Effectiveness and safety of the different endoscopic resection methods for 10- to 20-mm nonpedunculated colorectal polyps: A systematic review and pooled analysis

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INTRODUCTION

Colorectal cancer (CRC) evolves from colorectal polyps and other lesions through different molecular pathways.\(^1\) Due to the development and promotion of endoscopic techniques as well as increasing awareness of endoscopic examination for the prevention and treatment of CRC,
polyps <10 mm in size account for 90% of all colorectal polyps detected. However, diminutive and small polyps are rarely highly dysplastic, while large polyps, especially nonpedunculated polyps, tend to be high-grade neoplasias and have a high risk of being cancerous. Therefore, the removal of these lesions is of great significance for preventing CRC and reducing the related mortality.

At present, for the endoscopic resection of lesions without signs of submucosal invasion, cold snare polypectomy (CSP) is recommended for lesions smaller than 10 mm, and hot snare polypectomy (HSP) is suggested for pedunculated lesions larger than 10 mm. Furthermore, endoscopic mucosal resection (EMR) is recommended for nonpedunculated lesions larger than 20 mm according to the European Society of Gastrointestinal Endoscopy clinical guidelines and by the US Multi-Society Task Force. However, there is no high-quality evidence for the optimal resection of 10- to 20-mm (intermediate-size) nonpedunculated lesions or specific recommendations for such resection in recent guidelines. It remains unclear whether hot or cold resection is preferable, and if submucosal injection ought to be performed before resection. The main methods in use include EMR, cold EMR, underwater EMR (UEMR), CSP and HSP.

Ever since colonoscopy was introduced to treat colorectal diseases, many clinical studies on the resection of colorectal lesions have been published, but few studies have focused mainly on 10- to 20-mm polyps. Moreover, the sample size of some studies is not sufficient, and data on the effectiveness and safety of different resection methods for intermediate-size polyps have never been analysed or systematically reviewed.

Therefore, we performed this study to compare the results of different resection methods, with a focus on their effectiveness and safety outcomes.

**MATERIALS AND METHODS**

We performed this study based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations, and the study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/prospero/) in July (registration number: CRD42020180152).

**Inclusion and exclusion criteria**

We formulated the literature eligibility criteria according to PICO principles: P: patients who had undergone colonoscopy and had 10- to 20-mm nonpedunculated polyps; I and C: patients who had undergone colonoscopy via one of various common resection methods; and O: effectiveness (i.e. R0 resection rate, en bloc resection rate) and (or) safety (i.e. intraprocedural bleeding rate, delayed bleeding rate, perforation rate, and postpolypectomy syndrome rate). Retrospective and prospective studies including valid data were considered. Case reports and reviews were excluded.

**Search strategy and selection process**

We comprehensively searched the literature using PubMed, EMBASE, and the Cochrane Library (up to 15 April 2020) for studies related to the endoscopic treatment of nonpedunculated polyps. Electronic searches were conducted by two investigators (XY and ZZ) independently; the EMBASE search strategy is presented in Supplementary Table 1. After the removal of duplicate literature using an embedded Endnote (Endnote X9) function, the titles and abstracts were first screened according to the eligibility criteria, and then the full texts of the preliminarily screened articles were read to determine their further eligibility.

**Data extraction**

The eligible data were extracted by the two reviewers (JX and YZ) independently and recorded in a standard format in a Microsoft Excel spreadsheet. The extracted data included the type of study, name of the first author, year of publication, country of origin, method of lesion resection, number of complete resections, number of en bloc resections, number of cases of intraprocedural bleeding, number of cases of delayed bleeding, number of occurrences of perforation, number of occurrences of postpolypectomy syndrome, management of adverse events, duration of follow-up, and number of recurrences. We also extracted the number of centres, number of lesions, type and size of lesions, type of endoscope, type of snare, type and energy of electrocoagulation generator device, and number and experience of endoscopic operators. Any disagreement was settled by discussion with the arbitrator (LX).

**Outcome and quality assessment**

The primary outcomes were the R0 resection rate and en bloc resection rate. R0 resection was defined as complete resection with a histologically confirmed negative resection margin and no residual neoplastic tissue at any point on the horizontal or vertical cut margins, and en bloc resection was defined as endoscopically assessed removal of the lesion in one piece. Secondary outcomes were the rate of procedure-related adverse events and the recurrence rate after the procedure. Procedure-related adverse reactions were divided into intraprocedural bleeding, delayed bleeding,
perforation, and postpolypectomy syndrome (abdominal pain, fever, leukocytosis, and peritoneal inflammation in the absence of frank perforation that occurs after colonoscopic polypectomy with electrocoagulation).[9] Intraprocedural bleeding was defined as requiring endoscopy therapy after ineffective lavage and snare-tip soft coagulation during colonoscopy, and delayed bleeding was defined as requiring blood transfusion and/or the need for surgery, an interventional radiology procedure or repeat colonoscopy within 30 days. Perforation was defined as requiring intervention, including endoscopic closure or surgery.

The quality of the included studies was assessed by two reviewers (YZ and HL) using the modified Newcastle-Ottawa scale (NOS) for case control and cohort studies, which ranges from 0 (low quality) to 5 (high quality). The representativeness of the cohort, assignment of exposure, outcome that was not present at the start of the study, assignment of outcome and adequate follow-up were evaluated for each study.

Statistical analysis
For each outcome, the effect of interest was measured by pooled proportions (%) with 95% confidence intervals (CIs), and heterogeneity among studies was assessed using Cochran’s Q with the I² statistic. The pooled proportions were converted depending on the dependent variables modelled on the logit scale (R0 resection rate and en bloc resection rate) or double-arcsine scale (adverse event rate) and were pooled by a random effects model for a more conservative estimate if substantial heterogeneity (defined as I² statistic >50% and \( P < 0.10 \)) was observed; otherwise, a fixed effect model was used. We also calculated the adverse event rate and recurrence rate in the form of frequencies over the total number of included patients. In addition, meta-regression analysis of properties, including temporal-spatial properties, such as country of study, and methodology-related properties, such as study sample size and endoscopic techniques, was performed on the main outcomes, and prespecified subgroup analysis was carried out according to variables that may have affected the results, such as hot or cold resection.

