ASGE review of adverse events in colonoscopy

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Colonoscopy is the most commonly performed endoscopic procedure and overall is considered a low-risk procedure. However, adverse events (AEs) related to this routinely performed procedure for screening, diagnostic, or therapeutic purposes are an important clinical consideration. The purpose of this document from the American Society for Gastrointestinal Endoscopy's Standards of Practice Committee is to provide an update on estimates of AEs related to colonoscopy in an evidence-based fashion. A systematic review and meta-analysis of population-based studies was conducted for the 3 most common and important serious AEs (bleeding, perforation, and mortality). In addition, this document includes an updated systematic review and meta-analysis of serious AEs (bleeding and perforation) related to EMR and endoscopic submucosal dissection for large colon polyps. Finally, a narrative review of other colonoscopy-related serious AEs and those related to specific colonic interventions is included. (Gastrointest Endosc 2019;90:863-76.)

Colonoscopy is a commonly performed endoscopic procedure for various GI conditions and most routinely for the screening and surveillance of colorectal neoplasia. Overall, colonoscopy is considered a safe procedure, although a number of serious adverse events (AEs) have been reported. The definition of serious AEs is variable across studies but generally includes AEs that lead to an unplanned hospitalization, unplanned procedures or interventions, prolongation of an existing hospitalization, or death. Examples include bleeding, perforation, postpolypectomy syndrome, and cardiopulmonary AEs related to moderate or deep sedation.

Few population-based colonoscopy registries provide the exact magnitude of AEs associated with colonoscopy. Estimates of AEs related to colonoscopy in various studies differ by indications, patient population, asymptomatic versus symptomatic individuals, length, and completeness of follow-up after the procedure. In a 2008 systematic review of 12 studies totaling 57,742 colonoscopies performed for average-risk screening, the pooled overall AE rate was 2.8 per 1000 procedures (95% confidence interval [CI], 1.5-5.2),[1] whereas the reported incidence of AEs from mostly diagnostic colonoscopies performed in an integrated healthcare system in the United States was 5 per 1000 procedures (95% CI, 4.0-6.2).[2] In a 2016 evidence synthesis report by the Agency for Healthcare Research and Policy, the authors reported a pooled rate of major bleeding (22 studies; n = 3,347,101) of .8 per 1000 procedures (95% CI, .5-1.4) and rate of perforation of .4 per 1000 procedures (95% CI, .2-.5) for screening colonoscopy.[3] Although the

Abbreviations: AE, adverse event; ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; ESD, endoscopic submucosal dissection; IBD, inflammatory bowel disease; PEDS-CORI, Pediatric Endoscopy Database System-Clinical Outcomes Research Initiative; PPES, postpolypectomy electrocoagulation syndrome; WE, water exchange.

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risk of AEs in most studies are often not stratified by whether or not polypectomy was performed, according to 1 study, 85% of AEs are reported in patients undergoing colonoscopy with polypectomy.[1] With the widespread application of advanced endoscopic techniques for removal of colorectal polyps, including EMR and endoscopic submucosal dissection (ESD), the AEs associated with these advanced techniques are highly relevant.

The aims of this document are to provide evidence-based estimates of the 3 most common and important AEs of colonoscopy (bleeding, perforation, and mortality) from population-based studies, to provide evidence-based estimates of AEs related to EMR and ESD (bleeding and perforation) for large colon polyps, and to provide a narrative-based review of aspiration, splenic injury, and less common AEs. A narrative update of the previous Standards of Practice document[4] on other AEs, such as postpolypectomy syndrome, infection, and gas bloating, is addressed in this document. Risk of AEs as they relate to sedation and the pediatric population are also discussed. Details of various bowel preparations and their respective AEs are discussed in a separate American Society for Gastrointestinal Endoscopy (ASGE) document.[5]

METHODS

Panel composition and conflict of interest management

The panel was composed of 2 primary authors (S.T.K., R.J.H.), a content expert (A.S.), committee chair (S.W.), and members of the Standards of Practice Committee. All panel members disclosed possible intellectual and financial conflicts of interest in concordance with ASGE policies (https://www.asge.org/docs/default-source/about-asge/mission-and-governance/asge-conflict-of-interest-and-disclosure-policy.pdf).

Selection criteria

A search for population-level studies that provided estimates for the major postprocedural endpoints of perforation, bleeding, and mortality was conducted by a professional librarian using Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to present, Embase Classic+Embase 1947 to January 2018, and Wiley Cochrane. In cases of multiple studies from the same group using the same data source (such as a conference proceeding followed by a manuscript), we included only the more recent and extensive of the studies.

Only studies published in English were included for analysis. We included both retrospective and prospective cohort studies with data collected between January 2001 and March 2017 in the study. Prespecified medical subject headings, non–medical subject heading terms, and the search algorithm are shown in Appendix 1 (available online at www.giejournal.org). For estimates of perforation and bleeding after EMR and ESD, we chose case series and comparative trials published between January 2008 and January 2018; this decision was made given the rapid changes in advanced mucosal/submucosal resection techniques within the last decade. We adopted a search algorithm derived from Hassan et al,[6] which is available in Appendix 2 (available online at www.giejournal.org). For EMR, we restricted our analysis to polyps $\geq$20 mm in size.

Two reviewers (S.T.K. and R.J.H.) independently screened all abstracts. Case reports, review articles, cost-effectiveness or modeling studies, and animal studies were excluded. The full text of the remaining articles was evaluated to determine if they met inclusion criteria in the study. For each study the first author, time period, and date of publication were extracted. For population-level studies mean age, percentage of females in the cohort, rates of perforation, bleeding, mortality, and percentage of colonoscopies with polypectomy were recorded. Because only a subset of population-level studies reported the indication for colonoscopy (eg, screening, surveillance, or diagnostic), this variable was not included in the meta-regression analysis. For EMR/ESD studies mean age, percentage of females in the cohort, location of the study (East Asian or Other), rate of perforation, rate of delayed bleeding, and mean polyp size (in mm) was recorded. Delayed bleeding was defined as any clinically significant bleeding that occurred after completion of the procedure up to 30 days postprocedure. Intraprocedural bleeding was not recorded as a separate outcome given the heterogeneity in definition and because almost all cases of reported intraprocedural bleeding were controlled endoscopically during the procedure.

Statistical analysis

A random-effects model was used to calculate the pooled perforation and bleeding rate for both population-level and EMR/ESD studies. Pooled estimates were reported with 95% CIs. Covariates analyzed in regression analysis included mean population age, percentage of females in the cohort, and percentage of polypectomies in the cohort for population-level studies. Covariates analyzed in regression analysis included mean population age, percentage of females in cohort, and size of polyp in EMR/ESD studies. Pooled rates of perforation and bleeding were calculated and grouped by EMR or ESD status. Heterogeneity between studies was measured using the I^2 statistic. Analysis was performed using Comprehensive Meta-Analysis v 3.3.070 (Englewood, NJ).

POPULATION-LEVEL ESTIMATES OF SERIOUS AEs

Twenty-one population-level studies (11 from North America) reporting the rates of perforation, bleeding, or mortality after colonoscopy were identified (Supplementary Table 1, available online at www.giejournal.org). From these studies, data were extracted on 10,328,360 patients undergoing colonoscopy, of which 5,464,324 (54%) were women; the mean age of all patients was 62.3 years.

Perforation

Colonic perforation during colonoscopy may result from mechanical forces against the bowel wall, barotrauma, or a direct result of therapeutic procedures. Early symptoms include persistent abdominal pain and abdominal distention. Colonic perforation can be intraperitoneal or extraperitoneal. Intraperitoneal perforation leads to leak of air and colonic contents into the peritoneum. Plain radiographs of the chest and abdomen may demonstrate free air, although CT is superior to an upright chest film.[7] Therefore, an abdominal CT should be considered for patients with an unrevealing plain film in whom there is a high suspicion of perforation.[4] Rarely, colonic perforation can be extraperitoneal, leading to the passage of air into the retroperitoneal space, which can then diffuse along the fascial planes and large vessels, causing pneumo-retroperitoneum, pneumo-mediastinum, pneumopericardium, pneumothorax, and subcutaneous emphysema. Such patients can have an atypical presentation, including subcutaneous crepitus, neck swelling, chest pain, and shortness of breath after colonoscopy.[8]

The pooled rate of perforations among 10,328,360 colonoscopies was 5.8 per 10,000 colonoscopies (95% CI, 5.7-6.0) (Fig. 1A). Reported population-level perforation rates ranged from a low of 1.6 per 10,000 to a high of 11.9 per 10,000 with significant heterogeneity between studies ($I^2 = 97.6\%$). This heterogeneity in studies may reflect differences in indication, population age, comorbidity, geographic location, and rates of polypectomy between studies. In a meta-regression analysis (Supplementary Fig. 1A, available online at www.giejournal.org), neither age nor gender was significantly associated with perforation rate. Moreover, after adjusting for differences in age and gender between different population-level studies, polypectomy was not significantly associated with risk for perforation ($P = .9$). A previous meta-analysis of population-level studies found a trend toward higher rate of perforation in colonoscopies with polypectomy (8 per 10,000) compared with those without polypectomy (4 per 10,000, $P = .07$).[9] These data suggest that a substantial proportion of the risks of perforation from colonoscopy are related to procedural characteristics independent of the performance of polypectomy, such as the amount of torque or pressure applied to the bowel wall during advancement of the colonoscope or barotrauma from insufflation of the colon. Notably, as discussed later in this article, performance of advanced mucosal resection techniques (EMR and ESD) increases the risk for perforation; however, on a population level, the numbers of these advanced procedures as a percentage of all polypectomies are small. These risk estimates therefore likely accurately reflect the risk that most average-risk patients face when undergoing an examination for screening or surveillance purposes.

