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Texture and color enhancement imaging versus white light imaging for the detection of colorectal adenomas: a systematic review and meta-analysis

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:

Background

Texture and color enhancement imaging (TXI) is a novel optical technology designed to improve visibility during endoscopy by highlighting subtle differences in morphology and color. This systematic review and meta-analysis aimed to determine whether TXI, compared to conventional white light imaging (WLI), can improve important colonoscopy quality indicators, specifically the adenoma detection rate (ADR) and adenomas per colonoscopy (APC).

Methods

We searched PubMed, EMBASE, and the Cochrane Central for studies comparing TXI to WLI in patients undergoing colonoscopy for any indication. Risk ratios (RR) and mean differences (MD) were computed using a random-effects model.

Results

We included 1541 patients from 3 studies, of which 2 were randomized controlled trials (RCTs). TXI was used in 775 (50.3%) patients. The indications for colonoscopy varied, including positive fecal immunochemical test (FIT), surveillance, and diagnostic workup for abdominal symptoms. In the pooled data, TXI significantly increased both ADR (57,8% versus 43.6%; RR 1.32 [95% CI, 1.20–1.46]; $p < 0.001$; $I2 = 0\%$) and APC (MD 0.50 [95% CI, 0.37–0.64]; $p < 0.001$; $I2 = 0\%$), compared to WLI. Furthermore, TXI was more effective at detecting nonpolypoid/flat adenomas, proximal/right-sided adenomas, and adenomas ≥ 10 mm in size. Colonoscopies with TXI had shorter withdrawal times.

Conclusions

Our meta-analysis demonstrates that TXI significantly improves the detection of colorectal adenomas in patients undergoing colonoscopy for various indications. TXI has the potential to improve the overall quality of colonoscopy and contribute to colorectal cancer prevention.

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Thieme

Introduction

Colorectal cancer (CRC) ranks as the third most prevalent cancer and the second leading cause of cancer-related mortality globally [1]. Colonoscopy is typically used as either an initial or follow-up screening test that can reduce the risk of death from CRC by early detection and removal of precursor lesions such as colorectal adenomas [2]. However, colonoscopy is a highly operator-dependent procedure and failure to detect adenomas may increase the subsequent risk of cancer [3]. Approximately 26% of adenomas are missed during colonoscopy [4]. Therefore, various quality indicators and auxiliary strategies have been proposed to decrease the miss rate and lower the risk of CRC.

The adenoma detection rate (ADR) is an important quality benchmark recommended by professional societies [5]. It refers to the proportion of screening colonoscopies carried out by a physician that detect at least one histologically verified colorectal adenoma or adenocarcinoma. ADR is inversely correlated to post-colonoscopy CRC risk. For every 1.0% increase in ADR, there is a corresponding 3.0% decrease in CRC risk [2]. For this reason, ADR is widely accepted as the preferred surrogate marker for assessing colonoscopy quality. Nevertheless, ADR is subject to certain limitations. Endoscopists who prioritize ADR as the sole quality metric may perform a thorough examination until an adenoma is detected, after which they might unintentionally decrease the quality of the procedure thereafter. This could compromise the overall colonoscopy quality without impacting the ADR (‘One and done’ phenomenon) [6].

Adenomas per colonoscopy (APC) is an additional quality indicator that may overcome the limitations of ADR. It is sometimes referred to as the mean number of adenomas detected per procedure [7]. Endoscopists with comparable ADRs have shown significant variations in their overall adenoma detection, as measured by APC [8]. Since APC provides additional insights into endoscopist performance, it is preferable to report it alongside ADR.

Several technological advancements have been introduced to increase ADR through better visualization of the colonic surface [9]. Texture and color enhancement imaging (TXI; Olympus, Tokyo, Japan) is a novel optical technology featured in the EVIS X1 endoscopy system. TXI can enhance subtle tissue differences, including slight morphological and color changes, over conventional white light imaging (WLI) endoscopy [10]. TXI features two distinct modes regarding enhancement factors. Mode 1 (texture, brightness, and color enhancement) provides a greater red-white color contrast and gives the mucosa a redder appearance. Mode 2 (texture and brightness enhancement) generates images that more closely resemble the color tone of WLI [11].

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To determine if TXI can improve colonoscopy quality, we performed a systematic review and meta-analysis to compare its impact on ADR and APC with that of WLI in patients undergoing colonoscopy.

Materials and methods

All supporting data can be found within the article and its Supplementary Material.

Eligibility criteria

This systematic review and meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement [12,13]. This meta-analysis did not require Institutional Review Board approval because it used data from previously published and publicly available articles. Studies that met all of the following criteria were included in the meta-analysis: (1) Randomized controlled trials (RCTs) and observational cohort studies, (2) comparing TXI to WLI, (3) in a population of patients undergoing colonoscopy, and (4) reporting any of the prespecified outcomes of interest - ADR and APC. Studies without a WLI comparison group, review articles, and studies with overlapping populations were excluded. In the last instance, the study with the largest number of patients was the one included. This systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO), under protocol CRD42024549138.

Search strategy and data extraction

We systematically searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to May 2024 with the following search strategy: (Texture and Color Enhancement Imaging OR TXI) AND (Adenoma OR Adenomas OR ADR OR APC OR Colonoscopy OR Endoscopy OR Virtual chromoendoscopy OR Colorectal OR Colon OR Colonic OR Rectal OR Rectum OR Polyp OR Polyps OR Polypectomy). We manually searched the references of all included studies to identify any additional studies. The data was independently extracted by two authors (S.M. and H.S.) using predefined search criteria and quality assessment methods. Any disagreements were resolved through consensus.

