	Brazil	Single	Parallel	139	74/65	58.8	Experts	Sc	LASEREO
Suzuki *et al.*	2022	Multiple countries	Multiple	Parallel	3159	1736/1314	64.4	Experts + Trainees	Sc+ Su + Di	LASEREO or ELUXEO
Li *et al.*	2023	China	Multiple	Parallel	884	430/454	54.0	Experts + Trainees	Sc + Di	LASEREO or ELUXEO
Tanaka *et al.*	2023	Japan	Single	Parallel	594	371/223	53.1	Experts + Trainees	Sc+ Su + Di	LASEREO

Di, diagnosis; LCI, linked color imaging; M/F, male/female; NS, not stated; Sc, screening; Su, Surveillance; WLI, white light imaging.

The relative funnel plot is shown in Supplemental Figure 2(a). Four studies reported AMR. LCI significantly decreased the overall AMR compared with WLI (RR, 0.54; 95% CI, 0.41–0.73; $p < 0.0001$) with moderate heterogeneity [$I^2 = 34\%$; Figure 2(b)].

Mean number of adenomas per patient. Eleven studies reported the mean number of adenomas per patient in the LCI group and WLI group (n = 7995). The mean difference between the two groups was significantly higher for the LCI group compared with the WLI group (MD 0.28, 95% CI, 0.19–0.37, $p < 0.00001$) with mild heterogeneity [$I^2 = 30\%$; Figure 2(c)]. No statistical evidence of publication bias was found (Egger test: bias, −0.359; 95% CI, −2.020 to 1.303; $p = 0.637$). The relative funnel plot is shown in Supplemental Figure 2(b).

SSLs detection rate. The SSLs detection rate was derived from eight studies ($n = 6174$). The use of LCI showed a statistically significant increase in SSL detection rate when compared with the WLI group with mild heterogeneity [RR, 1.44; 95% CI, 1.12–1.84; $p = 0.005$; $I^2 = 24\%$; Figure 3(a)]. No statistical evidence of publication bias was found (Egger test: bias, −0.190; 95% CI, −2.101 to 1.720; $p = 0.815$). The relative funnel plot is shown in Supplemental Figure 2(c).

Mean number of SSLs per patient. Three studies reported the mean number of SSLs per patient ($n = 3811$). The mean number of SSLs per patient for LCI was significantly higher than that of WLI without heterogeneity [MD, 0.04; 95% CI, 0.02–0.06; $p = 0.001$; $I^2 = 0$; Figure 3(b)].

Advanced ADR. Nine studies provided the advanced ADR ($n = 6874$), which was significantly improved in the LCI group compared with the WLI group [RR, 1.14; 95% CI, 1.01–1.29; $p = 0.04$; Figure 4(a)]. Neither heterogeneity ($I^2 = 0$) nor evidence of publication bias (Egger test: bias, −0.382; 95% CI, −2.134 to 1.370; $p = 0.622$) was found. The relative funnel plot is shown in Supplemental Figure 2(d).

Mean number of AAs per patient. Three studies provided data allowing the mean number of AAs per patient to be calculated ($n = 3811$). The mean number of AAs per patient did not differ between the LCI and WLI arms [MD, 0.03; 95% CI, −0.00 to 0.06; $p = 0.07$; $I^2 = 0$; Figure 4(b)].

Secondary endpoints

SLs detection rate. Two studies reported SLs ($n = 3162$). The SLs detection rate for LCI was significantly higher than WLI with mild heterogeneity [RR, 1.60, 95% CI, 1.11–2.31; $p = 0.01$; $I^2 = 40\%$; Figure 3(c)].