Certain populations may face higher risks for perforation during colonoscopy, including patients with diverticulosis and inflammatory bowel disease (IBD).[1,10-13] Mukewar et al[14] found that patients with IBD undergoing colonoscopy were at an 8-fold higher risk for endoscopy-associated perforations compared with patients without IBD (18.91 per 10,000 procedures vs 2.5 per 10,000 procedures). The use of corticosteroids is associated with a 13-fold greater risk for perforation associated with colonoscopy. Certain comorbid conditions also increase the risk for AEs. In a study of U.S. Medicare beneficiaries, Warren et al[15] found that the presence of stroke, chronic obstructive pulmonary disease, atrial fibrillation, and congestive heart failure all significantly increased the risk of AEs due to colonoscopy. In addition to patient factors, provider factors may also influence the procedure risk. Ranasinghe et al[16] found significant variation (median, 12.3/1000; 5th to 95th percentile, 10.5 to 14.6/1000) in rates of AEs after outpatient colonoscopy between both hospital outpatient departments and free-standing ambulatory surgery centers, which could not be explained by case mix alone, raising the possibility that provider experience could be contributing to the variations in rates of AEs. Using administrative data from several large Canadian provinces, Rabeneck et al[17] found that endoscopists performing at volumes in the lowest quintile (<141 colonoscopies per year) had a 2.96 increase in odds of either perforation or bleeding compared with endoscopists performing at volumes in the highest quintile (>379 colonoscopies per year). In addition, Bielawska et al[10] reported that colonoscopies performed by surgeons and endoscopists of unknown specialty had higher perforation rates when compared with gastroenterologists (odds ratio, 2.00; 95% CI, 1.30-3.08).

Bleeding

Unlike perforation, risk for bleeding during colonoscopy appears to be strongly associated with the performance of polypectomy. Postpolypectomy hemorrhage may occur immediately or can be delayed for up to 4 weeks after the procedure. In our systematic review, the rate of bleeding based on 15 population-level studies, including 5,544,454 patients, was 2.4 per 1000 colonoscopies (95% CI, 2.4-2.5) (Fig. 1B). In a meta-regression analysis

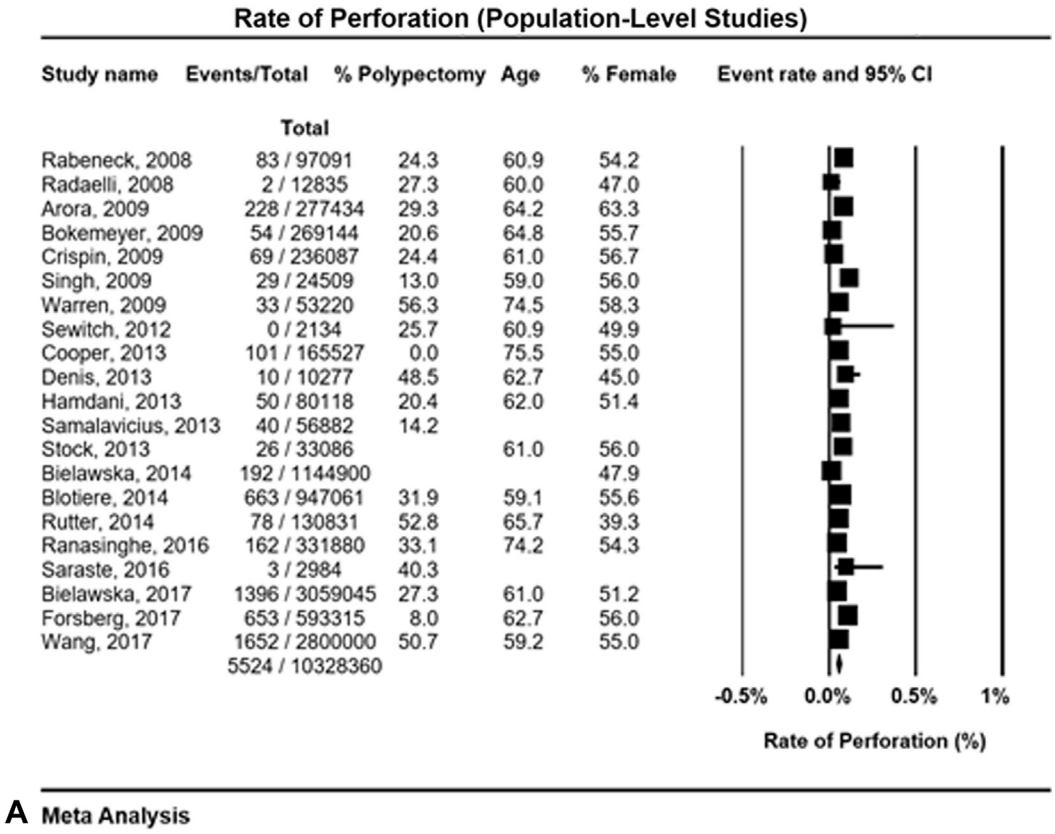


Figure 1. Pooled rates (and 95% CIs) of postcolonoscopy perforation (A), bleeding (B), and mortality (C) from population-level studies. Additional covariates included are percentage of colonoscopies with polypectomy (% polypectomy), mean age, and percentage of cohort that is female (% Female). Data analyzed with a random-effects model. Data for mortality presented as logit of event rate given low event rates. *CI*, Confidence interval.

(Supplementary Fig. 1B, available online at www.giejournal.org), the percentage of colonoscopies involving a polypectomy strongly predicted rates of bleeding, with a 2.7% increase in risk of bleeding for every 1% increase in rate of polypectomy ($P < .001$). This association remained significant after adjustment for age and gender ($P = .016$). The association between performance of polypectomy and risk for bleeding was also observed by Reumkens et al,[9] with findings of significantly more bleeding events after colonoscopies with polypectomy (9.8/1000) compared with colonoscopies without polypectomy (.6/1000, $P < .001$).

Polyp size has been reported as a risk factor for postpolypectomy bleeding in several studies.[18-20] Additional risk factors may include the number of polyps removed,[21,22] recent warfarin therapy,[20,23,24] right-sided colon segment location,[25,26] and polyp histology.[18] Patient comorbidities, such as cardiovascular disease,[18,20] may increase the risk for bleeding but also may be a marker for antithrombotic use.[24] Recommendations for the management of antithrombotic therapy in the periendoscopic period are discussed in detail in an ASGE guideline.[27] The prophylactic use of mechanical methods, such as clips or detachable snares, is commonly performed in practice; however, their efficacy in preventing delayed bleeding after non-EMR polypectomies has not been confirmed. Prospective, randomized studies and a meta-analysis have shown prophylactic clipping for polyps <2 cm does not prevent delayed bleeding,[28-30] but in case of nonpedunculated polyps >2 cm, endoscopic clip closure of the mucosal defect has been demonstrated to reduce the incidence of delayed bleeding events in the proximal colon after resection (see Serious AEs Related to Advanced Resection Techniques, Postprocedural bleeding). Injection of epinephrine before polypectomy was reported to reduce the incidence of intraprocedural bleeding, although there was no demonstrated effect on delayed bleeding.[31,32]

Mortality

Death after colonoscopy has been rarely reported. In a 2010 review of AEs based on prospective studies and retrospective analyses of large clinical or administrative databases, 128 deaths were reported among 371,099 colonoscopies, for an unweighted pooled death rate of .03%, or 3 in 10,000 colonoscopies[33]; all-cause mortality within 30 days occurred in .07% of patients, whereas colonoscopy-specific mortality occurred in .007% of patients. Our systematic review and meta-analysis included only colonoscopy-specific mortality, which was defined as

