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O IMPACTO DO "LINKED COLOR IMAGING (LCI)" NA TAXA DE DETECÇÃO DE ADENOMAS NA COLONOSCOPIA: REVISÃO SISTEMÁTICA E META-ANÁLISE.

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Orientador: Luiz Ronaldo Alberti

Coorientador: Fábio Gontijo Rodrigues

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ATA DE DEFESA DE DISSERTAÇÃO

Às 13:00, do dia vinte e nove de abril de dois mil e vinte e quatro, na sala 526 da Faculdade de Medicina, realizou-se a sessão pública para a defesa da Dissertação de **BRUNA HAUEISEN FIGUEIREDO ZWETKOFF**. A presidência da sessão coube ao prof. Luiz Ronaldo Alberti (orientador). Inicialmente, o presidente fez a apresentação da Comissão Examinadora assim constituída: Prof. Luiz Ronaldo Alberti (Orientador) – UFMG, Prof. Fábio Rodrigues Gontijo (Coorientador) – UFMG, Prof. José Celso Ardengh – UNIFESP e Prof. Carlos Eduardo Oliveira dos Santos – Hospital São Lucas da PUCRS. Em seguida, a candidata fez a apresentação do trabalho que constitui sua Dissertação de Mestrado, intitulada: O IMPACTO DO "LINKEDCOLOR IMAGING (LCI)" NA TAXA DE DETECÇÃO DE ADENOMAS NA COLONOSCOPIA: REVISÃOSISTEMÁTICA E META-ANÁLISE. Seguiu-se a arguição pelos examinadores e logo após, a Comissão reuniu-se, sem a presença da candidata e do público e decidiu considerar aprovada a Dissertação de Mestrado. O resultado final foi comunicado publicamente a candidata pelo presidente da Comissão. Nada mais havendo a tratar, o presidente encerrou a sessão e lavrou a presente ata que, depois de lida, se aprovada, será assinada pela Comissão Examinadora.

Belo Horizonte, 29 de abril de 2024.

Assinatura dos membros da banca examinadora:

Documento assinado eletronicamente por **Luiz Ronaldo Alberti**, **Professor do Magistério Superior**, em 10/01/2025, às 18:00, conforme horário oficial de Brasília, com fundamento no art. 5º do Decreto nº 10.543, de 13 de novembro de 2020.

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RESUMO

A prevenção do câncer colorretal fundamenta-se na vigilância com exames de colonoscopia de rotina. Entre os fatores de qualidade do exame, a taxa de detecção de adenomas (ADR) aparece como um dos principais índices de avaliação.

Dentro desse contexto, a tecnologia do "*linked color imaging* (LCI)" objetiva disponibilizar novos recursos que contribuam para aumentar a taxa de detecção de lesões adenomatosas, por meio de um sistema de diferenciação de espectros de luz que intensifica o contraste na topografia onde verifica-se esse tipo de lesão.

O objetivo desse trabalho é avaliar e quantificar, a partir de estudos vigentes, o impacto da utilização desse recurso no exame de colonoscopia de rotina.

Foram selecionados ensaios clínicos randomizados, em inglês, publicados até março de 2023 que avaliaram o uso do LCI em comparação com a luz branca (WL). O principal objetivo foi avaliar o impacto do LCI na taxa de detecção de adenomas. Também foram incluídos desfechos abrangendo o tamanho, morfologia, localização e o tipo das lesões, bem como o tempo total de avaliação cólica na retirada do aparelho a partir do ceco. O número de adenomas por paciente e a taxa de detecção adicional, foram analisados quando a metodologia do estudo permitiu tais avaliações. O estudo foi registrado no PROSPERO sob a identidade CRD42023438359.

Foram incluídos 16 estudos. O LCI mostrou acurácia superior na detecção de adenomas 1,20 (IC 95%: 1,13 a 1,28). Em relação ao tamanho, morfologia e localização, apesar dos resultados favoráveis ao LCI, não foram encontradas diferenças estatisticamente significativas nas análises de subgrupos. Também para a detecção de lesões serrilhadas, a adição do LCI não demonstrou resultados expressivos. Por outro lado, o uso do LCI aumentou as taxas de detecção de adenomas por paciente e a taxa de detecção adicional de adenomas em estudos de *crossover*. Em relação ao tempo de retirada, não houve diferenças estatisticamente significativas entre os exames realizados com ou sem LCI.

Assim, o LCI mostrou-se eficaz na identificação de lesões cólicas e aumentou a ADR e as taxas de detecção de adenomas por paciente, sem impacto negativo em outros

critérios de qualidade na colonoscopia, como o tempo de retirada. Além disso, o LCI demonstrou eficácia em aumentar a taxa de detecção adicional de lesões cólicas.

Palavras-chave: colonoscopia; cromoendoscopia; qualidade de colonoscopia; linked color imaging; taxa de detecção de adenoma.

ABSTRACT

The prevention of colorectal cancer is based on surveillance with routine colonoscopy. Among the factors of exam quality, adenoma detection rate (ADR) appears as one of the main. In this context, Linked Color Imaging (LCI) aims to intensifies the contrast of this type of lesion, improving exam performance.

Randomized clinical trials in English, published up to March 2023 evaluating the use of LCI compared to white light (WL) were selected. The main objective was to assess the impact of LCI on the ADR. In addition, the evaluated outcomes encompassed the size, morphology, location and type of lesions, the number of adenomas per patient, and the supplementary detection rate, as per study methodology's allowance for such assessments. The study was registered in PROSPERO with the ID CRD42023438359.

Sixteen studies were included, revealing LCI's superior accuracy in adenoma detection (1.20, 95% CI: 1.13–1.28) and increased rates per patient. Although LCI performed favorably in size, morphology, and location, subgroup analyses showed no statistically significant differences. The addition of LCI did not yield significant results for serrated lesion detection, and there were no statistically significant differences in withdrawal time between groups.

LCI has proved to be efficacious in the identification of colonic lesions and increased ADR, the adenoma detection rates per patient and the additional detection rate of colonic lesions, with no negative impact on other quality criteria in colonoscopy.

Keywords: colonoscopy; chromoendoscopy; quality colonoscopy; linked color imaging; adenoma detection

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ADR: adenoma detection rate

BLI: blue laser imaging

CRC: colorectal cancer

IEE: image-enhanced endoscopy

LCI: linked color imaging

LEDs: light-emitting diodes

NBI: narrow-band imaging

PDR: polyp detection rate

SADR: serrated adenoma detection rate

SSA/P: serrated adenoma/polyp

WL: white light

RCT: randomized prospective clinical trials

RR: risk ratio

SUMÁRIO

1. INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the world and represents the second most common cause of death by this disease [1].

The natural history of the disease shows the development of neoplasms from adenomatous lesions and the detection of those adenomatous polyps during colonoscopy has so far proved to be the most effective way of reducing CRC risk and mortality [2] and can be estimated by the adenoma detection rate (ADR), understood as the proportion of colonoscopies in which at least one adenomatous lesion is identified [3]. Despite this, there is still a non-negligible rate of unidentified polyps during a conventional examination, which can reach up to 20% [4].

Approximately 1% increase in the ADR leads to a 3% reduction rate in the incidence of colorectal cancer between colonoscopy screening intervals [5].

In an attempt to obtain better results in the identification of premalignant colonic lesions, great advances have been made, with the implementation of new technologies. Within this scenario, enhanced imaging techniques (*image-enhanced endoscopy* [IEE]) gained notoriety, mainly for its ease of use and no need of special preparations or additional devices. Initially, with good results in differentiating pre-malignant from benign lesions, allowing the evaluation of the surface pattern of these polyps [6], *narrow-band imaging (NBI) and blue laser imaging (BLI)* show controversial results in increasing the polyp detection rate [7,8].

In 2014, the Fujifilm Co. Ltd. (Tokyo, Japan) developed, *linked color imaging (LCI),* a technology that shows superiority in the illumination of the colorectal lumen when compared to other virtual chromoscopy techniques [9,10]. This technology uses the same standard of improvement of *BLI-bright,* separating the blue, red and green color spectra, expanding their differentiation, enhancing the color changes in the colonic mucosa and increasing the hemoglobin contrast, highlighting intestinal lesions that become more reddish than the rest of the mucosa surface [9].

LCI is available for both the Laser Endoscopic System (LASEREO) and the Light-Emitting Diode Endoscopic System (ELUXEO), both domains of Fujifilm Co. Ltd. (Tokyo, Japan) [7,11]. They differentiate based on the light sources employed. In the former, the laser light source generates two wavelengths of light at 410 ± 10 nm and 450 ± 10 nm [12]. The latter system, instead of a laser light source, utilizes light-emitting diodes (LEDs) as an endoscopic light source. The LED light source emits four wavelengths of light, namely blue-violet, blue, green, and red [13].

The low-wavelength 410-nm or violet light can penetrate only a short distance from the mucosa, particularly in more superficial regions. This is precisely where, in neoplastic lesions, there is a greater concentration of blood vessels, leading to easy absorption of this light spectrum by hemoglobin. Consequently, neoplastic lesions become even redder, while the adjacent mucosa takes on a violet hue, as it is located in deeper topographies [10].