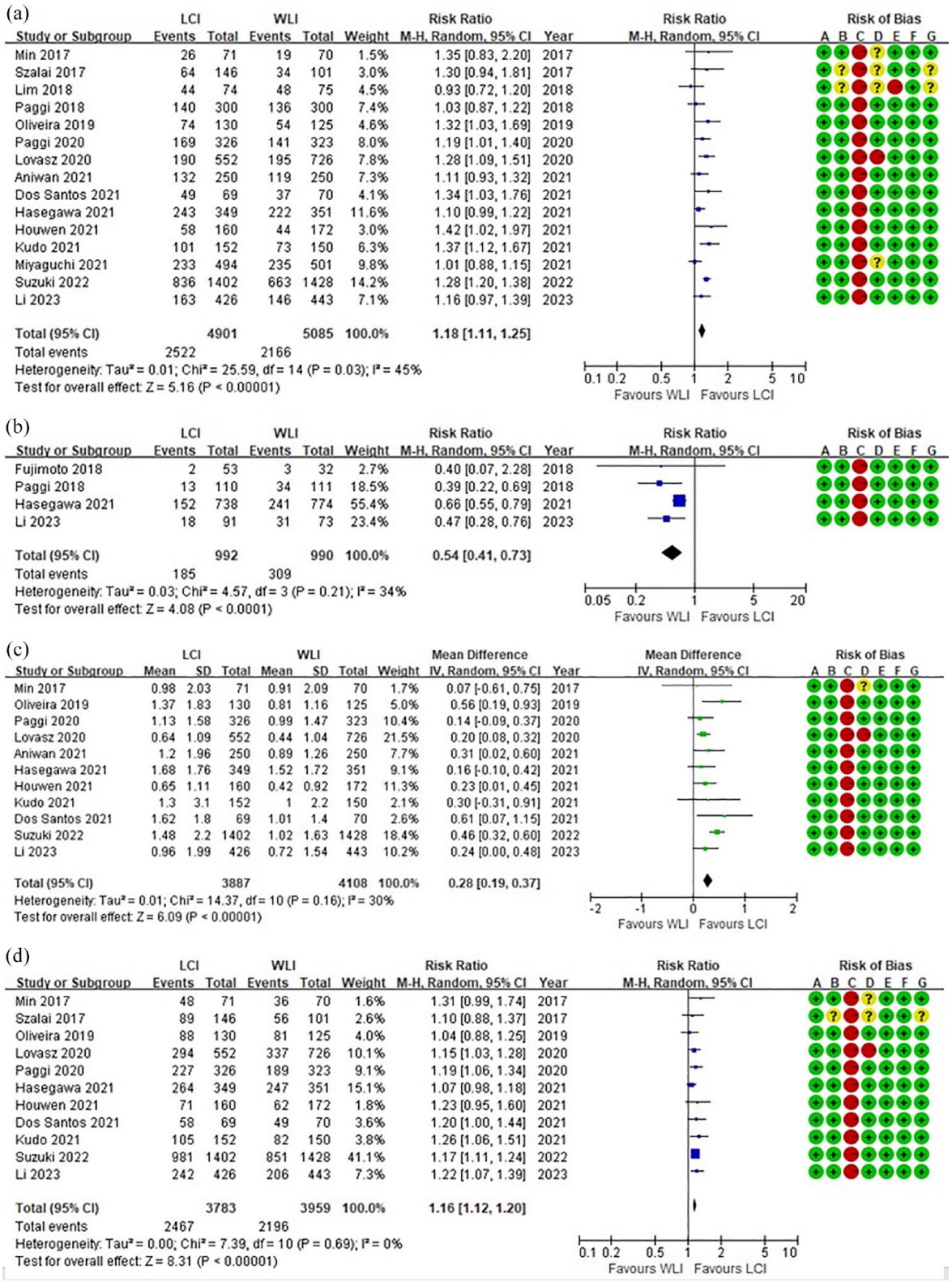

Figure 2. A quantitative analysis comparing LCI to WLI for the detection of overall adenomas. (a) Adenomas detection rate. (b) Adenomas miss rate. (c) Mean number of adenomas per patient. (d) Polyp detection rate. CI, confidence interval; IV, inverse variance; M–H, Mantel–Haenszel; SD, standard deviation. Risks of bias: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Symbols for risk of bias: +, low risk; _, high risk; ?, unclear risk.

