Underwater versus conventional endoscopic mucosal resection for colorectal lesions: An updated meta-analysis of randomized controlled trials

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Additional material is available at https://doi.org/10.1055/a-2150-9899

Key words
Polyps / adenomas / ..., Endoscopy Lower GI Tract, Endoscopic resection (polypectomy, ESD, EMRc, ...), Colorectal cancer

received 22.2.2023
accepted after revision 31.7.2023
accepted manuscript online 9.8.2023

Bibliography
Endosc Int Open 2023; 11: E935–E942
DOI 10.1055/a-2150-9899
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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ABSTRACT

Background and study aims Colorectal malignancy is a leading cause of death. Conventional endoscopic mucosal resection (CEMR) is a strategy used to resect precancerous lesions that involves injecting fluid beneath a polyp to create a gap for resection. Underwater endoscopic mucosal resection (UEMR) is a newer method that forgoes injection, instead filling the intestinal cavity with water to facilitate polyp resection. Our aim was to compare the safety and efficacy of these approaches by synthesizing the most contemporary evidence.

Methods PubMed, Embase, and Cochrane libraries were searched from inception through November 11, 2022 for randomized controlled trials (RCTs) comparing UEMR and CEMR for resection of colorectal lesions. The primary outcome was the rate of en bloc resection and secondary outcomes included recurrence, procedure time, and adverse events (AEs).

Results A total of 2539 studies were identified through our systematic literature search. After screening, seven RCTs with a total of 1581 polyps were included. UEMR was associated with significantly increased rates of en bloc resection (RR 1.18 [1.03, 1.35]; I^2 = 76.6%) versus conventional approaches. No significant differences were found in procedure time, recurrence, or AEs.

Conclusions UEMR is a promising effective technique for removal of colorectal lesions. The most contemporary literature indicates that it improves en bloc resection rate without increasing procedure time, recurrence, or AEs (PROSPERO ID CRD42022374935).

Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed malignancies in the world and a leading cause of cancer-related death. In the United States, lifetime incidence of developing CRC is around 4% for those at average risk [1]. Recent clinical guidelines have recommended decreasing the age of CRC screening from 50 to 45 years of age [2]. Widespread screening has reduced CRC incidence and mortality [3, 4, 5], with colonoscopy with resection serving as the primary intervention tool.

Endoscopic mucosal resection (EMR) is a strategy used to resect colorectal polyps and precancerous lesions. The conventional approach involves injecting fluid beneath the polyp into the submucosa to create a gap allowing for polyp resection [6]. However, incomplete resection and recurrence have been described with this technique as well as adverse events (AEs) including post-polypectomy syndrome, bleeding, and perforation [7]. Underwater endoscopic mucosal resection (UEMR) is a newer method of resection that does not involve submucosal injection but instead infuses the intestinal cavity with water [6, 8, 9]. This strategy was informed by the observation that filling the gastrointestinal lumen with water maintained the natural shape and thickness of the colon wall layers including the involution of the mucosa. In theory, this provides a better separation than air or carbon dioxide insufflation, which results in stretching, loss of rugae, and compression of the layers, and obviates the need for a submucosal lift [9].

Nevertheless, the results of initial randomized controlled trials (RCTs) comparing the two methods were conflicting [10, 11, 12, 13, 14]. In the past 3 years, this topic has been informed by several larger RCTs [15, 16]. The aim of our study was to address the relative safety and efficacy of UEMR and conventional EMR (CEMR) by synthesizing the most contemporary evidence.

Methods

Search strategy

Electronic databases including PubMed, Embase, and Cochrane Library, were searched from initiation to November 11, 2022 for trials investigating UEMR and CEMR for resection of colorectal lesions. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO ID CRD42022374935).

In collaboration with a health sciences librarian, the search query for each database was constructed using a combination of keywords and MeSH terms including underwater and conventional EMR, colorectal polyps, and colorectal lesions. A reproducible search strategy is provided in **Supplementary Table 1**. References from trials were reviewed to identify any additional studies (snowballing). No language or publication date filters were applied to the initial search to capture all appropriate studies. Endnote X7.7.1 (Clarivate Analytics, Philadelphia, Pennsylvania, United States) was used to capture citations and remove duplicates [17]. Covidence (Melbourne, Australia), a systematic review software program, was used for further abstract and title screening. For duplicate studies, or reports using the same data, only the most recently published results were included.