All meta-analytic computations were completed using R (version 3.6.2) and RStudio (RStudio Desktop version 1.1.463) statistical software with the meta and metafor packages.

RESULTS

Study characteristics and quality
Overall, 2397 articles were retrieved, and 36 studies were included in the final analysis [details in Figure 1], comprising data on 3212 polyps in total. Of the 36 studies [Table 1 and supplementary Table 2], 17 were retrospective, and the others were prospective. The number of studies of different origins were as follows: 9, United States; 8, Japan; 3, Australia; 3, China; 3, Greece; 2, Italy; and 1 each of Austria, Belgium, Brazil, Germany, Korea, Portugal, Spain and Sweden.

The quality scores assessed by modified NOS ranged from 4 to 5 (with a score of 4 accounting for 40.74% of studies, and a score of 5 accounting for 59.26%), excluding nine random controlled studies [Supplementary Table 3]. The heterogeneity was noted to be moderate–strong for the primary outcomes, as the majority of the studies were of one single group.

Different resection methods
Among the 36 articles with analysable data that we included, regardless of the type of resection method, 17 studies provided information on the R0 resection rate (representing 1201 lesions), and 28 studies provided information on the en bloc resection rate (representing 1391 lesions) [Figures 2 and 3]. The results

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Figure 1: Flowchart of the study selection process
of the multivariate meta-regression analysis of the main outcomes are presented in Table 2. The effect of the variable of study design on the R0 resection rate was significant (prospective study vs retrospective study; \( P = 0.03 \)), while the heterogeneity remained significant. Follow-up information was available for 329 lesions, and the median duration of follow-up was 15 months (range: 2–42). The pooled proportions of adverse events and recurrence were low, and the frequency rates are shown in Figure 4.

### Endoscopic mucosal resection (EMR)

A total of 21 studies employed EMR, including eight studies with analyzable data (381 lesions) on the R0 resection rate and 16 studies with analyzable data (814 lesions) on the en bloc resection rate.8,10–29 The pooled proportions for R0 resection rate and en bloc resection rate were 87% (95% CI 0.75–0.93, \( I^2 = 83% \)) and 88% (95% CI 0.79–0.93, \( I^2 = 89% \)), respectively.

The intraprocedural bleeding rate was 5.18% (19/367; pooled proportion 3%; 95% CI 0–0.08), ranking the highest among the intraprocedural bleeding rates of the conventional polypectomy methods. Other adverse events, such as delayed bleeding and postpolypectomy syndrome, had the lowest rates under EMR, but two perforations were reported. One was related to colonoscopy rather than EMR, and the other was caused by muscular involvement in snaring because of excessive suction.

### Underwater endoscopic mucosal resection (UEMR)

Nine studies (of which only four provided eligible data on R0 resection rate and nine presented data on

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**Table 1: Study characteristics**

| Author, year | Country | Lesions, n | Size and type of lesions* | Resection technique(s) | Quality** |
|--------------|---------|------------|---------------------------|------------------------|----------|
| Retrospective study |
| Yokota T,[39] 1994 | Japan | 40 | 11-20-mm nonpedunculated† | EMR (NS+E) | 4 |
| Su MY,[35] 2005 | China | 58 | 11-20-mm nonpolypoid‖ | EMR (NS) | 5 |
| Huang T,[31] 2009 | China | 30 | 10-19-mm LST | EMR (NS) | 5 |
| Serrano M,[32] 2012 | Portugal | 112 | 10-20-mm flat and sessile | EMR (NS/G+E+indigo) | 5 |
| Choksi N,[33] 2015 | USA | 8 | 10-20-mm adenoma | Cold EMR (NS+E+methylene blue) | 5 |
| Kashani A,[34] 2015†† | USA | 22 | 10-20-mm nonpedunculated | Cap-EMR | 4 |
| Muniraj T,[36] 2015 | USA | 15 | 10-20-mm sessile | Cold EMR (NS+indigo) | 5 |
| Hirose R,[37] 2017 | Japan | 72 | 10-14-mm nonpolypoid | CSP | 5 |
| Piraka C,[38] 2017 | USA | 35 | 10-20-mm nonpedunculated | Cap-cold EMR (NS+E+indigo) | 5 |
| Schenk R,[39] 2017 | USA | 34 | 15-20-mm nonpedunculated | EMR (NS) vs cap-UEMR | 5 |
| Cadon S,[34] 2018 | Italy | 121 | 10-19-mm flat and sessile | EMR vs UEMR | 5 |
| Chien HC,[40] 2019 | China | 148 | 10-19-mm flat and sessile | EMR vs UEMR | 4 |
| Gessl I,[41] 2019 | Austria | 432 | 11-20-mm sessile | CSP vs HSP | 4 |
| Kumar V,[42] 2019 | USA | 150 | 11-19-mm flat and sessile | EMR | 5 |
| Murakami T,[43] 2019 | Japan | 74 | 10-14-mm SSA/P | CSP | 5 |
| Van Overbeke L,[44] 2019 | Belgium | 63 | 11-19-mm flat and sessile | CSP/cold EMR | 5 |
| Ket SN,[45] 2020 | Australia | 604 | 10-20-mm flat and sessile | HSP/EMR vs CSP/cold EMR | 4 |
| Prospective study |
| Yosikane H,[46] 1999 | Japan | 7 | 10-20-mm LST | Cap-EMR (NS+E) | 5 |
| Bergmann U,[47] 2003 | Germany | 32 | 11-20-mm flat and sessile | Cap-EMR (NS+E) | 5 |
| Uraoka T,[48] 2005 | Japan | 140 | 10-19-mm flat and sessile | EMR (NS+G+fructose) vs EMR (NS) | 5 |
| Katsinelos P,[49] 2006 | Greece | 11 | 10-19-mm LST | EMR (D0,E) | 5 |
| Katsinelos P,[50] 2008 | Greece | 40 | 10-19-mm sessile | EMR (D0,E) vs EMR (NS+E) | RCT |
| Yoshida N,[51] 2012 | Japan | 46 | 11-20-mm nonpedunculated | EMR (0.13%H2+indigo) vs EMR (NS+indigo) | RCT |
| Pohl H,[52] 2013 | USA | 110 | 15-20-mm nonpedunculated | HSP | 4 |
| La Nauze R,[53] 2014 ††† | Australia | 129 | 10-20-mm sessile | CSP vs HSP | RCT |
| Uedo N,[54] 2015 | Japan | 10 | 15-20-mm lla | Cap-UEMR | 4 |
| Woodward T,[55] 2015 | USA | 11 | 16-20-mm flat and sessile | EMR (HPMC+NS+E+indigo) | RCT |
| Amato A,[56] 2016 | Italy | 14 | 10-20-mm flat and sessile | UEMR | 4 |
| Horuchi A,[57] 2016 | Japan | 102 | 10-19-mm flat and sessile | Cap-EMR (NS+E) vs cap-HSP | RCT |
| Tuttici NJ,[58] 2017 | Australia | 89 | 10-20-mm SSA/P | Cap-cold EMR (4%G+methyleneblue+E) | 5 |
| Chaves DM,[59] 2018 | Brazil | 9 | 10-20-mm LST | UEMR | 4 |
| Han SJ,[60] 2018 | Korea | 51 | 10-20-mm flat and sessile | EMR (NS+E) vs EMR (NS+E+indigo) | RCT |
| Papastergiou V,[61] 2019*** | Greece | 34 | 10-20-mm SSA/P | Cold EMR (methylene blue+NS) | 4 |
| Rodriguez‐Sánchez J,[62] 2019 | Spain | 69 | 15-20-mm nonpedunculated | EMR (NS+indigo) vs UEMR | RCT |
| Yamashina N,[63] 2019 | Japan | 210 | 10-20-mm nonpedunculated | EMR (NS) vs UEMR | RCT |
| Yan AW,[64] 2020 | USA | 86 | 10-19-mm LST | Cap-UEMR vs cap-EMR (HS+E+indigo) | RCT |

