Hypertonic solution as an optimal submucosal injection solution for endoscopic resection of gastrointestinal mucosal lesions: a systematic review and network meta-analysis.

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ABSTRACT

Objectives: Based on different physicochemical properties, common submucosal injection solutions could be classified into three categories: normal saline solution (NS), hypertonic solution (HS), and viscous solution (VS). We compared the efficacy and safety of various categories of solutions in this network meta-analysis of RCTs to identify the optimal submucosal injection fluid.

Methods: PubMed, Embase, Web of Science, and the Cochrane Library were searched for RCTs that compared the efficacy and safety of NS, HS, and VS during endoscopic resection for gastrointestinal mucosal lesions. Pairwise and network analyses were conducted to determine the ranking of different fluids.

Results: Thirteen RCTs were included in the final analysis with 1637 patients (1639 lesions). HS outperformed NS in rates of *en bloc* (pooled RR, 1.50; 95% CI, 1.10-1.90), overall bleeding (pooled OR, 0.33; 95% CI, 0.10-0.88; lesions$>$10mm OR, 4.65×10^{-2}; 95% CI, 1.10×10^{-3}-0.46), and intraoperative bleeding (lesions$>$10mm OR, 7.10×10^{-6}; 95% CI, 4.30×10^{-18}-0.26). HS showed the highest probability of ranking first in each outcome except for the volume of injection. Although VS was superior to NS in rates of *en bloc*, overall and intraoperative bleeding in lesions$>$10mm subgroup, and required less fluid in pooled analysis, it ranked last in cost of submucosal injection solution.

Conclusions: Both HS and VS were superior to NS in comparisons of efficacy and safety. Considering the better performance and potentially low cost, HS might be an optimal choice during gastrointestinal endoscopic resection, especially for colorectal EMR.

Introduction

With high morbidity and mortality rates, gastrointestinal (GI) neoplasms impose a significant socio-economic burden worldwide. [1-3] Compared to surgery, endoscopic resection (ER) including endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), may excise digestive tract lesions at an early stage without destroying the integrity of organs. Consequently, ER significantly improves patients' quality of life, shortens hospital stays, and cuts costs.[4-6] Due to these advantages, it has become widely accepted as an early intervention option for early GI mucosal lesions throughout the world.

During endoscopic resection, the submucosal injection generates a fluid cushion underneath the submucosal layer to reduce thermal injury or potential injury to muscular propria, thus contributing to safer and complete resection of the targeted lesion.[7-9] Recently, various submucosal injection solutions have been explored in clinical practice, and these solutions could be categorized as normal saline solution (NS), hypertonic solution (HS), and viscous solution (VS) [10-13](Supplementary Table 1). NS has been widely used owing to its low cost and simplicity to use without toxicity or tissue damage, however, the rapid absorption limits its duration of the fluid cushion.[10-12,14] The hypertonic solution, including hypertonic saline, 50% dextrose, mannitol solution, and Glyceol (10% glycerin and 5% fructose in NS), yielded relative long-lasting submucosal elevation and superior efficacy because of their hypertonic properties.[15,16] The European Society of Gastrointestinal Endoscopy (ESGE) recommended submucosal injection solutions with established safety, including VS (such as succinylated gelatin, and hydroxyethyl starch) and HS (Glyceol).[17] Since previous trials and meta-analyses predominantly used NS as a

control, few head-to-head studies comparing HS and VS exist, and the superiority among these submucosal injections is still debated.[18,19] Although the selection of submucosal injection solution varies from endoscopist to endoscopist, this network meta-analysis of RCTs compared the efficacy and safety of three categories of solutions aiming to give a universal recommendation that could be generalizable to a broader group of endoscopists in different endoscopy centers.

Methods

This systematic review and network meta-analysis was performed following PRISMA guidelines and was reported according to the PRISMA NMA Checklist. The protocol was registered on PROSPERO, the international prospective register of systematic reviews (CRD42022332854).

Search strategy

PubMed, Embase, Web of Science, and the Cochrane Library were searched for RCTs published in English until Aug 31, 2022. The retrieval strategy was provided in Supplementary Table 2. Manual search was performed for references of the included articles and important reviews.

Study selection

Only RCTs that investigated normal saline solution, hypertonic solution, and viscous solution as submucosal injection solutions in endoscopic resection, and reported *en bloc* resection rate were included, irrespective of publication status or blinding. Non-randomized controlled studies (such as cohort studies and case-control studies), reviews, editorials, case reports, letters, animal studies,

studies comparing different kinds of hypertonic solution or different kinds of viscous solution, and trials investigating other kinds of solutions were excluded.

Data extraction

Two investigators independently screened all titles and abstracts, then another two investigators extracted data utilizing a common data extraction form. When there was any disagreement, a third investigator intervened. The following data were extracted: details of study design, first author and publication year, country, resection method, number of participants, location, and size of lesions, type of submucosal injection solution, and result data.

The primary outcome of our network meta-analysis was the *en bloc* resection rate which was defined as the resection of the entire lesion in one piece. Secondary outcomes were complete resection rate, operation time, total injected volume, cost of submucosal injection solution, recurrence rate, overall bleeding rate, intraoperative bleeding rate, postoperative bleeding rate, and perforation rate. Complete resection was defined as the complete removal of the lesion with tumor-free lateral and vertical margins. Operation time was the period from the marking of the margins or the first injection, to the completion of the excision. The total injected volume was the total solution injected into the submucosa. The mean total injected volume multiplied by the mean or median prices of fluids makes the cost of submucosal injection solution. Recurrence was defined as recurrent adenoma at follow-up endoscopy. Overall bleeding included intraoperative bleeding and postoperative bleeding. Intraoperative bleeding was active bleeding requiring endoscopic therapy during the procedure. Postoperative bleeding was any post-ER bleeding requiring transfusion or endoscopic hemostasis because of hematochezia, an Hb concentration reduction of more than 2

g/dL, or melena. Perforation was detected either by endoscopy during the resection or by the presence of free air on a plain abdominal film or an abdominal CT.

Statistical analysis

We pooled all available data comparing the three categories of submucosal injection solutions using a random-effects model with the Bayesian framework[20,21] based on the assumption that between-studies variance is homogenous. The Markov Chain Monte Carlo (MCMC) simulation was performed using the following settings: the type of model, variance scaling factor for the starting values, number of chains, type of linear model, amount of adaptation iterations, amount of simulation iterations, and thinning factor were "consistency", 2.5, 4, "random", 10000, 50000, and 1, respectively. The trace plots and Gelman-Rubin plots in each outcome were presented in Supplementary Figure 1 and Supplementary Figure 2, respectively. Relative risk (RR) with a 95% confidence interval (CI) was reported for dichotomous data including *en bloc* and complete resection rate. The rates of overall bleeding, intraoperative bleeding, postoperative bleeding, recurrence, and perforation were reported as odds ratio (OR) with a 95% CI. The value of OR and RR are similar under the so-called "rare disease assumption", but OR may overestimate RR for outcomes with high incidences [22]. Considering the *en bloc* and complete resection rates are high while rates of bleeding, perforation, and recurrence are relatively low, we used RR for *en bloc* resection rate and complete resection rate, and OR for other binary data. Continuous data were reported as mean differences (MD) with a 95% CI. Bayesian estimates of the probability of ranking the best were conducted. Network inconsistency was evaluated by comparing the direct evidence with the indirect evidence utilizing the node-splitting technique. The I^2 statistic was employed to

evaluate statistical heterogeneity, and an I^2 value exceeding 50% was regarded to be indicative of substantial heterogeneity. Subgroup analyses were conducted for colorectal lesions, EMR, and lesions>10mm.