Outcomes

The primary outcome of our meta-analysis was rate of en bloc resection defined a priori as complete removal of the lesion as a single piece. The population of interest was adult patients (≥18 years old) undergoing EMR for colorectal lesions. The intervention was underwater EMR while the comparator was CEMR. Additional outcomes of the meta-analysis were defined as the proportion of recurrence at any point during the follow-up interval, AEs of bleeding, abdominal pain, perforation, and procedure time.

Study selection

All titles, abstracts, and full text underwent an initial screen by two independent reviewers. A third reviewer provided input about discrepancies until a consensus decision was reached. Inclusion criteria were as follows: [1] RCTs; [2] comparison of UEMR versus CEMR for resection of colorectal lesions; [3] publication in English; and [4] publication in a peer-reviewed journal or presentation as an abstract at a scientific meeting. Editorials, review papers, retrospective studies, prospective cohorts, case reports, and case-control studies were excluded. Our study includes the preferred reporting items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18].

Data extraction

All data were extracted by the independent reviewers with a third reviewer to resolve discrepancies. Data were entered into a Microsoft Excel spreadsheet (2020 Version 16.43; Microsoft Corp, Redmond, Washington, United States). The following information was extracted: author, title, journal, year, study country, type of study, type of EMR (underwater versus conventional) for colorectal lesions, total number of patients and number of patients in each study group, total number of polyps and number of polyps in each outcome group.

Risk of bias and quality of evidence

The Cochrane's risk of bias tool [19] was used to assess risk of bias in the studies included in our meta-analysis. This tool assesses six domains: selection bias, reporting bias, performance bias, detection bias, attrition bias, and other bias.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment was used to evaluate quality of evidence [20]. This assessment tool uses eight domains for evaluation: risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect size, dose response, and plausible confounders. The Cochrane Consumers and Communication Group supplementary material was also used as a source for evaluating each GRADE domain [21].

Data analysis

Pooled risk ratios (RR) and 95% confidence intervals (CIs) were used to compare the categorical variables of en bloc resection rate, recurrence, and AEs. Standardized mean difference (SMD) was used to analyze the continuous variable of procedure time. Random-effects models were used given our a priori assumptions about the heterogeneity of the source studies. Similar analysis was conducted for a subgroup of three studies that investigated large colorectal lesions (≥ 15 mm) [10, 11, 16].

We used Forest plots to present individual study contributions to pooled estimates. I^2 measure quantified heterogeneity. For the main outcome of en bloc resection we also used the rfdist command to estimate the 95% prediction interval which approximates the predictive interval of a future clinical trial. Given our meta-analysis had fewer than 10 studies included, funnel plots were not performed. A jackknife or leave-one-out analysis was used to determine if any individual study was overly influential. All quantitative analysis was performed using the statistical program STATA 14.2 (College Station, Texas, United States).