LCI also stands out for its ability to distinguish adenomatous lesions with neoplastic potential more accurately from inflammatory changes. Under white light illumination, both assume reddish tones, making differentiation challenging. However, under LCI, inflammatory changes also become purple, while neoplastic lesions remain red [10,11].

The objective of this work is to evaluate the impact of using LCI in the ADR and, therefore, the benefits associated with the use of this technology, which is increasingly available.

2. METHODS

Following the protocol established from the Preferred Reporting Items for Systematic reviews and Meta-Analyses [14], a literature review was carried out with the following question as a guide: “Does the use of virtual chromoscopy with LCI feature increase the ADR in the colonoscopy?”. The study was registered in PROSPERO with the ID CRD42023438359.

2.1 Search strategy

The search strategy was created by an experienced librarian and reviewed by another investigator (B.H.F.Z) and was developed with MeSH, DeCS descriptors and natural language with the following terms: Colonoscopy, chromoendoscopy, quality colonoscopy, Linked Color Imaging, polyp detection, adenoma detection. The databases for the research were PubMed, BIREME, LILACS, MEDLINE, and SciELO, as shown in Table 1.

2.2 Selection criteria

Two independent reviewers, B.H.F.Z and J.C.A, conducted article screening according to the PICO format (patient, intervention, control, and outcomes), wherein:

- Patients: Individuals aged 18 years and above undergoing colonoscopy examination.
- Interventions: Employment of LCI during colonoscopies.
- Control: Employment of WL during colonoscopies.
- Outcomes: Evaluation of the detection rate of adenomas, serrated lesions, colonic lesions larger or smaller than 5 millimeters, colonic lesions in the right and left colon, detection rate of flat and non-flat colonic lesions, number of adenomas per patient, additional polyp detection rate, and withdrawal time.

From the total, 24 articles were pre-selected based on the title and available abstract, using as the main inclusion criteria the relationship between the use of LCI and the rate of detection of polyps in the colonoscopy exam compared to the examination performed with WL. The selected papers were read and reviewed. Data in the articles were independently evaluated. Duplicate studies were excluded, as well as case reports, reviews and retrospective articles and experimental studies in animals, selecting only randomized prospective clinical trials in English published up to March 2023 with no initial date (Fig. 1).

2.3 Study definitions

ADR is defined as the proportion of colonoscopies with at least one adenoma detected in all colonoscopies. The serrated adenoma detection rate (SADR) is defined as the proportion of colonoscopies with at least one serrated adenoma/polyp (SSA/P) detected

in all colonoscopies. Numbers of adenomas per patient was defined as the total number of adenomas divided by the total number of patients in each study. Number of flat lesions is defined as the total number of lesions with a diameter at least twice the height of the lesion in each study. In many studies, flat lesions were defined as IIa, IIb and IIc lesions according to the Paris Classification [15]. In the non-flat lesion group, sessile, pedunculated, and subpedunculated lesions were included, respectively classified as Is, Ip, and Isp according to the Paris Classification [15]. Some studies [7,16] only differentiated lesions morphologically into polypoid and non-polypoid. The additional PDR was established as the number of polys seen in a second inspection divided by the total procedures.

The right colon accommodates the segments of the cecum and ascending colon, and the left colon corresponds to the descending colon and sigmoid colon. The withdrawal time was defined as the amount of time spent viewing as the colonoscope is withdrawn from the cecum.

2.4 Data extraction and study outcomes

The selected papers were evaluated in relation to the ADR and also in relation to the detection rate of serrated lesions. The benefit of LCI in the detection rate of lesions was evaluated taking into account its size (greater or smaller than 5 millimeters), location (right and left colon) and morphology, individualizing the results for the detection rate of flat and non-flat lesions. In addition, the number of adenomas per patient and the additional PDR were counted, when the study design allowed for such assessment.

For those crossover study designs, a duplicated assessment of colonic mucosa was done with both WL and LCI and for proper statistical comparison, only the number of lesions found in the initial examination was considered and included. Additionally, withdrawal time with and without this chromoscopy technology was also evaluated. Other data from studies, such as first author, year of publication, study period, type of study, study design, endoscopic system, number of participants, baseline demographics (age and gender), indications for colonoscopy, total study participants, and number of colonoscopists, were included.

Two independent reviewers (B.H.F.Z and J.C.A) tabulated the data collected on Microsoft Excel (Microsoft, Redmond, Washington, United States) and any discrepancy in data collection was resolved through mutual discussion. In case of a triple arm study, data for the LCI and WL groups we extracted.

2.5 Bias assessment

Using the Cochrane tool for assessing risk of bias 2 [17], the highlighted domains included the randomization process (D1), deviations from the intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4), and selection of the reported result (D5). The bias assessment for the primary outcome revealed considerations in domain D2, stemming from the inability to blind the performing colonoscopist, who inevitably became aware of the ongoing intervention. Some studies also encountered issues with pre-registration of proposed outcomes and problems with randomization.

2.6 Statistical analysis

Meta-analyses were conducted on the outcomes of interest. Combined results for continuous measures were presented as the mean difference, and aggregated results for dichotomous outcome measures were presented as the risk ratio (RR) between the LCI and WL methods. All analyses were performed using the meta package (version 6.5-0) implemented in the R programming language. Random-effects models were employed for all analyses. The choice to use random-effects models was based on their plausible assumptions in medicine and the extent of heterogeneity among studies. Meta-analysis results were depicted in forest plots.

2.6.1 Subgroup Analysis

When common trends in interventions considered clinically relevant emerged, post hoc subgroup analyses were conducted. The post hoc subgroup analyses included:

- 1. Polyp size (< 5 mm and > 5 mm).
- 2. Morphology (flat lesion and non-flat lesion).

- 3. Location (right and left).

2.6.2 Publication Bias Assessment

To assess publication bias in the meta-analyses, funnel plots were inspected, and findings were confirmed through the Egger regression test. If any publication bias was identified, its robustness was tested using the Trim-and-Fill method.

To explore heterogeneity for the primary outcome, the “leave-one-out” method was employed, systematically removing one study at a time, and ultimately assessing the effect size and the new heterogeneity encountered.

3. RESULTS

3.1 Study Selection

From the analysis and research in PubMed, BIREME, LILACS, MEDLINE and SciELO databases, 279 studies were selected. Of these, after reading the abstracts and titles, 24 studies remained. After that, selecting by eligibility criteria, 16 final studies [7,16,18-31] were used for the development of the research. The study selection process is illustrated in Figure 1.

3.2 Characteristics of the studies

We included 16 randomized clinical trials, published between 2017 and 2023, conducted in Japan, China, Brazil, Hungary, Thailand, and Italy and 2 international RCTs conducted in different countries [30,31], whose objectives were to analyze the effectiveness of LCI in the detection of polyps, compared to the examination performed with white light only (Table 2).

The majority of studies [7,16,18,20-22,24,25,27-29] employed the LASEREO, while in three studies [19,23,26] the ELUXEO was the prevailing system, utilizing LED as an endoscopic light source.

In 2023, Okada et al. [13] compared these two systems using the BLI mode to assess image quality for determining the Japan NBI expert team (JNET) classification, finding a concordance rate of 92.5%. The weighted κ-statistic was 0.99. Regarding the use of LCI, no similar studies exist. Extrapolating from these results, we consider there to be no significant differences or interference in outcomes between the laser and LED systems as light sources.

In three studies [13,18,19], results were extracted solely from the analysis of the right colon, and in another study [22], analysis extended to the splenic flexure, allowing for assessment of the benefit of incorporating this resource to identify lesions that might go unnoticed under WL." Min et al. [21], Dos Santos et al. [27] and Suzuki et al. [31] evaluated results with LCI and WL, individualizing each segment of the colon, while the others included an analysis of the entire colon, from the cecum to the rectum.

Seven studies [16,18,20,21,29–31] were multicenter, while the remaining were conducted in a single research center. Regarding indications, most studies included patients with different indications for colonoscopy, from surveillance and screening for investigation of gastrointestinal symptoms and positive occult blood fecal tests. Concerning gender and mean age of the participants, the studies exhibited notable similarities.Two studies only evaluated the detection rate of serrated lesions [16,22], considered in some studies to be more difficult to visualize due to their similarity with the adjacent mucosa [32].

The studies also exhibit design differences, with some employing a parallel design [7,16,20,23–31] while others use a cross-over design [19,21,22]. In Yoshida's study [18], an initial examination was conducted with WL, followed by additional assessments with either WL or LCI, combined with an extended 30-second duration for the second evaluation. Conversely, Hasegawa et al. [25] adopted a design in which the second observation was standardized using WL. Houwen et al. [30] included only Lynch syndrome patients ≥18 years undergoing surveillance colonoscopy.

3.2 Adenoma detection rate

The primary objective of this study was to comparatively evaluate the ADR using the LCI and WL.For this outcome, the systematic review encompassed a total of 15 studies [7,16,18–21,23–31] involving observations from 10,558 patients (5,200 in the LCI group and 5,358 in the WL group). The total number of recorded events was 4,751. The meta-analysis revealed that the ADR using LCI is 1.20 (95% CI: 1.13–1.28) times higher compared to WL examination (Fig. 2). The heterogeneity among the studies, quantified by I^2, was 44%, indicating moderate heterogeneity (p = 0.03). Analysis of the influence of each study on heterogeneity using the Leave-One-Out method is shown in Table 3. When the study by Miyaguchi is omitted, a substantial decrease in heterogeneity is observed, reaching values close to 24%; however, there are no alterations in the primary effect. In a sensitivity analysis using the random-effects model, the results appear consistently in favor of LCI (RR = 1.20; 95% CI: 1.13–1.28), and the true effect is likely close to this (Fig. 3).

