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How to increase proximal adenoma detection rate: a meta-analysis comparing water exchange, water immersion and air/CO_2 insufflation methods for colonoscopy

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Abstract

Background Recent meta-analyses have demonstrated a higher adenoma detection rate using the water exchange method (WE), compared to water immersion (WI) and air/CO_2 insufflation (ACI). Proximal adenomas have a high miss rate owing to their location and appearance. We performed a systematic review and meta-analysis of studies comparing the WE and WI methods to the ACI method, with a primary focus on proximal adenoma detection rate.

Methods The following databases were searched for our systematic review: Medline, Embase, Cochrane Library, CINAHL, and Web of Sciences. We included both randomized controlled trials and cohort studies. The primary outcome was proximal adenoma detection rate, and secondary outcomes were right adenoma detection rate and cecal intubation rate.

Results A total of 12 studies (17 arms) with 5660 patients (2260 ACI, 2281 WE, and 1119 WI) were included. A higher proximal adenoma detection rate (risk ratio [RR] 1.30, 95% confidence interval [CI] 1.11-1.53; P=0.001) and right adenoma detection rate (RR 1.43, 95%CI 1.19-1.71; P≤0.001; I^2=0%) were noted for the WE group compared to the ACI group. The WI group did not demonstrate a better detection rate of proximal or right adenomas.

Conclusions The water exchange method for colonoscopy holds promise and should be encouraged in the clinical setting to increase proximal and right adenoma detection rates. This will in turn decrease the incidence of colorectal cancer.

Keywords Colonoscopy, proximal adenoma detection rate, right adenoma detection rate, water exchange, water immersion

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Introduction

Recent years have seen the development of 2 water-aided methods, water exchange (WE) and water immersion (WI), for performing colonoscopy [1,2]. Cadoni *et al* defined the WE method as "a standardized technique that, through infusion and nearly simultaneous suction of water, entails substituting all colon content with a layer of clear water allowing gasless instrument progression to the cecum, minimizing distention, and maximizing cleanliness during insertion" [3]. These authors also defined the WI method as a "technique in which water is infused to facilitate cecal intubation, with limited use of insufflation when necessary. Opaque water is removed as needed to aid progression without maximizing cleanliness. Residual air pockets are used to bypass dirty content" [3]. The infused water is removed during the insertion phase in the WE method and during the withdrawal phase in the WI method [1-3]. Gas insufflation is used for the withdrawal phase in both water-aided methods [3].

Advantages of water-aided methods during colonoscopy potentially include less abdominal distension, improved mucosal visualization, and a higher rate of achieving cecal intubation, all of which should increase patient comfort and allow a thorough endoscopic examination. Rex *et al* also

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described a need for lower sedation medication dosages with the use of water-based methods [4]. Potential disadvantages of water-based methods include the increased overall procedural time, as highlighted by Cadoni *et al* [5]. On the other hand, the air/CO_2 insufflation (ACI) method is the most prevalent and has been associated with lower rates of perforation and post-procedural pain. The ACI method is also considered essential for procedures such as endoscopic mucosal dissection, wide-field endoscopic mucosal resection, and colorectal stent placement. The biggest challenge with this method is filling a gravity-dependent colon with gas, usually carbon dioxide [4].

Adenoma detection rate (ADR) is an important quality indicator during colonoscopy [6]. An increase in ADR has been strongly linked to a decrease in the incidence of colorectal cancer (CRC) and subsequent mortality [7]. Fuccio *et al* compared the WE, WI and ACI methods in a comparative meta-analysis and demonstrated the superiority of the WE method over both WI and ACI in terms of overall adenoma detection rate and right colon adenoma detection rate (RADR) [8]. Another network meta-analysis by Facciorusso *et al* supported the use of water techniques for improving overall ADR [9]. Critically, the authors of this study did not perform an analysis of the proximal adenoma detection rate (PADR).

Proximal colon adenomas, owing to their location and nature, have higher rates of being missed during colonoscopy [10-14]. Efforts are being made to increase PADR in order to decrease the overall interval incidence of CRC [15-17]. We performed a systematic review and meta-analysis of the available literature to compare the WE, WI and ACI techniques with a focus on the PADR obtained when each of these approaches were used.

Patients and methods

Study definitions

PADR is defined as the proportion of patients with at least 1 adenoma detected proximal to the splenic flexure. RADR is defined as the proportion of patients with at least 1 adenoma detected in the cecum and/or ascending colon. The ACI method is defined as insufflation of the colon using either air or CO_2, without the use of water.

Search strategy

We searched the following databases from inception through July 31st, 2019, to generate a comprehensive and up-to-date list of articles for the purposes of this systematic review: PubMed/MEDLINE, Embase, Cochrane Register of Controlled Trials, Web of Science Core Collection, and CINAHL. Controlled subject terms and keyword synonyms for the concepts of colonoscopy, adenoma/polyp detection rate, and water/underwater method were developed for PubMed and translated to the vocabularies and syntax of the other databases. The search strategy was created and performed by (WL-S) and cross checked by another reviewer (MA). Pertinent articles were finalized by 2 reviewers (MA and SS). We adhered to the PRISMA guidelines for this systematic review. The detailed search strategy for PubMed is highlighted in Supplementary Table 1.