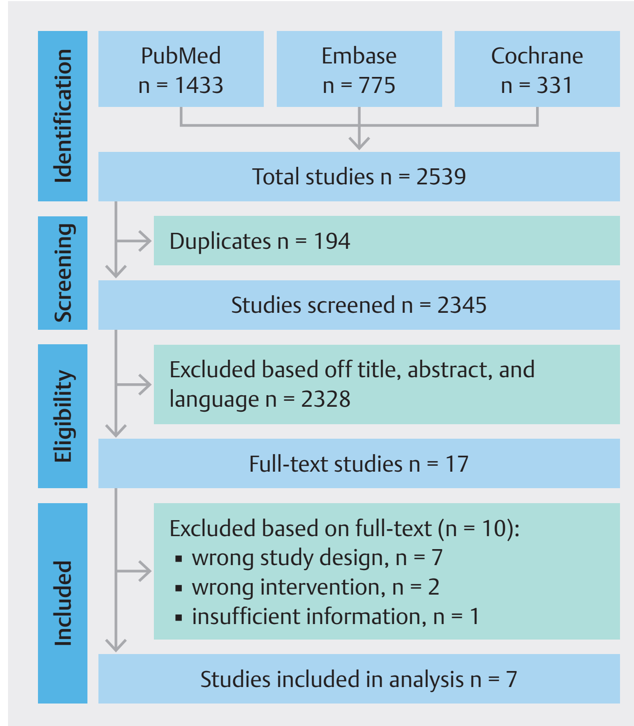
Results

Search results

The initial literature search revealed 2539 publications. After removing duplicates and studies excluded for irrelevance, 17 studies remained for full-text review. Of these, seven studies met inclusion criteria (▶**Fig. 1**). All seven studies were RCTs that were published as either full-text articles or abstracts comparing underwater EMR versus conventional EMR for resection of colorectal lesions.

Study characteristics

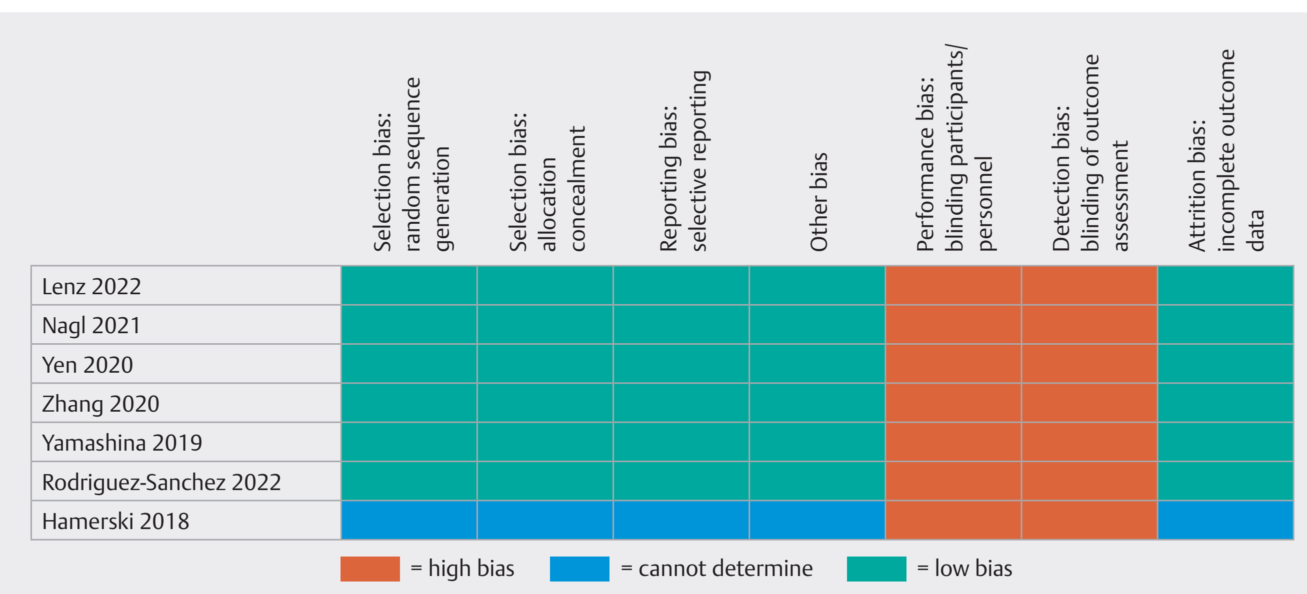
Baseline characteristics of each study are described in ▶**Table 1** while characteristics of the colorectal lesions and definitions are detailed in ▶**Table 2**. Briefly, the overall number of polyps included in the analysis across the seven studies was 1581, with 809 polyps undergoing UEMR and 772 undergoing CEMR. All seven studies were RCTs: two of them single center [11, 13] and five of them multicenter [10, 12, 14, 15, 16]. The trials took place in the United States [10, 13], Brazil [15], Germany [11], China [22], Japan [12], and Spain [16]. A recurrence interval was specified in five studies [10, 11, 13, 15, 16], a majority of which were between 3 to 6 months following endoscopy. Three studies only included larger polyps of either ≥ 15 mm [10] or ≥ 20 mm [11, 16] in size.