The network meta-analysis was performed by the package “gemtc” (version 1.0-1; Gert van Valkenhoef and Joel Kuiper) in R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria). The publication bias was assessed via Stata/MP 16.0. (StataCorp., T.X., USA).

Quality of evidence

The risk of bias and methodological quality of included studies was assessed utilizing the Cochrane Risk of Bias 2 (RoB 2) tool for RCTs.[23] The evaluation encompassed three categories: low risk of bias, some concerns, and high risk of bias.

Results

Study selection and characteristics

We searched 7335 records from databases and 126 citations from other relevant studies (Figure 1). After removing duplicated and irrelevant records, 134 records were included for full-length articles retrieval, and in which 121 records were removed for different reasons (Supplementary Table 3). Thirteen RCTs (26 arms of treatment) were included in the final network meta-analysis with 1637 patients (1639 lesions), and 61.6% of patients were male.[24-36] Three trials including 417 patients compared the efficacy and safety of HS with NS (222 in HS group vs. 195 in NS group), while nine trials compared NS with VS among 1057 patients (532 in NS group vs. 525

in VS group), and one trial with 163 patients compared HS with VS (82 in HS group vs. 81 in VS group). The baseline characteristics and number of events of included patients were provided in Table 1 and Supplementary Table 4, respectively.

Primary outcome

The network of eligible comparisons for *en bloc* resection rate was depicted in Supplementary Figure 3A. HS showed higher *en bloc* resection rates compared with NS according to pairwise (RR, 1.50; 95% CI, 1.10-2.10) and network meta-analysis (RR, 1.50; 95% CI, 1.10-1.90). However, no significant difference between VS and NS (pairwise RR, 1.10; 95% CI, 0.97-1.40; network RR, 1.10; 95% CI, 0.99-1.40), or between VS and HS (pairwise RR, 0.85; 95% CI, 0.52-1.40; network RR, 0.79; 95% CI, 0.60-1.00) was observed (Figure 2). According to the Bayesian framework, HS possessed the highest probability (95.7%) of being the optimal submucosal injection fluid (Figure 3).

In the subgroup of the colorectal lesions,[27-32,34-36] HS was preferable to NS according to the network meta-analysis (RR, 1.40; 95% CI, 1.10-1.90), but not significant in pairwise analysis (RR, 1.40; 95% CI, 0.95-2.20). In the subgroup of EMR,[24,25,27,28,30-32,35,36] HS showed higher *en bloc* resection rates compared with NS (pairwise RR, 1.50; 95% CI, 1.10-4.90; network RR, 1.40; 95% CI, 1.20-1.70) and VS (VS vs. HS in network meta-analysis: RR, 0.75; 95% CI, 0.61-0.91). In addition, VS performed better than NS only in the subgroup of lesions>10mm[24-27,29-31,33,35] (RR, 1.31; 95% CI, 1.01-1.80) (Figure 2). Based on the Bayesian framework, subgroup analyses did not alter the probable rank of HS as the optimal solution (Figure 3).

Secondary outcomes

The network plots of secondary outcomes were provided in Supplementary Figure 3B-3J. There was no head-to-head comparison between VS and HS for operation time, total injected volume, and cost of submucosal injection solution; thus, pooled comparisons of these three outcomes were obtained via network meta-analysis. Additionally, subgroup analyses were performed for colorectal lesions, EMR, and lesions >10 mm.

For secondary outcomes related to efficacy, no significant differences among the three categories of submucosal injection solutions in terms of the complete resection rate (Supplementary Table 5) and operation time (Supplementary Table 6) according to either pooled or subgroup analyses were discovered. However, compared with NS, VS required smaller volume of total injected fluids according to the pairwise (MD, -9.40; 95% CI, -19.00- -0.58) and network (MD, -9.40; 95% CI, -19.00 - -0.58) meta-analysis only in pooled analysis (Supplementary Table 7). As for the cost of submucosal injection solution, there were no differences among NS, HS, and VS (Supplementary Table 8), but VS showed the lowest probability of being the cheapest fluid according to the pooled and subgroup analyses (Figure 4D). As for recurrence rate, HS lowered recurrence rates than NS according to pairwise meta-analyses in pooled analysis (OR, 1.70×10^{-12}; 95% CI, 7.10×10^{-31}-0.11), the subgroup of colorectal lesions (OR, 7.40×10^{-10}; 95% CI, 5.50×10^{-28}-0.13), and the subgroup of EMR (OR, 5.70×10^{-10}; 95% CI, 1.80×10^{-30}-0.14). However, significant inconsistency was identified between direct and indirect estimates (HS vs. NS, P=0.033; VS vs. NS, P=0.043; VS vs. HS, P=0.024) (Supplementary Table 9).

Regarding adverse events, HS was associated with lower overall bleeding rates than NS in pooled analysis (network OR, 0.33; 95% CI, 0.10-0.88) and the subgroup of lesions>10mm (pairwise OR, 1.60×10^{-9}; 95% CI, 2.00×10^{-30}-0.09; network OR, 4.65×10^{-2}; 95% CI, 1.10×10^{-3}-0.46). Additionally, VS lowered the overall bleeding rate than NS in the subgroup of lesions>10mm according to network meta-analysis (OR, 0.43; 95% CI, 0.16-0.93) (Table 2). In terms of intraoperative bleeding rate, significant differences were discovered only in the subgroup of lesions>10mm (Table 3): HS was preferable to NS (pairwise OR, 7.80×10^{-12}; 95% CI, 9.80×10^{-31}-0.08; network OR, 7.10×10^{-6}; 95% CI, 4.30×10^{-18}-0.26) and VS (VS vs. HS OR, 9.16×10^{4}; 95% CI, 1.34-4.75×10^{19}); VS also showed lower rates of intraoperative bleeding compared with NS (OR, 0.39; 95% CI, 0.12-0.99). Notwithstanding, there were no significant differences among NS, HS, and VS in terms of postoperative bleeding (Supplementary Table 10) and perforation (Supplementary Table 11) rate. Considering tissue damage, only qualitative analysis was available owing to the deficiency of data. Only two studies that compared NS and VS described the deep resections containing muscularis propria and no statistical difference was found.[29,35] One reported 0 in 102 for SIC-8000 group and 4 in 109 for normal saline group, respectively, and the other observed 1 deep resection in each group (succinylated gelatin and normal saline).

HS showed the highest probability of ranking the best fluid in terms of complete resection rate, operation time, cost of submucosal injection solution, recurrence rate, overall bleeding rate, postoperative bleeding rate, and perforation rate according to the Bayesian framework in both pooled and subgroup analyses (Figure 4A-4B, 4D-4E, 5A, 5C-5D). In terms of intraoperative bleeding rate, HS seemed to be the best solution except for the subgroup analysis of colorectal lesions in which VS had the highest probability of ranking first (Figure 5B). Additionally, VS had a

superior performance in terms of total injected volume in both pooled and subgroup analyses (Figure 4C).

Risk of bias, inconsistency, and heterogeneity

Overall, four clinical trials possessed high risk of bias, seven showed some areas of concern, and only two had low risk of bias (Supplementary Figure 4). The publication bias evaluation results were reported in Supplementary Figure 5A to 5J, and there was no significant publication bias for each outcome except for cost of submucosal injection solution. The conclusion of the trim-and-fill test for cost of submucosal injection solution suggested 3 potential unpublished studies (Supplementary Figure 6).

The results of the inconsistency and the heterogeneity test were all summarized in the results of pairwise and network meta-analyses for each outcome (Figure 2, Table 2-3, Supplementary Table 5-11). Except for the recurrence rate, the direct and indirect comparison results showed consistency with all P values exceeding 0.05. Additionally, except for operation time, total injected volume, and cost of submucosal injection, significant heterogeneity was not observed for all other outcomes.