Inclusion and exclusion criteria

We restricted our systematic review to include only randomized controlled trials (RCT) and cohort studies. All other studies, including editorials, case reports, case series, and single-arm studies were excluded. Abstracts were also included in this review if they adhered to study design, i.e. RCT or cohort. Our search was not restricted to language or dates. If studies were found to contain duplicate data, the most recent available study was included.

Data collection

Baseline demographic data (age, sex), colonoscopy indication (screening/surveillance vs. diagnostic), and outcomes (PADR, RADR, and CIR) were extracted where applicable. Data extraction was performed by 2 individual reviewers (MA and SS) and cross-checked for any discrepancies.

Primary and secondary outcomes

The primary outcome of our analysis was PADR; secondary outcomes included RADR and CIR. We performed a comparative head-to-head meta-analysis of each technique for the WE, WI and ACI groups, where applicable. In addition, subgroup analysis was performed based on full articles and study design.

Statistical analysis

Data were extracted using Microsoft Excel (Microsoft, Redmond, Washington, United States). Risk ratio (RR) with 95% confidence interval (CI) were calculated for all pooled proportional outcomes. The DerSimonian-Laird method and a random-effects model were used as computing techniques and Open Meta Analyst (CEBM, University of Oxford, Oxford, United Kingdom) was used as the computing software for generating all outcomes. The fixed-effect model was used as a sensitivity tool. Heterogeneity was evaluated using the I^2 statistic between the studies, defined by Cochrane handbook for systematic reviews. Percentages of 25% (I^2=25), 50% (I^2=50), and 75% (I^2=75) were considered to represent low, moderate and high degrees of heterogeneity, respectively [18,19]. A P-value <0.05 was considered statistically significant for all outcomes between the 2 groups.

Table 1 Demographics and characteristics of patients included in the study

Study	Mean/Median Age, n		Male, n (%)		Indication for colonoscopy, n (%)		Study completion, n (%)	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Manuscripts								
Leung *et al* [24]	62.1	63.1	88 (97.8%)	91 (98.9%)	Sc/Su: 81 (90.0%) D/O: 9 (10.0%)	Sc/Su: 84 (91.3%) D/O: 8 (8.7%)	90 (100.0%)	92 (100.0%)
Ramirez *et al* [31]	59.3	60	184 (96.3%)	171 (96.6%)	Sc/Su: 191 (100.0%) D/O: 0 (0%)	Sc/Su: 177 (100.0%) D/O: 0 (0%)	191 (100.0%)	177 (100.0%)
Hsieh *et al* [34]	56.5	55.6	60 (66.7%)	108 (60.0%)	Sc/Su: 35 (38.9%) D/O: 55 (61.1%)	Sc/Su: 62 (34.4%) D/O: 118 (65.6%)	90 (100.0%)	180 (100.0%)
Cadoni *et al* [29]	60	58	204 (61.1%)	201 (59.5%)	Sc/Su: 140 (41.9 %) D/O: 194 (58.1%)	Sc/Su: 137 (40.5%) D/O: 201 (59.5%)	334 (82.3%)	338 (82.4%)
Cadoni *et al* [26,27]	59	59	239 (59.6%)	465 (58.2%)	Sc/Su: 97 (24.2%) D/O: 304 (75.8%)	Sc/Su: 191 (23.9%) D/O: 608 (76.1%)	401 (100.0%)	799 (100.0%)
Cadoni *et al* [28]	60.9	61.2	225 (55.1%)	447 (54.8%)	Sc/Su: 408 (100.0%) D/O: 0 (0%)	Sc/Su: 816 (100.0%) D/O: 0 (0%)	408 (100.0%)	816 (100.0%)
Hsieh *et al* [30]	54.8	55.8	105 (48.4%)	231 (53.2%)	Sc/Su: NR D/O: NR	Sc/Su: NR D/O: NR	217 (100.0%)	434 (100.0%)
Azevedo *et al* [25]	63.6	61.6	40 (56.3%)	41 (58.6%)	Sc/Su: 44 (62.0%) D/O: 27 (38.0%)	Sc/Su: 48 (68.6%) D/O: 22 (31.4%)	71 (87.7%)	70 (85.4%)
Leung *et al* [23]	60.8	60.5	145 (91.2%)	138 (85.7%)	Sc/Su: 159 (100.0%) D/O: NR	Sc/Su: 161 (100.0%) D/O: NR	159 (100.0%)	161 (100.0%)
Abstracts								
Boroff *et al* [32]	NR	NR	NR	NR	Sc/Su: 157 (100.0%) D/O: 0 (0%)	Sc/Su: 189 (100.0%) D/O: 0 (0%)	157 (100.0%)	189 (100.0%)
Chu *et al* [33	58.2	57.9	30 (50.0%)	29 (48.3%)	Sc/Su: 56 (93.3%) D/O: 4 (6.7%)	Sc/Su: 52 (86.6%) D/O: 8 (13.3%)	60 (100.0%)	60 (100.0%)

D/O, diagnostic/others; n, no. of patients; NR, not reported; Sc/Su, screening/surveillance

Bias assessment

Study quality was assessed using Cochrane risk-of-bias tools for RCTs and the Newcastle Ottawa score for cohort studies [20,21]. Publication bias was assessed using Egger's regression analysis, and was displayed using funnel plots generated using Review Manager V5.3 (The Cochrane Collaboration, Oxford, United Kingdom), where applicable.