▶**Fig. 1** Flowchart of the study selection process (PRISMA diagram) [18].

Bias and quality of evidence

A Cochrane risk of bias assessment for the studies is illustrated in ▶**Fig. 2**. Given the nature of the intervention, there was an inability to blind endoscopists, thus a high performance bias and detection bias in all seven studies. Most of the trials [11, 12, 13, 14, 16] used a 1:1 randomization strategy or permuted



▶**Fig. 2** Cochrane risk of bias assessment.

▶ **Table 1** Characteristics of included studies.

Author	Year	Country	Study type	Number of patients	Number of polyps		Primary outcome
					UEMR	CEMR	
Lenz [15]	2022	Brazil	RCT, dual center	105	61	59	Recurrence 6 months after resection
Nagl [11]	2021	Germany	RCT, single center	147	81	76	Recurrence 6 months after resection
Yen [13]	2020	United States	RCT, single center	255	248	214	Incomplete resection rate (from resection margins)
Zhang [14]	2020	China	RCT, multicenter	130	71	71	Complete and en bloc resection rate
Yamashina [12]	2019	Japan	RCT, multicenter	210	108	102	R0 resection rate
Rodriguez Sanchez [6]	2022	Spain	RCT, multicenter	298	149	162	Recurrence rate
Hamerski [10] (abstract)	2018	United States	RCT, multicenter	178	91	88	Curative resection rate

RCT, randomized controlled trial; UEMR, underwater endoscopic mucosal resection; CEMR, conventional endoscopic mucosal resection.

block technique [15], minimizing selection bias. These studies also described outcomes of interest with complete data reported in the results, which minimized risk of attrition bias. One study [10] was published as an abstract, and thus, insufficient information to assess most of the domains.

The starting quality of evidence for each outcome in our GRADE evaluation was high because all of the studies were RCTs (Supplementary Table 2). However, each outcome was downgraded for serious risk of bias given the inability to blind endoscopists and outcome assessors. The outcomes of en bloc resection, recurrence, and procedure time were further downgraded for inconsistency (high I^2). AEs were further downgraded for imprecision given low optimal information size (Supplementary Table 3). The overall final quality of evidence for each outcome was low.

Primary outcome

All seven trials reported en bloc resection. UEMR was associated with significantly increased rates of en bloc resection (RR 1.18 [1.03, 1.35]; I^2 = 76.6%), ▶ **Fig. 3a**. Similar results were noted when stratifying by a subgroup of studies that investigated larger polyps [10, 11, 16], with UEMR demonstrating increased rates of en bloc resection compared to CEMR (RR 1.78 [1.20, 2.63]; I^2 = 50.9%), ▶ **Fig. 4a**. The estimated 95% prediction interval for RR of en bloc resection was 0.8 to 1.74 (Supplementary Fig. 1).

Secondary outcomes

Four studies reported recurrence rates [10, 11, 15, 16] with no statistically significant difference in UEMR versus CEMR (RR 0.52 [0.24–1.11]; I^2 = 50.1%), ▶ **Fig. 3b**. Similar results of recurrence were found in the subgroup analysis of large polyps as well, ▶ **Fig. 4b**. There were also no statistically significant differences in AEs between the UEMR and CEMR groups (RR 0.64 [0.29–1.45]; I^2 < 0.1%), ▶ **Fig. 3c**. Of the five [11, 12, 13, 14, 16] studies that provided data on procedure times, there were no statistically significant differences in mean procedure times (SMD −1.17 [−2.68–0.33]; I^2 = 99.2%), ▶ **Fig. 3d**. UEMR reduced procedure time for the removal of large polyps compared to conventional approaches (SMD −0.43 [−0.73 to −0.13]; I^2 = 56.3%), ▶ **Fig. 4c**. Pooled rates of each outcome are provided in Supplementary Table 4.