To investigate publication bias with the presented results, a funnel plot was constructed (Fig. 4), and to formally assess the presence of asymmetry in this plot, the Egger's linear regression test was performed. The results of this analysis indicate no effect, with no significant asymmetry in the funnel plot (beta = 0.4851; p = 0.5067).

3.3 Serrated lesions

The incidence of identified serrated lesions, as indicated in studies that comparatively assessed total colonoscopy with and without the LCI resource, was reported in eleven studies [7,16,18–20,22,24,25,27,30,31]. In the analysis of the literature, we observed favorable outcomes for LCI, with low heterogeneity (I^2 0%, p = 0.51), however, with no statistical significance (RR = 1.11; 95% CI: 0.86–1.44) (Fig. 5).

3.4 Number of adenomas per patient

Among the selected studies, the number of adenomas per patient was evaluated in nine clinical trials [16,21,23–26,29–31], including observations from 7,845 patients (3,837 in the LCI group and 4,008 in the control group with WL) with a greater number of lesions identified in the groups in which the LCI was used. In the analysis of the average number

of adenomas per patient, the general average of all studies was 0.26 (95% CI: 0.16–0.37) more adenomas per patient in the LCI group. The heterogeneity was low (I^2 28%, p = 0.20) (Fig. 6).

3.5 Lesion morphology

With regard to lesion morphology, analyses were conducted by differentiating between flat and non-flat lesions. This analysis was feasible in ten studies [7,18–21,24,27,28,30,31], yielding results favoring LCI in the detection rate of flat lesions, with no significance. For non-flat lesions, specifically sessile, pedunculated, and subpedunculated lesions, the results were not favorable for LCI. Depressed lesions were not included in the analysis. It is noteworthy that in this analysis the results were not isolated solely for adenomas, converging towards the macroscopic morphological characterization of different colonic lesions, primarily based on the Paris Classification [15]. LCI demonstrated a tendency for superior detection rates for flat lesions when compared with non-flat lesions. In a comparative exploratory subgroup analysis, also, no statistically significant results were observed ($\chi^2_1 = 2.62$; p = 0.11) (Fig. 7).

3.6 Lesion size

We subdivided the observations by using a 5-millimeter size threshold for colonic lesions. Results for size analyses were identified in seven studies [7,15,19–21,24,30], demonstrating that, overall, LCI exhibits a trend with no statistical significance for identification of lesions under 5-millimeter. For larger lesions the results were not favorable for LCI. In a comparative exploratory subgroup analysis, no statistically significant results were observed ($\chi^2_1 = 2.82$; p = 0.09) (Fig. 8).

3.7 Lesion localization

In 8 studies [7,20,21,24,27,28,30,31], it was possible to comparatively assess the ADR in the right and left colon. Proportionally higher values were observed in the right colon (11% versus 2%). However, these differences were not statistically significant ($\chi^2 1 = 0.38$; p = 0.54) (Fig. 9).

3.8 Additional rate of detection of polyps

Three [19,21,22] of the 14 studies selected were a cross-over study and evaluated the impact of LCI for lesion identification on patients who had already undergone an initial study with WL. For comparative results, the detection rate of polyps with WL was also evaluated after initial comparison with LCI alone.

Thus, we see that the additional detection rate between studies is 60% higher for the group in which a second observation was performed with LCI, compared to WL (RR = 1.99, 95% CI: 1.30–3.06). The heterogeneity observed in the analysis was low (I^2 6%, p = 0.36) (Fig. 10).

3.9 Withdrawal time

The withdrawal time was interpreted as the removal time after cecal intubation was achieved. This time was evaluated by comparing the use of LCI or WL.

The LCI group presented a median time 0.14 longer than the other technique, but the difference is not statistically significant between the methods (RR = 0.15, 95% CI: −0.03 to 0.34). Heterogeneity was high (I2 = 86%, p = 0.10) (Fig. 11).

4. DISCUSSION

LCI is an innovative and promising technological resource that leads to better CRC screening results, and a growing number of studies are aimed at evaluating and quantifying its benefits. Pre- and post-processing programs produce higher-quality, clearer, and sharper images with a unique color pattern that allows neoplastic lesions to appear prominently with a more reddish color than the rest of the adjacent mucosa. By increasing the staining contrast and accentuating certain wavelength spectra, these lesions become more detectable by the examiner [9,10]. Current studies corroborate that the indiscriminate application of LCI increases the detection of polyps and colonic lesions across all histologies and sizes. Our meta-analysis consolidates the growing body of research aimed at assessing and quantifying the benefits of LCI, as evidenced by earlier

meta-analyses by Shinozaki et al [10], Wang et al [33], and Sun et al [34], which comprehensively summarized these advantages.

In the evaluation of our primary outcome, although we found results consistent with those previously reported, which primarily demonstrated an increase in ADR with the addition of LCI compared with WL, our subgroup analysis for the assessment of secondary outcomes revealed results that slightly diverged from those previously reported. Overall, although the results favored LCI, we did not find any statistically significant differences in lesion location, morphology, size, or histological type.

A comparative sub-analysis of lesion location demonstrated that LCI enabled greater detection of lesions in the right colon. However, no statistically significant differences were observed, consistent with the results reported by Wang et al [33], but differs from those demonstrated by Sun et al [34], who stratified the analyses by comparing lesions detected in proximal and distal colons.

In addition, we evaluated the effect of LCI on the detection of lesions based on lesion size and morphology. Although the addition of this feature improved the results, there was no statistical significance in the detection of flat lesions, with preferentially lateral growth, or lesions ≤ 5 mm. Both types are considered more challenging to visualize using WL alone. Wang et al [33], using a cutoff point of 10 mm demonstrated that the use of LCI provided even more pronounced and favorable results for the detection of these lesions. In contrast to our findings, Sun et al [34], reported statistically significant favorable results for LCI in the detection of flat lesions. A possible explanation for our discrepant results could be the more comprehensive inclusion of data in our review, which was approximately twice the number of studies included in previous reviews. To minimize publication bias, we attempted to include as many studies as possible, adhering to pre-established selection criteria.

In addition to the global ADR, we also individually evaluated the detection rate of serrated lesions, which are often difficult to assess because they present surface patterns similar to those of the adjacent colonic mucosa [32] accounting for 15–30% of the causes of CRC [35-38]. The results indicate a potential advantage with the incorporation of virtual

chromoendoscopy technology; however, in our analysis, the observed differences did not reach statistical significance, consistent with the findings reported by Wang et al [33], In contrast to the aforementioned meta-analyses, our study encompassed a broader range of investigations evaluating the number of serrated lesions. Our comprehensive approach involved the consideration of crossover study designs, exemplified in the study by Paggi et al [19], wherein duplicate assessments of colonic mucosa with both WL and LCI necessitated the inclusion of only lesions detected in the initial examination for proper statistical comparison. The inclusion of diverse studies beyond those specifically designed to detect serrated lesions may explain the disparities observed in our results. Our results are consistent with those reported by Wang et al [33]. Another possible explanation for the results found, in addition to the inclusion of a greater number of studies, is that serrated lesions are generally covered by a mucus cap, making it difficult to visualize them regardless of the technology used. To optimize these strategies, it is suggested that the mucus cap be removed in advance [39].

In these crossover studies [19,21,22] we observed significant benefits when LCI was used as an additional tool in patients who had already undergone prior evaluation with WL. This technology can overcome some of the deficiencies inherent in the conventional method, which is associated with a higher rate of unnoticed lesions. Instead of evaluating the adenoma miss rate, we assessed the additional PDR when incorporating LCI and observed that a second evaluation with the addition of this feature significantly increased PDR. Additionally, in the analysis of the number of adenomas per patient, we extracted data from more studies than those included in previously published reviews.

We also evaluated withdrawal time as an additional outcome. The results showed that despite a slight increase in the time to remove the colonoscope from the cecum when using LCI, there was no statistical significance in these data. Furthermore, considering the higher ADR with LCI, the longer procedure duration could be attributed to the additional time involved in the removal of these lesions.

The main limitations of our study are inherent in the heterogeneity of the included studies with different designs, populations, multiple indications for colonoscopy, and primary

outcomes. Altogether, these limitations made it difficult to homogenize the data for adequate meta-analysis and statistical analysis. Nevertheless, this more comprehensive approach minimized possible publication bias and provided more robustness to the outcomes evaluated.

It was concluded that LCI, an increasingly accessible and available technology, should be seen as a valuable tool in the arsenal of CRC prevention, mainly by reducing the rate of unnoticed lesions associated with interval CRCs [10], without negatively affecting other quality indicators in colonoscopy. However, our study stands out from those previously published by demonstrating that, in subgroup analyses, despite a favorable trend towards the use of LCI, no statistically significant differences were observed compared with WL.

5. CONCLUSION

It is concluded that LCI, an increasingly accessible and available technology, should be seen as an important tool in the arsenal of colorectal cancer prevention, mainly reducing the rate of unnoticed lesions associated with interval neoplasms [10], without negative impacts in other quality indicators of the colonoscopy examination.

6. REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Pineros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. *Int J Cancer* 2021;**149**: 778-789.

2. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;**366**: 687-696.

3. Floer M, Biecker E, Fitzlaff R, Roming H, Ameis D, Heinecke A, et al. Higher adenoma detection rates with endocuff-assisted colonoscopy - a randomized controlled multicenter trial. *PLoS One* 2014;**9**: e114267.

4. Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology* 1997;**112**: 24-28.

5. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014;**370**: 1298-1306.

6. Dos Santos CEO, Malaman D, Yoshida N, Pereira-Lima JC, Onófrio FQ, Furlan RG, et al. Blue laser imaging: a new image-enhanced endoscopy for the diagnosis of colorectal lesions. *Eur J Gastroenterol Hepatol* 2018;**30**: 1514-1520.

7. Dos Santos CEO, Malaman D, Pereira-Lima JC, de Quadros Onofrio F, Ribas Filho JM. Impact of linked-color imaging on colorectal adenoma detection. *Gastrointest Endosc* 2019;**90**: 826-834.

8. Dinesen L, Chua TJ, Kaffes AJ. Meta-analysis of narrow-band imaging versus conventional colonoscopy for adenoma detection. *Gastrointest Endosc* 2012;**75**: 604-611.

9. Shinozaki S, Osawa H, Hayashi Y, Lefor AK, Yamamoto H. Linked color imaging for the detection of early gastrointestinal neoplasms. *Therap Adv Gastroenterol* 2019;**12**: 1756284819885246.

10. Shinozaki S, Kobayashi Y, Hayashi Y, Sakamoto H, Sunada K, Lefor AK, et al. Colon polyp detection using linked color imaging compared to white light imaging: Systematic review and meta-analysis. *Dig Endosc* 2020;**32**: 874-881.

11. Yamamoto H, Shinozaki S, Hayashi Y, Miura Y, Khurelbaatar T, Osawa H, et al. Advanced treatment and imaging in colonoscopy: the pocket-creation method for complete resection and linked color imaging for better detection of early neoplastic lesions by colonoscopy. *Clin Endosc* 2019;**52**: 107-113.

12. Yoshida N, Hisabe T, Inada Y, Kugai M, Yagi N, Hirai F, et al. The ability of a novel blue laser imaging system for the diagnosis of invasion depth of colorectal neoplasms. *J Gastroenterol* 2014;**49**: 73-80.

13. Okada M, Yoshida N, Kashida H, Hayashi Y, Shinozaki S, Yoshimoto S, et al. Comparison of blue laser imaging and light-emitting diode-blue light imaging for the characterization of colorectal polyps using the Japan narrow-band imaging expert team classification: The LASEREO and ELUXEO COLonoscopic study. *DEN Open* 2024;**4**: e245.

14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**: n71.

15. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003;**58**(6 Suppl): S3-43.

16. Li J, Zhang D, Wei Y, Chen K, Wu R, Peng K, et al. Colorectal sessile serrated lesion detection using linked color imaging: A multicenter, parallel randomized controlled trial. *Clin Gastroenterol Hepatol* 2023;**21**: 328-336.e2.

17. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**: d5928.

18. Yoshida N, Inada Y, Yasuda R, Murakami T, Hirose R, Inoue K, et al. Additional Thirty seconds observation with linked color imaging improves detection of missed polyps in the right-sided colon. *Gastroenterol Res Pract* 2018;**2018**: 5059834.

19. Paggi S, Mogavero G, Amato A, Rondonotti E, Andrealli A, Imperiali G, et al. Linked color imaging reduces the miss rate of neoplastic lesions in the right colon: a randomized tandem colonoscopy study. *Endoscopy* 2018;**50**: 396-402.

20. Miyaguchi K, Takabayashi K, Saito D, Tsuzuki Y, Hirooka N, Hosoe N, et al. Linked color imaging versus white light imaging colonoscopy for colorectal adenoma detection: a randomized controlled trial. *J Gastroenterol Hepatol* 2021;**36**: 2778-2784.

21. Min M, Deng P, Zhang W, Sun X, Liu Y, Nong B. Comparison of linked color imaging and white-light colonoscopy for detection of colorectal polyps: a multicenter, randomized, crossover trial. *Gastrointest Endosc* 2017;**86**: 724-730.

22. Fujimoto D, Muguruma N, Okamoto K, Fujino Y, Kagemoto K, Okada Y, et al. Linked color imaging enhances endoscopic detection of sessile serrated adenoma/polyps. *Endosc Int Open* 2018;**6**: E322-E334.

23. Lovasz BD, Szalai M, Oczella L, Finta A, Dubravcsik Z, Madacsy L. Improved adenoma detection with linked color imaging technology compared to white-light colonoscopy. *Scand J Gastroenterol* 2020;**55**: 877-883.

24. Kudo T, Horiuchi A, Kyodo R, Horiuchi I, Arai N, Kajiyama M, et al. Linked colour imaging versus white-light colonoscopy for the detection of flat colorectal lesions: A randomized controlled trial. Colorectal Dis. 2021;**23**: 1414-1420.

25. Hasegawa I, Yamamura T, Suzuki H, Maeda K, Sawada T, Mizutani Y, et al. Detection of colorectal neoplasms using linked color imaging: a prospective, randomized, tandem colonoscopy trial. *Clin Gastroenterol Hepatol* 2021;**19**: 1708-1716.e4.

26. Aniwan S, Vanduangden K, Kerr SJ, Piyachaturawat P, Jangsirikul S, Luangsukrerk T, et al. Linked color imaging, mucosal exposure device, their combination, and standard colonoscopy for adenoma detection: a randomized trial. *Gastrointest Endosc* 2021;**94**: 969-977.

27. Dos Santos CEO, Malaman D, Arciniegas Sanmartin ID, Onofrio FDQ, Pereira-Lima JC. Effect of linked-color imaging on the detection of adenomas in screening colonoscopies. *J Clin Gastroenterol* 2022;**56**: e268-e272.

28. Tanaka S, Omori J, Hoshimoto A, Nishimoto T, Akimoto N, Tatsuguchi A, et al. Comparison of linked color imaging and white light imaging colonoscopy for detection of colorectal adenoma requiring endoscopic treatment: A single-center randomized controlled trial. *J Nippon Med Sch* 2023;**90**: 111-120.

29. Paggi S, Radaelli F, Senore C, Maselli R, Amato A, Andrisani G, et al. Linked-color imaging versus white-light colonoscopy in an organized colorectal cancer screening program. *Gastrointest Endosc* 2020;**92**: 723-730.

30. Houwen B, Hazewinkel Y, Pellise M, Rivero-Sanchez L, Balaguer F, Bisschops R, et al. Linked colour imaging for the detection of polyps in patients with Lynch syndrome: a multicentre, parallel randomised controlled trial. *Gut* 2022;**71**: 553-560.

31. Suzuki S, Aniwan S, Chiu HM, Laohavichitra K, Chirapongsathorn S, Yamamura T, et al. Linked-color imaging detects more colorectal adenoma and serrated lesions: an international randomized controlled trial. *Clin Gastroenterol Hepatol* 2023;**21**: 1493-1502.e4.

32. JE IJ, van Doorn SC, van der Brug YM, Bastiaansen BA, Fockens P, Dekker E. The proximal serrated polyp detection rate is an easy-to-measure proxy for the detection rate of clinically relevant serrated polyps. *Gastrointest Endosc* 2015;**82**: 870-877.

33. Wang J, Ye C, Wu K, Fei S. The effect of linked color imaging for adenoma detection. A meta-analysis of randomized controlled studies. *J Gastrointestin Liver Dis* 2022;**31**: 67-73.

34. Sun Y, Lv XH, Zhang X, Wang J, Wang H, Yang JL. Linked color imaging versus white light imaging in the diagnosis of colorectal lesions: a meta-analysis of randomized controlled trials. *Therap Adv Gastroenterol* 2023;**16**: 17562848231196636.

35. Zhu H, Zhang G, Yi X, Zhu X, Wu Y, Liang J, et al. Histology subtypes and polyp size are associated with synchronous colorectal carcinoma of colorectal serrated polyps: a study of 499 serrated polyps. *Am J Cancer Res* 2015;**5**: 363-374.

36. O'Brien MJ, Yang S, Mack C, Xu H, Huang CS, Mulcahy E, et al. Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and

traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. *Am J Surg Pathol* 2006;**30**: 1491-1501.

37. Kim KM, Lee EJ, Ha S, Kang SY, Jang KT, Park CK, et al. Molecular features of colorectal hyperplastic polyps and sessile serrated adenoma/polyps from Korea. *Am J Surg Pathol* 2011;**35**: 1274-1286.

38. Fujita K, Yamamoto H, Matsumoto T, Hirahashi M, Gushima M, Kishimoto J, et al. Sessile serrated adenoma with early neoplastic progression: a clinicopathologic and molecular study. *Am J Surg Pathol* 2011;**35**: 295-304.