Evidence rating

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the overall quality of evidence (high, moderate, low, very low) and provided summary of funding (SoF) Tables. We utilized GRADEpro GDT software (Evidence Prime Inc., Hamilton, Ontario, Canada) to generate the SoF Tables [22].

Results

A total of 12 studies with 17 arms were included in the final analysis for this systematic review and meta-analysis (Fig. 1) [23-34]. Of these, all were RCTs except one cohort study [32]. Nine of these studies were published as full manuscripts and 2 were published as abstracts. Two studies by Cadoni *et al* included data from the same RCT and hence we only included data once while comparing outcomes [26,27].

The risk-of-bias assessment is shown in Supplementary Table 2. All RCTs had high performance bias, as it was impossible to blind the endoscopist performing the procedure. We were unable to perform the bias assessment on the cohort study as it was an abstract. No significant publication bias was observed based on the funnel plot obtained (Supplementary Fig. 1) or Egger's regression test (P=0.34).

Study details and demographics of patients are summarized in Supplementary Table 3 and Table 1. Of all the studies included, 11 directly compared ACI to WE [23-34] and 4 directly compared ACI to WI [26,28,30,34]. The total number of patients included in these 11 studies was 5660 (2260 ACI, 2281 WE, 1119 WI). No statistically significant difference was observed in terms of age range (54.8-63.6, 55.7-63.1, and 54.3-61) or the proportion male sex (65.3%, 64.9%, and 55.3%) across the 3 groups for ACI, WE and WI, respectively. The primary and secondary outcomes for individual studies are summarized in Table 2.

Table 2 Primary and secondary outcomes for all studies

Study	PADR, n (%)		RADR, n (%)		CIR, n (%)	
	Control	Intervention	Control	Intervention	Control	Intervention
Manuscripts						
Leung *et al* [24]	ACI: 15 (16.7%)	WE: 27 (29.3%)	NR	NR	ACI: 81 (90.0%)	WE: 91 (99.0%)
Ramirez *et al* [31]	ACI: 66 (34.6%)	WE: 81 (45.8%)	NR	NR	ACI: 191 (100.0%)	WE: 163 (92.1%)
Hsieh *et al* [34]	ACI: 16 (17.8%)	WE: 29 (32.2%) WI: 25 (27.8%)	ACI: 10 (11.1%)	WE: 24 (26.7%) WI: 13 (14.4%)	ACI: 71 (78.9%)	WE: 82 (91.1%) WI: 83 (92.2%)
Cadoni *et al* [29]	ACI: 16 (4.8%)	WE: 34 (10.1%)	NR	NR	ACI: 330 (98.8%)	WE: 326 (96.4%)
Cadoni *et al* [26, 27]	ACI: 51 (21.3%)	WE: 60 (25.9%) WI: 48 (20.6%)	ACI: 48 (12.0%)	WE: 59 (14.9%) WI: 49 (12.1%)	ACI: 234 (97.9%)	WE: 228 (98.3%) WI: 228 (97.8%)
Cadoni *et al* [28]	NR	NR	ACI: 69 (16.9%)	WE: 98 (24.0%) WI: 78 (19.1%)	ACI: 399 (97.8%)	WE: 402 (98.5%) WI: 400 (98.0%)
Hsieh *et al* [30]	ACI: 44 (20.3%)	WE: 64 (29.5%) WI: 66 (30.4%)	ACI: 33 (15.3%)	WE: 47 (21.7%) WI: 38 (17.5%)	ACI: 197 (90.8%)	WE: 208 (95.9%) WI: 191 (88.0%)
Azevedo *et al* [25]	NR	NR	ACI: 4 (5.6%)	WE: 6 (8.6%)	NR	NR
Leung *et al* [23]	ACI: 83 (52.2%)	WE: 86 (53.4%)	NR	NR	ACI: 156 (98.1%)	WE: 161 (100.0%)
Abstracts						
Boroff *et al* [32]	ACI: 51 (32.5%)	WE: 64 (33.9%)	NR	NR	NR	NR
Chu *et al* [33]	NR	NR	ACI: 5 (8.3%)	WE: 7 (11.7%)	ACI: 56 (93.3%)	WE: 59 (98.3%)

ACI, air/CO_2 colonoscopy; CIR, cecal intubation rate; n, no. of studies; NR, not reported; PADR, proximal adenoma detection rate; RADR, right adenoma detection rate; WE, water exchange colonoscopy; WI, water immersion colonoscopy