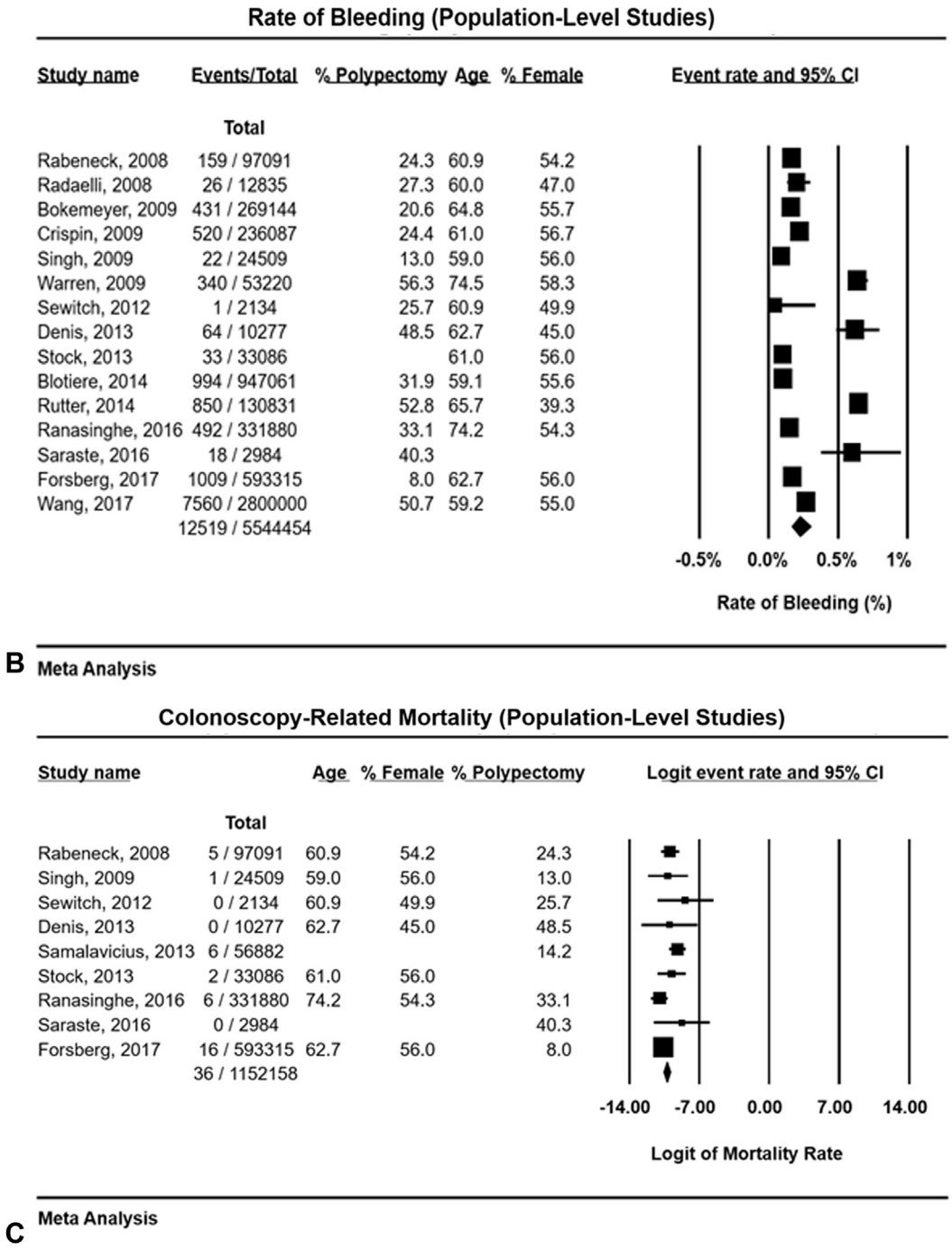


Figure 1. Continued.

death that could be directly attributable to a postprocedural AE (such as perforation) or the management of a postprocedural AE (such as surgery for a perforation). Nine studies reported colonoscopy-associated mortality rates. Thirty-six deaths occurred among 1,152,158 colonoscopies, for a pooled death rate of .003%, or 3 in 100,000 colonoscopies (Fig. 1C). Because of the small number of population-level studies reporting mortality data, meta-regression was not performed for the endpoint of mortality. Of the studies that reported both all-cause and colonoscopy-specific mortality, most deaths within 30 days of colonoscopy were not attributable to postcolonoscopy AEs but rather to underlying comorbidities such as cardiopulmonary disease, cirrhosis, and neurologic diseases. Most causes of death directly attributable to colonoscopy were either cardiopulmonary events that occurred

during or immediately after the procedure or sequelae of bowel perforation.

SERIOUS AEs RELATED TO ADVANCED RESECTION TECHNIQUES

With enhancements in endoscopic technology, the role of the endoscopist has expanded to removal of large benign polyps and polyps harboring early cancers using advanced techniques such as EMR and ESD. As with standard polypectomy, bleeding and perforation are the most common AEs with EMR and ESD, but they occur more frequently with these advanced techniques. The reported AE rates vary. Lesion size, location, and histology and operator experience may all contribute to this variability.[36-38]

We systematically analyzed the rates of the major endpoints of perforation and bleeding after both EMR of polyps ≥20 mm in size and ESD while also controlling for covariates of age, gender, location of the study, and polyp size. Rates of AEs were analyzed separately for EMR and ESD. Our search strategy yielded 29 studies, including 8237 unique procedures (Supplementary Table 2, available online at www.giejournal.org). Of the studies, 14 were reported from East Asia and 15 from either North America, Europe, or Oceania (Western).

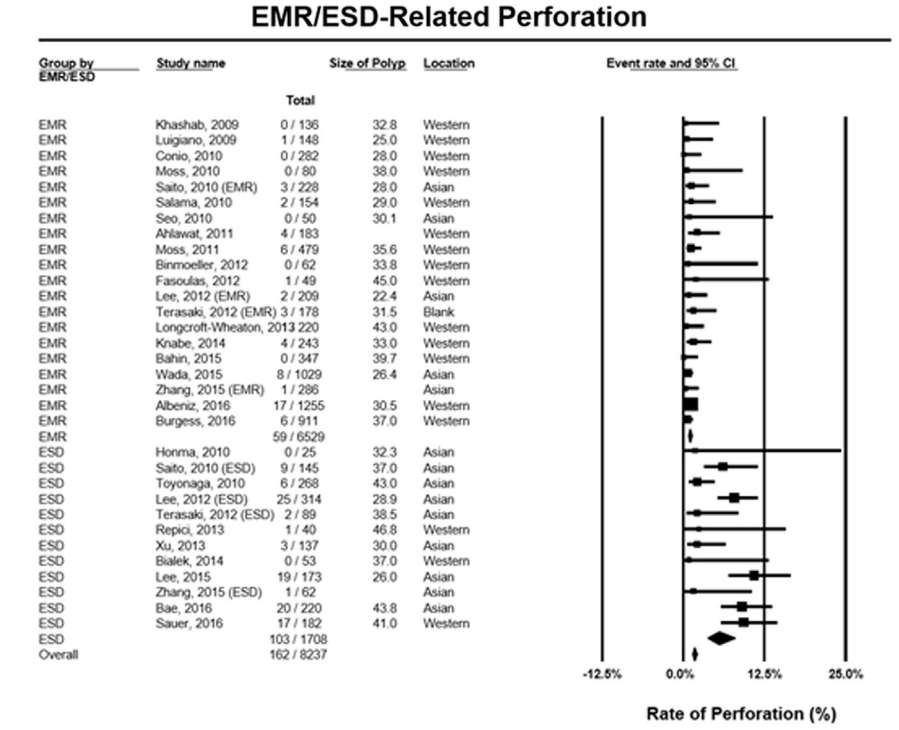
Perforation

Twenty studies included in this analysis reported data on perforation rate after EMR. Of 6529 procedures, 59 were complicated by a perforation for a pooled rate of 1.1% (95% CI, .9%-1.4%) (Fig. 2A). There was substantial heterogeneity between studies (I^2 = 83%), with reported rates ranging from .1% to 2.2%. Reasons for this heterogeneity include differences in definition of perforation, differences in polyp size and shape, center experience, and time period of study. Mortality appeared to be low, as no series reported fatalities as sequelae of perforation. Perforation is a term that may incorporate a spectrum of levels of deep mural injury; some have proposed a grading system for levels of mural injury ranging from muscularis propria exposure to full-thickness injury with a visualized hole and observed contamination.[34] Although delayed perforation can occur, most cases of perforation captured in this review were immediately apparent to the endoscopist. The "target sign," which represents concentric resection of progressively deeper layers of mural tissue and appears on the transected surface of the polypectomy specimen as a white to gray circular disk (the "target") surrounded by a web of submucosal tissue that is then encircled by the white cauterized mucosa (Fig. 3), has been suggested as an early marker of perforation that can be visualized endoscopically.[35] It represents a sign of muscle injury that can be either a full-thickness perforation or a partial muscle injury.

Twelve studies reported data on perforation after ESD, and the rate of perforation after ESD was nearly 7-fold higher than after EMR, with a pooled rate of 7.2% (103/1708 procedures; 95% CI, 6.0%-8.7%) (Fig. 2A); importantly, however, no fatalities from perforation were reported from these studies. Because perforation is frequently encountered by endoscopists performing colonic ESD, prompt recognition of muscularis propria tissue along the dissection plane is essential. Most series captured in this meta-analysis reported that immediate perforations could usually be closed by deployment of endoscopic clips with very few patients requiring surgery.[36-39] Meta-regression was performed analyzing factors predicting perforation from advanced resection techniques (Supplementary Fig. 2A, available online at www.giejournal.org), pooling both EMR and ESD. The strongest and only predictor of perforation was the performance of ESD (as compared with EMR). In the subgroup of studies that reported perforation after both EMR and ESD, rates of perforation after ESD were between 5- and 8-fold higher compared with EMR.[36,40,41] The mean size of the polyps removed, location of study, and study date were not associated with risk of perforation.

Postprocedural bleeding

Because intraprocedural bleeding prompts immediate therapy and because all advanced tissue removal techniques are usually associated with some degree of intraprocedural bleeding, we only included rates of postprocedural bleeding in our systematic review. We found 27 studies that reported delayed bleeding rates after EMR (19 studies) and ESD (11 studies) (with a follow-up period of up to 30 days after colonoscopy), with a pooled rate of 3.7% (95% CI, 3.2%-4.2%) (Fig. 2B) and a range of .2% to 8.4%. As with perforation, substantial heterogeneity was noted (I^2 = 66%). Unlike perforation, however, the rate of delayed bleeding was not statistically higher after ESD. Of the 11 studies reporting on rates of delayed bleeding after ESD (8 Asian and 3 Western), we found a pooled rate of 2.2% (95% CI, 1.5%-3.0%). By contrast, the EMR cohort experienced a pooled delayed bleeding rate of 4.0% (95% CI, 3.5%-4.5%). In a meta-regression analysis (Supplementary Fig. 2B, available online at www.giejournal.org), ESD was not associated with higher postprocedural bleeding rates compared with EMR. Polyp size, location, and year of study (temporal trend analysis) were also not associated with higher rate of delayed bleeding. The overwhelming majority of reported bleeding episodes were treated conservatively (blood transfusions, close observation with spontaneous resolution) or with endoscopic therapy. No fatalities from bleeding were reported. Other studies have reported that the following factors are associated with an increased risk for delayed bleeding: right-sided colon location, use of electrosurgical current not controlled by a microprocessor, intraprocedural bleeding at the time of polyp removal,