Quality assessment

The risk of bias in randomized studies was analyzed with the Cochrane Collaboration tool for assessing the risk of bias in randomized studies (RoB 2) [14]. Non-randomized studies were assessed with the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I)

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[15]. In the RoB 2 assessment, each trial is rated as high risk, low risk, or with some concerns across five domains. In the ROBINS-I evaluation, the risk of bias is categorized as low risk, moderate risk, serious risk, or critical risk. The assessment was independently performed by two authors (S.M. and H.S.), with any disagreements resolved through consensus. Publication bias was examined using funnel-plot analysis of individual study weights against point estimates. As per Cochrane guidelines, the Egger test was not performed because the meta-analysis included fewer than 10 studies [12].

Statistical analyses

Risk ratios (RRs) with 95% confidence intervals (CI) were computed to compare effects for binary endpoints. Means and standard deviations were extracted for continuous outcomes, and comparisons between groups were made using a weighted mean difference. Of note, missing standard deviations were computed from available data using the Review Manager Calculator or conversion methods recommended by the Cochrane Handbook [12,16]. Nonpolypoid and flat adenomas were analyzed together, as opposed to polypoid lesions. Proximal and right-sided adenomas, which include those located in the cecum, ascending colon, or transverse colon, were also examined as a single group. The Cochran Q test and I2 statistics were used to assess heterogeneity. Endpoints were regarded as having low heterogeneity if $p > 0.10$ and $I2 < 25\%$. The DerSimonian-Laird random-effects model was used for this meta-analysis, while the primary outcome of ADR was additionally assessed using the Mantel-Haenszel fixed-effects model. [17,18]. P values of <0.05 were considered statistically significant. To minimize the risk of selection bias, a subgroup analysis of RCTs was performed for the outcomes of ADR and APC. Statistical analyses were performed using Review Manager 5.4.1 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Study selection and baseline characteristics

The search strategy yielded a total of 229 results (Figure 1). After removal of duplicate records and unrelated articles or abstracts, the remaining 26 studies were fully reviewed whether they meet the inclusion and exclusion criteria. A total of three studies (2 RCTs and 1 retrospective cohort study) and 1541 patients were included in the meta-analysis [7,19,20]. The reasons for exclusion were: no outcome of interest reported (n = 9), overlapping populations (n = 8), no results available (n = 3), no WLI comparison group (n = 2), and review article (n = 1).

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Within the included studies, a total of 775 patients (50.3%) had a colonoscopy with TXI and 841 were male (54.6%). The studies had various indications for colonoscopy, including positive fecal immunochemical test (FIT), surveillance, and diagnostic workup for abdominal symptoms. Population characteristics are presented in Table 1.

Pooled analyses of all included studies

ADR was significantly higher in the TXI group than in the WLI group (57,8%; 448/775 versus 43.6%; 334/766, respectively; RR 1.32 [95% CI, 1.20–1.46]; $p < 0.001$; $I2 = 0\%$; Figure 2). Almost identical result was obtained when using the Mantel-Haenszel fixed-effects model (Supplementary figure 1). This absolute change of 14.2% indicates that seven colonoscopies with TXI are needed to detect one additional patient with an adenoma (number-needed-to-scope = 7). Similarly, APC was significantly higher in the TXI group than in the WLI group (MD 0.50 [95% CI, 0.37–0.64]; $p < 0.001$; $I2 = 0\%$; Figure 3). Furthermore, TXI was better at detecting nonpolypoid/flat adenomas (MD 0.27 [95% CI, 0.12–0.42]; $p < 0.001$; $I2 = 53\%$; Supplementary Figure 2), proximal/right-sided adenomas (MD 0.27 [95% CI, 0.14–0.40]; $p < 0.001$; $I2 = 0\%$; Supplementary Figure 3), and adenomas ≥ 10 mm in size (MD 0.07 [95% CI, 0.02–0.12]; $p = 0.008$; $I2 = 0\%$; Supplementary Figure 4).

Two studies reported mean withdrawal times [7,19]. Their pooled analysis showed shorter withdrawal times in the TXI group (MD -0.31 minutes [95% CI, -0.48 – -0.13]; $p < 0.001$; $I2 = 0\%$; Supplementary Figure 5). The third included study reported only median withdrawal time which was similarly shorter in the TXI group than in the WLI group (6 minutes, 55 seconds vs 7 minutes, 13 seconds, $p = 0.049$) [20].

In the subgroup analysis of RCTs, both ADR (57,6%; 310/538 versus 42.2%; 225/533; RR 1.37 [95% CI, 1.21–1.54]; $p < 0.001$; $I2 = 0\%$; Supplementary Figure 6) and APC (MD 0.51 [95% CI, 0.30–0.72]; $p < 0.001$; $I2 = 0\%$; Supplementary Figure 7) were significantly higher in the TXI group relative to the WLI group.

Quality assessment

The evaluation of RCTs is reported in Supplementary Figure 8. Both RCTs were judged to have low risk of bias [19,20]. In all the included studies, endoscopists could not be blinded due to the nature of the intervention. The nonrandomized study by Sakamoto et al. was judged to have serious risk of bias given the potential for confounding and selection bias inherent to observational studies (Supplementary Figure 9) [7]. Funnel plot analysis of the

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primary outcome (ADR) revealed a symmetric distribution, indicating no evidence of publication bias (Figure 4).