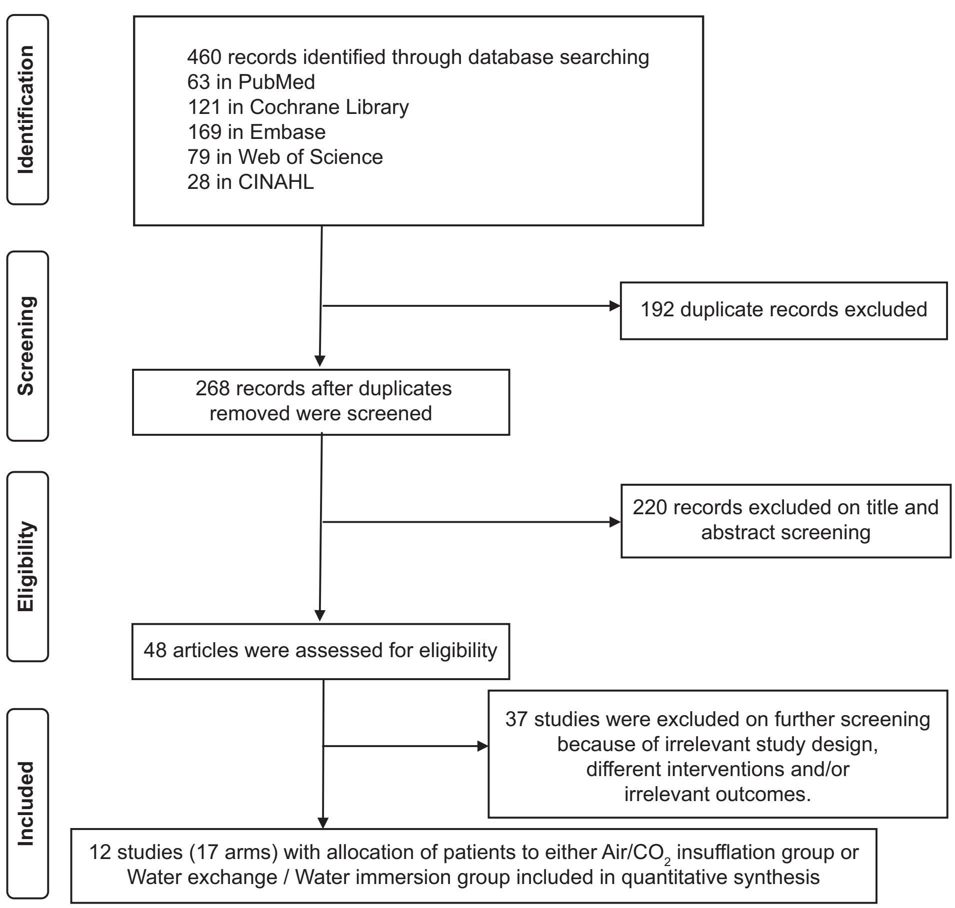

Figure 1 Flow diagram representing the selection of studies

Table 3 Summary of findings

Water exchange technique compared to air/CO_2 insufflation for colonoscopy

Patient or population: Patients undergoing colonoscopy
Setting: Inpatient or outpatient
Intervention: water exchange technique
Comparison: air/CO_2 insufflation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with air/CO2 insufflation	Risk with water exchange technique			
PADR assessed with: colonoscopy, biopsy, histology	220 per 1000	**287 per 1000** (231 to 357)	**RR 1.30** (1.05 to 1.62)	2627 (7 RCTs)	⊕⊕⊕○ MODERATE[a]
RADR assessed with: colonoscopy, biopsy, histology	138 per 1000	**198 per 1000** (164 to 236)	**RR 1.43** (1.19 to 1.71)	2367 (5 RCTs)	⊕⊕⊕○ MODERATE[a]
CIR assessed with: colonoscopy	953 per 1000	**972 per 1000** (944 to 1,000)	**RR 1.020** (0.991 to 1.051)	2891 (8 RCTs)	⊕⊕⊕○ MODERATE[a,b]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)

CI, confidence interval; CIR; cecal intubation rate; PADR, proximal adenoma detection rate; RADR, right adenoma detection rate; RCTs, randomized controlled trials; RR, risk ratio/ relative risk

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Participants and endoscopist were not blinded during colonoscopy for practical reasons