CSP: cold snare polypectomy; D0, 50% dextrose; E, epinephrine; EMR, endoscopic mucosal resection; G, glucose; HA, hyaluronic acid; HPMC, hydroxypropyl methylcellulose; HSP, hot snare polypectomy; LST, lateral spreading tumour; NS, normal saline; SSA/P, sessile serrated adenoma/ polyp; UEMR, underwater endoscopic mucosal resection. *type of lesion according to the Paris classification. **quality evaluation using modified Newcastle-Ottawa scale. ***Only the abstract is available. †Nonpedunculated refers to all lesions except those classified as I., ‖Nonpolypoid includes lesions of types IIa, IIb, IIc, and II:**
en bloc resection rate) analysed the effectiveness of UEMR.\textsuperscript{[8,23,24,26,28-32]} The pooled proportions were quite encouraging with this method (pooled proportion for R0 resection rate 90%, 95% CI 0.74–0.97, $I^2 = 61$%; pooled proportion for en bloc resection rate 82%, 95% CI 0.71–0.90, $I^2 = 77$%).

The rate of adverse events resembled that under EMR, with two cases of delayed bleeding reported in 271 lesions, although without a need for surgery. The recurrence rate (6.67%; 1/15) was only available from one study of 15 lesions.

**Cold EMR**

Five studies involving 181 lesions used cold EMR.\textsuperscript{[33-37]} Only one of these studies provided analysable data (89 lesions) on the R0 resection rate, and among all of the resection rates, cold EMR yielded the highest pooled proportion (proportion 98%; 95% CI 0.91–0.99). There were no available data on the en bloc resection rate.

Only one in 124 lesions (0.81%) had intraprocedural bleeding, and one in 58 (1.72%) lesions had abdominal pain. No perforations were observed in 92 lesions.
Cold snare polypectomy (CSP)

Only one eligible study (55 lesions) among the four studies (222 lesions) using CSP provided data on the R0 resection rate, but the pooled proportion was only 82% (95% CI 0.69–0.90). The en bloc resection rate was reported in two studies involving 127 lesions, with values of 0.53 and 0.93, and the pooled proportion was 80% (95% CI 0.39–0.96, $I^2 = 91\%$).

Seldom, no adverse events were noted, representing approximately 200 lesions. One patient using warfarin experienced delayed bleeding 4 days after CSP, but the bleeding was controlled with subsequent endoscopic clipping and did not require blood transfusion. Among the conventional polypectomy methods, CSP yielded the lowest recurrence rate, at 5.41% (4/74), according to the available data.

Hot snare polypectomy (HSP)

Four studies employed HSP: three with analysable data (538 lesions) on the R0 resection rate and one (76 lesions) with analysable data on the en bloc resection rate. The R0 resection rate pooled proportion was 82% (95% CI 0.78–0.85, $I^2 = 0\%$), similar to that under CSP, and among

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**Figure 3:** Forest plot reporting the en bloc resection rates of different types of resection methods. (95% CI, 95% confidence interval; CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; UEMR, underwater endoscopic mucosal resection)

| Study       | Events Total | Proportion | 95%-CI |
|-------------|--------------|------------|--------|
| **EMR**     |              |            |        |
| Yoshikane H, 1999 | 7            | 7          | 1.00 [0.59; 1.00] |
| Bergmann U, 2003  | 30           | 32         | 0.94 [0.79; 0.99] |
| Su MY, 2005       | 58           | 58         | 1.00 [0.94; 1.00] |
| Uraoka T, 2005    | 107          | 140        | 0.76 [0.69; 0.83] |
| Katsinelos P, 2006 | 11           | 11         | 1.00 [0.72; 1.00] |
| Katsinelos P, 2008 | 38           | 40         | 0.95 [0.83; 0.99] |
| Huang Y, 2009     | 28           | 30         | 0.93 [0.78; 0.99] |
| Serrano M, 2012   | 76           | 112        | 0.68 [0.58; 0.76] |
| Yoshida N, 2012   | 43           | 46         | 0.93 [0.82; 0.99] |
| Woodward T, 2015  | 8            | 11         | 0.73 [0.39; 0.94] |
| Schenck RJ, 2017  | 19           | 19         | 0.47 [0.24; 0.71] |
| Cadoni S, 2018    | 46           | 58         | 0.79 [0.67; 0.99] |
| Chien HC, 2019    | 71           | 74         | 0.96 [0.88; 0.99] |
| Rodríguez-Sánchez J, 2019 | 32       | 40         | 0.80 [0.64; 0.91] |
| Yamashina T, 2019 | 76           | 102        | 0.75 [0.65; 0.83] |
| Yen AW, 2020      | 25           | 34         | 0.74 [0.56; 0.87] |
| **Random effects model** | 814     |            | 0.88 [0.79; 0.93] |