Discussion

In this systematic review and meta-analysis of 3 studies and 1541 patients, we compared TXI with WLI for the detection of adenomas in patients undergoing colonoscopy. The major findings from the pooled data are summarized below: (1) TXI improved ADR by 32% (relative change; 57,8% versus 43.6%) and APC by 0.5 adenomas as compared to WLI; (2) This improvement persisted in the subgroup analysis of RCTs; (3) TXI was similarly better at detecting nonpolypoid/flat adenomas, proximal/right-sided adenomas, and adenomas ≥ 10 mm in size; (4) Colonoscopies with TXI had shorter withdrawal times.

Previous studies with colonoscopy videos and still images have demonstrated that TXI mode 1 enables improved visualization of colorectal lesions, compared to WLI [21,22]. Both subjective visibility scores and objective color difference values of TXI were significantly higher than those of WLI [22]. TXI technology brightens dark areas and enhances surface texture for both protruding and flat colorectal lesions [21]. Therefore, improved visibility during colonoscopy is the most likely reason for the superior performance of TXI over WLI in detecting adenomas.

Other image-enhanced endoscopic modalities have been compared to WLI for the detection of colorectal lesions. For example, a meta-analysis of 11 RCTs found that second-generation Narrow band imaging (NBI; Olympus, Tokyo, Japan) improved ADR only in cases of optimal bowel preparation (50.2% for NBI versus 44.4% for WLI). The results were not statistically significant when the bowel preparation was adequate and when first-generation NBI was used [23]. A meta-analysis of 17 RCTs found that colonoscopies with Linked color imaging (LCI; Fujifilm, Tokyo, Japan) had higher ADR (51.4% versus 42.6%) and higher APC (MD 0.28) than WLI, respectively [24]. In a systematic review and meta-analysis of 5 studies, I-scan (PENTAX, Tokyo, Japan) improved ADR compared to WLI (43.4% vs 39.7%, respectively). However, the improvement in APC was not statistically significant [25].

TXI is a novel image processing algorithm compared to other optical technologies. We believe the inclusion of 1541 patients in our meta-analysis provides a reliable basis for evaluating ADR. We acknowledge that an increase in ADR may be driven primarily by the detection of diminutive adenomas (less than 5 mm in size), which can introduce potential downsides such as increased financial burdens on endoscopy units and pathology laboratories. Increased detection may lead to more intensive surveillance, exemplifying the

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"high adenoma detector paradox" [26]. These concerns align with the principles of green endoscopy, aiming to balance clinical benefit with resource utilization. Furthermore, a pooled analysis of 12 international cohorts of patients undergoing screening, surveillance, or diagnostic colonoscopy found that diminutive polyps with advanced histologic features do not increase the risk for metachronous advanced neoplasia [27]. Despite these considerations, we believe that TXI implementation may have substantial clinical benefits. Our subgroup analyses indicate that TXI increases the detection of adenomas ≥ 10 mm. These findings suggest that TXI can detect advanced adenomas and other clinically relevant adenomas such as proximal/right-sided, and nonpolypoid/flat adenomas that might otherwise be missed with WLI.

Bowel preparation is a key component of high-quality colonoscopy. Adequate bowel preparation (usually defined as a Boston Bowel Preparation Scale score ≥6, with each segment score ≥2) should be achieved in at least 90% of screening and surveillance colonoscopies [5]. As mentioned previously, second generation NBI improved ADR only when the bowel preparation was optimal. A likely explanation is that under NBI, the residual liquid appears reddish, which darkens the endoscopic view. Conversely, TXI maintains its brightness, as the residual liquid appears yellowish, even with poor preparation. Therefore, TXI could facilitate lesion detection under suboptimal conditions. In the two RCTs included in this study, fewer than 5% of patients were excluded from the per-protocol analysis due to inadequate bowel preparation [19,20]. The rest of the patients had either adequate or optimal preparation, and subsequent analyses confirmed the superiority of TXI over WLI for adenoma detection under such conditions.

Colonoscopy withdrawal time, usually defined as time spent inspecting the mucosa minus time spent on washing, suctioning, and therapeutic procedures, is an important quality indicator that has been linked to adenoma detection [28]. In all the included studies, the withdrawal time, reported as a mean or median value, met the minimum recommended threshold of ≥6 minutes [5]. Our pooled analysis showed shorter withdrawal times in the TXI group compared to the WLI group. The reason for this finding currently remains unknown. Despite being statistically significant, the mean difference of 0.31 minutes (about 19 seconds) may be too low to be clinically relevant in routine colonoscopy practice. Nevertheless, TXI improved important colonoscopy quality indicators without increasing the withdrawal time.

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Sessile serrated lesions (SSLs) were not included in our meta-analysis. Approximately 25% of sporadic CRCs originate from serrated precursor lesions, emphasizing their significance in screening programs [29]. SSLs may be missed during colonoscopy due to their flat morphology and color similar to the surrounding mucosa. Thus, the proximal serrated polyp detection rate (PSPDR) has been proposed as a quality indicator for CRC prevention. PSPDR is inversely related to the incidence of interval post-colonoscopy CRC. Each one percent increase in PSPDR corresponds to a 7% reduction in the adjusted hazard of interval post-colonoscopy CRC [30]. In a study with endoscopic images of histologically confirmed serrated polyps, TXI significantly improved visibility scores over WLI [31]. A recent meta-analysis found that TXI significantly increased the detection of SSLs, compared to WLI (RR, 1.44; 95% CI 1.02–2.02) [32]. These results further validate the superiority of TXI over WLI for detection of colorectal lesions.