6. TABLES

Table 1. Search strategy

Database	Search strategy
PubMed	(Colonoscopy OR chromoendoscopy OR quality colonoscopy) AND (Linked Color Imaging) AND ((polyp detection) OR (adenoma detection))
BIREME/ LILACS/MEDLINE	(Colonoscopy OR chromoendoscopy OR quality colonoscopy) AND (Linked Color Imaging) AND ((polyp detection) OR (adenoma detection))
SciELO	Colonoscopy OR chromoendoscopy OR quality colonoscopy) AND (Linked Color Imaging) AND ((polyp detection) OR (adenoma detection)

Table 2. Characteristics of the studies

Author	Country	Year	Study design	Participants (n)	Gender	Mean age	System	Indications	Colonoscopists participants
Min et al. [21]	China	2017	RCT Multi	141	53% male	46.8 ± 12.9	LASEREO	Symptoms, screening	-
Fujimoto et al. [22]	Japan	2018	RCT Single	44	45% male	63.5 ± 10.6	LASEREO	Screening after resection of SSA/P	5
Yoshida et al. [18]	Japan	2018	RCT Multi	130	55% male	65.9 ± 14.3	LASEREO	Screening, positive FIT	3
Paggy et al. [19]	Italy	2018	RCT Single	600	57% male	65.0 ± 10.2	ELUXEO	Symptoms, screening, positive FIT	6
Dos Santos et al. [7]	Brazil	2019	RCT Single	379	37% male	58.7	LASEREO	Symptoms, screening	1
Lovasz et al. [23]	Hungary	2020	RCT Single	1278	49.5% male	51.95	ELUXEO	Screening	3
Paggy et al. [29]	Italy	2020	RCT Multi	649	50% male	60.8 ± 7.3	LASEREO	Screening, positive FIT	14

Kudo et al. [24]	Japan	2021	RCT Single	302	51% male	63.2	LASEREO	Screening	2
Miyaguchi et al. [20]	Japan	2021	RCT Multi	1000	62% male	65.0 ± 14.4	LASEREO	Screening, symptoms, positive FIT	20
Hasegawa et al. [25]	Japan	2021	RCT Single	700	63% male	66.5 ± 12.3	LASEREO	Screening, symptoms	14
Aniwan et al. [26]	Thailand	2021	RCT Single	1000	35.1% male	63.1	ELUXEO	Primary screening colonoscopy	20
Li et al. [16]	China	2022	RCT Multi	884	48.6% male	54 ± 10.9	ELUXEO/LASEREO	Screening	11
Dos Santos et al. [27]	Brazil	2022	RCT Single	205	49% male	58.8 ± 9	LASEREO	Screening	-
Houwen et al. [30]	Belgium, Italy, Netherlands, Poland, Spain, United Kingdom	2022	RCT Multi	332	42% male	48.4 ± 14.1	-	Screening in cohort of patients with Lynch syndrome	22

Suzuki et al. [31]	Japan, Singapore, Taiwan, and Thailand	2022	RCT Multi	3050	57% male	64.4	ELUXEO/LASEREO	Screening, symptoms, positive FIT	97
Tanaka et al. [28]	Japan	2023	RCT Single	594	63.4% male	53	LASEREO	Screening, symptoms, positive FIT	9

Table 3. Leave-one-out

First author	RR	95% CI	valor P	tau^2	tau	I^2
Leaving Min [21]	1.2018	(1.1282; 1.2802)	< 0.0001	0.0056	0.0748	47.8%
Leaving Yoshida [18]	1.1995	(1.1274; 1.2762)	< 0.0001	0.0053	0.0728	42.9%
Leaving Paggy [19]	1.2144	(1.1415; 1.2921)	< 0.0001	0.0049	0.0701	39.8%
Leaving Dos Santos [7]	1.1978	(1.1229; 1.2777)	< 0.0001	0.0057	0.0756	46.8%
Leaving Lovasz [23]	1.1970	(1.1198; 1.2794)	< 0.0001	0.0061	0.0778	46.7%
Leaving Paggy [29]	1.2057	(1.1260; 1.2911)	< 0.0001	0.0067	0.0818	47.9%
Leaving Kudo [24]	1.1944	(1.1197; 1.2740)	< 0.0001	0.0055	0.0741	45.6%
Leaving Miyaguchi [20]	1.2233	(1.1594; 1.2908)	< 0.0001	0.0019	0.0435	24.8%
Leaving Hasegawa [25]	1.2176	(1.1392; 1.3015)	< 0.0001	0.0055	0.0742	40.7%
Leaving Aniwan [26]	1.2117	(1.1335; 1.2953)	< 0.0001	0.0061	0.0784	46.2%
Leaving Dos Santos [27]	1.1972	(1.1229; 1.2764)	< 0.0001	0.0056	0.0748	46.5%
Leaving Houwen [30]	1.1868	(1.1176; 1.2603)	< 0.0001	0.0041	0.0638	39.2%
Leaving Suzuki [31]	1.1956	(1.1142; 1.2829)	< 0.0001	0.0066	0.0812	41.9%
Leaving Li [16]	1.2069	(1.1279; 1.2915)	< 0.0001	0.0065	0.0809	47.8%
Leaving Tanaka [28]	1.1959	(1.1218; 1.2750)	< 0.0001	0.0055	0.0742	46.0%
Pooled estimate	1.2028	(1.1302; 1.2800)	< 0.0001	0.0054	0.0735	44.0%

7. FIGURES

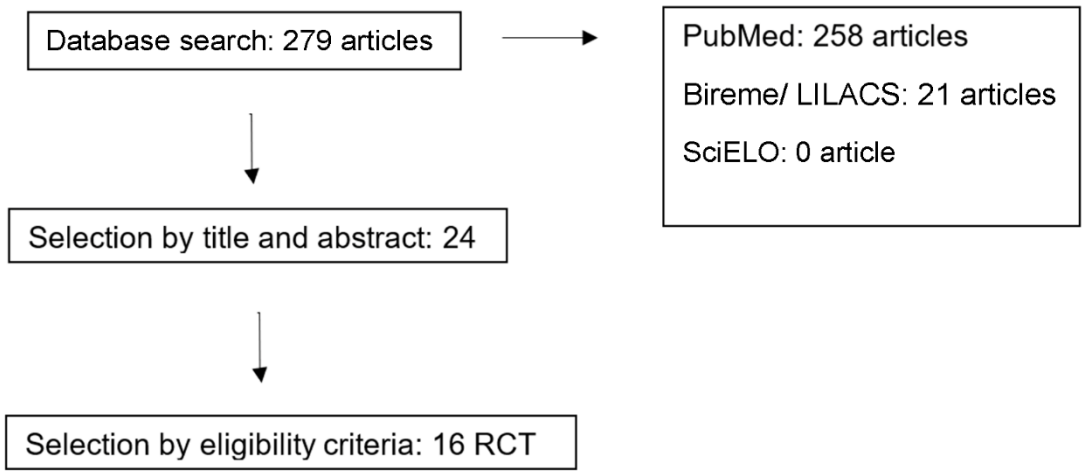

Figure 1: Work selection flowchart

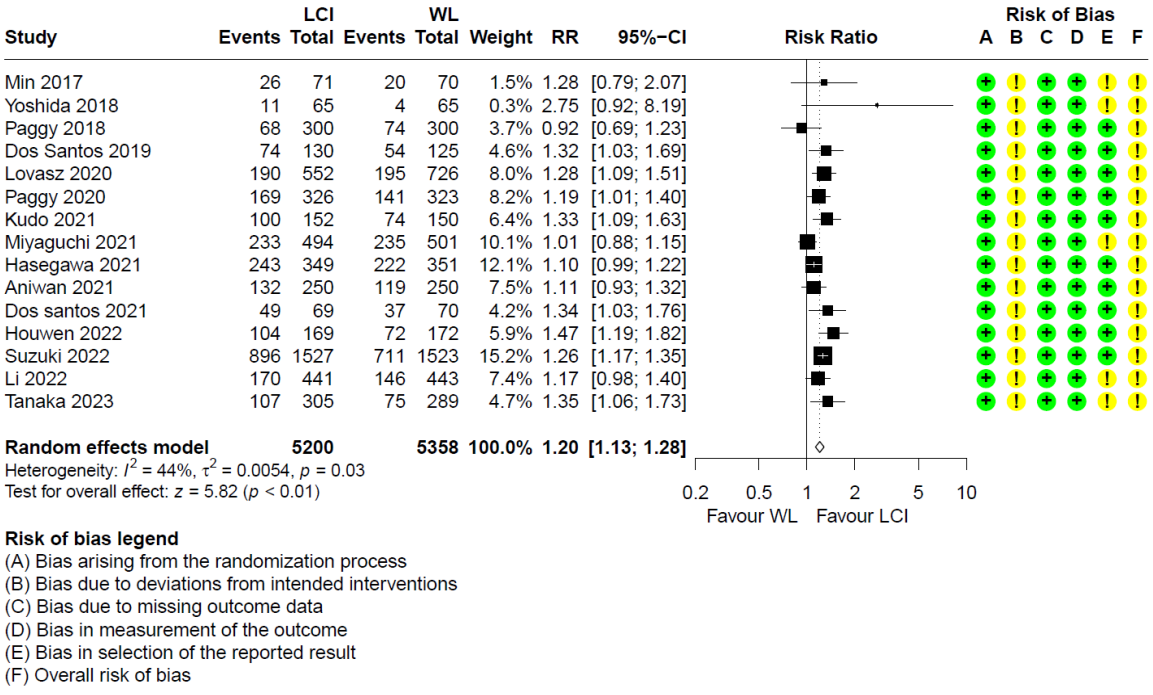

Figure 2: A quantitative analysis comparing linked color imaging (LCI) versus white light (WL) for the primary outcome: adenoma detection rate (ADR).