Discussion

To the best of our knowledge, this systematic review and network meta-analysis was the first to perform a network meta-analysis of submucosal injection solutions categorized as NS, HS, and VS based on the physicochemical property which led to the differences in clinical effects. Traditional meta-analyses couldn’t establish solid evidence on the relative effectiveness of several

treatments. While indirect evidence is available when direct comparisons between two or more treatments may not exist. Then the network meta-analysis combines both direct and indirect evidence and allows us to infer which type of treatment may be preferable.[21] For now, the difference between HS and VS is still unclear owing to the deficiency of head-to-head study. To provide robust evidence on the relative performance of NS, HS, and VS for endoscopists, we conducted this network meta-analysis. According to this meta-analysis, HS outperformed NS in rates of *en bloc* resection, overall bleeding, and intraoperative bleeding. Interestingly, in the subgroup of lesions﹥10mm, VS demonstrated a higher *en bloc* resection rate than NS, and both HS and VS showed better performance compared with NS in terms of overall and intraoperative bleeding rates. Additionally, HS also performed better than VS in terms of intraoperative bleeding rate in lesions﹥10mm. According to Bayesian estimates, HS seemed to rank first in terms of most outcomes except for total injected volume. Consequently, HS had the greatest potential to be the optimal fluid based on comparisons of the efficacy and safety of the three fluids especially during colorectal EMR.

From the efficacy aspect, HS's superiority over NS and VS in terms of *en bloc* resection rate was discovered. Moreover, HS showed the highest probability of being the optimal fluid in rates of *en bloc* resection, complete resection, operation time, and recurrence. Although HS tends to dissipate more rapidly than VS, it is easier to inject into the submucosal layer and generates a relatively high elevation quickly. In addition, HS has a longer-lasting "fluid cushion" due to its higher osmotic pressure compared to NS. Considering the majority of the studies conducted EMR, more consideration was given to the initial elevation other than the duration of the submucosal "fluid cushion".[37] Fujishiro et al. found VS (sodium hyaluronate solution) produced equal initial

elevation with HS (Glyceol) and pretty higher elevation than NS.[38] This finding suggests that HS could achieve comparable initial elevation to VS, which likely contributes to its superiority observed in our meta-analysis. Interestingly, VS seemed to be preferable to NS in *en bloc* resection rate in the subgroup of lesions>10mm, which is consistent with common sense that VS was more suitable for ER of larger lesions. Particularly, during ESD or EMR procedures for larger lesions, the higher viscosity of VS ensures prolonged confinement within the submucosal layer. This extended duration facilitates the procedure and minimizes the need for additional injections, simplifying the achievement of *en bloc* resection. In terms of recurrence rate, the results could not provide a definitive conclusion due to significant inconsistency, thus more studies with large sample sizes are necessary.

From a cost-effectiveness aspect, the low prices of normal saline, hypertonic saline, and 50% dextrose are well known.[10,11] Glycerol, a type of hypertonic solution, is relatively inexpensive (U.S. $0.1–$0.2/10mL) as well.[11] In contrast, VSs including sodium hyaluronate (U.S. $495-$1280/10 mL), Eleview™ (U.S. $81/10 mL), and ORISE gel (U.S. $150/10 mL) are much more expensive than NS and HS.[11,14] No differences among NS, HS, and VS notwithstanding, the price gap between VS and NS or HS is undeniably huge. In addition, VS showed a trend toward higher cost, and ranked last according to the Bayesian framework. However, significant heterogeneity and publication bias was observed in this analysis. That could be attributed to the fact that owing to the absent data on cost-effectiveness, we calculated the costs based on the injected volume and the prices of fluid. As a result, the interpretation of these findings should be approached with caution, and future studies regarding this aspect are critical to reveal the cost-effectiveness of different fluids.

From a safety aspect, HS lowered overall and intraoperative bleeding rates compared with NS. Also, HS decreased the rates of intraoperative bleeding compared with VS in the subgroup of lesions>10mm. Along with estimates of probable rank, the network meta-analysis revealed that HS might be the optimal choice. One of the advantages of HS is its ability to generate a "fluid cushion" that lasts for a relatively long duration. This prolonged cushioning effect allows for the compression of local surrounding tissues, thereby contributing to the reduction in bleeding rates when compared to NS. Notably, the hypertonic solution was used for variceal bleeding through osmotic dehydrating and sclerosant effect.[39] And a previous study reported that hypertonic solutions might obliterate the local vasculature, thus minimizing the risk of local bleeding during endoscopic resection.[24] The combined compression of surrounding tissue and the effect of dehydrating and sclerosant may explain the superiority of HS. VS decreased the rates of overall bleeding and intraoperative bleeding compared with NS in the subgroup of lesions>10mm. This finding aligns with the widely accepted notion that VS proves to be superior to NS in the endoscopic resection (ER) of larger lesions. The high viscosity of VS enables it to persist for a longer duration compared to NS. This prolonged duration allows for the compression of surrounding tissues, effectively minimizing bleeding during the ER procedure, particularly for larger lesions.

The superiority of hypertonic solution was recognized in previous studies while possible tissue damage remains a concern.[24,27,28,36] Unfortunately, quantitative analysis of tissue damage was deficient owing to the insufficient data of included studies. In a previous study, Fujishiro et al. observed tissue damage only in 20% and 50% DW, while no tissue damage after injection of Glyceol or 15% dextrose water, which indicated tissue damage was related to concentration or some specific type of solutions.[40] Nevertheless, the elevation and duration of the submucosal fluid

cushion generated by HS were related to the osmotic pressure. Glyceol, for instance, demonstrated excellent efficacy and safety due to a 7 times higher osmotic pressure than the extracellular fluid.[36,41] Hence, considering the hypertonicity, Glyceol could be confined to the submucosa without penetrating into deeper muscular layers if injected into the submucosa carefully, thus providing the duration for the endoscopist to securely remove the mucosal lesion.[24,28] The viscous solution also showed superiority over NS due to its high viscosity while high cost may hamper utilization.[42] Additionally, novel VS including ORISE and SIC-8000 could cause foreign body granuloma post-endoscopic resection and induce submucosal distortion in the zone of ER scars, which must be careful before clinical utilization.[43-45]

Our study had some limitations. Firstly, inherent heterogeneity was inevitable since the included trials compared various submucosal injection solutions across different types of endoscopic resection (ESD and EMR), and different lesion sites (colorectum, and stomach). Although it was challenging to compare the efficacy and safety of submucosal injection fluids in different organs through different resection methods, we performed this network meta-analysis aiming to identify the optimal submucosal injection fluid which could be generalizable to upper and lower gastrointestinal endoscopic resection. What’s more, there was no heterogeneity for most outcomes except for the operation time, total injected volume, and cost of submucosal injection solution. We inferred that the high level of heterogeneity which couldn’t be decreased by subgroup analyses was primarily due to variations in definitions, measurements of these three outcomes, and the endoscopists’ experience of included studies. The interpretation of results of operation time, total injected volume, and cost of solution should be approached with caution. Secondly, the number of studies compared HS with other solutions is limited (4 in 13 included studies). Among

them, only one study including 163 patients compared HS (dextrose solution) and VS (sodium hyaluronate solution, SHA) head-to-head, and VS was associated with a higher immediate bleeding rate compared with HS while no differences were found between them in terms of complete resection, perforation, and postoperative bleeding rates.[27] Consequently, more studies that compare HS and VS with larger sample sizes are warranted. Thirdly, the limited quantity of available studies has hindered us from carrying out the planned subgroup analyses effectively. Concerning the specific sites of lesions, our subgroup analysis focused solely on colorectal lesions, we were unable to aggregate studies related to lesions either in esophagus, stomach or duodenum. For the resection methods, only subgroup analysis for EMR was obtained. Similarly, our analysis regarding lesion sizes was confined to those larger than 10mm. Therefore, to obtain a generalizable and definitive conclusion, further research that studies submucosal injection solutions for upper gastrointestinal (esophagus, stomach, and duodenum) ER and colorectal ESD with larger sample sizes is necessary. Fourthly, the majority of the included studies were randomized controlled trials of moderate to high quality, of which only two RCTs possessed a low risk of bias. We found that most of the risk originated from the selection of the reported result since protocols were not registered. Fifthly, new injection techniques were not evaluated as most studies used injection needles and only one study used a needle knife. However, hybrid knives, which combine the functions of the knife and the injector, have been demonstrated to reduce the injection time and operation time.[46-48] Therefore, future research on submucosal injection solutions that utilize new injection techniques is required.