| **UEMR**        |              |            |        |
| Uedo N, 2015    | 5            | 10         | 0.50 [0.18; 0.81] |
| Amato A, 2016   | 13           | 14         | 0.93 [0.66; 1.00] |
| Schenck RJ, 2017 | 8            | 15         | 0.53 [0.27; 0.79] |
| Cadoni S, 2018  | 51           | 63         | 0.81 [0.69; 0.90] |
| Chaves DM, 2018 | 6            | 9          | 0.67 [0.30; 0.93] |
| Chien HC, 2019  | 72           | 74         | 0.97 [0.91; 1.00] |
| Rodríguez-Sánchez J, 2019 | 23       | 29         | 0.79 [0.60; 0.92] |
| Yamashina T, 2019 | 96           | 108        | 0.89 [0.81; 0.94] |
| Yen AW, 2020    | 44           | 52         | 0.85 [0.72; 0.93] |
| **Random effects model** | 374     |            | 0.82 [0.71; 0.90] |

| **CSP**        |              |            |        |
| La Nauze R, 2014 | 28           | 53         | 0.53 [0.39; 0.67] |
| Murakami T, 2019 | 69           | 74         | 0.93 [0.85; 0.98] |
| **Random effects model** | 127    |            | 0.80 [0.39; 0.96] |

| **HSP**        |              |            |        |
| La Nauze R, 2014 | 52           | 76         | 0.68 [0.57; 0.79] |
| **Random effects model** | 76     |            | 0.68 [0.57; 0.78] |

**Residual heterogeneity:** $I^2 = 87\%$, $τ^2 = 1.0798$, $p < 0.01$

**Residual heterogeneity:** $I^2 = 75\%$, $p < 0.01$

0.2 0.4 0.6 0.8 1
the methods, HSP was associated with the lowest en bloc resection rate (pooled proportion 68%; 95% CI 0.57–0.78).

The incidence rates of adverse events in HSP were 0.47% for intraprocedural bleeding (2/428; pooled proportion 0; 95% CI 0–0.01), 1.57% for delayed bleeding (2/127; pooled proportion 1%; 95% CI 0–0.05), and 0.4% for perforation (2/504; pooled proportion 0; 95% CI 0–0.01). No postpolypectomy syndrome was observed (0/127).

Subgroup analysis according to submucosal uplifting effect

Resection methods with a submucosal uplifting effect included EMR, UEMR and cold EMR. Thirteen studies (608 lesions) reported outcomes for the R0 resection rate, and 23 studies (978 lesions) reported data on the en bloc resection rate. The pooled proportions for complete and en bloc resection were 90% (95% CI 0.81–0.94, $I^2 = 84\%$) and 85% (95% CI 0.79–0.91, $I^2 = 83\%$), respectively.

For resection without a submucosal uplifting effect, four studies representing 593 lesions yielded a pooled R0 resection rate of 82% (95%CI 0.78–0.85, $I^2 = 0\%$); three studies involving 203 lesions yielded a pooled en bloc resection rate of 74% (95%CI 0.47–0.94, $I^2 = 94\%$).

The intraprocedural bleeding rate was slightly higher in the submucosal uplifting effect group (35/826; rate 4.24%; pooled proportion 3%; 95% CI 0.01–0.05, $I^2 = 43\%$) than in the no uplifting effect group (2/629; rate 0.3%; pooled proportion 0%; 95% CI 0–0.01, $I^2 = 0\%$). For delayed bleeding, perforation and postpolypectomy syndrome, the rates in both groups were low [Table 3a].

Subgroup analysis according to electrocautery usage (hot vs cold resection)

Removal methods using electrocautery were considered hot resection methods, such as HSP, EMR and UEMR. Based on the data reported for R0 resection rate by 17 studies (15 studies with 1057 hot resection-treated lesions and 2 studies with 144 cold resection-treated lesions), the pooled proportions were 86% (95% CI 0.80–0.91, $I^2 = 81\%$) and 93% (95% CI 0.72–0.99, $I^2 = 77\%$) for hot resection and cold resection, respectively.

The pooled proportions of adverse events for both groups were similar. However, intraprocedural bleeding was more frequent in the hot resection group, at 3% (95% CI 0.01–0.05, $I^2 = 68\%$), than in the cold resection group (pooled proportion 0%; 95% CI 0–0.01, $I^2 = 0\%$), whereas delayed bleeding exhibited the opposite pattern (pooled proportion for hot resection group 0%, 95% CI 0.01–0.03, $I^2 = 6\%$; pooled proportion for cold resection group 4%; 95% CI 0–0.07, $I^2 = 54\%$) [Table 3b].

**DISCUSSION**

The purpose of this systematic review was to summarize the available evidence and recommend the best method to remove 10- to 20-mm nonpedunculated colorectal polyps. Analysis of all the existing data showed that the resection methods with a submucosal uplifting effect (EMR, UEMR, cold-EMR), especially cold EMR, were safe and more effective than the methods without such an effect for removing 10- to 20-mm nonpedunculated colorectal polyps.

| Variable                        | R0 resection rate | en bloc resection rate |
|---------------------------------|-------------------|------------------------|
| Time period of the study        |                   |                        |
| ≤2015                           |                  | Reference              |
| >2015                           | -0.07             | 0.43                   |
| Origin of study                 |                   |                        |
| Asia                            | Reference         | Reference              |
| Western countries               | 0.12              | 0.10                   |
| Study design                    |                   |                        |
| Prospective                     | Reference         | Reference              |
| Retrospective                   | -0.17             | 0.03†                  |
| Sample size                     |                   |                        |
| <50                             | Reference         | Reference              |
| ≥50                             | 0.13              | 0.18                   |
| Resection with uplifting effect |                   |                        |
| No                              | Reference         | Reference              |
| Yes                             | 0.11              | 0.21                   |
| Resection with electrocautery   |                   |                        |
| No                              | Reference         | Reference              |
| Yes                             | -0.08             | 0.44                   |