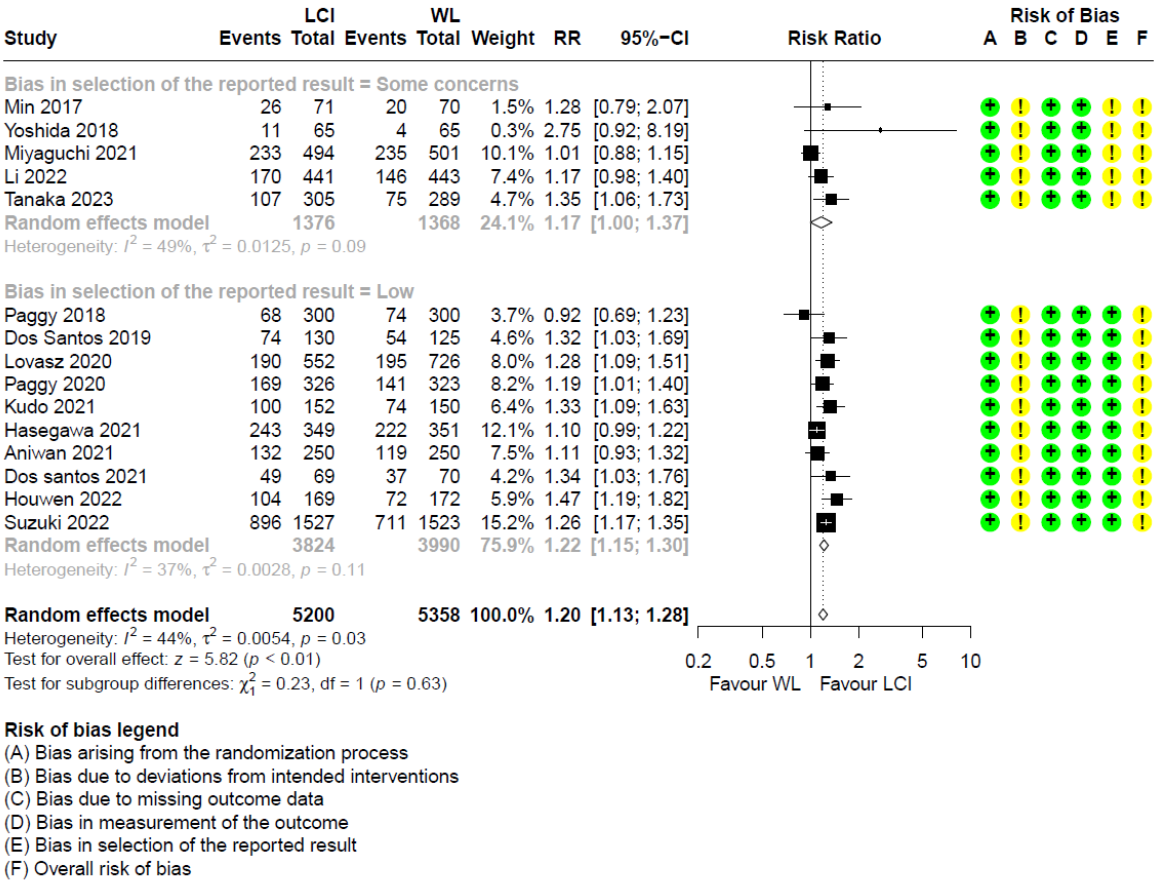

Figure 3: Sensitivity analysis for adenoma detection rate (ADR).

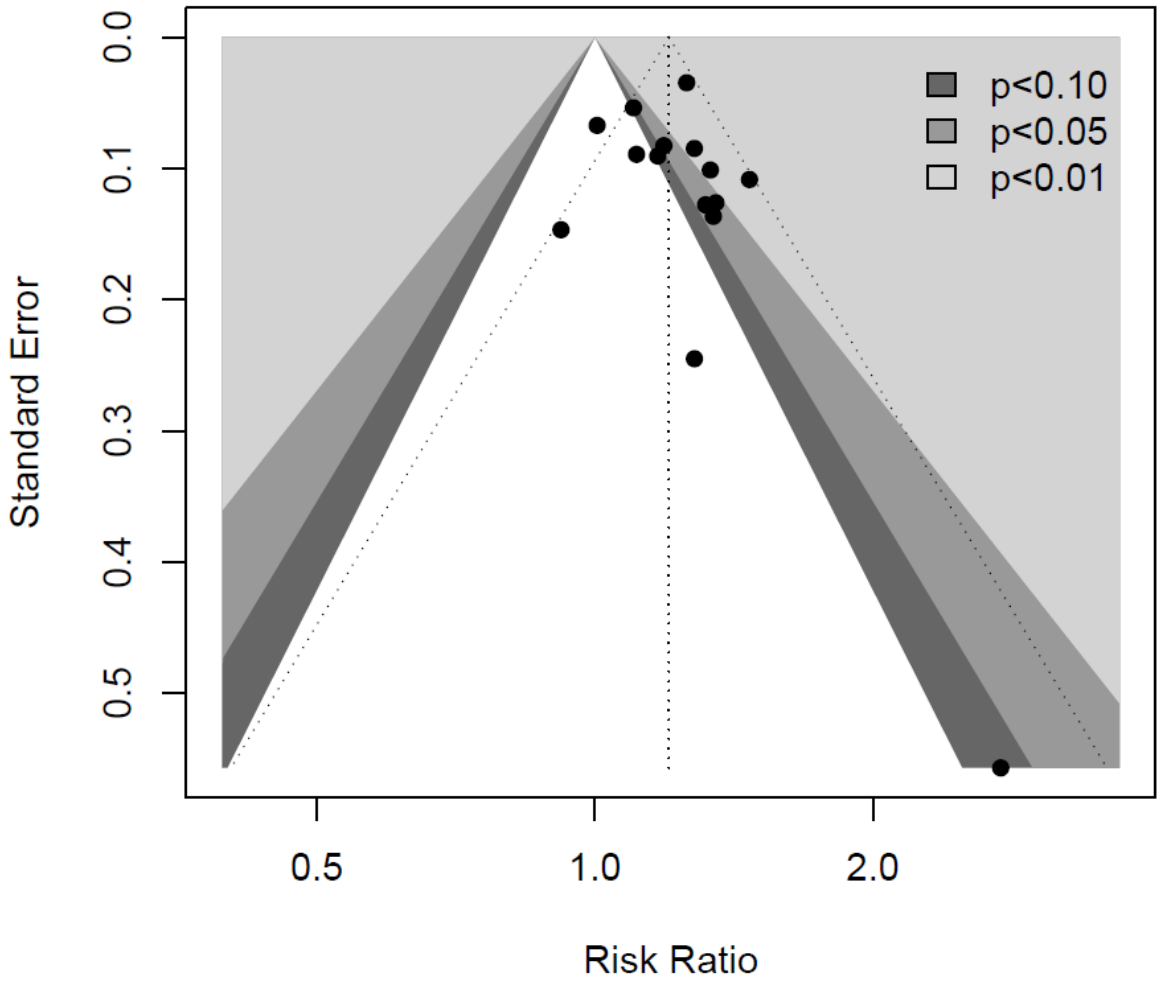

Figure 4:A funnel plot to investigate publication bias for adenoma detection rate (ADR).

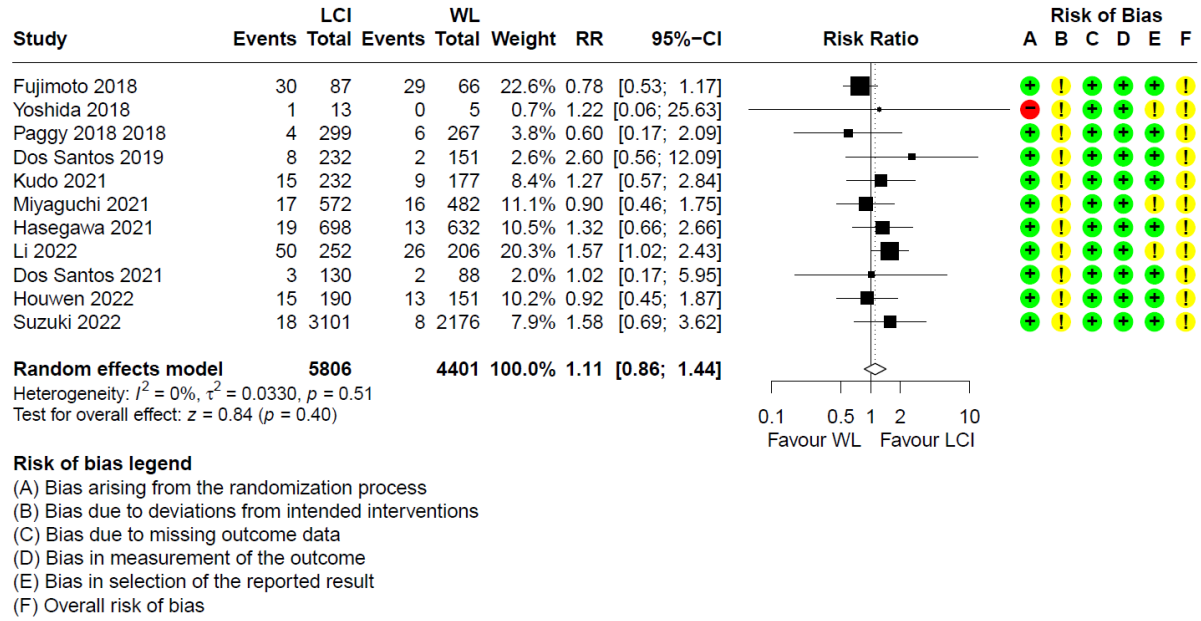

Figure 5: A quantitative analysis comparing linked color imaging (LCI) versus white light (WL) for serrated lesions.