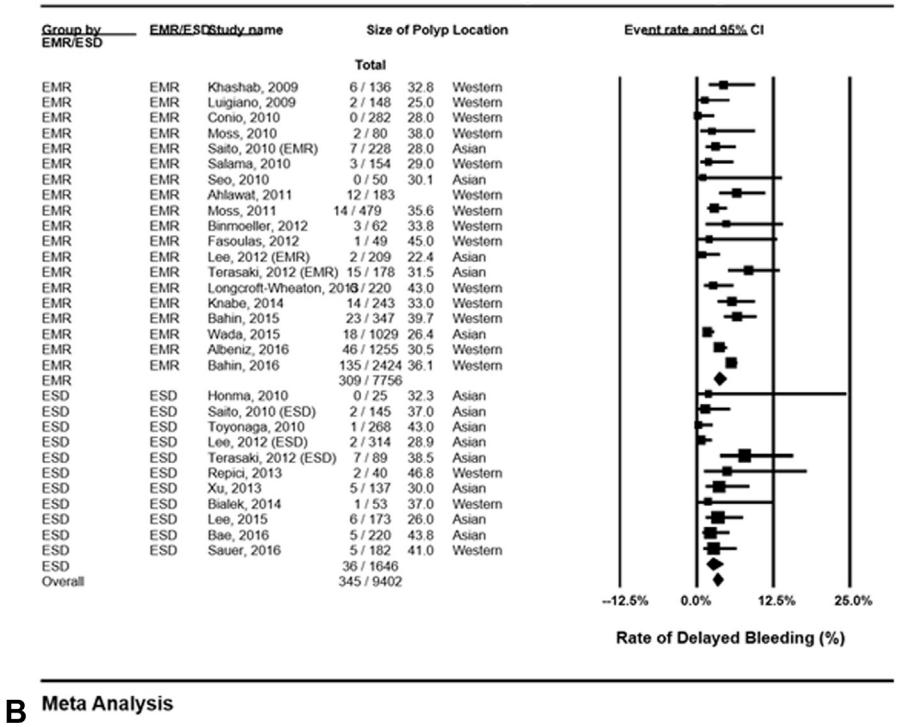


Figure 2. Pooled rates (and 95% CIs) of EMR/ESD-related perforation (A) and delayed bleeding (B) stratified by performance of EMR or ESD. Additional covariates included are mean diameter of polyp and location of study (Asian or Western). Data analyzed with a random-effects model. *CI*, Confidence interval; *ESD*, endoscopic submucosal dissection.

Figure 3. The "target sign" appears on the transected surface of the polypectomy specimen as a white to gray circular disk (the "target") surrounded by a web of submucosal tissue that is then encircled by the white cauterized mucosa.

exposed vessels of the post-EMR ulcer, signs of coagulation injury to the resection bed, and use of anticoagulants.[22,42-44]

The intraprocedural bleeding rate in the literature is over 10% in several large series, with delayed bleeding reported in 1.5% to 14% of cases.[45,46] In their large case series of 479 large sessile polyps that underwent EMR, Moss et al[47] reported the following rates of AEs: hospitalization, 7.7%; postprocedural pain, 2.1%; serositis, 1.5%; bleeding (mostly immediate), 2.9%; and perforation, 1.3%. There were no deaths. Others have reported rates of immediate and delayed bleeding of 11% and 7%, respectively.[48] Immediate bleeding can be treated with endoscopic therapy during the procedure but adds to procedure time. Most clinical bleeding AEs stop without intervention, although the need for transfusions has been reported.[49] Previous studies on prophylactic hemoclip placement for minimizing risk of postpolypectomy bleeding in patients not on anticoagulation have not shown a reduction in bleeding rates.[30,50] However, recent data from a randomized controlled trial demonstrated that endoscopic clip closure of the mucosal defect after resection of large colon polyps (≥20 mm) reduces the risk of postpolypectomy bleeding (3.5% for the clip group vs 7.1% for the control group; absolute risk difference, 3.6%; 95% CI, .7-6.5), an effect that appeared to be restricted to large polyps in the proximal colon (3.3% in the clip group vs 9.6% in the control group; absolute risk difference, 6.3%; 95% CI, 2.5-10.1.[51] Prophylactic clipping postresection of polyps <20 mm in size has not been shown to reduce the risk of postpolypectomy bleeding.[29]

OTHER AEs RELATED TO COLONOSCOPY

In this section we provide a narrative review of other AEs related to colonoscopy.

Postpolypectomy electrocoagulation syndrome

Postpolypectomy electrocoagulation syndrome (PPES) is the result of electrocoagulation-induced thermal injury during standard polypectomy, EMR, or ESD to the bowel wall that causes a transmural burn and localized peritonitis without evidence of frank perforation on radiographic studies. Typically, patients with PPES present 1 to 5 days after colonoscopy with fever, localized abdominal pain, localized peritoneal signs, and leukocytosis without any radiologic evidence of perforation. The reported incidence varies widely, from 1 in 100 (1%) to 3 per 100,000 (.003%).[2,33,52,53] The incidence is higher (7%-8%) in patients undergoing ESD.[54] PPES usually is managed with intravenous hydration, broad-spectrum parenteral antibiotics, bowel rest, and nothing by mouth until symptoms subside.[2,53] In a large multicenter study, hypertension, large lesion size (>2 cm), and nonpolypoid morphology were found to be independent predictors of PPES. Thirty-four patients had PPES in this study, with 2.9% of patients requiring intensive care unit stay and no mortality.[53] Full-thickness burns may result in bowel necrosis and delayed perforation, thereby requiring surgical management. Removal of right-sided lesions is likely to be associated with a higher risk of wall injury because of the thinner colonic wall.[55] Submucosal injection of saline solution and other lifting agents are frequently performed to minimize the risk of PPES during endoscopic removal of large polyps.[55,56] Other techniques reported to decrease the risk of PPES include tenting the polyp away from the colonic wall before applying electrocautery, cutting the stalk of pedunculated polyps one-half or one-third of the distance from the base of the pedicle, and suctioning air out of the colon, especially in the right-sided colon segment, to minimize tension on the wall and increase colonic wall thickness.[57]

Abdominal discomfort and/or bloating

Postcolonoscopy abdominal pain can be because of a host of serious AEs as discussed above; however, abdominal discomfort and/or bloating is a less severe but very common AE postcolonoscopy and can affect patient compliance with future colonoscopies.[33,58] The discomfort may be caused by colonic spasm, gaseous distention of the colon, and mechanical or barotrauma. The most commonly reported minor AEs of colonoscopy are bloating (2.6%-25%) and abdominal pain and/or discomfort

(2.5%-11%).[58-61] Appropriate techniques, such as avoiding and reducing endoscope looping and minimizing air insufflation, should help reduce these symptoms.[62] In addition, a systematic review and meta-analysis of randomized controlled trials demonstrated less postprocedure pain with carbon dioxide compared with standard air insufflation.[63] Water immersion and water exchange (WE) techniques that avoid air insufflation also may reduce pain, especially when minimal or no sedation is used. A meta-analysis and systematic review comparing air insufflation and water-aided methods (water immersion and WE) for procedure-related pain revealed both water immersion and WE to be superior to air insufflation.[64] Studies comparing water-aided colonoscopy with CO_2 insufflation have reported water immersion and WE significantly reduced colonoscopy insertion pain, and WE was the least painful technique but was the most time consuming.[65,66] Postcolonoscopy abdominal discomfort because of gaseous distention is usually self-limited and rarely requires hospitalization.

Gas explosion

Explosive AEs from colonoscopy are rare but have serious consequences.[4] A 2007 review reported 9 cases, each resulting in colonic perforation and in 1 case, death.[67] Gas explosion can occur when combustible levels of hydrogen or methane gas are present in the colonic lumen, oxygen is present, and electrosurgical energy is used (eg, electrocautery or argon plasma coagulation). Suspected risk factors are use of nonabsorbable or incompletely absorbable carbohydrate preparations, such as mannitol, lactulose, or sorbitol,[68,69] and incomplete colonic cleansing either because a sigmoidoscopy preparation was used (eg, enemas) or because of inadequate colonoscopic preparation.[70] Some authors have advocated use of CO_2 during colonoscopy and avoiding enema-only bowel prep before applying argon plasma coagulation for treatment of radiation proctitis.[71] Bowel preps such as polyethylene glycol and sodium phosphate are reportedly safer before use of electrocautery and argon plasma coagulation because they do not result in combustible levels of hydrogen and methane.

Infection

Transient bacteremia after colonoscopy, with or with polypectomy, causing bacterial translocation of normal colonic flora to the bloodstream can occur in approximately 4% of procedures, with a range of 0% to 25%.[72] However, signs or symptoms of infection are rare. Bacteremia is uncommon (6.3%) even after therapeutic colon procedures such as colonic stent insertion.[73] Although individual cases of infection after colonoscopy have been reported, there is no definite causal link with the endoscopic procedure and no proven benefit for antibiotic prophylaxis.[74] Therefore, current guidelines from the American Heart Association and ASGE recommend against antibiotic prophylaxis for patients undergoing colonoscopy.[75] The 2016 update of the multisociety guideline on reprocessing flexible GI endoscopes reported cases of transmission of infection resulting from defective equipment and/or failure to adhere to reprocessing guidelines.[76] Pneumonia and perirectal abscess have been reported after colonoscopy.[77] Pneumonia is mostly because of aspiration related to sedation and less commonly directly related to the procedure, as discussed in detail below in Sedation-related AEs.