Discussion

Our systematic review and meta-analysis (SRMA) compared the efficacy and safety of UEMR versus CEMR for removal of colorectal lesions in more than 1000 patients. Our results suggest UEMR is superior to CEMR for en bloc resection of colorectal polyps. These findings were even more pronounced in the subgroup analysis of large (≥ 15 mm) polyps where UEMR also reduced procedure time. These gains were achieved without an increase in AEs.

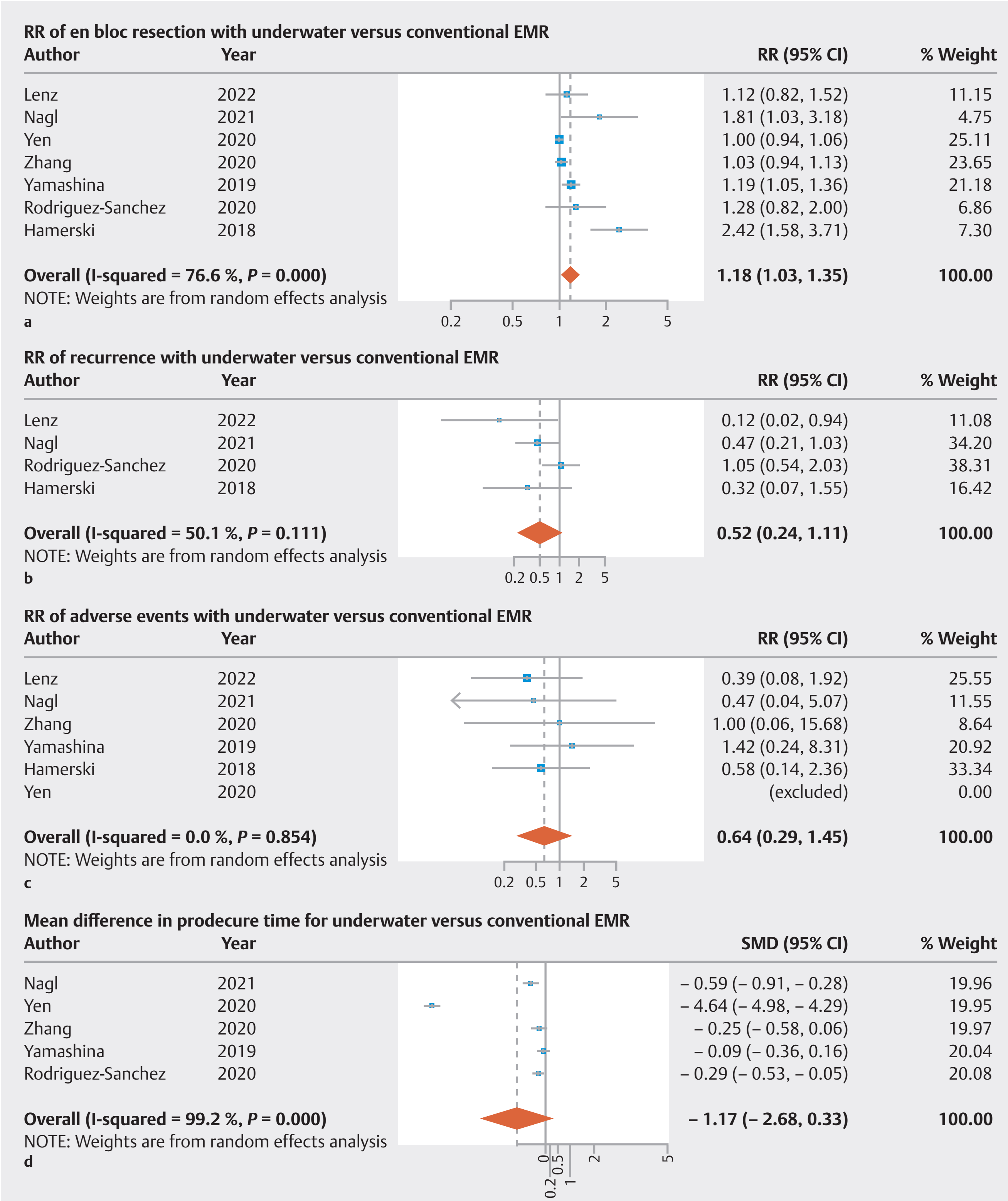
Excessive air insufflation used to visualize the colon lumen may compress the wall layers together, making capture of mucosa more difficult and theoretically increase the risk of deep injury with resection due to the fact that the muscularis propria becomes thinner on full air insufflation. CEMR involves submucosal injection to separate the mucosa from the muscularis propria with the aim to improve safety; nevertheless, this may make lesions difficult to grasp and resect en bloc. As a result, piecemeal resection may be required and the risk of recurrence increased [6, 23, 24]. Binmoeller et al. described the UEMR technique in 2012 as a novel endoscopic method to reduce colonic wall tension when resecting colonic lesions that allows the layers to separate and maintains the natural shape (involutions) of the mucosa [9]. This reduces the need for submucosal injection and favors the more precise and complete (en bloc) resec-