All in all, hypertonic solution might be the optimal choice during gastrointestinal endoscopic resection especially colorectal EMR considering its better performance and potentially low cost.

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Acronyms and abbreviations

NS – Normal saline solution
HS – Hypertonic solution
VS – Viscous solution
RCT - Randomized Controlled Trial
GI – Gastrointestinal
RR – Relative risk
OR – Odds ratio
MD – Mean difference
SD – Standard deviation
ER – Endoscopic resection
EMR - Endoscopic mucosal resection
ESD - Endoscopic submucosal dissection
ESGE - The European Society of Gastrointestinal Endoscopy
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NMA – Network meta-analysis
CT - Computed Tomography
RoB – Risk of bias

Figure legends

Figure 1. Flow chart of study selection.

Figure 2. Forest plot of *en bloc* resection rate.

Inconsistency p-values for each split comparison between direct and indirect comparisons are provided. P-value > 0.05 denotes the absence of inconsistency. I^2 pair represents the heterogeneity of pairwise comparisons. I^2 cons represents the heterogeneity of network comparisons. An I^2 >50% indicates high heterogeneity, whereas I^2＜50% denotes low heterogeneity.

NS, normal saline solution; HS, hypertonic solution; VS, viscous solution; RR, Relative risk; CI, confidence interval; NA, data not available.

Figure 3. The probability of ranking for *en bloc* resection rate. NS, normal saline solution; HS, hypertonic solution; VS, viscous solution.

Figure 4. The probability of ranking for efficacy of secondary outcomes. NS, normal saline solution; HS, hypertonic solution; VS, viscous solution. A. The probability of ranking for complete resection rate. B. The probability of ranking for operation time. C. The probability of ranking for total injected volume. D. The probability of ranking for cost of submucosal injection solution. E. The probability of ranking for recurrence rate.

Figure 5. The probability of ranking for safety of secondary outcomes. NS, normal saline solution; HS, hypertonic solution; VS, viscous solution. A. The probability of ranking for overall bleeding rate. B. The probability of ranking for intraoperative bleeding rate. C. The probability of ranking for postoperative bleeding rate. D. The probability of ranking for perforation rate.

Table 1. Baseline characteristics of included studied.

Table 2. Summarized results of pairwise and network meta-analyses for overall bleeding rate.

Table 3. Summarized results of pairwise and network meta-analyses for intraoperative bleeding rate.

Supplementary files legends

Supplementary Figure 1. Trace plots of each outcome.

Supplementary Figure 2. Gelman-Rubin plots of each outcome.

Supplementary Figure 3. The network plots of each outcome.

A. Network plot of *en bloc* resection rate. B. Network plot of complete resection rate. C. Network plot of operation time. D. Network plot of total injected volume. E. Network plot of cost of submucosal injection solution. F. Network plot of recurrence rate. G. Network plot of overall bleeding rate. H. Network plot of intraoperative bleeding rate. I. Network plot of postoperative bleeding rate. J. Network plot of perforation rate.

Supplementary Figure 4. Risk of bias in included RCTs.

Supplementary Figure 5. Funnel plot of publication bias for each outcome.

A. Funnel plot of *en bloc* resection rate. B. Funnel plot of complete resection rate. C. Funnel plot of operation time. D Funnel plot of total injected volume. E. Funnel plot of cost of submucosal injection solution. E. Funnel plot of recurrence rate. F. Funnel plot of overall bleeding rate. F. Funnel plot of intraoperative bleeding rate. H. Funnel plot of postoperative bleeding rate. I. Funnel plot of perforation rate.

Supplementary Figure 6. Trim-and-fill test for cost of submucosal injection solution.

○ The 3 potential unpublished studies.

Supplementary Table 1. Commonly used submucosal injection solutions and their classification according to different physicochemical properties.

Supplementary Table 2. Search strategy.

Supplementary Table 3. Exclusion reasons for retrieved records.

Supplementary Table 4. The number of events of included studies.

Supplementary Table 5. Summarized results of pairwise and network meta-analyses for complete resection rate.

Supplementary Table 6. Summarized results of pairwise and network meta-analyses for operation

time.

Supplementary Table 7. Summarized results of pairwise and network meta-analyses for total injected

Supplementary Table 8. Summarized results of pairwise and network meta-analyses for cost of submucosal injection solution.

Supplementary Table 9. Summarized results of pairwise and network meta-analyses for recurrence rate.

Supplementary Table 10. Summarized results of pairwise and network meta-analyses for postoperative bleeding rate.

Supplementary Table 11. Summarized results of pairwise and network meta-analyses for perforation rate.

Supplementary Table 12. PRISMA NMA checklist.

Table 1. Baseline characteristics of included studies.

Author, Year	Location of lesions	Resection methods	Country	Submucosal injection solutions	Use of epinephrine	Sample size	Male /Female	Age (Mean ± SD), year	Lesion Size (Mean±SD), mm
Wang, 2019	Colorectum	EMR	China	Glycerol fructose	Yes	150	98/52	58±6	9.3±2.3
				Normal saline		125	70/55	58±6	9.8±2.1
Repici, 2018	Colorectum	EMR	Italy	SIC-8000 (Eleview®)	NA	102	127/99	65±39	31.6±12.8
				Normal saline		109			32.3±12.1
Kim, 2015	Stomach & colorectum	EMR& ESD	Korea	Sodium hyaluronate solution	No	80	62/22	61±10	26/37/21 [#]
				Normal saline		74	45/33	60±11	32/30/16 [#]
Kim, 2013	Stomach	ESD	Korea	Sodium hyaluronate solution	Yes	33	25/12	63±9	14.2±5.5
				Normal saline		36	26/13	62±9	13.5±4.4
Fasoulas2012	Colorectum	EMR	Greece	Hydroxyethyl starch	Yes	25	16/9	68±10	45±9.5
				Normal saline		24	8/16	67±10	46±9.75
Kishihara, 2012	Colorectum	EMR	Japan	Sodium hyaluronate solution	No	46	21/25	61±9	11.3±3.0
				Normal saline		48	32/16	65±8	12.5±4.0
Yoshida, 2012	Colorectum	EMR	Japan	Sodium hyaluronate solution	No	93	62/31	66±16	8.9±4.0
				Normal		96	63/3	67±14	8.2±2.5

				saline			3		
Moss, 2010	Colorectum	EMR&ESD	Australia	Succinylated gelatin	NA	41	22/19	69±9	40.0±14.8
				Normal saline		39	23/16	67±12	35.0±14.8
Hurlstone, 2008	Colorectum	EMR	UK	Dextrose solution	Yes	82	42/40	57±14	18.0±7.3
				Sodium hyaluronate solution		81	39/42	58±13	20.2±9.0
Katsinelos, 2008	Colorectum, distal	EMR	Greece	50% dextrose solution	Yes	45	20/25	65±10	2.0±1.8
				Normal saline		47	27/20	69±13	2.5±1.8
Yamamoto, 2008	Stomach	EMR&ESD	Japan	Sodium hyaluronate solution	Yes	69	57/12	65±8	41/20/8 #
				Normal saline		70	51/19	66±8	32/25/13 #
Lee, 2006	Stomach	EMR	Korea	Fibrinogen mixture	Yes	36	27/9	61±11	19.2±6.2
				Normal saline		36	21/15	60±11	16.8±6.1
Varadarajulu, 2006	Stomach & colorectum	EMR	USA	50 % dextrose solution	NA	27	12/15	67±13	25.0±12.0
				Normal saline		25	14/9	61±10	22.0±9.0

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NA, not available; SD, standard deviation.