b. Studies reported varying intubation rate

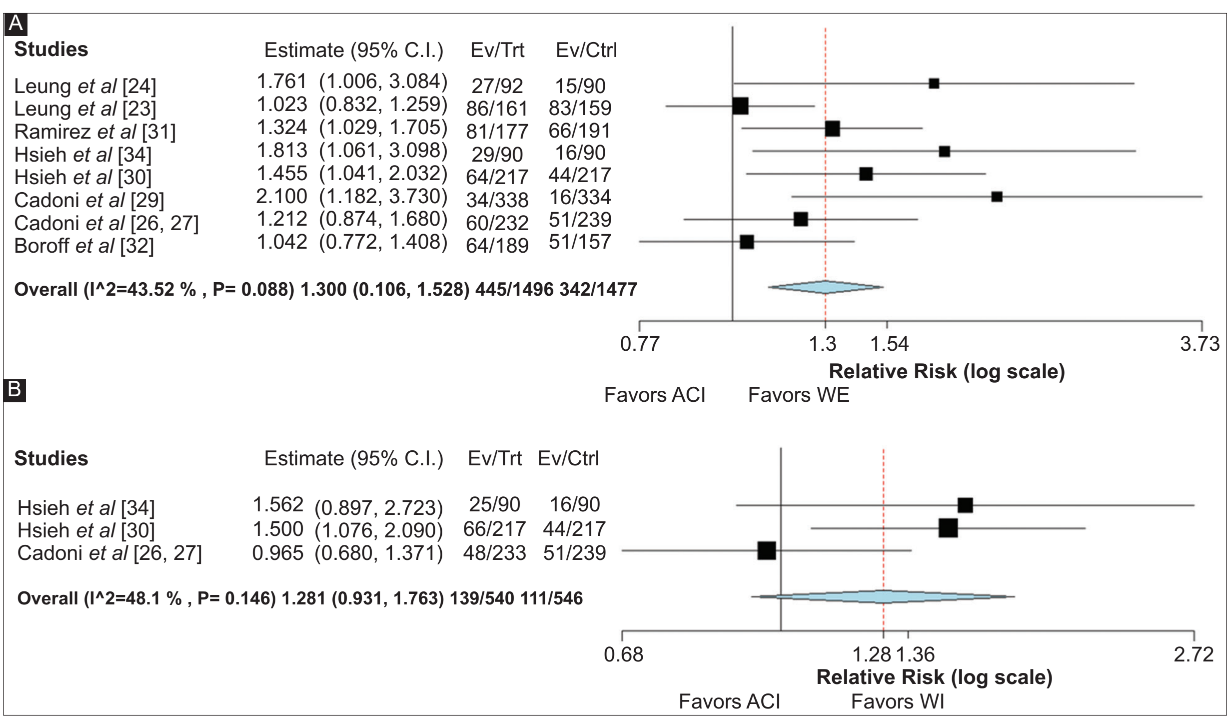

Figure 2 Forest plot comparing PADR in (A) WE versus ACI group (B) WI versus ACI group

C.I., confidence interval; ACI, air/CO_2 insufflation colonoscopy; Trt, WE group; Ctrl, ACI group; PADR, proximal adenoma detection rate; WE, water exchange colonoscopy; WI, water immersion colonoscopy

PADR

Overall, 8 studies reported PADR [23,24,27,29-32,34]. The 8 arms comparing WE to ACI revealed a higher PADR for the WE group (WE: 29.7%, 95%CI 21.8-41.9% vs. ACI: 23.2%, 95%CI 14.1-33.8%; RR 1.30, 95%CI 1.11-1.53; P=0.001; I^2=43.5%) (Fig. 2A). Only 3 arms compared WI to ACI and found no difference in PADR between them (WI: 26.0%, 95%CI 19.4-33.3% vs. ACI: 20.3%, 95%CI 17.2-23.9%; RR 1.28, 95%CI 0.93-1.76; P=0.13; I^2=48.1%) (Fig. 2B).