▶ **Table 2** Lesion characteristics and definitions.

Author	Inclusion criteria	Exclusion criteria	Polyp criteria	Recurrence interval	Recurrence definition	Adverse events definition
Lenz [15]	≥ 18 years old	Pregnancy, familial polyposis, inflammatory bowel disease, severe organ failure	Naïve non-pedunculated (sessile or flat) colorectal lesions 10–40 mm in size, without involving dentate line, ileocecal valve or appendiceal orifice	6 months	Histologically-proven adenomas in control colonoscopy at the resection site	Bleeding, hemorrhage, perforation
Nagl [11]	≥ 18 years old	Pregnancy, American Society of Anesthesiologists class III or higher, familial polyposis syndrome, inflammatory bowel disease	Flat or sessile colorectal lesions, 20–40 mm in size without deep submucosal invasion and excluding residual lesions from prior resection attempts	6 months	Macroscopic evaluation and histologic assessment of the resection scar	Bleeding, hemorrhage, perforation requiring transfusion or endoscopic/ surgical intervention
Yen [13]	≥ 18 years old	Antithrombotic therapy (except aspirin), uncorrected coagulopathy or thrombocytopenia, American Society of Anesthesiologist classification ≥ 4, hospitalization	> 5 mm in size without evidence of deep submucosal invasion	3–6 months	Presence of any adenomatous or serrated pathology in the biopsy specimen	Bleeding, hemorrhage, perforation requiring transfusion or endoscopic/ surgical intervention
Zhang [14]	18–75 years old	Pregnant, inflammatory bowel disease, familial polyposis, severe organ failure, anticoagulant or antiplatelet therapy	Non-pedunculated colorectal polyp 4–9 mm in size without evidence of deep submucosal invasion	–	–	Bleeding, perforation
Yamashina [12]	≥ 20 years old	Inflammatory bowel disease, familial polyposis, coagulopathy, severe organ failure, electrolyte abnormalities	Non-pedunculated colorectal mucosal lesions (adenoma, intramucosal adenocarcinoma, or sessile serrated adenoma/polyp) that were 10–20 mm in diameter	–	–	Bleeding, perforation, hyponatremia
Rodriguez Sanchez [16]	≥ 18 years old	Pregnant, inflammatory bowel disease, lesions with submucosal invasion	Complex colorectal lesions > 2 cm in size	6 months	Presence of polyp tissue at site of original lesion on surveillance colonoscopy	Bleeding, hemorrhage, perforation
Hamerski [10] (abstract)	–	–	Colorectal laterally spreading tumors ≥ 15 mm, excluding involvement of the appendiceal orifice, ileocecal valve or dentate line or lesions concerning for invasive malignancy	3–6 months	Frequency of residual neoplasia documented on surveillance colonoscopy	Bleeding, perforation, post-polypectomy syndrome