Positive meta-regression coefficients express an increased rate compared with the reference group. *statistically significant
When resecting lesions of this size, endoscopists often encounter two major challenges: one is determining whether submucosal uplifting or injection is needed, and the other is in deciding between cold and hot resection. At present, EMR is the preferred method of resection in clinical practice. This method takes advantage of the thermal effect of electricity to produce local hyperthermia, local tissue cell water liquefaction and protein coagulation denaturation after submucosal injection. With this method, a high-frequency current is used to produce hyperthermia of the tissues that come into contact with the snare; the polyp is then cauterized and cut off. Another new technology, UEMR, is similar in principle to EMR but does not involve submucosal injection. Since it was first proposed by Binmoeller et al. in 2012, many studies of UEMR have been conducted. Yamashina et al. recently compared the effectiveness and safety of UEMR and EMR in the resection of intermediate-size colorectal polyps with encouraging results, suggesting that UEMR is a technique worth popularizing. It requires local insufflation with water instead of air in the bowel lumen, and the optical zoom effect can magnify the mucosal structure and indirectly enhance the sensitivity of the examination. In addition, surgery with water perfusion can alleviate pain in patients.

In the subgroup analysis according to submucosal uplifting effect, we found that the R0 resection rate and en bloc resection rate were higher in the submucosal uplifting group (R0 resection rate 90% vs 82%, en bloc resection rate 85% vs 74%). A retrospective study of 10- to 20-mm neoplastic polyp resection with follow-up for 0.5 to 5 years found that incomplete resection, especially a high proportion of piecemeal resections, may be a risk for recurrence and interval CRC. We believe that the submucosal uplifting effect can allow these flatter lesions to be more easily exposed, thus facilitating complete and en bloc resection. Although UEMR is not injected directly into the submucosal layer, the mucosa and submucosa float due to water immersion, while the muscularis external layer remains circumferential such that the two layers are separated from each other, which produces submucosal uplift.

However, the analysis of adverse events showed that there was a larger proportion of adverse rates among the methods involving a submucosal uplifting effect. The incidence rates of intraprocedural bleeding were higher for EMR and UEMR (for EMR, 5.18%; 19/367; pooled proportion 3%; 95% CI 0–0.08; for UEMR, 4.48%; 15/335; pooled proportion 3%; 95% CI 0.01–0.06) than for the other methods. Intraprocedural bleeding leads to the extension of operation time and complicates postoperative management. Considering that this phenomenon may be caused by electrocautery, we conducted a subgroup analysis by electrocautery, i.e. cold vs hot resection. The results revealed that thermal resection was associated with a higher intraprocedural bleeding rate than cold resection, which confirmed our conjecture. Cold resection is generally believed to be typically associated with more intraprocedural bleeding; however, we found that the intraprocedural bleeding rate of hot resection was higher than that of cold resection. Chandrasekar et al. reported similar intraprocedural bleeding rates (2% for hot EMR but 0.7% for cold EMR). We found that technical proficiency may be one of the influencing factors. The operators in the study by Cadoni et al. came from a community hospital, and the study did not mention EMR operation experience. The operator in Chien’s study had only about 200 cases of EMR resection experience. The rate of intraprocedural bleeding was significantly higher in these two studies than in the other studies. Therefore, improving...
the operation skills of doctors may improve the safety of the operation. Takayanagi et al. studied the histology of cold and hot snare resection and demonstrated that hot snare resection may cause deeper damage than cold snare resection and often reaches the muscularis propria. Owing to the electrocautery damage to the larger and greater number of blood vessels in the deep layer of the submucosa, it is believed that hot resection is more likely than cold resection to cause bleeding and even perforation after the procedure. Nevertheless, in analysing the available data, we found that these postpolypectomy adverse events were rare. Among the studies employing hot resection methods, only two cases of delayed bleeding after HSP, two cases of delayed bleeding after UEMR, and one case of delayed perforation after EMR were reported after different durations of follow-up of nearly 2000 cases of lesions. We suspect that the liquid cushion under the mucosa or the broader distance from the muscularis propria may play a buffering role [Figure 5].

Since cold resection was introduced to remove medium-size sessile polyps in 1989, mechanical resection without electrocautery has been advocated and has attracted increasing interest from endoscopists in recent years due to its fewer complications. In addition, the cauterization of lesions leading to poor-quality resected specimens will eventually result in inaccurate histopathological evaluations and mistakes in postoperative treatment and follow-up. In contrast, cold resection ensures a complete specimen, including normal tissue at least 1–2 mm around the lesion. The submucosal uplifting effect makes the resection of the bottom of the lesion more complete. All of these features are helpful for obtaining a higher R0 resection rate. In clinical practice, protrusions are commonly observed after cold polypectomy, which creates concern for residual polyps. Although research on residual tissue is not clear, a study by Tuttici et al. in 2015 revealed that the protrusions were mainly composed of submucosa and muscularis mucosa and did not contain residual polyp tissue or large vascular structures.

The most obvious limitation of this review was the marked statistical heterogeneity in the majority of primary outcomes, which persisted after meta-regression analysis and subgroup analyses. This heterogeneity precluded the robustness of the results and represents a critical issue. Variations in clinical procedures (such as differences in endoscope type, snare type, current, type of submucosal injection solution, use of an assistant instrument and endoscopist experience) and lesion type (sessile, flat, nonpolypoid, lateral spreading tumour, adenoma, sessile serrated adenoma/polyp) among included studies are inevitable. In addition, variable definitions of the R0 resection rate may have contributed to the results, although only histological negativity was considered to define complete resection in this study. Second, the follow-up time to determine lesion recurrence varied among the studies, and available data were limited, which may reflect the fact that management is often not satisfied after lesion resection in real clinical practice. Finally, there were few studies on cold resection techniques, and comparative data for inclusion in this study were lacking. CSP is strongly recommended in existing guidelines for the removal of small polyps but not for that of large polyps, and many endoscopists consider cold resection to have a higher risk of bleeding during operation; therefore, it is rarely used in daily practice for 10- to 20-mm polyps. However, many studies have indicated that cold snare resection may be an effective and safer technique than hot snare resection for >10-mm polyp resection.

CONCLUSIONS

Methods with submucosal uplifting effects seem to show better effectiveness than those without for the complete resection of 10- to 20-mm nonpedunculated polyps. In particular, cold EMR seems to be a promising method that exploits the advantages of cold resection; however, further research is needed.