Splenic injury

Splenic injury is a rare but serious AE of colonoscopy. It can develop immediately or up to several days after the procedure, making diagnosis difficult. The true incidence is unknown because of variability in reporting, but the reported rates from large series are 1 in 10,000 to 4.5 per 10,000 colonoscopies.[78,79] These patients are usually women (71.5%) in their sixth decade.[79] A high degree of suspicion is necessary because the clinical presentation can be nonspecific and variable in timing. Because of the high morbidity and mortality (up to 5%) associated with this entity, early identification and treatment are critical. Suggested mechanisms that may cause splenic injury during colonoscopy include direct trauma as the colonoscope traverses the splenic flexure of colon or rupture of the splenic capsule because of traction on the splenocolic ligament or adhesions. Suggested risk factors for splenic injury can be divided into patient-related and procedure-related factors. Suggested patient-related risk factors for splenic injury include prior abdominal surgery, presence of splenocolic adhesions, splenomegaly, endometriosis, inflammation (diverticular disease, IBD, pancreatitis), infection (malaria, typhoid, Epstein-Barr virus–induced infectious mononucleosis), and anticoagulant use.[79,80] Proposed procedure-related risk factors include difficult colonoscopy, deep sedation with propofol, operator inexperience, supine position, maneuvers such as hooking the splenic flexure to straighten the colon, "slide by" technique and alpha maneuver, and applying abdominal pressure in the left hypochondrium. The splenic injury can be intraparenchymal, subcapsular, or with intraperitoneal extension.

There are 5 grades of splenic injury based on severity (Table 1).[81] Clinical presentation can vary, and the patient may present with nonspecific abdominal discomfort or abdominal pain that can be diffuse or localized to the left upper quadrant of the abdomen or left shoulder pain (Kehr's sign) occurring within 24 hours of the procedure or, less commonly, delayed by days. Rarely, patients present with hemodynamic shock. Laboratory tests can reveal anemia. The criterion standard for diagnosis is contrast-enhanced CT of the abdomen that enables evaluation of the grade and extent

TABLE 1. Spleen injury scale

Grade	Injury description
I	Hematoma subcapsular <10% surface area Laceration capsular tear <1 cm parenchymal depth
II	Hematoma subcapsular 10%-50% surface area; intraparenchymal <5 cm in diameter Laceration 1-3 cm parenchymal depth that does not involve a trabecular vessel
III	Hematoma subcapsular >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma Intraparenchymal hematoma >5 cm or expanding Laceration >3 cm parenchymal depth or involving trabecular vessels
IV	Laceration involving segmental or hilar vessels producing major devascularization (>25% of spleen)
V	Completely shattered spleen Hilar vascular injury that devascularizes spleen

of the splenic injury. US can be useful in assessing splenic injury in patients with hemodynamic instability and for those with contraindication to contrast-enhanced CT (allergy, renal insufficiency, etc). Management options include a conservative approach, splenic artery embolization, and surgery. The treatment option chosen is based on the presentation, underlying comorbidities, and imaging findings. Hemodynamically stable patients can be managed conservatively with close monitoring, intravenous fluids, blood transfusion, and antibiotics. However, some patients may fail a conservative approach and require surgery or splenic artery embolization. For hemodynamically stable patients with grades I to IV lacerations and no history of splenic disease, embolization of the splenic artery has been reported to be an effective therapeutic option.[82] Splenectomy is usually reserved for cases with active bleeding and hemodynamic instability.

Sedation-related AEs

In hospital- and population-based studies, the incidence of aspiration events requiring hospitalization after colonoscopy with moderate or deep sedation is generally low ($\leq$1 in 1000). In a population-based study, the incidence of aspiration requiring hospitalization during 165,527 outpatient diagnostic colonoscopies in 100,359 Medicare patients age 66 years and older (mean age, 76 years) was .14% for patients having colonoscopy under deep sedation with anesthesia assistance and .10% for patients under moderate sedation without anesthesia assistance (P = .02).[83] A study of 23,508 outpatient colonoscopies at 3 hospitals in Australia reported 1 case (.004%) of aspiration requiring hospitalization in a patient undergoing colonoscopy with general anesthesia.[84] A study of 3155 colonoscopies performed with patients under sedation managed by an anesthesiologist in adults at a single hospital in Italy reported that .16% of patients undergoing colonoscopy had an aspiration requiring "some intervention by an anesthesiologist."[85] Aspiration requiring hospitalizations was not reported. Others have investigated the risk of colonoscopy-associated aspiration using monitored anesthesia care/anesthesia assistance, with mixed results. Wernli et al[86] did not find an increased risk of aspiration pneumonia between anesthesia-assisted colonoscopy and standard sedation (odds ratio, 1.03; 95% CI, 1.00-1.06). However, their study population was limited to patients aged 40 to 64 years. A recent population-based cohort study of 3,059,045 outpatient colonoscopies, of which 862,817 were anesthesia assisted, reported that use of anesthesia assistance was associated with an increased risk of aspiration pneumonia (odds ratio, 1.63; 95% CI, 1.11-2.37) compared with colonoscopies performed without anesthesia assistance.[78]

It is commonly believed that aspiration risk is related to duration of nothing by mouth status before colonoscopy. A recent systematic review and meta-analysis[87] found 6 studies (4 randomized controlled trials and 2 observational studies; sample size ranging from 115 to 1345) that reported risk of aspiration based on different durations of nothing by mouth status.[88-93] In 5 studies no aspirations occurred during colonoscopy and none was reported within 30 days after colonoscopy.[88-91,93] In 4 studies bowel preparation was completed at least 2 to 4 hours before colonoscopy. Overall, this systematic review found low-grade evidence that risk of aspiration is not related to duration of nothing by mouth status beyond 2 hours. Similarly, consumption of split-dose bowel prep within 3 to 4 hours of propofol sedation has not shown to increase risk of aspiration.[94]

AEs IN THE PEDIATRIC POPULATION

Overall rates of AEs from pediatric colonoscopy are uncommon, occurring in 1.1% to 2.4% of cases. Data collected prospectively from the Pediatric Endoscopy Database System-Clinical Outcomes Research Initiative (PEDS-CORI), a pediatric component of CORI, on 7792 colonoscopies reported 88 cases with at least 1 serious AE (1.1%).[95] From this database the most common AE was bleeding, occurring in .38% of cases. During colonoscopy,

71% of bleeding occurred in children under 10 years of age. Of 348 patients undergoing polypectomy, 5 (1.4%) had clinically significant bleeding. Hypoxemia was reported in 25% of those with an AE, with more cases using moderate sedation compared with general anesthesia ($P < .001$). Perforation during colonoscopy has been reported in several large series.[95-98] Kramer and Narkewicz[96] reported a perforation rate of 3.1% during polypectomy but none during diagnostic colonoscopy. PEDS-CORI reported a single case (.1%) of perforation in a patient with active IBD. Similarly, in a retrospective single-center study based on surgical records, 3 colonoscopy-related perforations occurred out of 3269 procedures (.09%).[96] All perforations were recognized within 24 hours, including 1 intraprocedure, and all were operatively repaired. In another large retrospective study based on physician recall of 7100 patients, 2 perforations occurred, both in patients with IBD: 1 was recognized periprocedure and the other 3 days postprocedure.[97] Several case reports also describe an increased risk of perforation in patients with Ehlers-Danlos type 4, because these patients may also have spontaneous perforation.[99,100]

One of the limitations of PEDS-CORI is that it predominantly reflects intraprocedure information and likely underestimates postprocedural events. A single-center prospective observational study of 9577 procedures (1819 diagnostic colonoscopies) with designated AE terminology tracked pediatric patients within 72 hours of an endoscopic procedure.[96] The authors identified an AE rate of 2.4% (with a minimum of referral to an emergency department) and a polypectomy AE rate of 10.9%, taking into account events beyond the immediate postprocedure threshold. This disproportionate rate likely reflects a bias in children toward increased evaluation when there is a concern for a postprocedure AE. Bleeding risk and serious infection rates were .11% and .07%, respectively; however, data included both upper and lower endoscopic procedures. This study also provided more global AE rates rather than procedure-specific rates.

At least in children under 3 years of age, there is a potential neurocognitive risk for prolonged and repeated procedures.[101] Thus, prolonged, incomplete, or nondiagnostic studies necessitating additional procedures may have longer term effects beyond standard 24-hour or 30-day AE rate statistics. Pediatric-specific colonoscopy quality indicators (eg, bowel preparation quality and ileal intubation rates) may indirectly assess these risks beyond costs, patient inconvenience, and other factors compared with adult patients.[102-104]

Taken together, overall rates of AEs during pediatric colonoscopy are uncommon (1.1%-2.4%) and most often associated with polypectomy. As in adults, significant AEs include bleeding and perforation (.02%-.1%). Pediatric patients with IBD and those with polyps may also be at higher risk of AEs. Research gaps include standardizing AE definitions in pediatric patients and assessing disease-specific risks, the relationship of AEs to pediatric quality indicators, and the role of postprocedural bleeding and closure techniques.

OTHER RARE AEs RELATED TO COLONOSCOPY

Other rare AEs associated with colonoscopy and interventions, such as acute appendicitis and acute diverticulitis, are summarized in the Supplementary Text (available online at www.giejournal.org).

CONCLUSION

Colonoscopy is the most commonly performed endoscopic procedure, and AEs are inherent to its performance. This document provides evidence-based estimates of AEs related to colonoscopy based on population-based studies, AEs related to advanced mucosal resection techniques (EMR and ESD), and a narrative update on other AEs associated with colonoscopy. Even though significant heterogeneity was seen in several analyses, the overall estimates of AEs have remained stable. Because endoscopy has assumed a more therapeutic role in the management of various colonic disorders, the potential for AEs increases. Improved knowledge of potential endoscopic AEs, their expected frequency, and the risk factors associated with their occurrence may help to minimize the incidence by careful selection of measures to help mitigate the risks associated with colonoscopy and other specific colonoscopic interventions[4] Endoscopists are expected to carefully select patients for the appropriate intervention, be familiar with the planned procedure and available technology, and be prepared to manage any AE that may arise. Early recognition and prompt intervention are essential as soon as an AE occurs to help minimize associated morbidity and mortality. Tracking and monitoring AEs as part of a continuing quality improvement process may serve to educate endoscopists, help to reduce the risk of future AEs, and improve the overall quality of colonoscopy. Also, centralized reporting of AEs in the future may help in the development of a robust database, allowing for a better understanding of the true estimates of AEs and thereby serve for safety and quality targets in colonoscopy practice.