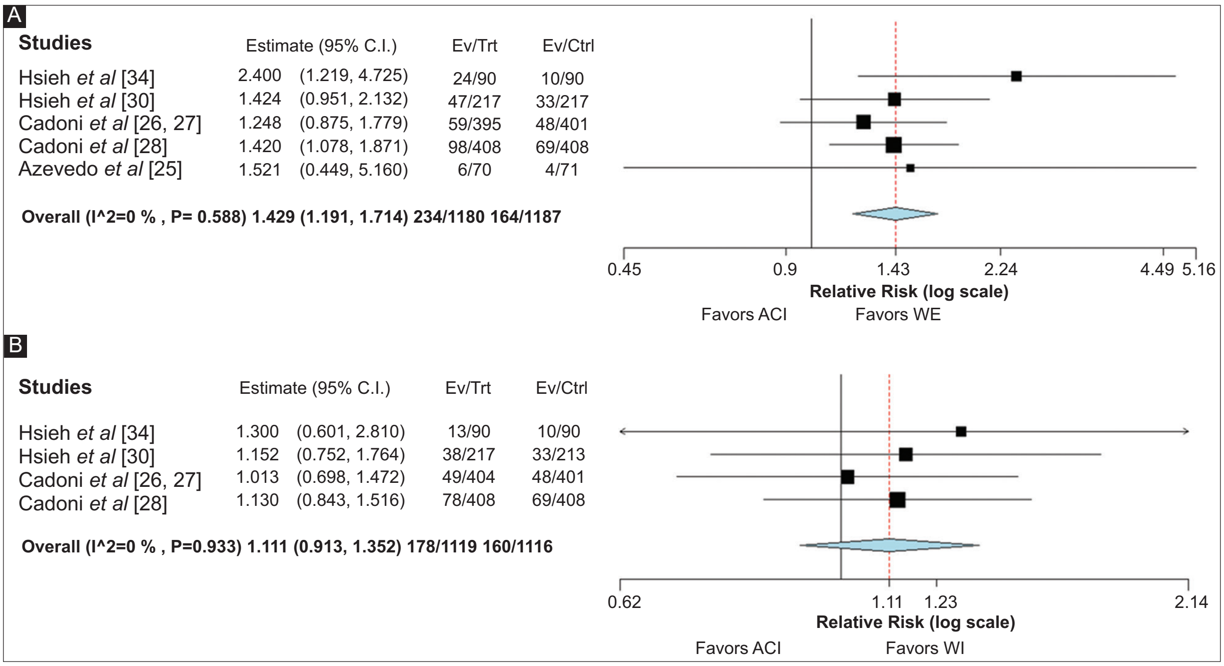

Figure 3 Forest plot comparing RADR in (A) WE vs. ACI group (B) WI vs. ACI group
C.I., confidence interval; ACI, air/CO_2 insufflation colonoscopy; Trt, WE group; Ctrl, ACI group; RADR, right adenoma detection rate; WE, water exchange colonoscopy; WI, water immersion colonoscopy

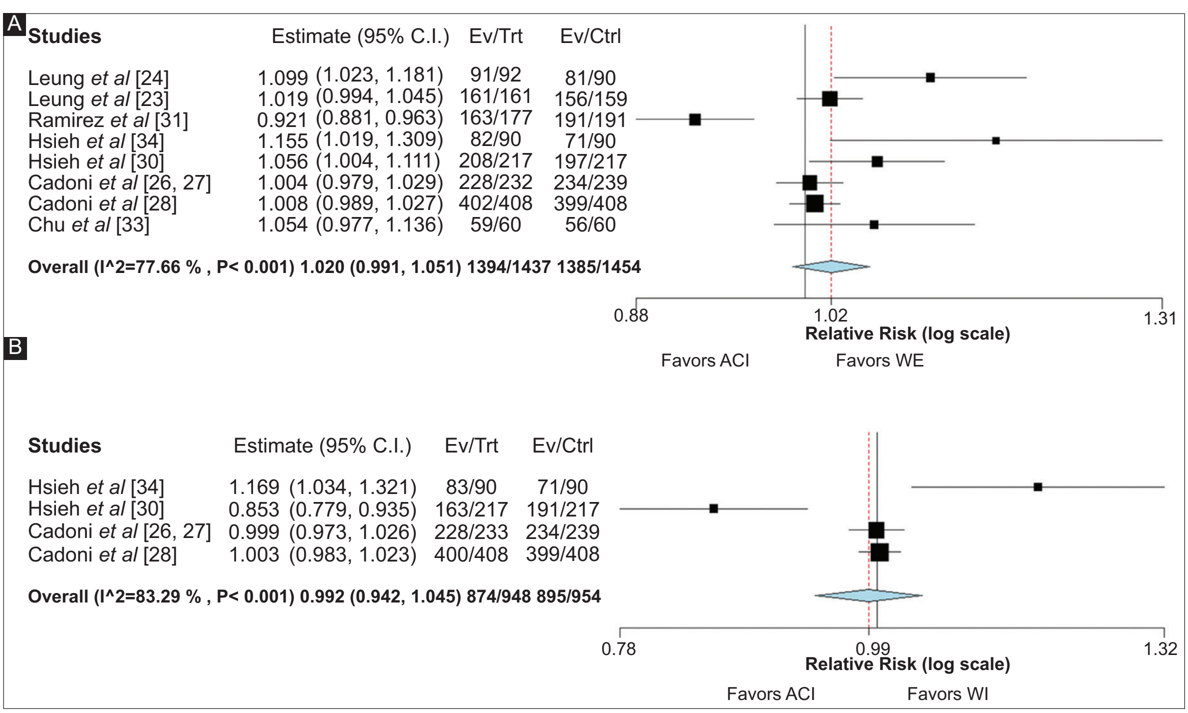

Figure 4 Forest plot comparing CIR in (A) WE vs. ACI group (B) WI vs. ACI group
C.I., confidence interval; ACI, Air/CO_2 insufflation colonoscopy; Trt, WE group; Ctrl, ACI group; CIR, cecal intubation rate; WI, water exchange colonoscopy

RADR

Overall 5 studies reported RADR [25,28,30,31,34]. RADR was significantly greater in the WE group compared to the ACI group, with a direct comparison in 5 arms (WE: 19.8%, 95%CI 14.6-25.4% vs. ACI: 13.8%, 95%CI 10.4-16.9%; RR 1.43, 95%CI 1.19-1.71; P≤0.001; I^2=0%) (Fig. 3A). Four arms compared the WI to the ACI group and found no difference in RADR (WI: 15.9%, 95%CI 12.4-19.9% vs. ACI: 14.3%, 95%CI 11.7-17.3%; RR 1.11, 95%CI 0.91-1.35; P=0.29; I^2=0%) (Fig. 3B).

CIR

No significant difference was observed in CIR for either comparison: i.e. WE vs. ACI (97.0% vs. 95.3%, RR 1.02, 95%CI 0.99-1.05; P=0.18; I^2=77.7%) (Fig. 4A) and WI vs. ACI (92.2% vs. 93.8%, RR 0.99, 95%CI 0.94-1.05; P=0.76; I^2=83.3%) (Fig. 4B).