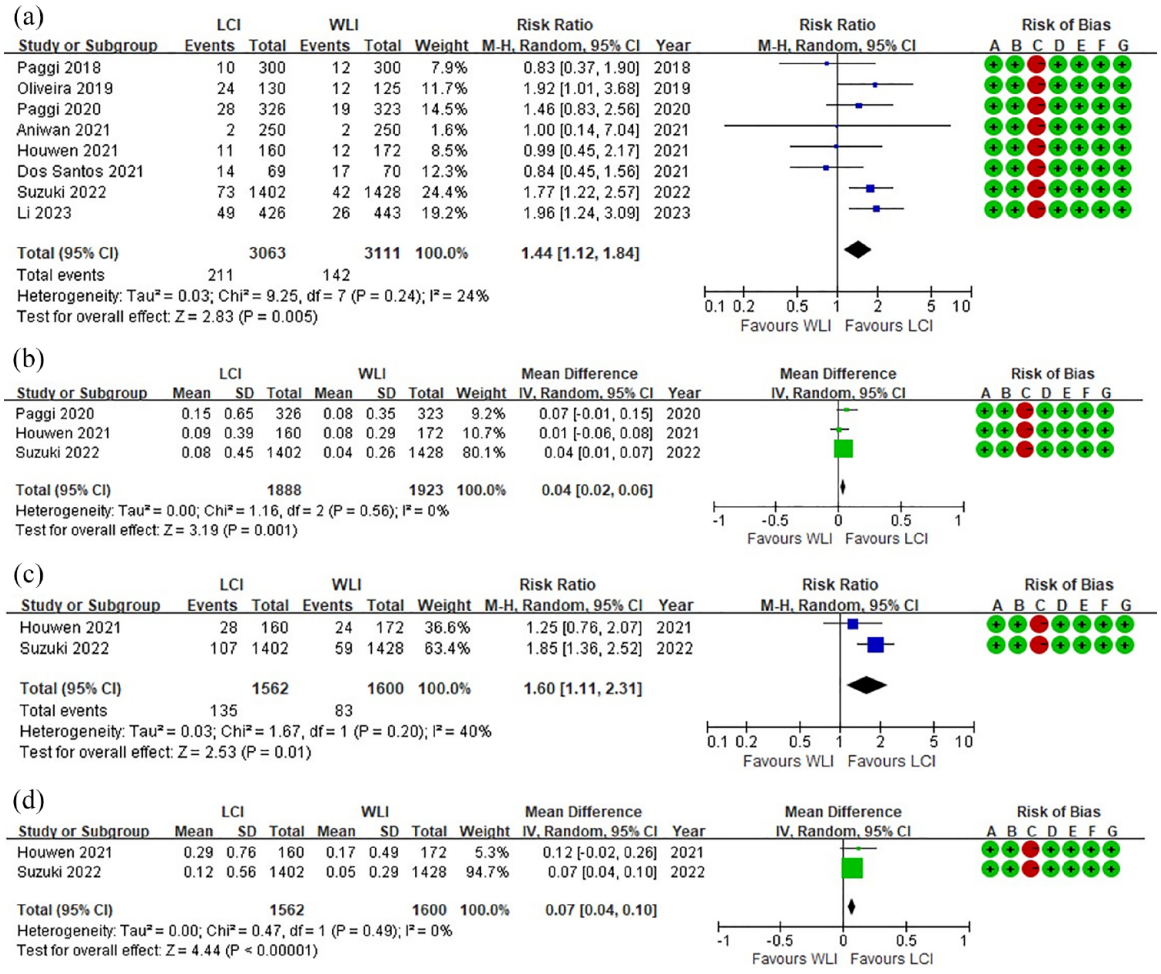

Figure 3. A quantitative analysis comparing LCI to WLI for the detection of SLs. (a) Sessile serrated lesions detection rate. (b) Mean number of SSLs per patient. (c) Overall SLs detection rate. (d) Mean number of SLs per patient. CI, confidence interval; IV, inverse variance; M–H, Mantel–Haenszel; SD, standard deviation. Risks of bias: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Symbols for risk of bias: +, low risk; _, high risk.
LCI, linked color imaging; SLs, serrated lesions; SSLs, sessile serrated lesions; WLI, white light imaging.

Mean number of SLs per patient. We also evaluated the mean number of SLs per patient in these two studies, showing that the mean difference between these two groups was statistically significantly higher for LCI compared with WLI without heterogeneity [MD 0.07, 95% CI, 0.04–0.10, $p < 0.00001$; $I^2 = 0$; Figure 3(d)].

DLs detection rate. The DLs detection rate was calculated from data provided in three studies ($n = 2479$). LCI resulted in the detection of more DLs than WLI without heterogeneity [RR, 1.39; 95% CI, 1.22–1.59; $p < 0.00001$; $I^2 = 0\%$; Figure 5(a)].

Mean number of DLs per patient. Three studies reported the mean number of DLs per patient ($n = 4031$). The mean number of DLs per patient for LCI was significantly higher than WL with mild heterogeneity [MD, 0.24; 95% CI, 0.12–0.37; $p < 0.0001$; $I^2 = 38\%$; Figure 5(b)].

Flat lesions detection rate. Five studies provided data on FL detection rate ($n = 5675$). Among these studies, LCI was found to have a significantly higher FL detection rate compared with WLI with mild heterogeneity [RR, 1.37; 95% CI, 1.19–1.58; $p < 0.0001$; $I^2 = 42\%$; Figure 5(c)]. No evidence of publication bias (Egger test: bias,