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APPENDIX 1. SEARCH STRATEGY FOR POPULATION-LEVEL STUDIES

Search date: March 19, 2017

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to present, Embase Classic+Embase 1947 to 2017 March 17, Wiley Cochrane

Ovid MEDLINE, Embase

#	Searches	Results
1	*Colonoscopy/	27,391
2	*endoscopic polypectomy/ use emczd or Colonic Polyps/su	4512
3	colonoscop*.ti.	22,610
4	(colon* adj2 polypectom*).ti,ab.	2031
5	or/1-4	35,626
6	exp *Postoperative Complications/ use ppez	243,109
7	exp *postoperative complication/ use emczd	172,778
8	exp *Intraoperative Complications/ use ppez	22,563
9	exp *peroperative complication/ use emczd	6076
10	exp *Gastrointestinal Hemorrhage/	68,570
11	((gi or gastrointestin* or intestin* or colon) adj2 (bleed* or hemorrag* or haemorrag*)).ti,ab.	50,205
12	exp *Intestinal Perforation/ use ppez	8581
13	exp *digestive system perforation/ use emczd	18,243
14	((gi or gastrointestin* or intestin* or colon) adj2 perforation*).ti,ab.	10,029
15	exp Mortality/	1,339,415
16	mortality.ti,ab.	1,467,173
17	exp Anesthesia/ae, mo [Adverse Effects, Mortality]	24,321
18	exp *anesthesia complication/ use emczd	4365
19	exp Colon/in [Injuries]	1691
20	exp colon injury/ use emczd	2802
21	(adverse or complication*).ti.	351,154
22	or/6-21	2,814,327
23	5 and 22	5594
24	limit 23 to english language	4834
25	limit 24 to yr="1980 -Current"	4690
26	animals/ not (humans/ and animals/)	5,550,858
27	25 not 26	4667
28	limit 27 to (case reports or comment or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,Embase; records were retained]	1012
29	Case Report/	4,116,817
30	27 not (28 or 29)	3264
31	remove duplicates from 30	2452

Wiley Cochrane

Search Name: Colonoscopy-Adverse Events

Date Run: 19/03/17 15:32:25.423

Description:

ID	Search	Hits
#1	medical subject headings (MeSH) descriptor: [Colonoscopy] explode all trees	1914
#2	colonoscop*:ti	1738
#3	#1 or #2	2718
#4	MeSH descriptor: [Postoperative Complications] explode all trees	33,491
#5	MeSH descriptor: [Intraoperative Complications] explode all trees	4022
#6	MeSH descriptor: [Gastrointestinal Hemorrhage] explode all trees	1901
#7	((gi or gastrointestin* or intestin* or colon) near/2 (bleed* or hemorrag* or haemorrag*)):ti,ab	1443
#8	MeSH descriptor: [Intestinal Perforation] explode all trees	148
#9	((gi or gastrointestin* or intestin* or colon) near/2 perforation*):ti,ab	188
#10	MeSH descriptor: [Mortality] explode all trees	12981
#11	mortality:ti,ab	37,315
#12	(adverse or complication*):ti	7476
#13	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	87,576
#14	#2 and #13	93

APPENDIX 2. SEARCH STRATEGY FOR COLONOSCOPIES WITH EMR/ENDOSCOPIC SUBMUCOSAL DISSECTION

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to present, Embase Classic+Embase 1947 to 2017, Wiley Cochrane

MEDLINE/Embase

1	exp Colon/ or exp Rectum/	20,3534
2	(colon or rectum or colorectal).ti,ab.	63,8072
3	1 or 2	72,4789
4	exp Colonic Polyps/ use ppez	7675
5	exp Colon Polyp/ use emczd	19,639
6	exp Polyps/ use ppez	29,762
7	exp Polyp/ use emczd	67,959
8	exp Adenoma/	198,527
9	exp Neoplasms/ use ppez	3,034,373
10	exp Neoplasm/ use emczd	4,099,596
11	(colon* and polyp*).ti,ab.	51,289
12	(colonic polyps or colon polyp* or polyps or polyp* or lesion* or adenoma* or adenomatous or neoplasia*).ti,ab.	2,574,943
13	or/4-12	8,798,252
14	(Polypectomy or removal or EMR or ESD).ti,ab.	722,293
15	(endoscopic resection or mucosectomy or endoscopic submucosal resection).ti,ab.	12,082
16	exp Colonoscopy/	89,383
17	tu.fs.	2,074,126
18	th.fs.	3,105,206
19	16 and (17 or 18)	8307
20	14 or 15 or 19	738,992
21	3 and 13 and 20	17,176
22	limit 21 to yr="2014 - 2017"	4424
23	remove duplicates from 22	3442
24	(30 mm or 3 cm or large or 20 mm or 2 cm).ti,ab.	2,907,929
25	23 and 24	938

Wiley Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Colon] explode all trees	1504
#2	MeSH descriptor: [Rectum] explode all trees	1358
#3	(colon or rectum or colorectal):ti,ab	15,101
#4	MeSH descriptor: [Colonic Polyps] explode all trees	371
#5	MeSH descriptor: [Polyps] explode all trees	832
#6	MeSH descriptor: [Adenoma] explode all trees	1053
#7	MeSH descriptor: [Neoplasms] explode all trees	61,680
#8	(colon* and polyp*):ti,ab	1037
#9	(colonic polyps or colon polyp* or polyps or polyp* or lesion* or adenoma* or adenomatous or neoplasia*):ti,ab	31,393
#10	#1 or #2 or #3	16,364
#11	#4 or #4 or #6 or #7 or #8 or #9	88,559
#12	(Polypectomy or removal or EMR or ESD):ti,ab	11,648
#13	(endoscopic resection or mucosectomy or endoscopic submucosal resection):ti,ab	750
#14	MeSH descriptor: [Colonoscopy] explode all trees	1947
#15	#12 or #13 or #14	13,971
#16	(30 mm or 3 cm or large or 20 mm or 2 cm):ti,ab	70,321
#17	#10 and #11 and #15 and #16 Publication Year from 2014 to 2017, In trials	105

SUPPLEMENTARY TABLE 1. Evidence table for the population studies

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
Beilawska et al. (2014)	Retrospective analysis using Clinical Outcomes Research Initiative National Endoscopic Database	**Inclusion Criteria:** All complete and incomplete colonoscopies. Colonoscopies involving patients over 18 years of age from January 2000 through March 2011 **Exclusion criteria:** Flexible sigmoidoscopies Procedures performed by Pediatric Gastroenterologists.	N = 1,144,900 Male 596220 (52.1) Female 548484 (47.9) Age = <60 years 566913 (49.5) 60 - 74 yrs 426222 (37.2) >= 75 yrs 151140 (13.2) Unknown 433 (0.04)	0.017% or 1 in 5882 procedures.	Not reported	Not reported	" Early perforation" recorded referred to a perforation discovered before the procedure report is signed off at the end of the colonoscopy Patients aged 60-74 years had an OR of 2.69 (95% CI, 1.83 - 3.98) and those 75 years and older had an OR of 5.63 (95% CI, 3.73 -8.49) toward increased early perforation compared with those aged 60 years and younger. Increasing ASA class was also associated with increasing early perforation risk, with patients in ASA Class III and above having greatest risk. Female gender was also a significant independent risk factor (OR 2.00). Any therapy (OR 3.93) and large polyp size (OR 4.14) were highly significant risk factors for early perforation
Blotiere et al. (2014)	Retrospective study based on SNIIRAM and the PMSI databases.	**Inclusion Criteria:** Total or partial colonoscopy in 2010 **Exclusion Criteria:** patients with a history of chronic inflammatory bowel disease (ICD10 codes K50 and K51) or colorectal cancer (ICD10 code C16-C26) Patients who had already undergone colonoscopy during the 12 months preceding the first colonoscopy performed in 2010	N = 947,061 Men = 420,852 (44.4%) Age = 0—39 92,188 (9.7%) 40—49 143,604 (15.2%) 50—59 249,746 (26.4%) 60—69 252,689 (26.7%) 70—79 155,861 (16.5%) 80 and older 52,973 (5.6%)	Between 4.5 and 9.7 per 10,000 procedures	Between 9.9 and 11.0 per 10,000 procedures	Not reported	The main risk factors associated with perforation and hemorrhage were patient's age (over 80 years compared to under 40, OR = 7.51 and 3.23), resection of polyps larger than 1 cm or more than 4 polyps (compared to no polypectomy, OR = 2.72 and 5.12) and emergency colonoscopy (OR = 4.63 and 5.99). Colonoscopy performed by a gastroenterologist performing less than 244 colonoscopies per year was associated with an increased risk of perforation (OR = 2.29).