Subgroup analysis

A subgroup analysis of only published RCTs showed higher PADR (28.8% vs. 22.8%, RR 1.30, 95%CI 1.05-1.62; P=0.02; I^2=51.5%) and RADR (19.8% vs. 13.8%, RR 1.43, 95%CI 1.19-1.71; P≤0.001; I^2=0%) in the WE group compared to the ACI group. PADR for screening colonoscopies was available in 3 studies and a higher detection rate was found for the WE group; however, the results were not statistically significant (41.9% vs. 33.5 %, RR 1.31, 95%CI 0.93-1.85; P=0.13; I^2=70.9%).

Evidence rating

Using the GRADE approach, the certainty of evidence was moderate for PADR and RADR assessed for WE vs. ACI colonoscopy (Table 3). The certainty of evidence was low and moderate for PADR and RADR, respectively, when the WI and ACI techniques were compared (Table 4).

Discussion

The results of our systematic review and meta-analysis demonstrate a greater PADR and RADR for the WE compared to the ACI method. This was also consistent with our subgroup analysis of RCTs. No difference in detection

Table 4 Summary of findings

Water immersion technique compared to air/CO2 insufflation for colonoscopy

Patient or population: Patients undergoing colonoscopy
Setting: Inpatient or outpatient
Intervention: water immersion technique
Comparison: air/CO2 insufflation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with air/ CO2 insufflation	Risk with water immersion technique			
PADR assessed with: colonoscopy, biopsy, histology	203 per 1000	**260 per 1000** (189 to 358)	**RR 1.280** (0.931 to 1.763)	1086 (3 RCTs)	⊕⊕○○ LOW[a,c]
RADR assessed with: colonoscopy, biopsy, histology	143 per 1000	**159 per 1000** (131 to 194)	**RR 1.111** (0.913 to 1.352)	2235 (4 RCTs)	⊕⊕⊕○ MODERATE[b,c]
CIR assessed with: colonoscopy	938 per 1000	**931 per 1000** (884 to 980)	**RR 0.992** (0.942 to 1.045)	1902 (4 RCTs)	⊕○○○ VERY LOW[a,b,c]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
a. Studies reporting varying results
b. very low number of studies, difficult to assess publication bias
c. Participants and endoscopist were not blinded during colonoscopy for practical reasons
CI, confidence interval; CIR, cecal intubation rate; PADR, proximal adenoma detection rate; RADR, right adenoma detection rate; RCTs, randomized controlled trials; RR, risk ratio/ relative risk

rates was observed when the WI group was compared with the ACI group.

The exact mechanism through which WE improves colonoscopy outcome metrics, such as ADR, RADR and PADR, is not fully understood. One possible theory points to the greater cleanliness throughout the colon achieved through simultaneous water infusion and suction in the WE method, as shown by Fuccio *et al* [8]. Another possible mechanism is the magnifying effect of water itself on the endoscope optics during the insertion phase, leading to higher detection rates [34]. Lastly, a thorough examination is possible, as the WE technique eliminates the need for constant washing and suctioning and hence reduces the incidence of luminal collapse [35]. A combination of the aforementioned factors may increase the yield of colonoscopy outcome metrics and decrease the incidence of interval CRC.

Proximal lesions can be challenging to detect, because of their location and subtle appearance. Sessile serrated adenomas/polyps (SSA/Ps), a subset of these lesions, are particularly important, as they may account for ~20% of all CRC cases [36]. Yang *et al* previously showed that 61.2% of SSA/Ps were found in the proximal colon [37]. This further necessitates the improvement of techniques to increase detection of these proximal lesions. Only one study directly evaluated SSA/Ps, showing a significantly greater detection rate of these lesions using the WE method compared to the ACI method (23.6% vs. 11.3%, P<0.01) [23]. Our meta-analysis is important, as we pooled data from all available studies regarding proximal adenomas and our results demonstrate the superiority of the WE method in detecting these lesions; this, in turn, should increase the detection rate for SSA/Ps.

The current meta-analysis has some limitations. Not all studies reported both PADR and RADR for each technique; however, a sufficient number of patients were analyzed to generate a pooled outcome for each metric. Our results for PADR showed some degree of heterogeneity and hence the results should be interpreted with caution. The heterogeneity can be explained by a combination of endoscopist skill, the inclusion of cohort study design, the indications for colonoscopy, procedural technicalities such as method of sedation, use of adjunctive modalities such as distal attachments or chromoendoscopy, etc. To compensate for this, we tried to limit our search criteria to exclude studies that used additional adjunctive modalities. The subgroup analysis for only RCTs also showed consistent results for both PADR and RADR using the WE method compared to the ACI method. The studies included were reported from limited institutions with expert endoscopists and the results may not be generalizable to a general population. Lastly, the impracticality of blinding the endoscopist and patient during a study does bring performance and detection bias into play. The limitations are partly attenuated by the combined statistical power of large number of studies with diverse study populations. All studies except one were RCTs and we used strict inclusion and exclusion criteria for screening studies.