With the expansion of population-based screening programs globally, the demand for high-quality colonoscopies will increase, potentially creating substantial burdens on healthcare systems. Higher ADR is associated with improved long-term outcomes in reducing CRC incidence and mortality [33]. As an important quality metric, widespread ADR improvement is needed to maximize the effectiveness of endoscopic screening and its public health benefits. Incorporating image enhancement modalities, such as TXI, to improve visibility during colonoscopy may significantly contribute to CRC prevention.

Our study has limitations. First, we chose to include both RCTs and observational studies in the pooled analyses. Nonrandomized studies are prone to confounding, selection bias, and other biases. Nevertheless, a subgroup analysis of only RCTs focusing on ADR and APC showed similar results to those including the observational study (Supplementary figures 6 and 7), confirming a stable effect size and robustness of the meta-analysis. The absence of heterogeneity (I2 = 0%) for both outcomes suggests that variability in effect sizes is likely due to sampling error. These results justify the inclusion of an observational study, enhancing the generalizability of the meta-analysis. Second, due to the nature of the intervention, endoscopists could not be blinded. This might have introduced performance and diagnostic biases, with more thorough inspection of the colonic mucosa when using TXI. However, ADR in the WLI group was notably high (43.6%), indicating that patients in the control group underwent high-quality colonoscopic evaluation. Third, while the imaging processor (Evis X1) was the same in all studies, different colonoscope series with varying image qualities (high definition versus 4K) were employed. The role of 4K resolution in the detection of colorectal lesions remains unclear at this time. Fourth, since the included studies were conducted predominantly in tertiary care centers, the results may not be generalizable to community hospitals. Fifth, the results of the RCTs may have been

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influenced by the Hawthorne effect. Knowing that they were participating in a trial and that their results were being measured, the endoscopists might have performed more careful inspections, leading to higher ADRs than would be seen in real-world settings. Finally, there may have been differences in the colonoscopy procedures within the included studies. For example, two studies did not specify the imaging modality used during insertion [7,20], and none detailed how polyps found during insertion were handled. Notably, a repeated observation of the ascending colon was routinely done in Sakamoto et al., alternating the imaging modality during the second observation of the ascending colon [7]. Despite these limitations, we remain confident in our study findings due to the rigorous methodologies employed, the consistency of the results, and the clinical plausibility.

In conclusion, our meta-analysis demonstrates that TXI improves the detection of colorectal adenomas in patients undergoing colonoscopy for various indications. As a novel image processing algorithm, TXI has the potential to improve the overall quality of colonoscopy and contribute to CRC prevention. Further research is needed to confirm these findings in diverse clinical settings and to evaluate the practical aspects of implementing TXI in routine practice.

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Figure Legends

Figure 1: PRISMA flow diagram of study screening and selection
From: 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. doi: 10.1136/bmj.n71

Available at: https://www.prisma-statement.org/prisma-2020-flow-diagram

Figure 2: Forest plot of studies comparing adenoma detection rate (ADR); CI = confidence interval; M-H = Mantel-Haenszel method; TXI = Texture and color enhancement imaging; WLI = White light imaging

Figure 3: Forest plot of studies comparing adenomas per colonoscopy (APC); CI = confidence interval; IV = inverse variance; SD = standard deviation; TXI = Texture and color enhancement imaging; WLI = White light imaging

Figure 4: Funnel plot analysis of the primary outcome (adenoma detection rate; ADR); RR = risk ratio; SE = standard error

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Table 1: Baseline characteristics of the included studies

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Table 1: Baseline characteristics of the included studies

	Antonelli 2023	Young 2024	Sakamoto 2023
Design	RCT	RCT	Non-RCT*
Patients, (n) TXI/WLI	375/372	163/161	237/233
Study population	Individuals aged > 40 years	Individuals aged > 18 years	Individuals aged ≥ 20 years
Indications for colonoscopy	Positive FIT, CRC screening, Surveillance, Diagnostic	Positive FIT, Surveillance, Diagnostic, Other	Positive FIT, CRC screening, Surveillance, Diagnostic, Polyp follow-up, Pretreatment workup
Location	Italy, Germany, Japan	Australia	Japan
Age, y TXI/WLI	62.8 (9.6)/62.2 (9.3)†	60 (50-69)/61 (52-70)‡	64.2 (12.1)/63.7 (12.8)†
Male, n (%) TXI/WLI	187 (49.9)/188 (50.5)	187 (49.9)/188 (50.5)	154 (65.0)/147 (63.1)
Cecal intubation, n (%) TXI/WLI	366 (97.6)/365 (98.1)	NA	237 (100)/232 (99.6)
Bowel preparation, n (%) TXI/WLI	BBPS score ≥ 2 in all segments: 363 (96.8)/351 (94.4)	BBPS score ≥ 6: 163 (100)/161 (100)	Aronchik scale, Excellent and good: 226 (95.3)/220 (94.4)
Withdrawal time TXI/WLI	Mean 7.7 minutes/8.0 minutes	Median 6 minutes, 55 seconds/ 7 minutes, 13 seconds	Mean 8.6 minutes/9.0 minutes