#Lesions expressed in the order of 5-10mm/11-15mm/16-20mm.

Table 2. Summarized results of pairwise and network meta-analyses for overall bleeding rate.

Comparisons	Pairwise meta-analysis (OR, 95%CI)	Network meta-analysis (OR, 95%CI)	P-value	I^2 pair (%)	I^2 cons (%)
Pooled analysis					
HS vs. NS	0.41 (0.11, 1.30)	**0.33 (0.10, 0.88) ***	0.387	26.10%	19.50%
VS vs. NS	0.65 (0.33, 1.10)	0.68 (0.36, 1.10)	0.375	4.00%	0.00%
VS vs. HS	5.60 (0.53, 1.70x10^2)	2.00 (0.69, 6.80)	0.381	NA	0.00%
Subgroup of colorectal lesions					
HS vs. NS	0.56(0.13,2.10)	0.42(0.11,1.30)	0.262	0.00%	0.00%
VS vs. NS	0.62(0.25,1.40)	0.69(0.30,1.50)	0.292	0.00%	0.00%

VS vs. HS	5.30(0.44,2.10x10^{2})	1.60(0.46,6.70)	0.304	NA	11.60%
Subgroup of EMR					
HS vs. NS	0.38 (7.20x10^{-2},1.40)	0.31 (7.00x10^{-2},0.94)	0.390	28.70%	20.80%
VS vs. NS	0.54 (0.17,1.50)	0.60 (0.22,1.50)	0.394	0.00%	0.00%
VS vs. HS	5.80 (0.39,2.40x102)	1.90 (0.52,9.80)	0.379	NA	0.00%
Subgroup of lesions＞10mm					
HS vs. NS	**1.60x10^{-9} (2.00x10^{-30}, 0.09) ***	**4.65x10^{-2} (1.10x10^{-3}, 0.46) ***	0.08	NA	0.00%
VS vs. NS	0.45 (0.17, 1.00)	**0.43 (0.16, 0.93) ***	0.10	0.80%	0.00%
VS vs. HS	5.30 (0.40, 2.00x10^{2})	9.14 (0.93, 3.56x10^{2})	0.10	NA	0.00%

Inconsistency p-values for each split comparison between direct and indirect comparisons are provided. P-value > 0.05 denotes the absence of inconsistency. I^2 pair represents the heterogeneity of pairwise comparisons. I^2 cons represents the heterogeneity of network comparisons. An I^2 >50% indicates high heterogeneity, whereas I^2＜50% denotes low heterogeneity.

NS, normal saline solution; HS, hypertonic solution; VS, viscous solution. OR, odds ratio; CI, confidence interval. NA, data not available. *Significant difference.

Table 3. Summarized results of pairwise and network meta-analyses for intraoperative bleeding rate.

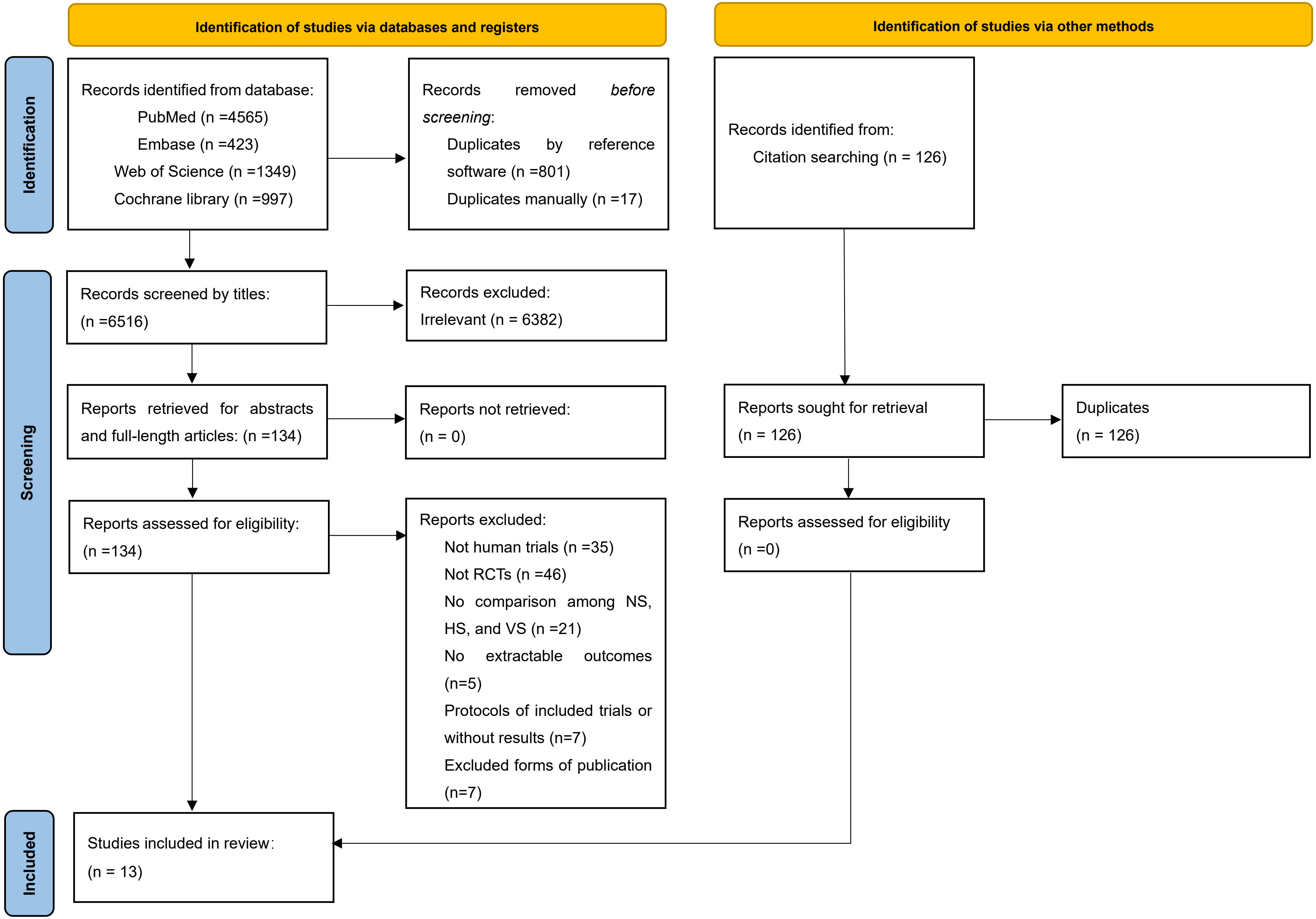
Comparisons	Pairwise meta-analysis (OR, 95%CI)	Network meta-analysis (OR, 95%CI)	P-value	I^2 pair (%)	I^2 cons (%)
Pooled analysis					
HS vs. NS	0.37 (0.04, 2.00)	0.38 (0.05, 1.98)	0.486	64.80%	28.10%
VS vs. NS	0.60 (0.23, 1.30)	0.61 (0.23, 1.26)	0.633	5.20%	0.00%
VS vs. HS	2.10x10^{-5} (1.20x10^{-31}, 5.50x10^{11})	1.58 (0.24, 13.96)	0.586	NA	0.00%
Subgroup of colorectal lesions					
HS vs. NS	0.83 (0.09, 6.80)	0.79 (0.09, 6.8)	0.462	NA	0.00%
VS vs. NS	0.52 (0.16, 1.50)	0.52 (0.16, 1.47)	0.760	3.70%	0.00%
VS vs. HS	9.30x10^{-5} (1.60x10^{-20}, 6.80x10^{8})	0.64 (0.05, 6.8)	0.554	NA	0.00%
Subgroup of EMR					
HS vs. NS	0.32 (0.02, 2.30)	0.34 (0.02, 2.46)	0.682	68.70%	36.20%
VS vs. NS	0.42 (0.07, 1.90)	0.42 (0.07, 1.89)	0.556	1.30%	0.00%
VS vs. HS	2.70x10^{-7} (2.40x10^{-34}, 5.00x10^{12})	1.23 (0.09, 28.25)	0.529	NA	0.00%
Subgroup of lesions＞10mm					