In conclusion, the use of WE during colonoscopy showed significantly better PADR and RADR compared to the ACI method. Given the importance of SSA/Ps, future studies should be conducted to directly assess the use of the WE method to evaluate the detection rate of these lesions.

Summary Box

What is already known:

- The water exchange technique has been found to have significantly better detection rates for polyps and adenomas
- Previous meta-analyses have demonstrated the efficacy of water exchange techniques in improving overall adenoma detection rate (ADR), right ADR (RADR), and polyp detection rate

What the new findings are:

- Our meta-analysis evaluated proximal adenoma detection rate (PADR), which is another outcome metric
- The water exchange technique showed significantly better PADR and RADR compared to standard (air/CO_2) insufflation colonoscopy
- Given the efficacy of water exchange techniques, clinicians should be encouraged to utilize them to further improve their colonoscopy outcome metrics

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Supplementary material

Supplementary Table 1 PubMed search strategy

Search	Query	Items found
#1	(Underwater* OR water OR "Water" [Mesh: NoExp])	939742
#2	("Colonoscopy" [Mesh] OR colonoscop* OR coloscop*)	42494
#3	("Adenoma" [Mesh] OR "Polyps" [Mesh] OR adenoma* OR polyp OR polyps)	172518
#4	([Detect* OR miss] AND [rate or rates])	291521
#5	#3 AND #4	4737
#6	#1 AND #2	642
#7	#5 AND #6	82
#8	#7 NOT (["case reports"] [Publication Type] OR "guideline" [Publication Type] OR "introductory journal article" [Publication Type] OR "review" [Publication Type])	63

Supplementary Table 2 Risk of bias in the included randomized controlled trials (RCTs)

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Leung *et al* [24]	Unclear	Unclear	High	Unclear	Low	Low
Ramirez *et al* [31]	High	Unclear	High	High	Low	Low
Hsieh *et al* [34]	Low	Low	High	High	Low	Low
Cadoni *et al* [29]	Low	Unclear	High	Low	Low	Low
Cadoni *et al* [26, 27]	Unclear	Unclear	High	Low	Low	Low
Cadoni *et al* [28]	Low	Low	High	Low	Low	Low
Hsieh *et al* [30]	Unclear	Low	High	Unclear	Low	Low
Azevedo *et al* [25]	Low	Low	High	Low	Low	Low
Leung *et al* [23]	Low	Low	High	Low	Low	Low

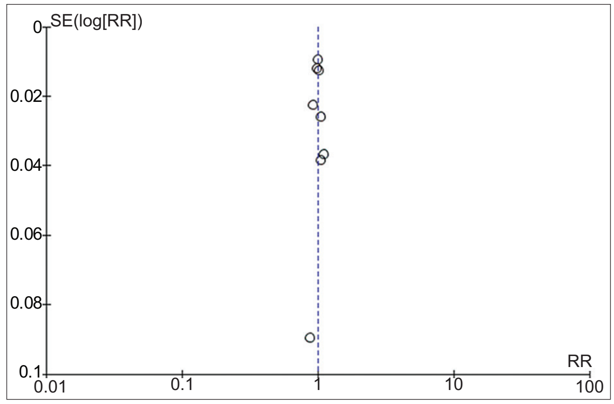
*Cadoni 2, 3 included data from the same RCT and are hence included as one here

Supplementary Table 3 Study details

S. No	Study-year	Type of Study	Year	Techniques compared	Total (n)	Control group (n)	Intervention group (n)
Manuscripts							
1.	Leung *et al* [24]	RCT	2011	WE vs. ACI	182	90	92
2.	Ramirez *et al* [31]	RCT	2011	WE vs. ACI	368	191	177
3.	Hsieh *et al* [34]	RCT	2014	WE vs. WI vs. ACI	270	90	180 (WE: 90, WI: 90)
4.	Cadoni *et al* [29]	RCT	2014	WE vs. ACI	816	406	410
5.	Cadoni *et al* [26,27]	RCT	2016	WE vs. WI vs. ACI	1200	401	799 (WE: 395 WI: 404)
6.	Cadoni *et al* [28]	RCT	2017	WE vs. WI vs. ACI	1224	408	816 (WE: 408, WI: 408)
7.	Hsieh *et al* [30]	RCT	2017	WE vs. WI vs. ACI	651	217	434 (WE: 217, WI: 217)
8.	Azevedo *et al* [25]	RCT	2018	WE vs. ACI	163	81	82
9.	Leung *et al* [23]	RCT	2019	WE vs. ACI	320	159	161
Abstracts							
1.	Boroff *et al* [32]	Cohort	2015	WE vs. ACI	346	157	189
2.	Chu *et al* [33]	RCT	2015	WE vs. ACI	120	60	60

*Cadoni (2, 3) included data from the same RCT and hence included as one here

CI, air/CO_2 insufflation colonoscopy; n, no. of patients; RCT, randomized controlled trials; WE, water exchange colonoscopy; WI, water immersion colonoscopy



Supplementary Figure 1 Funnel plot demonstrating no visible asymmetry (signifying no publication bias), based on cecal intubation rate
RR, risk ratio; SE, standard error