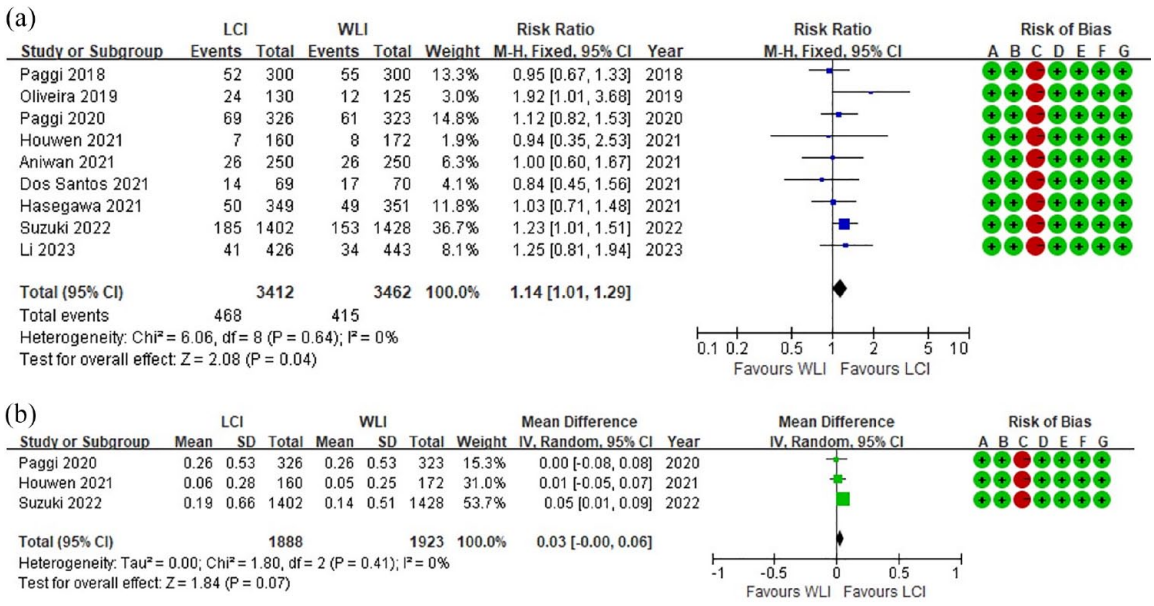

Figure 4. A quantitative analysis comparing LCI to WLI for the detection of AAs. (a) Overall advanced adenomas detection rate. (b) Mean number of advanced adenomas per patient. CI, confidence interval; IV, inverse variance; M–H, Mantel–Haenszel; SD, standard deviation. Risks of bias: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Symbols for risk of bias: +, low risk; _, high risk.

−0.363; 95% CI, −4.904 to 4.178; $p = 0.816$) was found. The relative funnel plot is shown in Supplemental Figure 2(e).

Proximal and distal ADR. The proximal ADR was reported in three studies ($n = 1481$), and the distal ADR was reported in two studies ($n = 1149$). The use of LCI did not improve the distal ADR but did improve the proximal ADR compared with WLI: [RR, 1.08; 95% CI, 0.91–1.28; $p = 0.37$; $I^2 = 0$; Figure 5(d)] for distal ADR and [RR, 1.20; 95% CI, 1.02–1.42; $p = 0.03$; $I^2 = 5\%$; Figure 5(e)] for proximal ADR, respectively.

Mean number of proximal adenomas per patient. The mean number of proximal adenomas per patient was derived from three studies (n = 3811). The mean difference was significantly higher for the LCI group compared with the WLI group with mild heterogeneity [MD 0.25, 95% CI, 0.16–0.35, $p < 0.00001$; $I^2 = 29\%$; Figure 5(f)].

Polyp detection rate. Eleven studies reported PDR ($n = 7742$). The PDR for LCI was significantly higher than that of WLI without heterogeneity [MD, 1.16; 95% CI, 1.12–1.20; $p < 0.00001$; $I^2 = 0$; Figure 2(d)].

Procedure time

For the withdrawal time reported in 13 studies ($n = 9028$), LCI showed no superiority over WLI (MD −0.18, 95% CI, −0.46 to 0.11, $p = 0.22$) with high heterogeneity [$I^2 = 94\%$; Figure 6(a)]. No statistical evidence of publication bias was found (Egger test: bias, −0.359; 95% CI, −2.020 to 1.303; $p = 0.637$). The relative funnel plot is shown in Supplemental Figure 2(f). For the intubation time reported in six studies ($n = 3741$), LCI also did not show any superiority over WLI (MD −0.15, 95% CI, −0.45 to 0.14, $p = 0.30$) without heterogeneity [$I^2 = 0\%$; Figure 6(b)].

Sensitivity analyses

Sensitivity analyses were performed to justify this meta-analysis including conference abstracts and non-parallel studies. First, we evaluated ADR after excluding two conference abstracts[17,18], and LCI significantly increased the ADR compared to WLI (RR 1.19, 95% CI, 1.12–1.26, $p < 0.00001$;