HS vs. NS	**$7.80x10^{-12}$ ($9.80x10^{-31}$, 0.08) ***	**$7.10x10^{-6}$ ($4.30x10^{-18}$, 0.26) ***	0.181	NA	0.00%
VS vs. NS	0.39 (0.11, 1.00)	**0.39 (0.12, 0.99) ***	0.107	0.00%	0.00%
VS vs. HS	$3.10x10^{-5}$ ($7.30x10^{-38}$, $5.20x10^{7}$)	**$9.16x10^{4}$ (1.34, $4.75x10^{19}$) ***	0.270	NA	19.30%

Inconsistency p-values for each split comparison between direct and indirect comparisons are provided. P-value > 0.05 denotes the absence of inconsistency. I^2 pair represents the heterogeneity of pairwise comparisons. I^2 cons represents the heterogeneity of network comparisons. An I^2 >50% indicates high heterogeneity, whereas I^2＜50% denotes low heterogeneity.

NS, normal saline solution; HS, hypertonic solution; VS, viscous solution. OR, odds ratio; CI, confidence interval. NA, data not available. *Significant difference.

Figure 1



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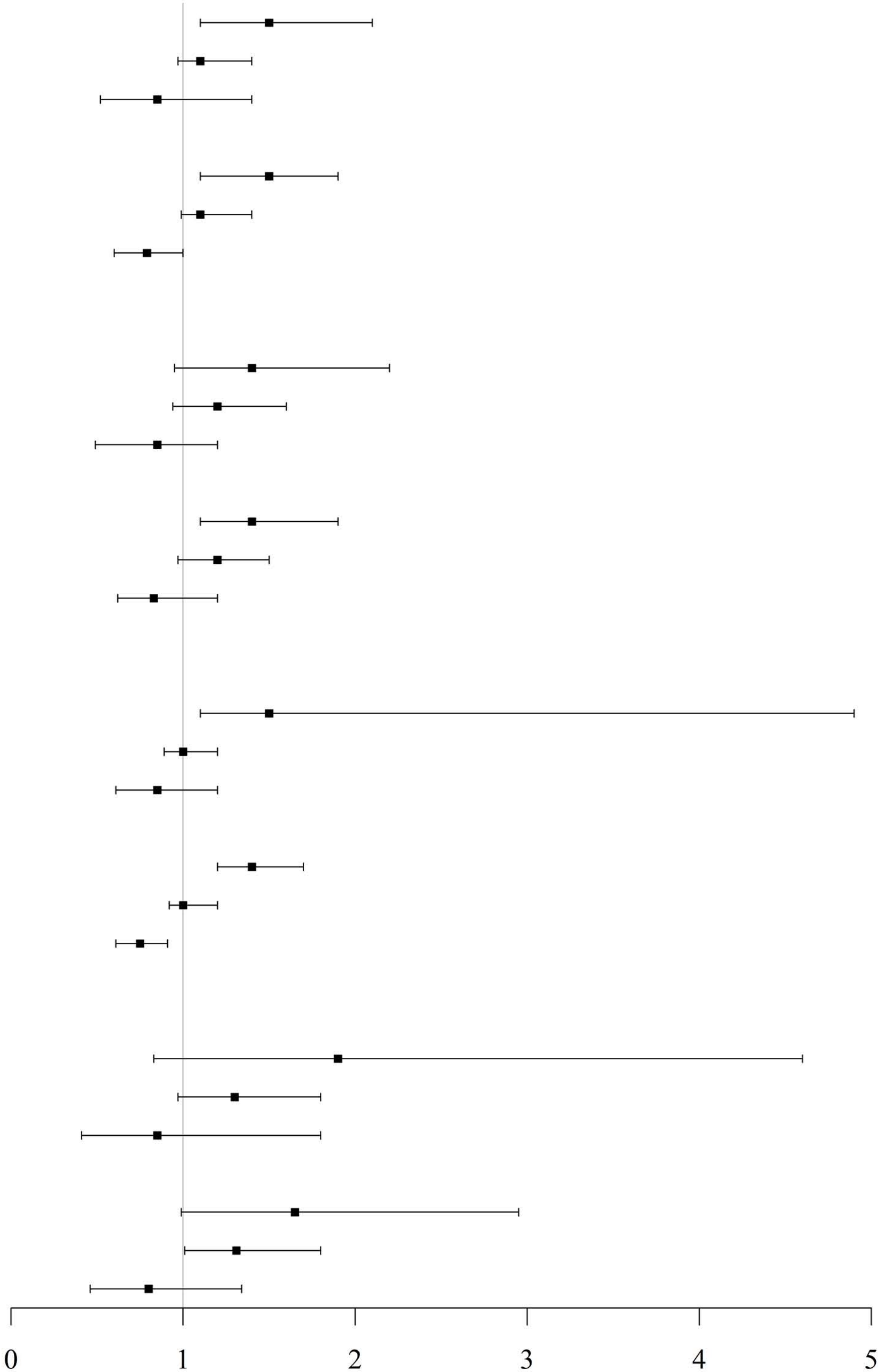
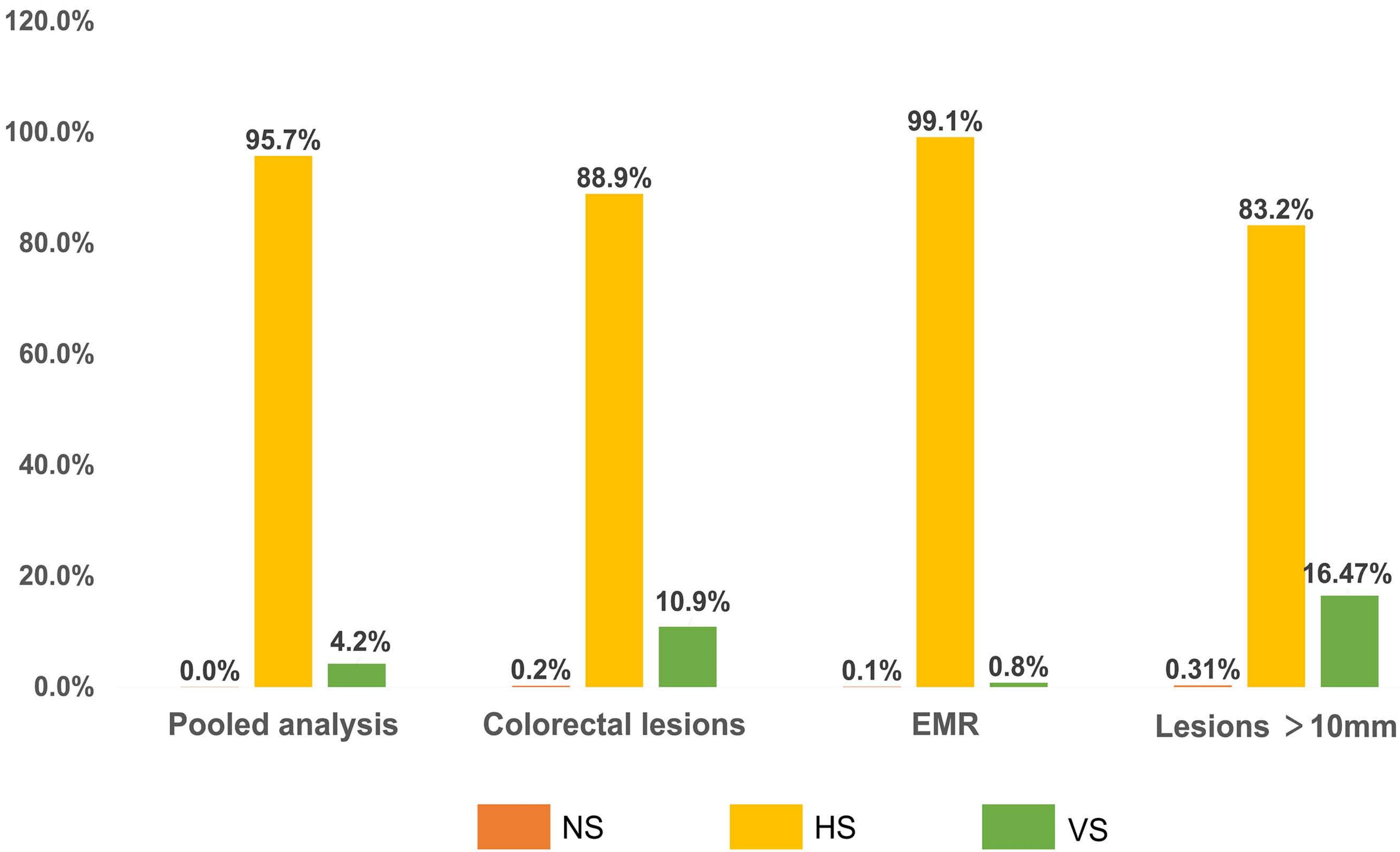
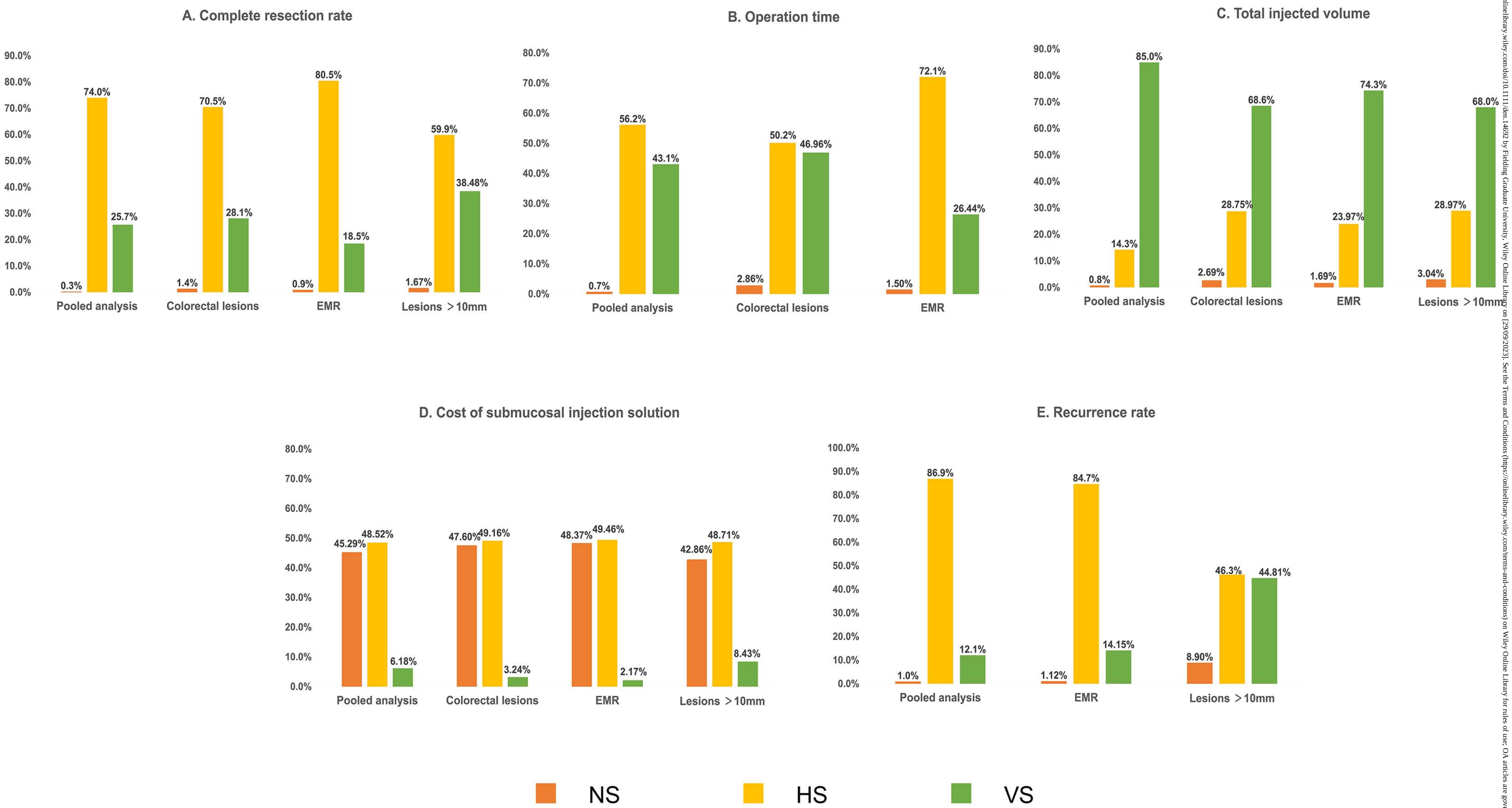
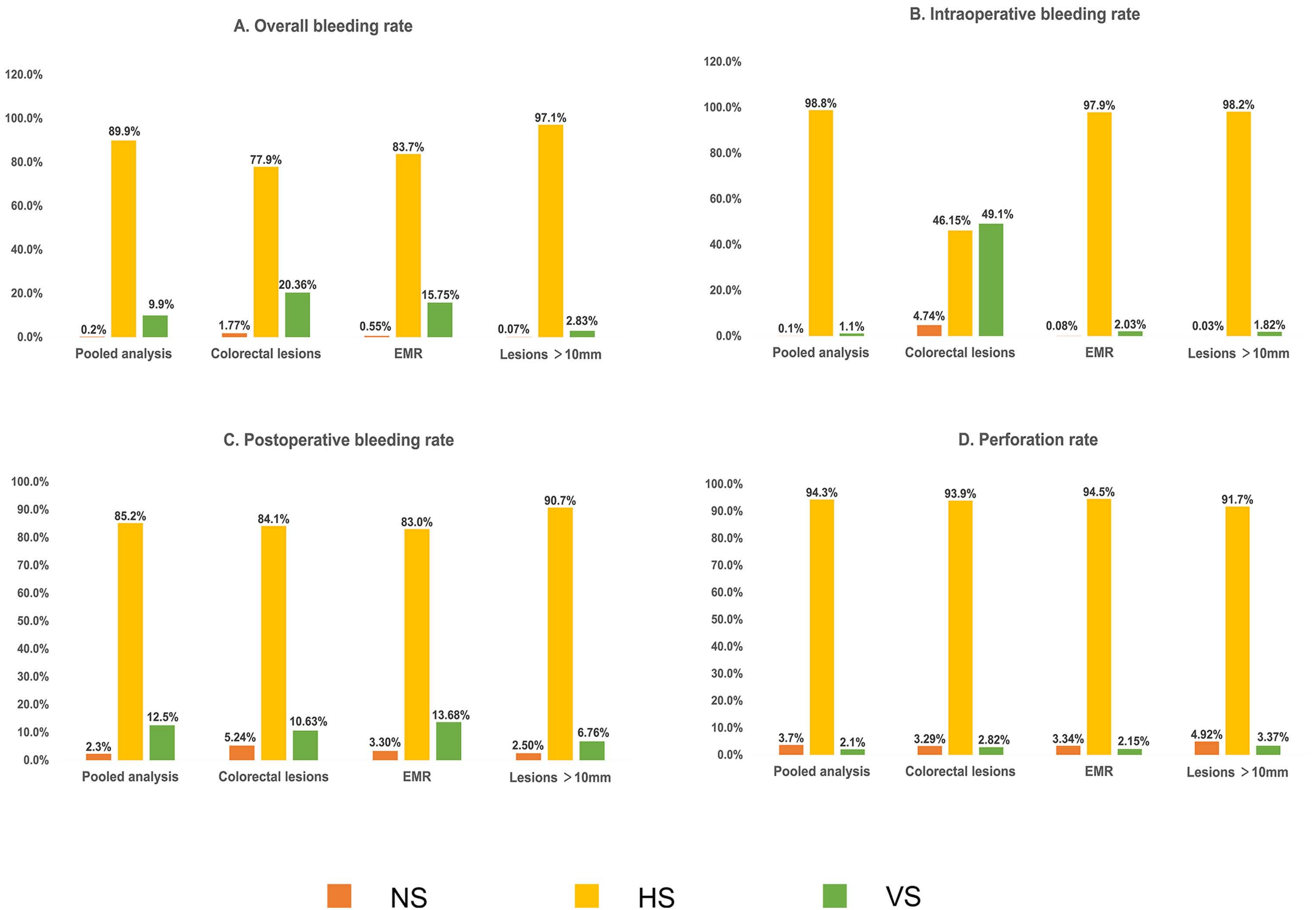
Not RCTs (n =46)
No comparison among NS, HS, and VS (n =21)
No extractable outcomes (n=5)
Protocols of included trials or without results (n=7)
Excluded forms of publication (n=7)
Reports assessed for eligibility
(n =0)
Included
Studies included in review:
(n = 13)