*Retrospective cohort study; †Mean (SD); ‡Median (interquartile range); CRC: Colorectal carcinoma; BBPS: Boston bowel preparation scale; FIT: Fecal immunochemical test; NA: Not available; RCT: Randomized controlled trial; TXI: Texture and color enhancement imaging; WLI: White light imaging

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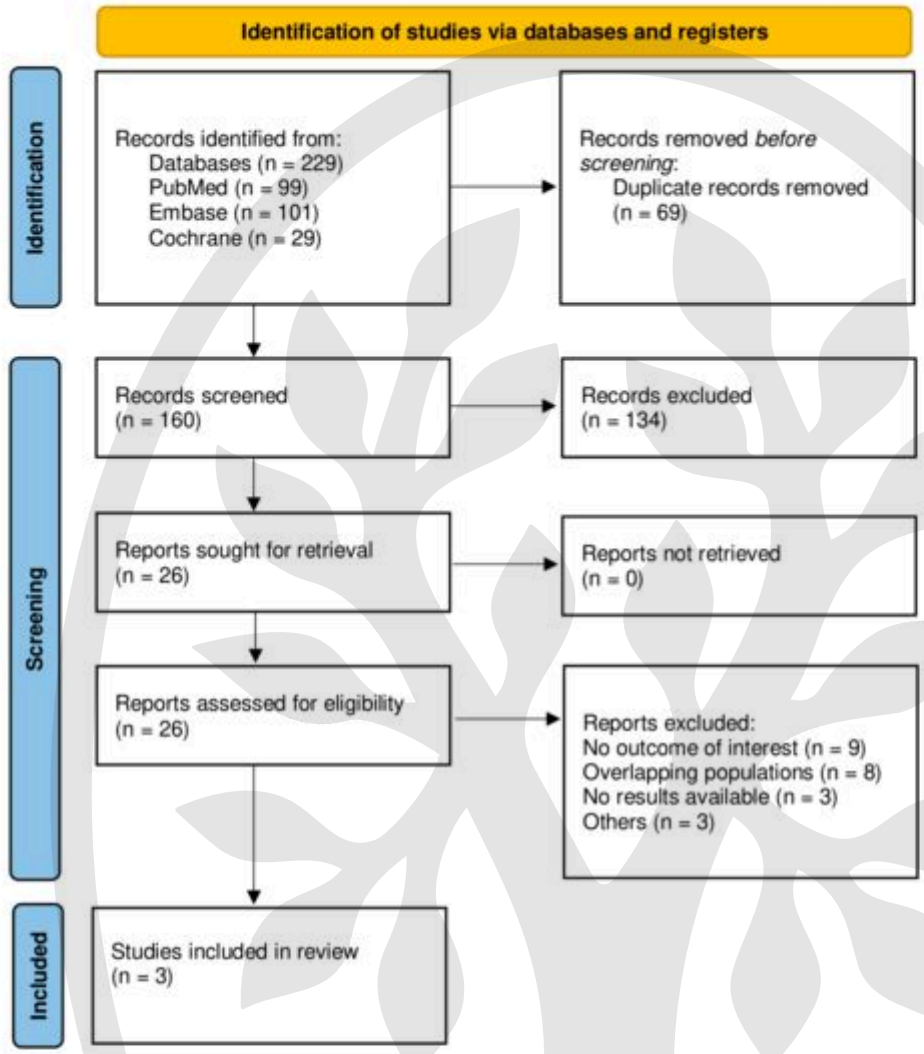
Figure 1 PRISMA flow diagram of study screening and selection



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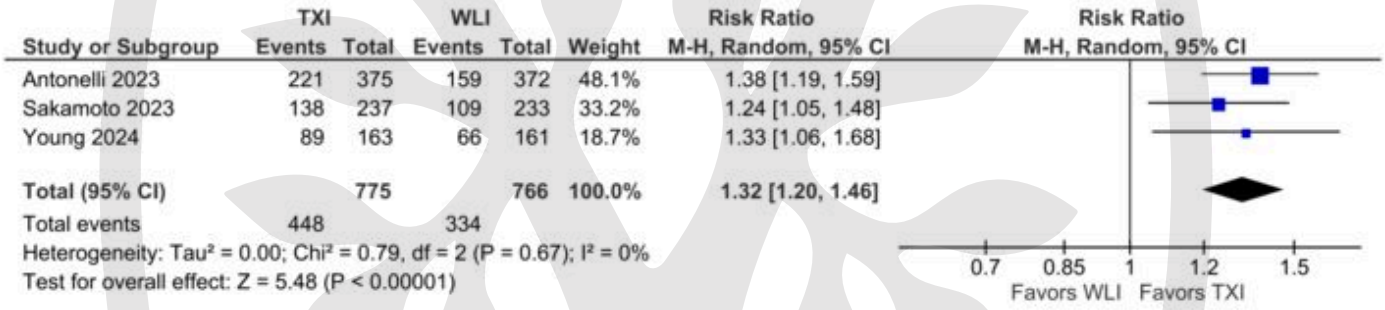