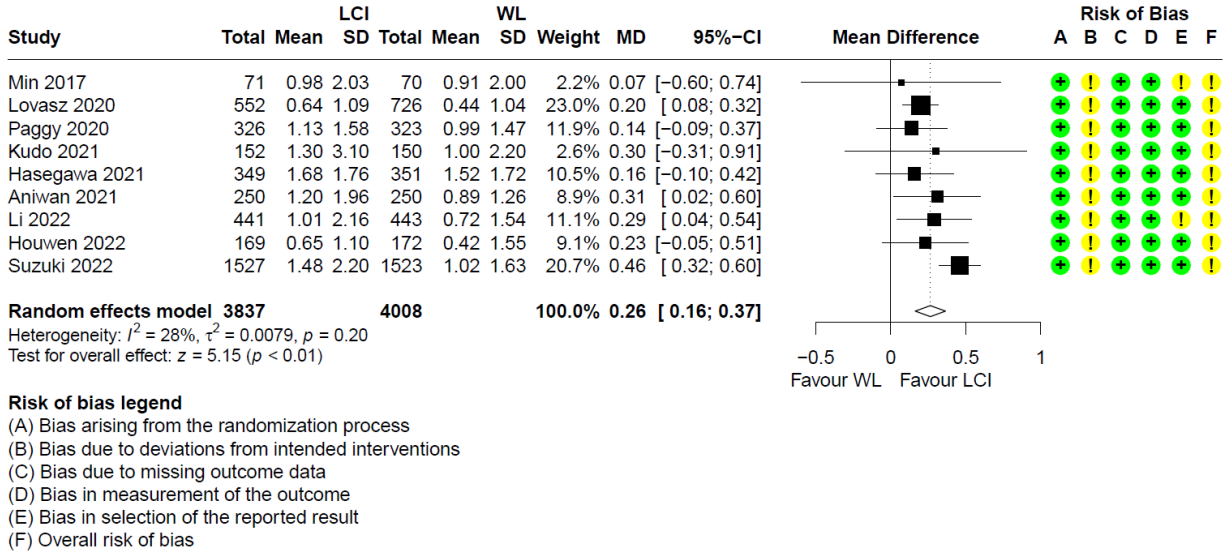

Figure 6: A quantitative analysis comparing linked color imaging (LCI) versus white light (WL) for mean number of adenomas per patient.

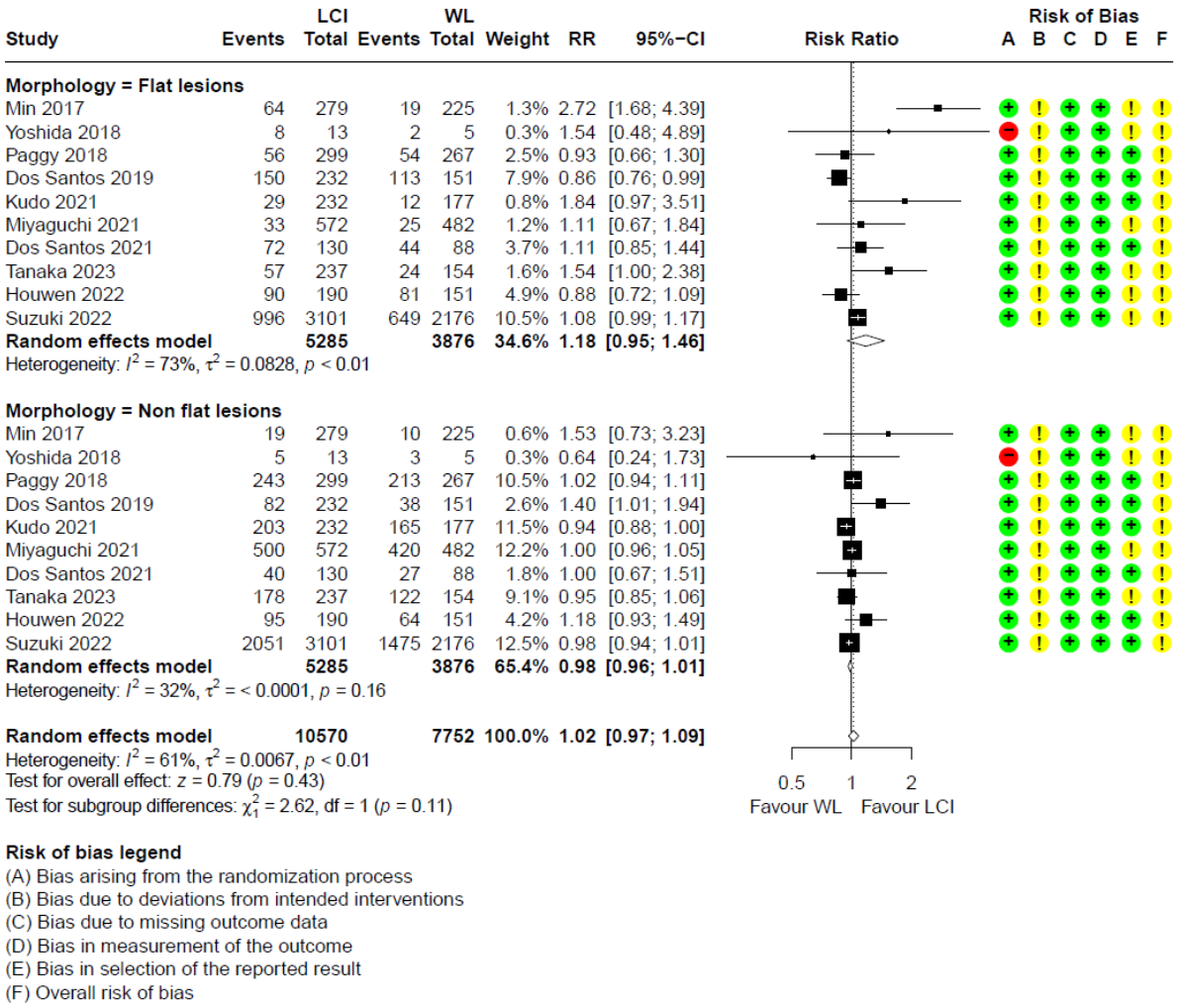

Figure 7: A comparative exploratory subgroup analysis for morphology comparing flat and non-flat lesions.

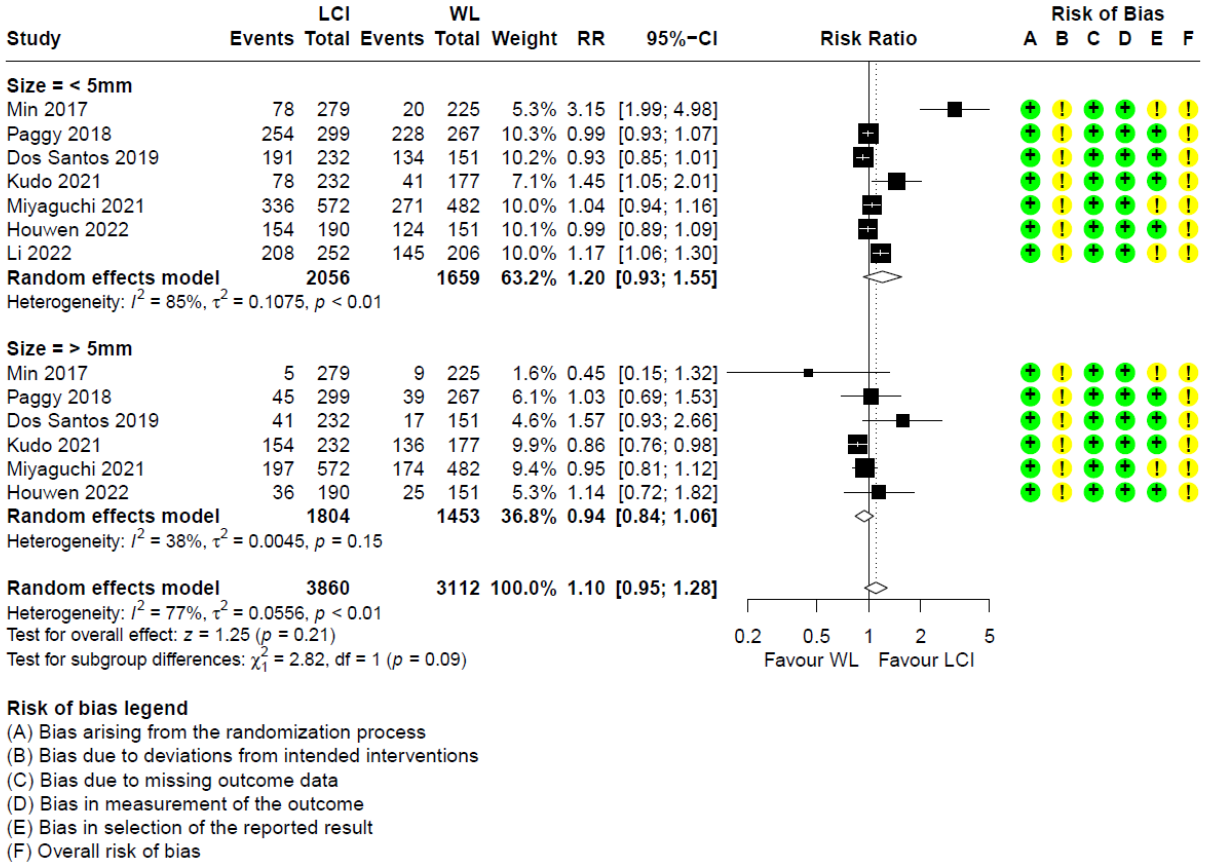

Figure 8: A comparative exploratory subgroup analysis for size comparing lesions under and larger than 5 millimeters.