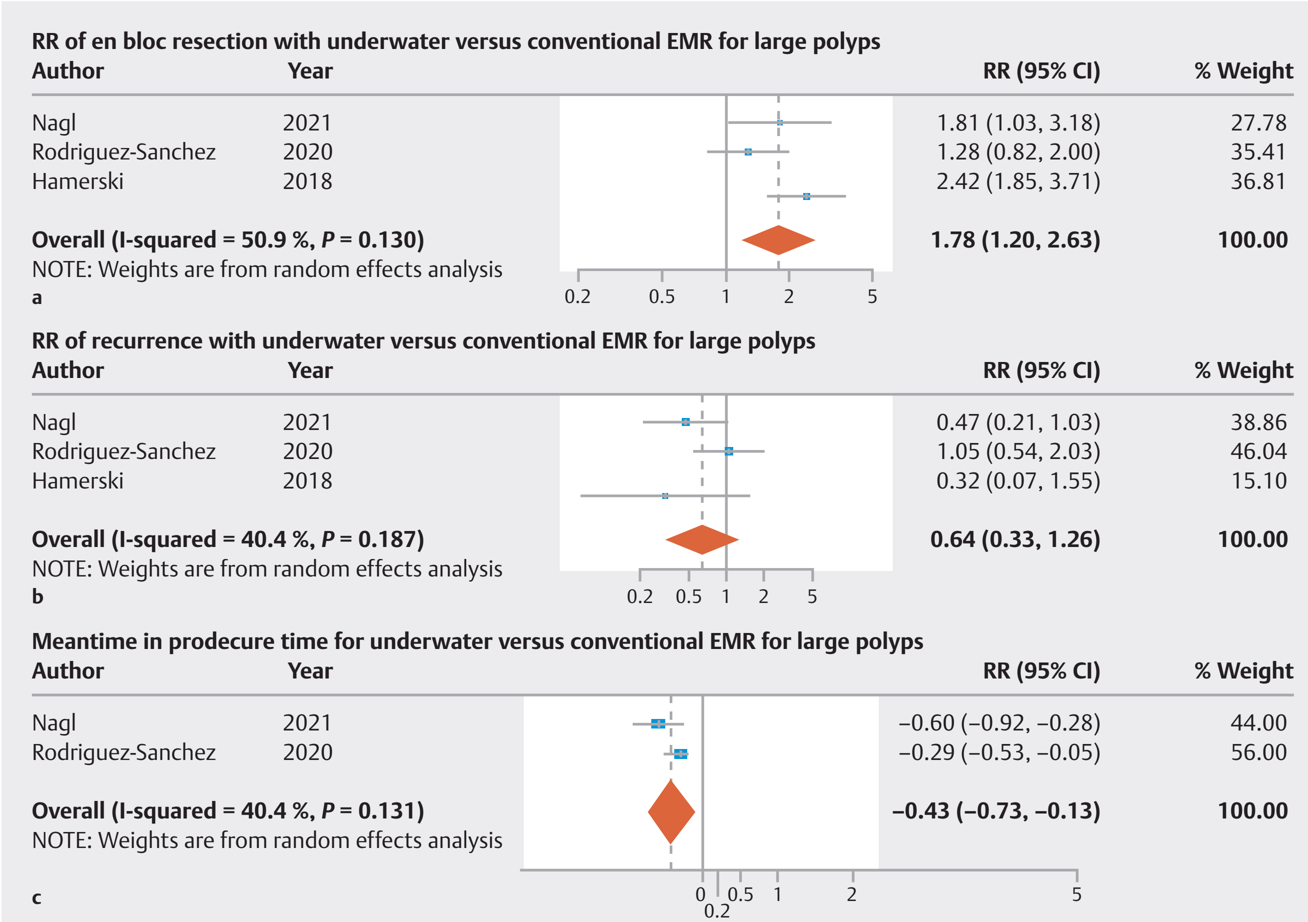
tion of polyps [6, 9]. Following the introduction of this technique, several initial RCTs have aimed to compare the efficacy and safety UEMR versus CEMR. Two trials [11, 12] demonstrated significantly increased rates of en bloc resection in the UEMR groups while other trials [13, 14, 15] showed no statistically significant differences. This SRMA of RCTs harmonized the best evidence on the subject and indicates that underwater EMR improves en bloc resection.