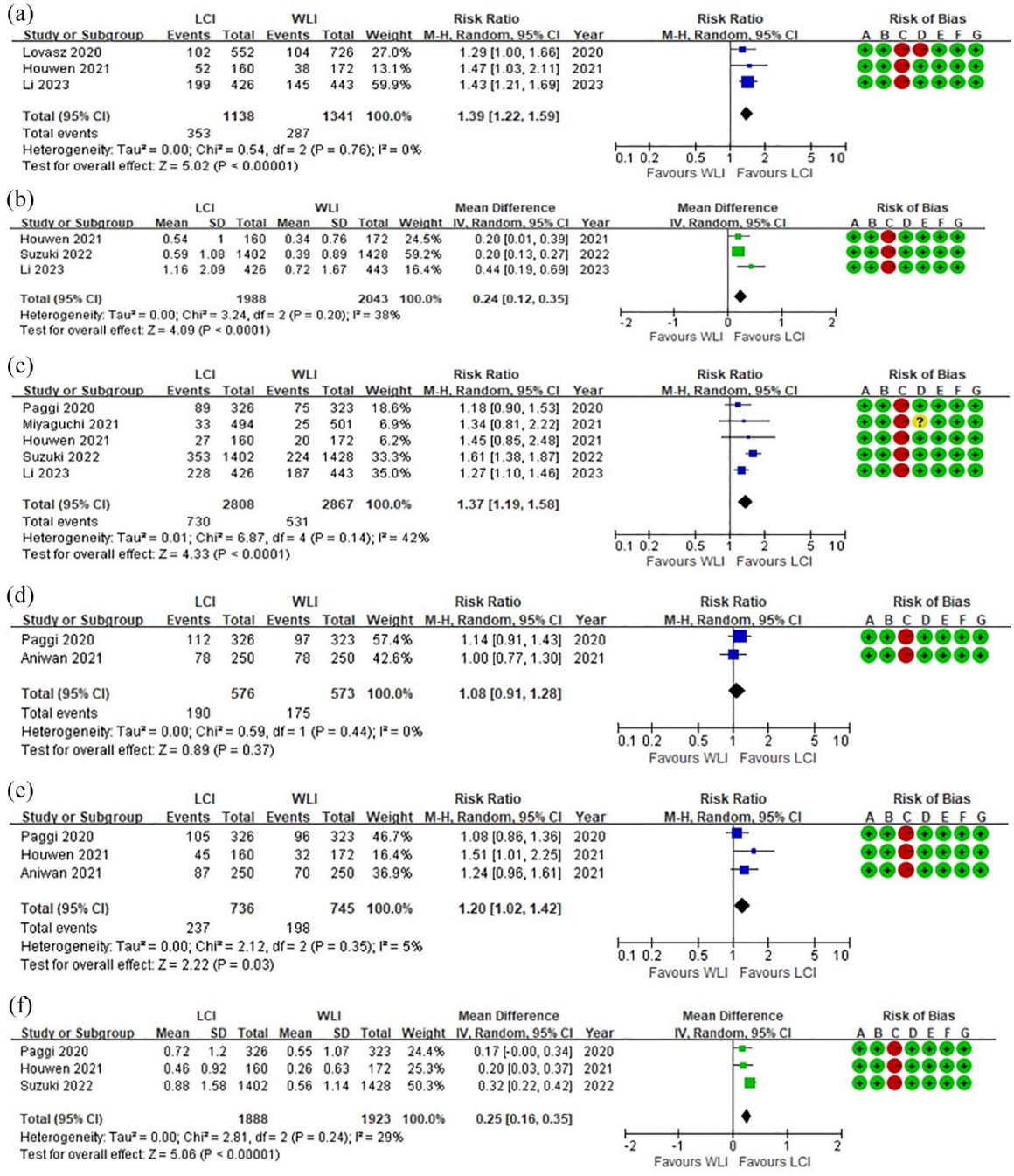

Figure 5. A quantitative analysis comparing LCI to WLI for the detection of colorectal lesions. (a) DLs detection rate. (b) Mean number of DLs per patient. (c) Flat lesions detection rate. (d) Distal adenomas detection rate. (e) Proximal adenomas detection rate. (f) Mean number of proximal adenomas per patient. CI, confidence interval; IV, inverse variance; M–H, Mantel–Haenszel; SD, standard deviation. Risks of bias: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Symbols for risk of bias: +, low risk; _, high risk; ?, unclear risk.
DL, Diminutive lesions.