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
Rutter et al. (2014)	Population based study	**Inclusion criteria:** All colonoscopies performed in the NHSBCSP between the start of the program in 2006 and January 2012 **Exclusion criteria:** Not reported	N = 130831 colonoscopies (167208 polypectomies) were analyzed, including 30 881 single polypectomies. Male = 60.7% Mean age = 65.7 years (59-92 years)	Overall 0.06% Diagnostic colonoscopy 0.03% Therapeutic colonoscopy 0.09%	Overall 0.65% Diagnostic colonoscopy 0.10% Therapeutic colonoscopy 1.14%		The overall rate of adverse events was 1.42% (1 in 71 procedures). Polypectomy increased bleeding risk 11.14-fold and perforation risk 2.97-fold. Cecal location (but not elsewhere in the proximal colon) and increasing polyp size were the two most important risk factors for bleeding and perforation
Ranasinghe et al. (2016)	Population based study	**Inclusion criteria:** Medicare FFS patients aged ≥65 years undergoing outpatient colonoscopy at HOPDs, ASCs, and physician office settings. Common nonhigh-risk outpatient diagnostic and therapeutic colonoscopy procedures with or without biopsy, lesion ablation, and/or polypectomy. only patients with continuous enrollment in Medicare FFS Parts A and B in the 12 months before the procedure **Exclusion criteria:** High-risk patient groups undergoing colonoscopy Colonoscopies that occurred concurrently with high-risk upper gastrointestinal endoscopies, such as for control of bleeding; and colonoscopies for patients with a history	N = 331,880 Number of facilities = 8140 Female = 180,313 (54.3%) Age = 65-69 = 98,248 (29.6%) 70-74 = 101,555 (30.6%) 75-79 = 72,984 (22 %) 80-84 = 42,021 (12.7%) 85 + = 17,072 (5.1%) Mean age = 74.2 years	3 %	6.4%	6/331,880 . 0.002%	Outpatient colonoscopies were followed by 5412 unplanned hospital visits within 7 days (16.3/1000 colonoscopies). A history of disorders of fluid and electrolyte balance (odds ratio [OR] . 1.43; 95% confidence interval [CI]: 1.29_1.58), psychiatric disorders (OR . 1.34; 95% CI: 1.22_1.46), and, in the absence of a history of arrhythmia, increasing age >65 years (age >85 years vs 65 - 69 years; OR . 1.87; 95% CI: 1.54_2.28) were the strongest predictors of unplanned hospital visits.

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
		of inflammatory bowel disease or diverticulitis in the year preceding the colonoscopy Colonoscopies for patients who lacked continuous enrollment in Medicare FFS Parts A and B in the 1 month after the procedure.					
Saraste et al. (2016)	Population based study	**Inclusion criteria:** All patients with a positive FOBT followed by a colonoscopy performed between 1 January 2008 and 30 June 2012 . (Swedish study) **Exclusion criteria:**	N = 2984	Overall 1/1000 2.5/1000 after colonoscopy with polypectomy	14/1000	1/2984 (unrelated to colonoscopy)	Mortality and complications within 30 days after colonoscopy or subsequent surgery were identified through national registers, and complications were assessed through review of medical charts Overall complications 1%
Bielawska et al. (2017)	Population based	**Inclusion criteria:** Adults aged 18 and older who underwent outpatient colonoscopy in Ontario, Canada between January 1, 2005 and December 31, 2012 **Exclusion criteria:** 1) Colonoscopies performed during hospital admission 2) Flexible sigmoidoscopy 3) Other procedures like EGD performed with the colonoscopy	N = 3,059,045 patients Male = Anesthesia assisted 421,352 (48.8%) Unassisted 1,070,723 (48.8%) Total Anesthesia Assisted Colonoscopy N=862,817 Total Unassisted Colonoscopy N=2,196,228 Age: 18 - 29 AA 18,699 (2.2%) UA 58,957 (2.7%) 30 - 39 AA 39,434 (4.6%) UA 116,517 (5.3%) 40 - 49 AA 125,883 (14.6%) UA 329,597 (15.0%) 50 - 59 AA 293,419 (34.0%) UA 693,237 (31.6%) 60 - 69 AA 227,585 (26.4%) UA 560,976 (25.5%) 70 - 79 125,129 (14.5%) 339,402 (15.5%)	1396 colonoscopy related bowel perforations (0.046%)	Not reported	Not reported	138 splenic injuries (0.0045%) 186 aspiration pneumonia (0.0061%) Risk of perforation was significantly associated with standard polypectomy (OR 1.78), large polypectomy (OR 7.60) and stenting or stricture dilation (OR 16.80), compared to no intervention AA not associated with perforation After propensity matching, use of AA was associated with a statistically significant (P = 0.012) 63% increase in the odds of aspiration pneumonia

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
			80+ AA 32,668 (3.8%) UA 97,542 (4.4%)				
Forsberg et al. (2017)	Retrospective population-based cohort study	**Inclusion criteria:** Colonoscopies performed during the years 2001–2013 on adults ≥ 18 years identified in the Swedish health registers (National Hospital Discharge Register and the National Outpatient Register) Individuals with at least one colonoscopy during 2001–2013 **Exclusion criteria:** Polypectomy performed in the colon or rectum (e.g., a rectoscopy) during a procedure other than a colonoscopy Individuals for whom there was only a code for polypectomy and no code for endoscopy	N = 593,315 colonoscopies performed on the 426,560 individuals Female = 56% Median Age = 62.7 years (range 18-105 years) Inpatient colonoscopies = 14.9%	0.11% For colonoscopy with polypectomy perforation rate was 0.25% The multivariate RR for perforation when general anaesthesia was employed was 2.65 (p<.001; 95% CI 1.71–4.12).	0.17% For colonoscopy with polypectomy bleeding rate was 0.53%	0.68%	Adverse events were recorded for within 30 days of the procedure 31 splenic injuries (1:20,000 colonoscopies) reported. 1.^% colonoscopies performed with general anesthesia In 47,492 of the colonoscopies performed (8%), polypectomies Were performed. There was a significant increased risk for perforation observed when general anesthesia was employed (RR 2.65; 95% CI 1.71–4.12) Risk of bleeding and perforation were higher in age > 60 and when polypectomy performed.
Wang et al. (2017)	Population based study	**Inclusion criteria:** Screening or surveillance colonoscopy and non-screening/non-surveillance colonoscopy performed in California hospital-owned and nonhospital owned ambulatory facilities, emergency departments, and hospitals from January 1, 2005 through December 31, 2011. For persons who underwent multiple colonoscopies, the first colonoscopy encounter was	N = S-Colo was performed on 1,580,318 patients and included biopsy/ intervention in 59.2%, NS-Colo was performed on 1,222,070 patients and included biopsy/ intervention in 39.7%. Average age = 60.4 years for SC 57.7 years for NSC Male = 768,858 (48.7%) for SC 490,826 (40.2%) for NSC Race = White =	After screening/ surveillance 2.9/10000 (95% CI, 2.5–3.3) without biopsy or intervention With biopsy or intervention 6.3/10000 (95% CI, 5.8–6.8) Total SC 4.9 (4.5–5.2) Nonscreening/ nonsurveillance colonoscopy without intervention 4.8 (4.3–5.3) Nonscreening/ nonsurveillance colonoscopy with intervention 10.8 (9.9–11.7) Total NSC 7.2 (6.7–7.7)	Lower bleeding after screening /surveillance 5.3/10000 (95% CI 4.8–5.9) Without biopsy or intervention With biopsy or intervention 36.4/10000 (95% CI, 35.1–37.6) Total SC: 23.7 (22.9–24.5) Nonscreening/ nonsurveillance colonoscopy without intervention 18.9 (17.9–19.8) Nonscreening/ nonsurveillance colonoscopy with intervention 50.2 (48.2–52.2)	After screening /surveillance 2.1 (1.7–2.4) Without biopsy or intervention With biopsy or intervention 4.1 (3.6–4.5) Total SC: 3.2 (3.0–3.5) Nonscreening/ nonsurveillance colonoscopy without intervention 5.0 (4.5–5.5) Nonscreening/ nonsurveillance colonoscopy with intervention 9.1 (8.3–10.0) Total NSC 6.6 (6.2–7.1)	30-day GI and non-GI complication rates in patients undergoing outpatient colonoscopy. Complications were documented within 30 days in 109 (95% CI 107–112) per 10,000 S-Colo-Diag patients, and in 218 (95% CI 215–221) per 10,000 S-Colo-Int patients Overall complications were seen in 239 (236–243) and in 400 (395–406) NS colonoscopy without and with interventions respectively Biopsy/intervention was an independent predictor of lower GI bleeding and perforation (adjusted odds ratios

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
		used. **Exclusion criteria:**	1,042,493 (66%) SC 739,335 (60.5%) NSC		Total NSC 31.3 (30.3–32.3)		3.07 [95% CI 2.91–3.25] and 1.89 [95% CI 1.70–2.11], respectively).
Rabeneck et al. (2008)	Population based	**Inclusion criteria:** Individuals 50 to 75 years old who underwent an outpatient colonoscopy during April 1, 2002, to March 31, 2003 **Exclusion criteria:** In the 5 years preceding the index colonoscopy, had a colonoscopy, a diagnosis of colorectal cancer, a hospital admission with inflammatory bowel disease, or a colonic resection. In the 7 days prior to or on the day of the index colonoscopy, had an upper endoscopy Underwent colonoscopy for endoscopic hemostasis of a bleeding colonic lesion, insertion of a colonic stent, endoscopic colonic dilatation, or endoscopic reduction of a sigmoid volvulus.	N = 97,091 Mena age = 60.9 years Female = 52,641 (54.2%)	Pooled rate = 1.64/1000	Pooled rate = 0.85/1000	5/67,632 or 0.074/1000	Bleed or a perforation within 30 days following the index colonoscopy recorded. 23,623 (24.3%) had polypectomy performed during the procedure. Older age and having a polypectomy were associated with higher odds of bleeding or perforation.
Radaelli et al. (2008)	Cross-sectional, prospective multicenter study.	**Inclusion criteria:** Data from 278 centers in Italy and 12,835 consecutive colonoscopies were evaluated The main features of each endoscopy center (structure indicators) were collected through the use of a standardized questionnaire, completed by the head of each participating centers (questionnaire	N = 12835 colonscopies Gender = Male 6740 (52.5%) Female 5910 (Age (years) = >75 2005 (15.6%) 65–75 3727 36–64 6056 ≤35 933	2/12835 (0.02%)	26/12835 (0.20%)	Not reported	About 93% of colonoscopies were performed for diagnostic purpose; screening and surveillance accounted for 13.7% and 25.3% of the indications, respectively. Sedation and/or analgesia was administered in about half of the patients. Immediate complications related to the procedure included intestinal perforation and post-polypectomy bleedings