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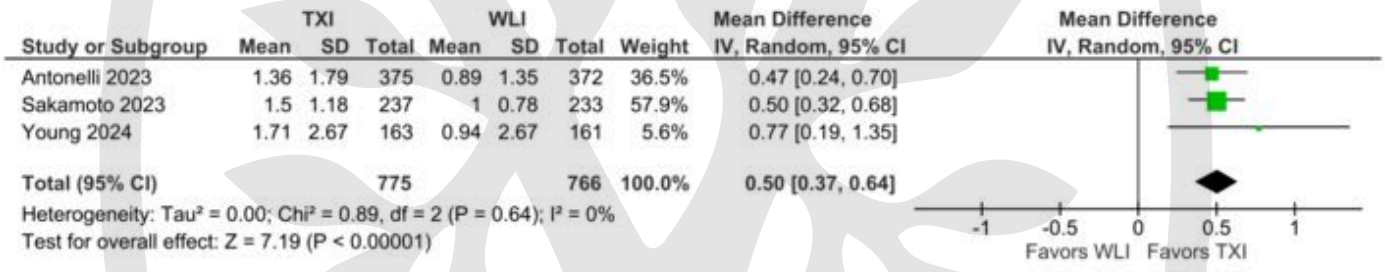

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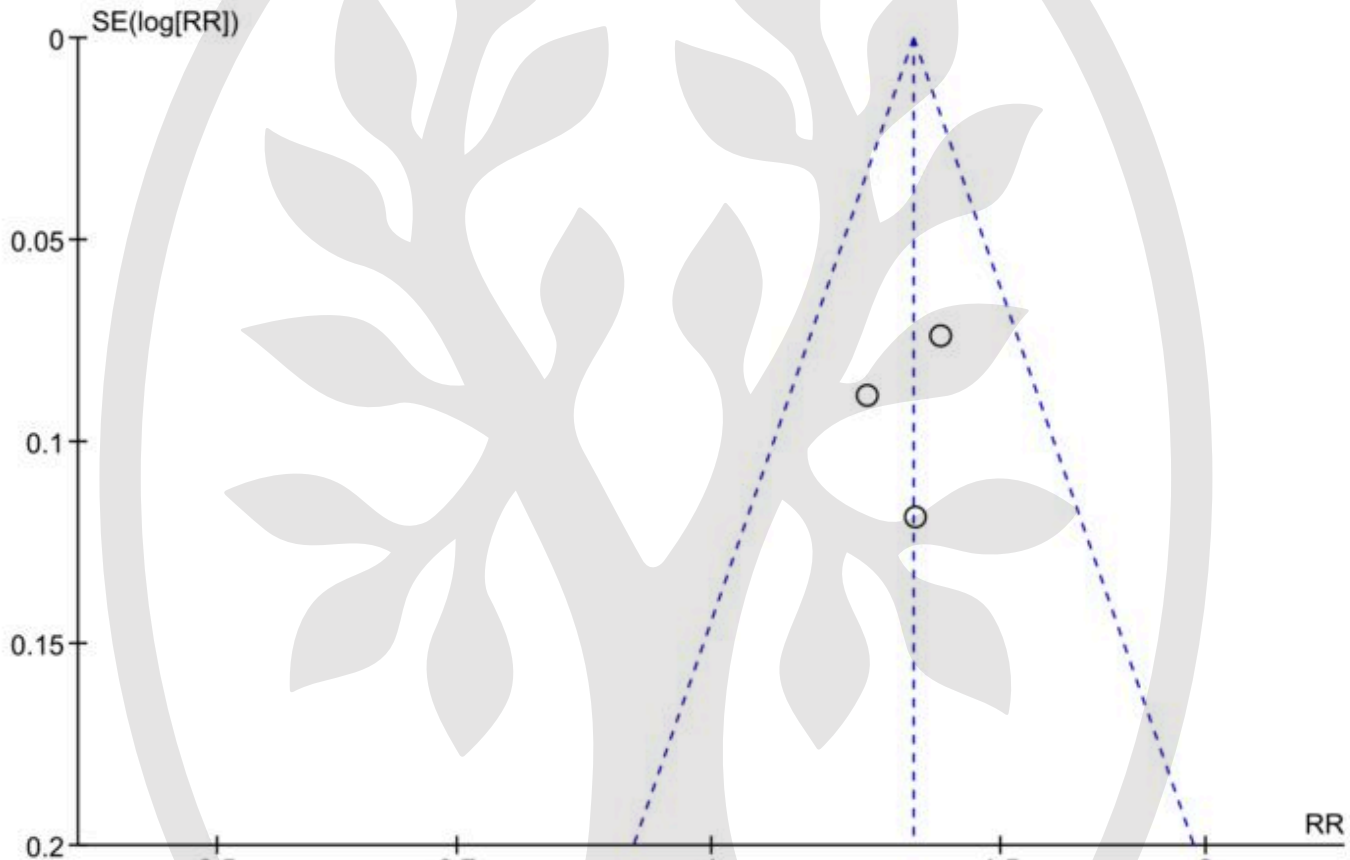

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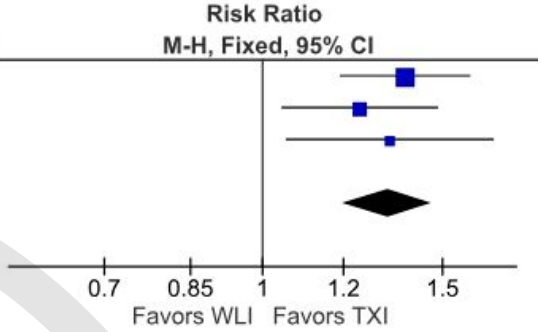
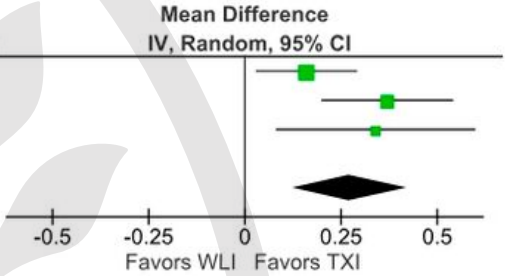
Study or Subgroup	TXI Events	TXI Total	WLI Events	WLI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonelli 2023	221	375	159	372	47.5%	1.38 [1.19, 1.59]
Sakamoto 2023	138	237	109	233	32.7%	1.24 [1.05, 1.48]
Young 2024	89	163	66	161	19.8%	1.33 [1.06, 1.68]
Total (95% CI)		**775**		**766**	**100.0%**	**1.33 [1.20, 1.47]**
Total events	448		334			