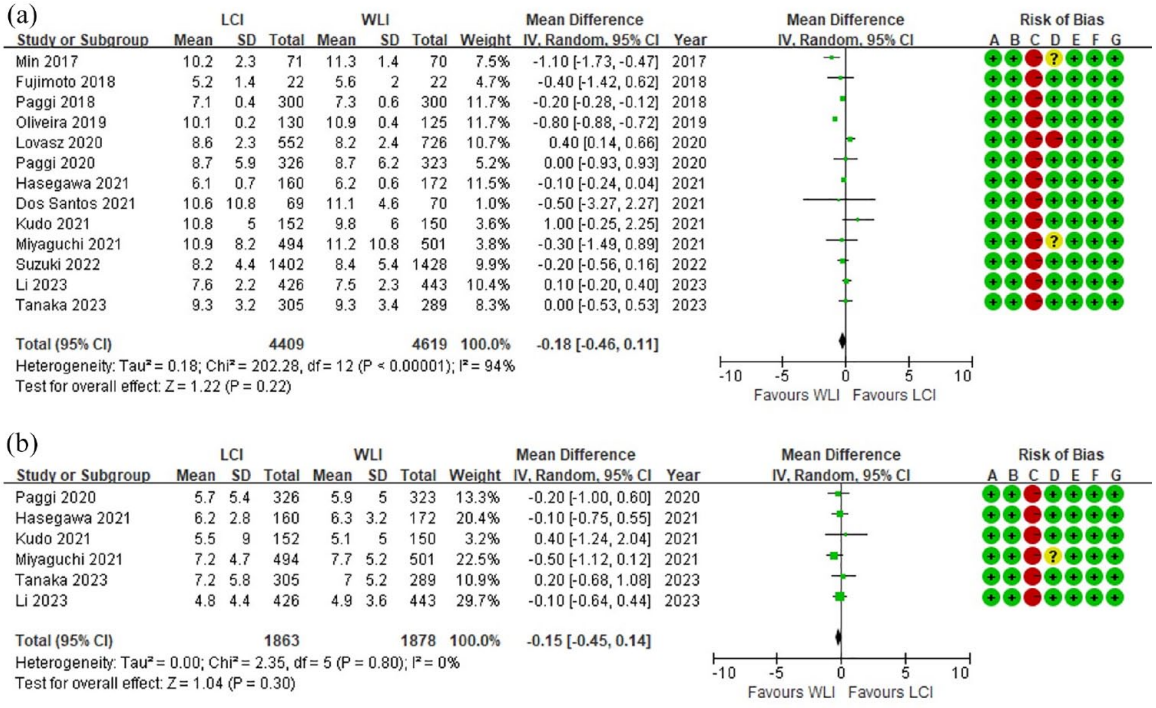

Figure 6. A quantitative analysis comparing LCI to WLI for the procedure time. (a) Withdrawal time. (b) Intubation time. CI, confidence interval; IV, inverse variance; M–H, Mantel–Haenszel; SD, standard deviation. Risks of bias: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Symbols for risk of bias: +, low risk; _, high risk; ?, unclear risk.

Supplemental Figure 3). Second, we evaluated the SSL detection rate, advanced ADR, ADR, and the mean number of adenomas per patient after excluding relative crossover[18,25] and tandem[26–28] group studies. LCI had significantly higher SSL detection rate [RR 1.67, 95% CI, 1.32–2.13, $p<0.0001$; Supplemental Figure 4(a)], advanced ADR [RR 1.19, 95% CI, 1.03–1.37, $p=0.02$; Supplemental Figure 4(b)], ADR [RR 1.22, 95% CI, 1.14–1.30, $p<0.00001$; Supplemental Figure 4(c)], and the mean number of adenomas per patient [MD 0.30, 95% CI, 0.20–0.40, $p<0.00001$; Supplemental Figure 4(d)] than WLI. These data were similar to the original results.

Subgroup analyses

Subgroup analyses were performed based on a number of factors, including the country in which the study was conducted (Asian and non-Asian), the study cohort (screening and not limited to screening), and the experience of endoscopists (experts and mixed). The results are shown in Table 2. There was no significant difference in ADR between all the subgroups. Interestingly, LCI resulted in a significantly higher SSL detection rate [MD, 1.82; 95% CI, 1.37–2.42; $p<0.0001$; $I^2=0$; Supplemental Figure 5(a)], advanced ADR [MD, 1.21; 95% CI, 1.02–1.43; $p=0.03$; $I^2=0$; Supplemental Figure 5(b)], and FL detection rate [MD, 1.41; 95% CI, 1.17–1.71; $p=0.0004$; $I^2=62\%$; Supplemental Figure 5(c)] when colonoscopy was conducted by both experts and trainees (mixed), but there was no significant difference when outcomes from studies conducted by only experts. A subgroup analysis according to the study cohort showed a similar increased SSL detection rate [MD, 1.52; 95% CI, 1.01–2.30; $p=0.04$; $I^2=47\%$; Supplemental Figure 6(a)], advanced ADR [MD, 1.21; 95% CI, 1.02–1.43; $p=0.03$; $I^2=0$; Supplemental Figure 6(b)], and FL detection rate [MD, 1.42; 95% CI, 1.21–1.66; $p<0.0001$; $I^2=44\%$; Supplemental Figure 6(c)] with LCI as compared with WLI in the mixed population, when the analysis was restricted to only screening population, no significant difference was reported

Table 2. Subgroup analysis of main outcomes for the comparisons between LCI and WLI colonoscopy.