Group	RR(95%CI)	I2(%)	P-value
Pooled analysis			
Pairwise meta-analysis			
HS vs. NS	1.50 (1.10, 2.10)	23.30%	-
VS vs. NS	1.10 (0.97, 1.40)	54.60%	-
VS vs. HS	0.85 (0.52, 1.40)	-	-
Network meta-analysis			
HS vs. NS	1.50 (1.10, 1.90)	0.00%	0.647
VS vs. NS	1.10 (0.99, 1.40)	49.20%	0.664
VS vs. HS	0.79 (0.60, 1.00)	0.00%	0.655
Colorectal lesions			
Pairwise meta-analysis			
HS vs. NS	1.40 (0.95,2.20)	0.00%	-
VS vs. NS	1.20 (0.94,1.60)	26.70%	-
VS vs. HS	0.85 (0.49,1,50)	-	-
Network meta-analysis			
HS vs. NS	1.40 (1.10, 1.90)	0.00%	0.474
VS vs. NS	1.20 (0.97, 1.50)	14.10%	0.475
VS vs. HS	0.83 (0.62, 1.20)	0.00%	0.475
EMR			
Pairwise meta-analysis			
HS vs. NS	1.50 (1.10,4.90)	0.00%	-
VS vs. NS	1.00 (0.89,1.20)	26.70%	-
VS vs. HS	0.85 (0.61,1.20)	-	-
Network meta-analysis			
HS vs. NS	1.40 (1.20,1.70)	0.00%	0.474
VS vs. NS	1.00 (0.92,1.20)	14.10%	0.475
VS vs. HS	0.75 (0.61,0.91)	0.00%	0.475
Larger than 10mm lesions			
Pairwise meta-analysis			
HS vs. NS	1.90 (0.83, 4.60)	-	-
VS vs. NS	1.30 (0.97, 1.80)	82.80%	-
VS vs. HS	0.85 (0.41, 1.80)	-	-
Network meta-analysis			
HS vs. NS	1.65 (0.99, 2.95)	0.00%	0.672
VS vs. NS	1.31 (1.01, 1.80)	80.80%	0.694
VS vs. HS	0.80 (0.46, 1.34)	0.00%	0.686




120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.0%
95.7%
4.2%
0.2%
88.9%
10.9%
0.1%
99.1%
0.8%
0.31%
83.2%
16.47%
Pooled analysis
Colorectal lesions
EMR
Lesions ＞10mm
NS
HS
VS


A. Complete resection rate
0.3%
74.0%
25.7%
1.4%
70.5%
28.1%
0.9%
80.5%
18.5%
1.67%
59.9%
38.48%
Pooled analysis
Colorectal lesions
EMR
Lesions >10mm
B. Operation time
0.7%
56.2%
43.1%
2.86%
50.2%
46.96%
1.50%
72.1%
26.44%
Pooled analysis
Colorectal lesions
EMR
C. Total injected volume
0.8%
14.3%
85.0%
2.69%
28.75%
68.6%
1.69%
23.97%
74.3%
3.04%
28.97%
68.0%
Pooled analysis
Colorectal lesions
EMR
Lesions >10mm
D. Cost of submucosal injection solution
45.29%
48.52%
6.18%
47.60%
49.16%
3.24%
48.37%
49.46%
2.17%
42.86%
48.71%
8.43%
Pooled analysis
Colorectal lesions
EMR
Lesions >10mm
E. Recurrence rate
1.0%
86.9%
12.1%
1.12%
84.7%
14.15%
8.90%
46.3%
44.81%
Pooled analysis
EMR
Lesions >10mm
NS
HS
VS


A. Overall bleeding rate
120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.2%
89.9%
9.9%
1.77%
77.9%
20.36%
0.55%
83.7%
15.75%
0.07%
97.1%
2.83%
Pooled analysis
Colorectal lesions
EMR
Lesions ＞10mm
B. Intraoperative bleeding rate
120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.1%
98.8%
1.1%
4.74%
46.15%
49.1%
0.08%
97.9%
2.03%
0.03%
98.2%
1.82%
Pooled analysis
Colorectal lesions
EMR
Lesions ＞10mm
C. Postoperative bleeding rate
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
2.3%
85.2%
12.5%
5.24%
84.1%
10.63%
3.30%
83.0%
13.68%
2.50%
90.7%
6.76%
Pooled analysis
Colorectal lesions
EMR
Lesions ＞10mm
D. Perforation rate
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
3.7%
94.3%
2.1%
3.29%
93.9%
2.82%
3.34%
94.5%
2.15%
4.92%
91.7%
3.37%
Pooled analysis
Colorectal lesions
EMR
Lesions ＞10mm
NS
HS
VS