Heterogeneity: Chi² = 0.79, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 5.50 (P < 0.00001)



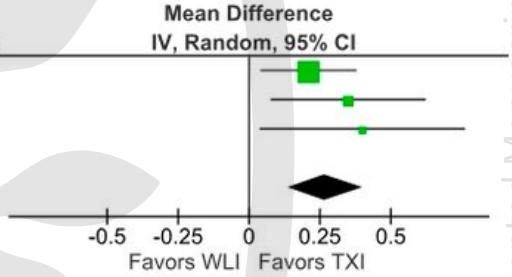
Study or Subgroup	TXI Mean	TXI SD	TXI Total	WLI Mean	WLI SD	WLI Total	Weight	Mean Difference IV, Random, 95% CI
Antonelli 2023	0.58	0.97	375	0.42	0.83	372	42.9%	0.16 [0.03, 0.29]
Sakamoto 2023	1.06	1.03	237	0.69	0.83	233	35.0%	0.37 [0.20, 0.54]
Young 2024	0.58	1.18	163	0.24	1.18	161	22.1%	0.34 [0.08, 0.60]
Total (95% CI)			**775**			**766**	**100.0%**	**0.27 [0.12, 0.42]**

Heterogeneity: Tau² = 0.01; Chi² = 4.26, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 3.58 (P = 0.0003)



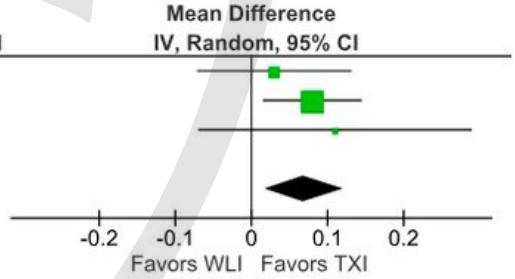
Study or Subgroup	TXI Mean	TXI SD	TXI Total	WLI Mean	WLI SD	WLI Total	Weight	Mean Difference IV, Random, 95% CI
Antonelli 2023	0.76	1.26	375	0.55	1.05	372	62.8%	0.21 [0.04, 0.38]
Sakamoto 2023	0.98	1.64	237	0.63	1.34	233	23.7%	0.35 [0.08, 0.62]
Young 2024	1.13	1.65	163	0.73	1.65	161	13.5%	0.40 [0.04, 0.76]
Total (95% CI)			**775**			**766**	**100.0%**	**0.27 [0.14, 0.40]**

Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 4.00 (P < 0.0001)



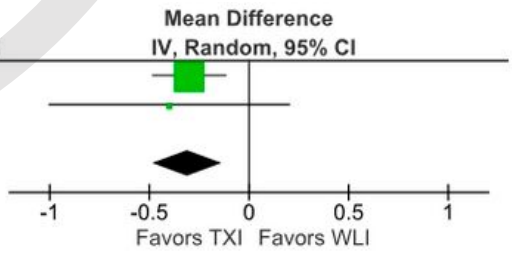
Study or Subgroup	TXI Mean	TXI SD	TXI Total	WLI Mean	WLI SD	WLI Total	Weight	Mean Difference IV, Random, 95% CI
Antonelli 2023	0.29	0.71	375	0.26	0.69	372	26.4%	0.03 [-0.07, 0.13]
Sakamoto 2023	0.16	0.4	237	0.08	0.3	233	65.3%	0.08 [0.02, 0.14]
Young 2024	0.26	0.82	163	0.15	0.82	161	8.3%	0.11 [-0.07, 0.29]
Total (95% CI)			**775**			**766**	**100.0%**	**0.07 [0.02, 0.12]**

Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.63 (P = 0.008)



Study or Subgroup	TXI Mean	TXI SD	TXI Total	WLI Mean	WLI SD	WLI Total	Weight	Mean Difference IV, Random, 95% CI
Antonelli 2023	7.7	0.74	375	8	1.63	372	91.6%	-0.30 [-0.48, -0.12]
Sakamoto 2023	8.6	3.1	235	9	3.5	230	8.4%	-0.40 [-1.00, 0.20]
Total (95% CI)			**610**			**602**	**100.0%**	**-0.31 [-0.48, -0.13]**

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 3.47 (P = 0.0005)