In addition to maintenance of wall layers and helpful mucosal features, water appears to have a magnifying effect on colonic mucosa, which may enhance the endoscopist's ability to delineate between normal and adenomatous tissue to identify borders for resection. Furthermore, continuous infusion of wa-



▶ **Fig. 3** Forest plots of randomized controlled trials investigating underwater EMR versus conventional EMR for the following outcomes. **a** En bloc resection. **b** Recurrence. **c** Adverse events. d Procedure time.

ter helps remove blood and other obscuring debris away from the targeted area of interest, which improves visibility [9]. These endoscopic advantages during UEMR forgo the need for piecemeal resection, which is often used in CEMR for larger lesions, and may contribute to the reduced rates of recurrence described.



► **Fig. 4** Forest plots of randomized controlled trials investigating underwater EMR versus conventional EMR in large (≥ 15 mm) colorectal lesions for the following outcomes. **a** En bloc resection. **b** Recurrence. **c** Procedure time.

There was no statistically significant difference in AEs between UEMR and CEMR in our study. In contrast to the CEMR technique, UEMR may be performed safely without a submucosal injection. Injection poses a small risk of bleeding, dysplastic seeding, and other mucosal injury [6]. Nevertheless, this SRMA did not reveal an impact of approach on overall safety.

With regard to effects on procedure time, studies have shown mixed results. A few RCTs [10, 11, 13, 16] suggested decreased procedure times with UEMR compared to CEMR while others did not [12, 14]. Theoretically, procedure time could be shortened during UEMR because submucosal injection is not needed, which reduces the number of steps prior to actual resection. We found that UEMR reduced procedure time for large polyp resection; however, only two trials provided sufficient information for this subgroup analysis [11, 16]. There was substantial heterogeneity for procedure time, which may be partially explained by variations in endoscopist expertise and differences in reporting of total procedure time versus resection time. Regardless, UEMR does not appear to increase procedure duration.

Prior reviews on this topic [23, 25] have included variable study types including RCTs, prospective cohorts, and retrospective cohorts. Inclusion of various study designs may limit interpretability of results and may account for high heterogeneity seen in these reviews (i. e. I^2 = 97% for Li et al). A strength of our design is restriction to RCTs and utilization of very recent work to answer relevant questions about the role of UEMR versus conventional EMR. In addition, we performed subgroup analysis of trials investigating large polyps to evaluate the efficacy of UEMR for these more difficult lesions. A limitation of meta-analysis is that it can harmonize secondary outcomes from source studies and compound the problem of multiple testing. While adjustments for multiplicity are not routinely used in meta-analysis, we attempted to mitigate this problem by defining our outcomes a priori in PROSPERO prior to our literature search and review. This strategy and inclusion of populations from multiple continents increases our study's generalizability.

Nevertheless, there are several limitations to consider. While all seven trials investigated our primary outcome of en bloc resection, inclusion of each trial in our secondary outcomes was limited due to lack of reporting on the outcome or lack of measurement of dispersion (i. e. standard deviation or interquartile ranges) for analytic purposes. For example, although Hamerski et al. [10] reported shorter resection duration in their abstract for the UEMR cohort, given the lack of time range or other indication of time dispersion, we were unable to include their study in our final analysis for this outcome. There is also a critical susceptibility to performance and detection bias as it is difficult to blind the endoscopists from the intervention they are performing. Furthermore, from our GRADE evaluation, the overall final quality of evidence for each outcome was low, diminishing our ability to draw definitive conclusions from our findings. In addition, we did find large heterogeneity for our primary outcome (I^2 = 76.6%). Potential factors include a range of expertise ([12, 14] and relative polyp size.

Conclusions

In conclusion, in our comprehensive meta-analysis of RCTs, we demonstrated that underwater EMR significantly increases the en bloc resection rate for colorectal lesions, and these results may be more pronounced in larger lesions. There were no significant differences in AEs, recurrence, and procedure time, suggesting that UEMR is a safe and effective technique for resection of colorectal polyps and should be considered as an alternative approach to CEMR, especially for larger lesions.

Conflict of Interest

The authors declare that they have no conflict of interest.

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