Financial support and sponsorship

This study was funded by the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (No. 2016KYB257, 2017KY581, and 2018269382).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. East JE, Atkin WS, Bateman AC, Clark SK, Dolwani S, Ket SN, et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut 2017;66:1181-96.
2. Vleugels JL, Hazewinkel Y, Fockens P, Dekker E. Natural history of diminutive and small colorectal polyps: A systematic literature review. Gastrointest Endosc 2017;85:1169-76.e1.
3. Turner KO, Genta RM, Sonnenberg A. lesions of all types exist in colon polyps of all sizes. Am J Gastroenterol 2018;113:303-6.
4. Zhan T, Hahn F, Hielscher T, Bilge A, Grüger J, Weers J, et al.
Multiple behavioral factors are associated with occurrence of large, flat colorectal polyps. Int J Colorectal Dis 2017;32:575-82.

5. Fettisch M, Moss A, Hassan C, Bhardwaj P, Dumonceau JM, Paspatis G, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European society of gastrointestinal endoscopy (ESGE) clinical guideline. Endoscopy 2017;49:270-97.

6. Kaltenbach T, Anderson JC, Burke CA, Dominitz JA, Gupta S, Lieberman D, et al. Endoscopic removal of colorectal lesions—recommendations by the US multi-society task force on colorectal cancer. Gastrointest Endosc 2020;91:486-519.

7. Rex DK, Dekker E. How we resect colorectal polyps <20 mm in size. Gastrointest Endosc 2019:89:449-52.

8. Yamashita T, Uedo N, Akasaka T, Iwasubo T, Nakatani Y, Akamatsu T, et al. Comparison of underwater vs conventional endoscopic mucosal resection of intermediate-size colorectal polyps. Gastroenterology 2019;157:451-61.e2.

9. Yokota T, Sugihara K, Yoshiha S. Endoscopic mucosal resection for colorectal neoplastic lesions. Dis Colon Rectum 1994;37:1108-11.

10. Su M-Y, Hsu C-M, Ho Y-P, Lien J-M, Lin C-J, Chiu C-T, et al. Endoscopic mucosal resection for colorectal non-polypoid neoplasms. Am J Gastroenterol 2005;100:2174-9.

11. Huang Y, Liu S, Gong W, Zhi F, Pan D, Jiang B. Clinicopathologic features and endoscopic mucosal resection of lateral spreading tumors: Experience from China. Int J Colorectal Dis 2009;24:1441-50.

12. Serrano M, Miao de Ferro S, Fidalgo P, Lage P, Chaves P, Dias Pereira A. Endoscopic mucosal resection of superficial colorectal neoplasms: Review of 140 procedures. Acta Medica Portuguesa 2012;25:288-96.

13. Choksi N, Elmunzer BJ, Stidham RW, Shuster D, Piraka C. Cold snare piecemeal resection of colonic and duodenal polyps >/=1 cm. Endosc Int Open 2015;3:E508-13.

14. Kashani A, Lo SK, Jamil LH. CAP-assisted endoscopic mucosal resection is highly effective and safe for non-pedunculated colorectal polyps when performed by an experienced gastroenterologist. Gastrointest Endosc 2015;81:AB295.

15. Muniraj T, Sahakian A, Aslanian HR. Cold snare polypectomy (CSP) for large sessile colonic polyps: A single-center experience. Gastroenterol Res Pract 2015;2015;79:AB437.

16. Hirose R, Yoshiha N, Murakami T, Ogiso K, Inada Y, Dohi O, et al. Histopathological analysis of cold snare polypectomy and its indication for colorectal polyps 10-14 mm in diameter. Dig Endosc 2017;29:594-601.

17. Piraka C, Saeed A, Waljeck AC, Pillai A, Stidham R, Elmunzer BJ. Cold snare polypectomy for non-pedunculated colon polyps greater than 1 cm. Endosc Int Open 2017;5:E184-9.

18. Schenck RJ, Jahann DA, Patrie JT, Stelow EB, Cox DG, Uppal DS, et al. Underwater endoscopic mucosal resection is associated with fewer recurrences and earlier curative resections compared to conventional endoscopic mucosal resection for large colorectal polyps. Surg Endosc 2017;31:4174-83.

19. Cadoni S, Liggi M, Galliutu P, Mura D, Fuccio L, Koo M, et al. Underwater endoscopic colorectal polyp resection: Feasibility in everyday clinical practice. United European Gastroenterol J 2018;6:454-62.

20. Chien H-C, Uedo N, Hsieh P-H. Comparison of underwater and conventional endoscopic mucosal resection for removing sessile colorectal polyps: A propensity-score matched cohort study. Endosc Int Open 2019;7:F1528-36.

21. Gessi I, Waldmann E, Penz D, Majcher B, Dokladanska A, Hinterberger A, et al. Resection rates and safety profile of cold vs hot snare polypectomy in polyps sized 5-10 mm and 11-20 mm. Dig Liver Dis 2019;51:536-41.

22. Kumar V, Broadley H, Rex DK. Safety and efficacy of hot avulsion as an adjunct to EMR (with video). Gastrointest Endosc 2019;89:999-1004.

23. Murakami T, Yoshida N, Yasuda R, Hirose R, Inoue K, Dohi O, et al. Local recurrence and its risk factors after cold snare polypectomy of colorectal polyps. Surg Endosc 2020;34:2918-25.
and long-term outcomes of underwater EMR compared to the traditional procedure in the real clinical practice. Rev Esp Enferm Dig 2019;111:543-9.

43. Yen AW, Leung JW, Wilson MD, Leung FW. Underwater versus conventional endoscopic resection of nondiminutive nonpedunculated colorectal lesions: A prospective randomized controlled trial (with video). Gastrointest Endosc 2020;91:643-54.e2.

44. Reumkens A, Sanduleanu S. Response to Jacobo Dib Jr. Am J Gastroenterol 2017;112:390.

45. Tate DJ, Desomer L, Heitman SJ, Forbes N, Burgess NG, Awadie H, et al. Clinical implications of decision making in colorectal polypectomy: An international survey of Western endoscopists suggests priorities for change. Endosc Int Open 2020;8:E445-55.

46. Binmoeller KF, Weilert F, Shah J, Bhat Y, Kane S. “Underwater” EMR without submucosal injection for large sessile colorectal polyps (with video). Gastrointest Endosc 2012;75:1086-91.

47. Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: Systematic review and meta-analysis. Endoscopy 2014;46:388-402.

48. Adler J, Toy D, Anderson JC, Robertson DJ, Pohl H. Metachronous neoplasias arise in a higher proportion of colon segments from which large polyps were previously removed, and can be segmented to estimate incomplete resection of 10-20 mm colorectal polyps. Clin Gastroenterol Hepatol 2019;17:2277-84.

49. Chandrasekar VT, Aziz M, Patil HK, Sidhu N, Duvvuri A, Dasari C, et al. Efficacy and safety of endoscopic resection of sessile serrated polyps >10 mm. A systematic review and meta-analysis. Br J Surg 2020;107:219-229.

50. Rajendran A, Pannick S, Thomas-Gibson S, Oke S, Anele C, Sevdalis N, et al. Systematic literature review of learning curves for colorectal polypectomy techniques in lower gastrointestinal endoscopy. Colorectal Dis 2020;22:1085-1100.

51. Takayanagi D, Nemoto D, Isohata N, Endo S, Aizawa M, Utano K, et al. Histological comparison of cold versus hot snare resections of the colorectal mucosa. Dis Colon Rectum 2018;61:964-70.

52. Meeroff JC. Removal of colonic medium size sessile polyps without diathermy. Gastrointest Endosc 1989;35:136.

53. Hewett DG. Colonoscopic polypectomy: Current techniques and controversies. Gastroenterol Clin North Am 2013;42:443-58.

54. Tutticci N, Burgess NG, Pellise M, McLeod D, Bourke MJ. Characterization and significance of protrusions in the mucosal defect after cold snare polypectomy. Gastrointest Endosc 2015;82:523-8.

55. Thoguluva Chandrasekar V, Spadaccini M, Aziz M, Maselli R, Hassan S, Fuccio L, et al. Cold snare endoscopic resection of nonpedunculated colorectal polyps larger than 10 mm: A systematic review and pooled-analysis. Gastrointest Endosc 2019;89:929-36 e3.

56. Dumoulin FL, Hildenbrand R. Endoscopic resection techniques for colorectal neoplasia: Current developments. World J Gastroenterol 2019;25:300-7.
**Supplementary Table 1: EMBASE search strategy**

| Query                                                                 | Results |
|-----------------------------------------------------------------------|---------|
| colonic: ab, ti OR colon: ab, ti OR colorectal: ab, ti                | 450782  |
| polyp: ab, ti OR polyps: ab, ti OR lesion: ab, ti OR lesions: ab, ti OR adenomas: ab, ti OR neoplasms: ab, ti | 1369082 |
| nonpedunculated: ab, ti OR 'nonpedunculated':ab, ti OR sessile: ab, ti OR nonpolypoid: ab, ti OR 'nonpolypoid':ab, ti OR excavated: ab, ti OR 'laterally spreading tumors':ab, ti OR 'laterally spreading lesions':ab, ti OR elevated: ab OR flat: ab, ti OR depressed: ab, ti | 905822  |
| #1 AND #2 AND #3                                                     | 8484    |
| polypectomy: ab, ti OR removal: ab, ti OR resection: ab, ti           | 821732  |
| colonoscopy: ab, ti OR coloscopy: ab, ti                             | 52020   |
| #5 AND #6                                                            | 9709    |
| #4 AND #7 NOT review: it                                             | 1182    |
## Supplementary Table 2: Original data of the included studies.