Country	Adenoma detection rate			Sessile serrated lesion detection rate			Advanced adenoma detection rate			Flat lesions detection rate		
	RR [95%CI]	I^2 (%)	*p* Value	RR [95%CI]	I^2 (%)	*p* Value	RR [95%CI]	I^2 (%)	*p* Value	RR [95%CI]	I^2 (%)	*p* Value
Asian countries	1.17 [1.07–1.28]	62	0.0007	1.82 [1.37–2.42]	0	<0.0001	1.17 [1.00–1.37]	0	0.04	1.41 [1.17–1.71]	62	0.0004
Non-Asian countries	1.19 [1.09–1.31]	30	0.0003	1.23 [0.77–1.96]	19	0.38	1.08 [0.89–1.32]	9	0.44	1.23 [0.97–1.56]	0	0.09
Indication												
Screening	1.23 [1.12–1.34]	0	<0.0001	1.43 [0.85–2.39]	0	0.18	1.07 [0.90–1.27]	0	0.46	1.18 [0.90–1.53]	NA	0.23
Not limited to screening	1.16 [1.06–1.26]	59	0.0006	1.52 [1.01–2.30]	47	0.04	1.21 [1.02–1.43]	0	0.03	1.42 [1.21–1.66]	44	<0.0001
Experience												
Experts	1.19 [1.11–1.29]	29	<0.00001	1.23 [0.77–1.96]	19	0.38	1.07 [0.90–1.27]	0	0.46	1.23 [0.97–1.56]	0	0.09
Experts + Trainees	1.14 [1.01–1.30]	74	0.04	1.82 [1.37–2.42]	0	<0.0001	1.21 [1.02–1.43]	0	0.03	1.41 [1.17–1.71]	62	0.0004

LCI, linked color imaging; WLI, white light imaging; RR, risk ratio.

between those two groups. In the Asian population, again there was a significant difference in SSL detection rate [MD, 1.82; 95% CI, 1.37–2.42; $p < 0.0001$; $I^2 = 0$; Supplemental Figure 7(a)], advanced ADR [MD, 1.17; 95% CI, 1.00–1.37; $p = 0.04$; $I^2 = 0$; Supplemental Figure 7(b)], and FL detection rate [MD, 1.41; 95% CI, 1.17–1.71; $p = 0.0004$; $I^2 = 62\%$; Supplemental Figure 7(c)] between the LCI and WLI groups. In terms of the non-Asian population, the combined results were not significantly different in subgroups.

Discussion

In this systematic review and meta-analysis, based only on high-quality trials (17 RCTs with more than 10,000 patients), we showed a significantly increased detection rate in SLs, SSL, and AAs when comparing LCI to WLE. In addition, there was an increased detection rate of DLs, FLs, and proximal adenomas in the LCI arm. Meanwhile, LCI significantly increases the number of SLs/SSLs/DLs/FLs/proximal adenomas per patient compared with WLI. LCI also showed a significant increase in ADR and a decrease in AMR when compared to WLI. There was no significant difference in the number of AAs per patient, the intubation time, or withdrawal time between the two groups.

Previous meta-analyses in the literature have investigated the role of LCI and WLI in the overall ADR and PDR only, whereas other modalities did not reveal any significance.[15,16] In this meta-analysis, our goal was to further understand the utility of LCI and WLI to detect SLs, SSL, and AAs, which play an important role in the adenoma to carcinoma and alternative carcinogenetic pathways. The reason these favorable outcomes were shown in our meta-analysis but not in previous studies received in the years 2019[15] and 2021[16] is because of the approximately fivefold and twofold increase in the magnitude of the pooled population (10,624 *versus* 2464; 10,624 *versus* 5510). We had a large patient population that was randomized across different studies, allowing for collective analysis. Meanwhile, we only included RCTs so as to generate the evidence at the highest level.

This is the first meta-analysis to compare the number of SLs, SSL, and AAs detected per patient comparing LCI with WLI. Interestingly, different from other aspects, the discordance between lesion detection rate and the mean

number of lesions per patient was detected regarding AAs. A possible explanation could be the limited number of studies reporting on mean number of AAs per patient. Considering that nine studies were included to explore the advanced ADR, whereas only three of them provided data on mean number of AAs per patient. Moreover, it could also be possible that LCI more often causes the first AAs detection, therefore increasing the advanced ADR. However, it does not reveal additional AAs in those patients with one AAs already detected; thus, its influence on the mean number of lesions per patient remains minimal.

Unlike prior meta-analyses, we were able to assess the detection of DLs, FLs, and proximal and distal adenomas. Our results showed that LCI could significantly improve the diminutive/FLs detection rate and the number of DLs per patient. The possible reason may be that the color enhancement provided by LCI enables observation of the wide colorectal lumen, allowing the operators to identify diminutive or flat polyps compared to WLI. Considering that diminutive or flat polyp are more commonly missed than other types of lesions during colonoscopy, the benefit of LCI for the detection of them might have significant clinical implications. Additionally, it has been reported that the use of LCI could reduce the rate of missed polyps of the proximal colon compared with WLI in the previous meta-analysis.[15] Conversely, Miyaguchi *et al.* and Min *et al.* both reported that the ADR with LCI is significantly higher than that with WLI in the distal colon.[25,34] Given these controversial results, we further detected the distal ADR, proximal ADR, and the mean number of proximal ADR per patient. It showed that the use of LCI did not improve the distal ADR but did improve the proximal ADR and mean number of proximal adenomas per patient compared with WLI. However, considering that only a few studies were included to calculate this, we thus recommend defined RCTs and longitudinal studies to further validate it.