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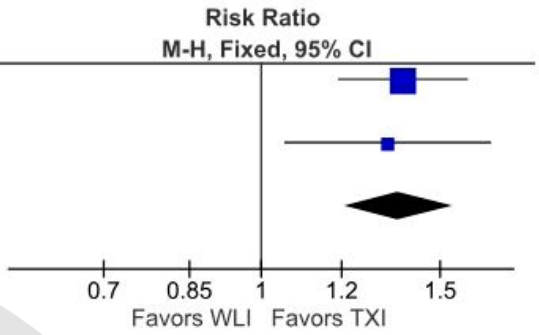
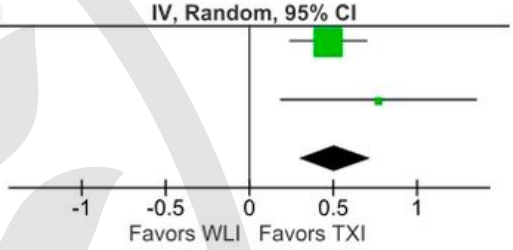
Study or Subgroup	TXI Events	TXI Total	WLI Events	WLI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonelli 2023	221	375	159	372	70.6%	1.38 [1.19, 1.59]
Sakamoto 2023	138	237	109	233	0.0%	1.24 [1.05, 1.48]
Young 2024	89	163	66	161	29.4%	1.33 [1.06, 1.68]
Total (95% CI)		**538**		**533**	**100.0%**	**1.37 [1.21, 1.54]**
Total events	310		225			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 4.96 (P < 0.00001)



Study or Subgroup	TXI Mean	TXI SD	TXI Total	WLI Mean	WLI SD	WLI Total	Weight	Mean Difference IV, Random, 95% CI
Antonelli 2023	1.36	1.79	375	0.89	1.35	372	86.7%	0.47 [0.24, 0.70]
Sakamoto 2023	1.5	1.18	237	1	0.78	233	0.0%	0.50 [0.32, 0.68]
Young 2024	1.71	2.67	163	0.94	2.67	161	13.3%	0.77 [0.19, 1.35]
Total (95% CI)			**538**			**533**	**100.0%**	**0.51 [0.30, 0.72]**

Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 4.72 (P < 0.00001)



Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
Low

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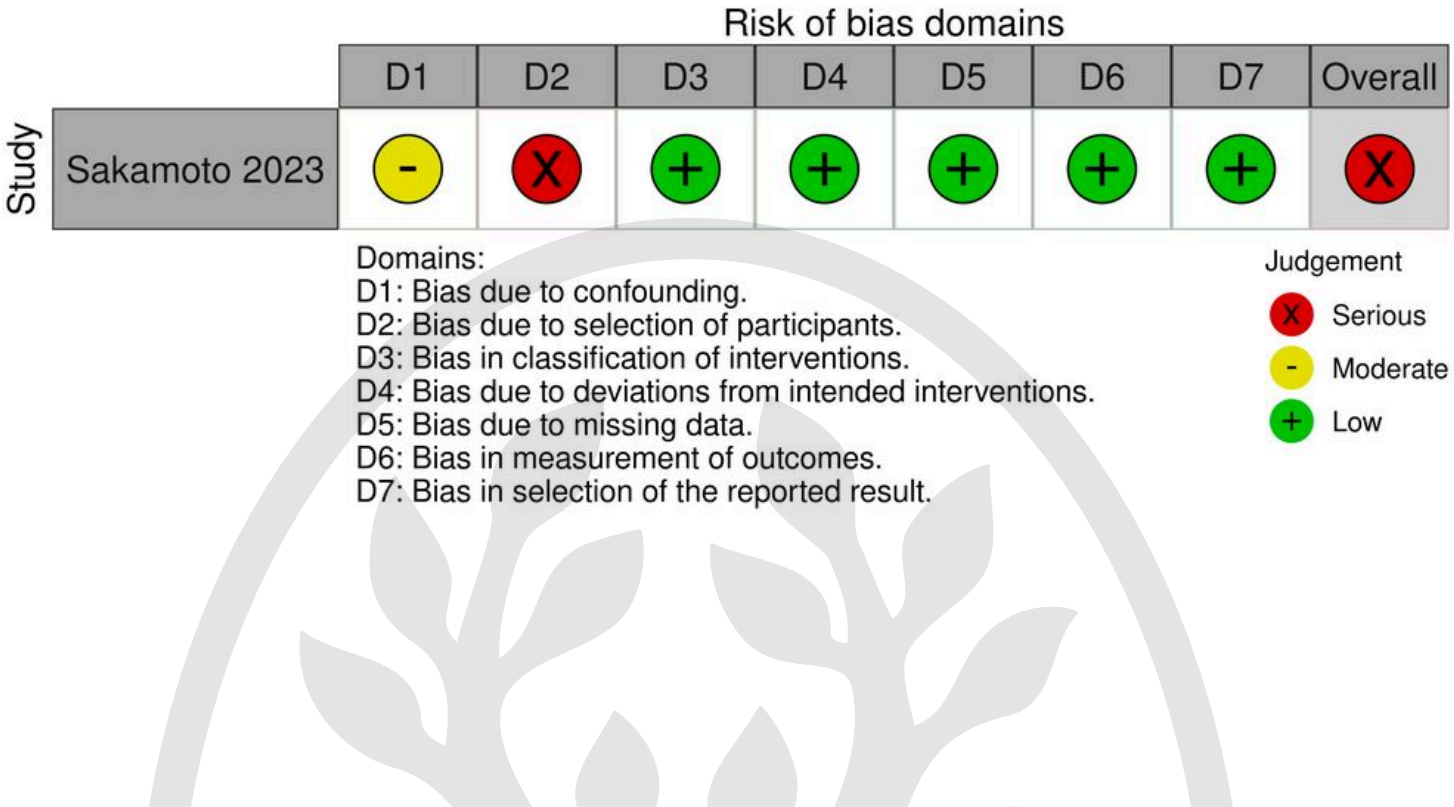

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