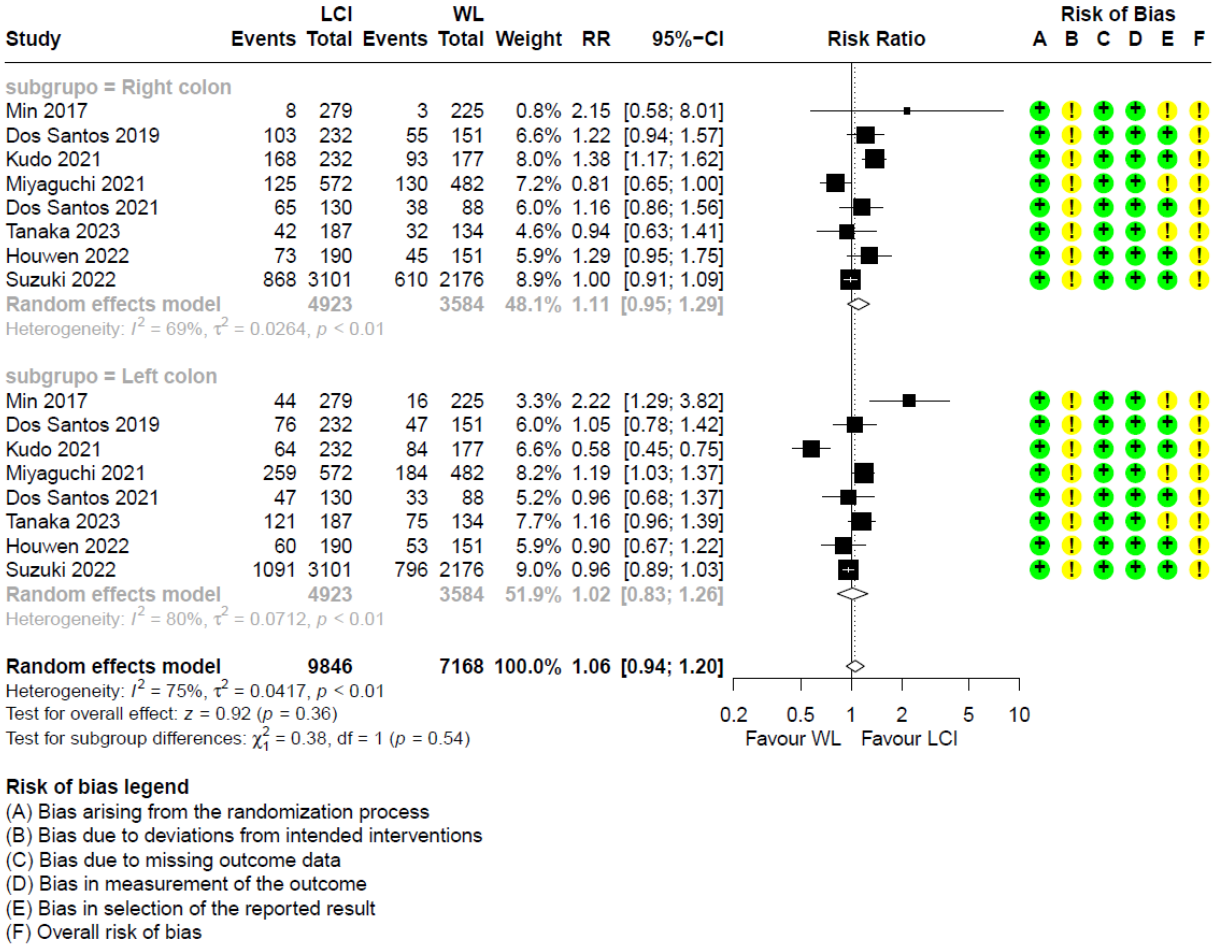

Figure 9: A comparative exploratory subgroup analysis for location comparing lesions in right and left colon.

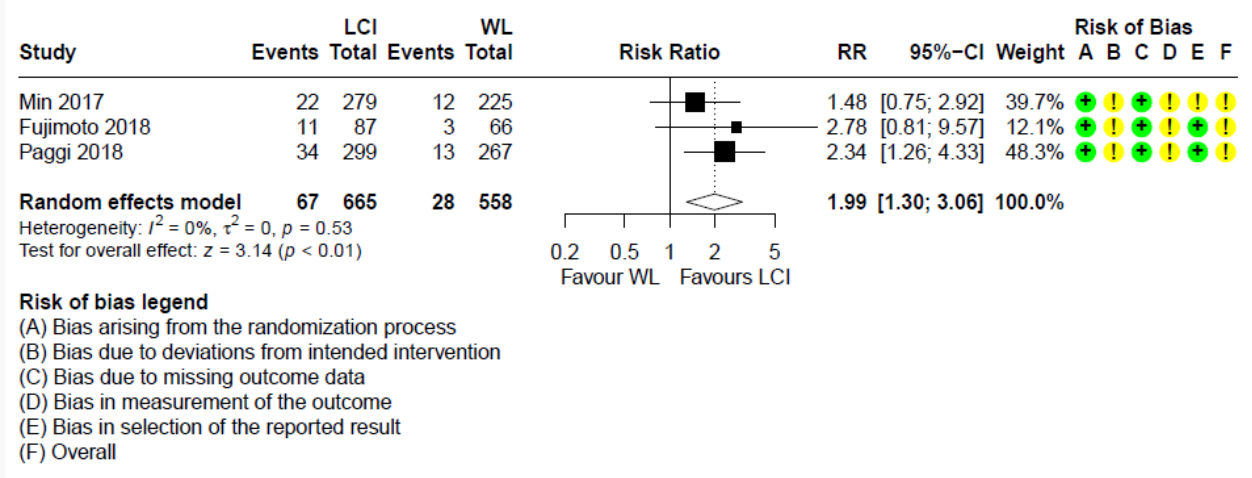

Figure 11: Additional rate of detection of polyps.

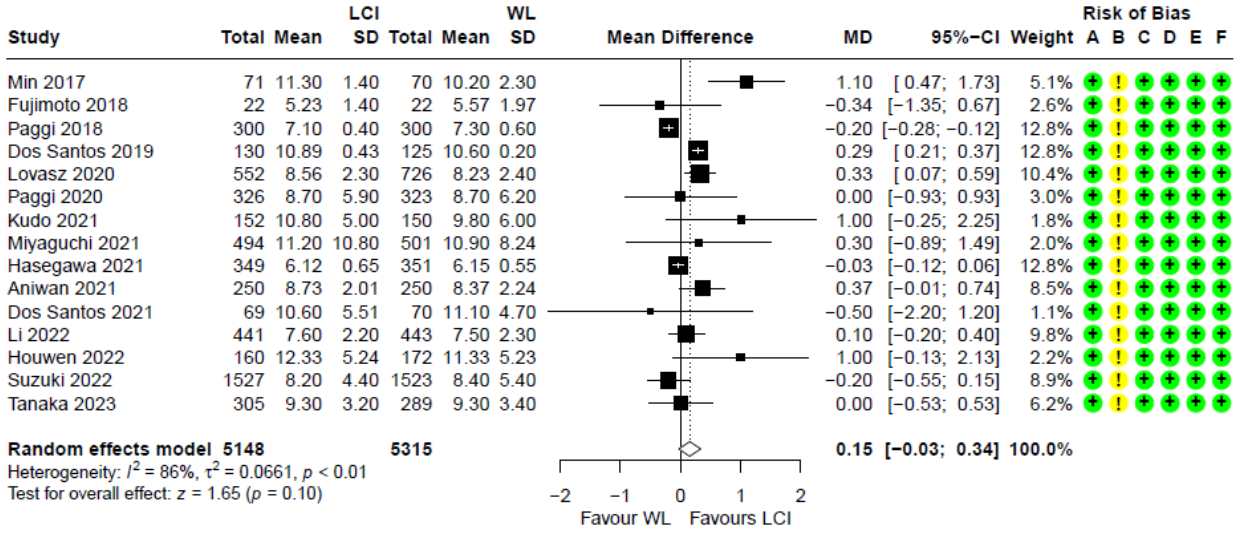

Figure 101: Withdrawal time.