Interestingly, we found that the beneficial effect of the LCI group on advanced ADR, SSL detection rate, and FL detection rate was maintained only for studies when experts and trainees are included during the subgroup analysis. However, when the analysis was restricted to studies only including experienced endoscopists, LCI did not show superiority over WLI. It has been reported that the experience of endoscopists was significantly associated with adenoma detection when using WLI,[35] which means that experts could perform well even when they use WLI but trainees could not. Considering that AAs, SSL, and FLs are difficult to detect during colonoscopy, it is reasonable that there is no significant difference between LCI and WLI for experts. But when trainees are included, LCI showed improved detecting ability of such lesions compared with WLI. This phenomenon suggests that LCI is more reliable and easier to set up compared with WLI, especially for trainees. We also found that in the subgroup of the screening population, LCI could not improve advanced ADR, SSL detection rate, and FL detection rate. A possible reason may be that when the purpose is screening, endoscopists did the procedure much more carefully, so they could find more lesions even in WLI. Another crucial reason may be that studies included in the screening subgroup were very limited. In this way, the result may be changed in a larger population, so further evaluation is needed.

Due to the characteristic nature of the 410-nm violet light of LCI, which penetrates only a short distance and is easily absorbed by hemoglobin in the vessels, neoplastic lesions remain red while the vessels of the surrounding mucosa become purple because of the deeper location where the 410-nm violet light cannot reach.[36] So, using LCI leads to the enhancing architecture visualization and/or mucosa vasculature of neoplastic lesions. ADR is associated with the long-term prevention of CRC and has been recognized as a key measurement for a quality colonoscopy.[37] To improve the ADR, chromoendoscopy, distal attachments including cuff or a transparent cap, and computer-aided detection (CADe)-assisted colonoscopy have been reported.[38–40] In detail, second-generation cuff could lead to a consistent improvement in ADR. More recently, Spadaccini *et al.* reported that the combination of CADe and EndoCuff Vision during colonoscopy could increase ADR and adenomas per colonoscopy without increasing withdrawal time compared to CADe alone.[41] Our analysis showed that ADR and mean number of adenomas per patient were significantly higher with LCI. However, ADR remains an imperfect quality indicator. In this regard, the AMR, measured in tandem and crossover design studies, has been considered a surrogate colonoscopy quality indicator.[42,43] Our

analysis showed that LCI significantly decreases the AMR when compared to WLI. The combination of ADR, mean number of adenomas per patient, and AMR provided further insights into how LCI improved colonoscopy outcomes.

There are several limitations in this meta-analysis. First, endoscopists were not blinded in both groups, which is common in most studies designed for assessing different endoscopic devices. Second, there were different scoring criteria used to grade the quality of bowel preparation in the included studies, making it difficult to analyze the outcomes, but individual studies did not have a significant difference in bowel preparation between both groups. Third, the polyp size, polyp location, and AMR were calculated using data from a few studies. Therefore, future large studies are necessary to conduct. Fourth, the 2019 WHO Classification introduce the term 'SSL' to replace 'SSA/*p*'. In the past some reports, SSA/P and SSL might be mixed. Further study compared the detection efficacy of LCI in SSL should be conducted. Fifth, the conclusion of subgroup analysis is limited because there were no follow-up data directly on the relationship between endoscopists' experience and adenoma detection, highlighting the need for such studies in the future. Sixth, different study design, experience of the operators, and different equipment may cause clinical heterogeneity. Although we did subgroup analyses based on the study cohort and the experience of endoscopists, conceptual heterogeneity may still exist.

Conclusion

In this large meta-analysis of data from 10,624 individual patients in RCTs, we found that LCI showed superiority over WLI for the detection of clinically relevant lesions such as SLs and AAs. Moreover, this result was evident also for DLs, FLs, and proximal adenomas. Subgroup analysis suggests that LCI has the potential to be easier set-up for trainees. Therefore, LCI increases key quality parameters in colonoscopy, supporting its use in everyday clinical practice, especially for trainees.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Yining Sun: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Writing – original draft.

Xiu-He Lv: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Software; Writing – original draft.

Xian Zhang: Data curation; Formal analysis; Methodology; Software.

Jin Wang: Funding acquisition; Methodology; Validation.

Huimin Wang: Data curation; Software.

Jin-Lin Yang: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

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Competing interests

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Supplemental material

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