| First author, year | R0 resection | En bloc resection | Intraprocedural bleeding | Delayed bleeding | Perforation | Post-polypectomy syndrome | Follow-up time | recurrence |
|--------------------|--------------|-------------------|--------------------------|-------------------|-------------|---------------------------|----------------|------------|
| **EMR**            |              |                   |                          |                   |             |                           |                |            |
| Yokota T, 1994     | 29           | NA                | NA                       | NA                | NA          | NA                        | NA             |            |
| Yoshikane H, 1999  | NA           | 7                 | NA                       | 1                 | NA          | 13.9±7.2 m                | 0/7            |            |
| Bergmann U, 2003   | 31           | 30                | NA                       | NA                | NA          | 18±6 m                    | 0/30           |            |
| Su MY, 2005        | NA           | 58                | NA                       | 0                 | NA          | 22±8.5 m                  | 0/58           |            |
| Uraoka T, 2005     | NA           | 107               | NA                       | NA                | 0           | NA                        | 339±210 d      | 6/107      |
| Katsinelos P, 2006 | NA           | 11                | NA                       | 0                 | 0           | NA                        | NA             |            |
| Katsinelos P, 2008 | NA           | 38                | NA                       | NA                | NA          | NA                        | NA             |            |
| Huang Y, 2009      | NA           | 28                | NA                       | 0                 | 0           | NA                        | NA             |            |
| Serrano M, 2012    | NA           | 76                | NA                       | 1                 | NA          | 15.9±8.9 m                | 12/74          |            |
| Yoshida N, 2012    | 31           | 43                | NA                       | NA                | 0           | NA                        | NA             |            |
| Kashani A, 2015    | NA           | NA                | 1                        | NA                | 0           | NA                        | NA             |            |
| Woodward T, 2015   | NA           | 8                 | NA                       | NA                | NA          | 129±49.6 d                | 2/7            |            |
| Horiiuchi A, 2016  | 47           | NA                | 0                        | 0                 | 0           | NA                        | NA             |            |
| Schenck RJ, 2017   | NA           | 9                 | 0                        | 0                 | 0           | 3-6 m                     | 1/19           |            |
| Cadoni S, 2018     | 46           | 46                | 9                        | 0                 | 0           | 14±12.96 m                | NA             |            |
| Han SJ, 2018       | 69           | NA                | NA                       | NA                | NA          | NA                        | NA             |            |
| Chien HC, 2019     | NA           | 71                | 6                        | NA                | 0           | NA                        | NA             |            |
| Kumar V, 2019      | NA           | NA                | NA                       | NA                | 0           | NA                        | NA             |            |
| Rodríguez-Sánchez J, 2019 | NA | 32 | NA | NA | NA | NA | NA |            |
| Yamashina T, 2019  | NA           | 76                | 2                        | 0                 | 0           | NA                        | NA             |            |
| Yen AW, 2020       | 25           | 25                | 1                        | 0                 | 0           | 0                         | NA             |            |
| **UEMR**           |              |                   |                          |                   |             |                           |                |            |
| Uedo N, 2015       | NA           | 5                 | NA                       | 0                 | 0           | NA                        | NA             |            |
| Amato A, 2016      | 13           | 13                | 2                        | 0                 | 0           | NA                        | NA             |            |
| Schenck RJ, 2017   | NA           | 8                 | 0                        | 1                 | 0           | 3-6 m                     | 1/15           |            |
| Cadoni S, 2018     | 49           | 51                | 5                        | 1                 | 0           | 14±12.96 m                | NA             |            |
| Chaves DM, 2018    | 7            | 6                 | 0                        | 0                 | 0           | NA                        | NA             |            |
| Chien HC, 2019     | NA           | 72                | 3                        | NA                | 1           | NA                        | NA             |            |
| Rodríguez-Sánchez J, 2019 | NA | 23 | NA | 0 | NA | NA | NA |            |
| Yamashina T, 2019  | NA           | 96                | 3                        | 0                 | 0           | 0                         | NA             |            |
| Yen AW, 2020       | 51           | 44                | 2                        | 0                 | 0           | 0                         | NA             |            |
| **Cold-EMR**       |              |                   |                          |                   |             |                           |                |            |
| Choksi N, 2015     | NA           | NA                | NA                       | 0                 | 0           | 1 (abdominal pain)        | 3 m            | NA         |
| Muniraj T, 2015    | NA           | NA                | NA                       | 0                 | 0           | 0                         | NA             |            |
| Piraka C, 2017     | NA           | NA                | 0                        | 0                 | 0           | 0                         | NA             |            |
| Tutticci NJ, 2017  | 87           | NA                | 1                        | NA                | NA          | NA                        | NA             |            |
| Papastergiou V, 2019 | NA | NA | NA | 0 | 0 | 0 | NA |            |
| **CSP**            |              |                   |                          |                   |             |                           |                |            |
| La Nauze R, 2014   | NA           | 28                | NA                       | 0                 | 0           | 0                         | NA             |            |
| Hirose R, 2017     | NA           | NA                | 0                        | 1                 | 0           | NA                        | NA             |            |
| Gessl I, 2019      | 45           | NA                | 0                        | NA                | 0           | NA                        | NA             |            |
| Murakami T, 2019   | NA           | 69                | 0                        | 0                 | 0           | NA                        | 10-24 m        | 4/74       |
| **HSP**            |              |                   |                          |                   |             |                           |                |            |
| Pohl H, 2013       | 91           | NA                | NA                       | NA                | NA          | NA                        | NA             |            |
| La Nauze R, 2014   | NA           | 52                | NA                       | 2                 | 1           | 0                         | NA             |            |
| Horiiuchi A, 2016  | 43           | NA                | 0                        | 0                 | 0           | 0                         | NA             |            |
| Gessl I, 2019      | 305          | NA                | 2                        | NA                | 1           | NA                        | NA             |            |

CSP: cold snare polypectomy; d, day; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; m, month; NA, not available; UEMR, underwater endoscopic mucosal resection
Supplementary Table 3: Modified Newcastle-Ottawa scale

| First author, year | Selection | Outcome | Score |
|--------------------|-----------|---------|-------|
| Yokota T, 1994     | 1 1 1 1 0 | 4       |
| Yoshikane H, 1999  | 1 1 1 1 1 | 5       |
| Bergmann U, 2003   | 1 1 1 1 1 | 5       |
| Su MY, 2005        | 1 1 1 1 1 | 5       |
| Uraoka T, 2005     | 1 1 1 1 1 | 5       |
| Katsinelos P, 2006 | 1 1 1 1 1 | 5       |
| Katsinelos P, 2008 | - - - -   | -       |
| Huang Y, 2009      | 1 1 1 1 1 | 5       |
| Serrano M, 2012    | 1 1 1 1 1 | 5       |
| Yoshida N, 2012    | - - - -   | -       |
| Pohl H, 2013       | 1 1 1 1 0 | 4       |
| Serrano M, 2012    | - - - -   | -       |
| Huang Y, 2009      | 1 1 1 1 1 | 5       |
| Serrano M, 2012    | 1 1 1 1 1 | 5       |
| Yoshida N, 2012    | - - - -   | -       |
| Pohl H, 2013       | 1 1 1 1 0 | 4       |
| Choksi N, 2015     | 1 1 1 1 1 | 5       |
| Kashani A, 2015    | 1 1 1 1 0 | 4       |
| Muniraj T, 2015    | 1 1 1 1 1 | 5       |
| Uedo N, 2015       | 1 1 1 1 0 | 4       |
| Woodward T, 2015   | - - - -   | -       |
| Amato A, 2016      | 1 1 1 1 0 | 4       |
| Horiiuchi A, 2016  | - - - -   | -       |
| Hirose R, 2017     | 1 1 1 1 0 | 4       |
| Piraka C, 2017     | 1 1 1 1 1 | 5       |
| Schenck RJ, 2017   | 1 1 1 1 1 | 5       |
| Tuticci NJ, 2017   | 1 1 1 1 1 | 5       |
| Cadoni S, 2018     | 1 1 1 1 1 | 5       |
| Chaves DM, 2018    | 1 1 1 1 0 | 4       |
| Han SJ, 2018       | - - - -   | -       |
| Chien HC, 2019     | 1 1 1 1 0 | 4       |
| Gessel I, 2019     | 1 1 1 1 0 | 4       |
| Kumar V, 2019      | 1 1 1 1 1 | 5       |
| Murakami T, 2019   | 1 1 1 1 1 | 5       |
| Papastergiou V, 2019 | 1 1 1 1 0 | 4       |
| Rodríguez-Sánchez J, 2019 | - - - - | -RCT |
| Van Overbeke L, 2019 | 1 1 1 1 1 | 5       |
| Yamashina T, 2019  | - - - -   | -       |
| Ket SN, 2020       | 1 1 1 1 0 | 4       |
| Yen AW, 2020       | - - - -   | -       |

Selection variables: 1 = representativeness of cohort; 2 = assignment of exposure; 3 = outcome not present at start. Outcome variables: 1 = assignment of outcome; 2 = adequate follow-up