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
		No. 1). A second questionnaire was used to prospectively record details of all the consecutive colonoscopies performed in a 2-week study period in 2004 (process indicators). **Exclusion criteria:** Not reported					either during the examination or before discharge, and cardiac and/or respiratory complications serious enough to oblige the endoscopist to stop the examination were recorded. 32 (0.25%) cardiopulmonary complications were noted.
Arora et al. (2009)	Retrospective, population-based, cohort study	**Inclusion criteria:** Colonoscopy performed in patients 18 years or older enrolled in the Medi-Cal program during the period from January 1, 1995, to June 30, 2005. Only one (first) colonoscopy per patient was studied. **Exclusion criteria:** Patients not enrolled in Medi-Cal continuously for the 7 days after their date of first colonoscopy	N = 277,434 Control N = 1,072,723 Mean (SD) age = 64.20 ± 14.80 years (range 18-107.8 years) Mean age control = 63.97 ± 14.99 years (range 18-107.9 years) Gender = Women: 175,816 (63.4%) Men: 101, 618 Race= White 108,946 (39.3%) AA: 26,824	228/277434 (0.082%) 82/100,00	Not reported	Not reported	Risk of perforation 7 days post colonoscopy recorded The OR of getting a perforation from a colonoscopy compared with matched controls (n Z 1,072,723) who did not undergo a colonoscopy was 27.6 (95% CI, 19.04-39.92), P < .001. increasing age (> 65 yrs), significant comorbidity, obstruction as an indication for the colonoscopy, and performance of invasive interventions during colonoscopy were significant risk factors for perforation.
Bokemeyer et al. (2009)	Population study	**Inclusion criteria:** Asymptomatic individuals over 55 years of age undergoing screening colonoscopy under outpatient conditions. Data were collected prospectively in 280 practices of gastroenterology and/or internal medicine as well as endoscopy units in hospitals between 1 October 2003 and 31 December 2006 and included the entire number of complete investigations	N = 269144 colonoscopies Male 119 264 (44.3%) Female 149 880 (55.7%)	0.02% of the colonoscopies and 0.09% of polypectomies.	0.16% of colonoscopies and 0.8% of polypectomies	No mortality seen in study group	Cardiopulmonary complication in 0.10% of the colonoscopies Most of the bleeding managed endoscopically 0.03% needed surgery 90% procedures performed with conscious sedation

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
		of the colon in the centers during the respective time period. Completeness of colonoscopy was a prerequisite for inclusion in the study **Exclusion criteria:** If participants reported symptoms suggestive of disease of the lower gastrointestinal tract, including rectal bleeding 6 months earlier, marked changes in bowel habits or lower abdominal pain that would itself require colonoscopy. Other exclusion criteria were earlier bowel surgery, surveillance after previous polypectomy or surgery of colorectal adenomas or cancer or positive hemoccult tests.					
Crispin et al. (2009)	Population study	**Inclusion criteria:** Age > 18 yrs Data from compulsory health insurance (CHI) members who underwent colonoscopies in 2006. Data were documented prospectively in the Electronic Colonoscopy Documentation of the Bavarian Association of CHI Physicians, a registry of outpatient colonoscopies performed in practices throughout Bavaria, Germany	N = 236087 Median age = 61 years Male = 43.29%	69/236087 (0.03%)	520/236087 (0.22%)	Not reported	Less than a quarter (23.72 %) were screening cases, the rest had specific indications (60.53% clinical signs and symptoms, 10.98% adenoma surveillance, 4.78% cancer aftercare). A total of 735 patients (0.31 %) suffered complications 152 (0.06%) cardiopulmonary complications seen 50/69 (72%) perforations required surgery. Male sex, higher age, nonscreening indication, biopsies, polypectomies, and absence of sedation/

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
		Exclusion criteria: Younger than 18 yrs Duplicate records					analgesia were indicative of a higher bleeding risk. Perforations were also related to biopsies and polypectomies. Biopsy performed in 30.67% and polypectomy in 24.38%. Patients with large lesions > 3 cm exhibited an approximately 30-fold bleeding risk compared with patients with small ones < 0.5 cm (OR: 27.522, 17.198–44.049). The risk of perforation with the largest lesions (compared with the smallest ones) was augmented by a factor of approximately 30 (OR for lesions > 3 cm: 31.485, 95%CI 6.368–155.664)
Singh et al. (2009)	Retrospective study	**Inclusion criteria:** Lower GI endoscopies performed on adult (aged > 16 years) outpatients at 6 Winnipeg hospitals between April 1, 2004, and March 31, 2006. **Exclusion criteria:**	N = 24,509 Mean age ±SD = 59 ± 15 yrs Women = 56%	Perforation post polypectomy 1.8/1000 Perforation after colonoscopy 1/1000 After stricture dilation 58.8/1000 After colonoscopy with biopsy 0.5/1000 Flex sig without additional procedure 0.8/1000 Flex sig with biopsy 3.1/1000	Bleeding post polypectomy 6.4/1000	1/24509 Due to post op complications after surgery for perforation after snare polypectomy of small polyp in cecum	General surgeons performed 13,705 (56%), gastroenterologists 9618 (39%), and family physicians 1180 (5%) of the procedures. There were 303 admissions with potential complications The overall rate of complications was 2.9/1000 procedures The complication rate was highest for endoscopists performing fewer than 200 procedures per year (5.4/1000 vs 2.7/1000 for the rest, P = .02, relative risk 2 [95% CI, 1.1-3.7] The mean (± SD) age of the individuals who had procedure-related complications was 65 ±15 years; 65% were men. The rate of complications for individuals older

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
							than 50 years was 3.3 per 1000 procedures (60/17,918).
Sewitch et al. (2012)	Prospective cohort study	**Inclusion criteria:** Between 2007 and 2009, individuals 50 to 75 years of age who underwent outpatient colonoscopy and were covered by the provincial health insurance plan (Régie de l'assurance maladie du Québec [RAMQ]) Recruited from seven university-affiliated hospitals in Montreal (Quebec); they were approached by the research assistant before colonoscopy and explained the purpose of the study. Individuals who provided written informed consent were included **Exclusion criteria:** Not reported	N = 2134 Mean age = 60.9 yrs Male = 50.1%	0% [95% CI 0.00% to 0.17%]).	1/2134 Post polypectomy	0% [95% CI 0.00% to 0.17%]).	33/2134 (1.55% [95% CI 1.06% to 2.16%]) were hospitalized within 30 days. Rate of serious complications was 0.05% (95% CI 0.00% to 0.26%) for all colonsocopies and 0.18% (95% CI 0.00% to 1.01%) for colonoscopies with at least one polypectomy
Cooper et al. (2013)	Population based study	**Inclusion criteria:** Patients undergoing outpatient diagnostic colonoscopy was identified using the January 1, 2000, through November 30, 2009, Medicare Carrier and Outpatient files Patients 66 years or older (to allow measurement of comorbidities during the year prior to the colonoscopy procedure) and were receiving Medicare benefits through Part A and Part B for at least 1 year prior to and 30 days after the colonoscopy	N = 165 527 procedures in 100 359 patients, including 35 128 procedures with anesthesia services (21.2%) and 130399 colonoscopies (78.8%) without anesthesia. Mean (SD) age = 75.5 (6.4) years Female = 55% White = 85.1%	101/165527	0	Overall 30-day mortality 0.29% It was similar in the anesthesia (0.32%) and nonanesthesia (0.28%) groups (P = .29) overall 1-year mortality 2.68% It was similar in the anesthesia (2.82%) and nonanesthesia (2.64%) groups (P = .06).	Patients were monitored from the index colonoscopy for up to 30 days after the procedure for the occurrence of specific complications and up to 1 year for death. Complications were documented after 284 procedures (0.17%), included aspiration (n=173), splenic injury (n=12). Overall complications were more common in cases with anesthesia assistance (0.22% [95% CI, 0.18%-0.27%]) than in others (0.16% [0.14%-0.18%]) (P<.001), as was aspiration (0.14% [0.11%-0.18%] vs 0.10%

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
		Exclusion criteria: Patients enrolled in Medicare-sponsored managed care plans during the 1-year period prior to and 30-day period after the colonoscopy were excluded because of the high likelihood of incomplete claims					[0.08%-0.12%], respectively; P = .02). Predictors Of complications included age greater than 70 years, increasing comorbidity, and performance of the procedure in a hospital setting. In multivariate analysis, use of anesthesia services was associated with an increased complication risk (odds ratio, 1.46 [95% CI, 1.09-1.94]).
Denis et al. (2013)	Retrospective cohort study	**Inclusion criteria:** Colonoscopies performed in patients aged 50–74 undergoing a colonoscopy for a positive guaiac-based fecal occult blood test between September 2003 and February 2010 within the population-based CRC screening programme organized in Alsace, a region in eastern France **Exclusion criteria:** People with serious illness, recent CRC screening or high CRC risk	N = 102777 colonoscopies	10 (1.0‰, 95% CI 0.4–1.6)	31 (3.0‰, 95% CI 2.0–4.1)	0	All events definitely, probably and possibly related to colonoscopy occurring within 30 days of the colonoscopy were taken into account. Overall 250 (24.3‰ colonoscopies) AEs were recorded in 249 patients. They were classed as mild (n = 202, 80.8%), moderate (n = 29, 11.6%) and severe (n = 19, 7.6%) The rate of moderate and severe AEs was 4.7‰ (95% CI 3.4–6.0), 8.8‰ for therapeutic and 0.8‰ for diagnostic colonoscopies (p < 0.001)
Hamdani et al. (2013)	Retrospective cross-sectional study	**Inclusion criteria:** 18 years and older and had an inpatient or outpatient colonoscopy procedure code in any facility within the Geisinger Health System during the period from January 1, 2002 to August 25, 2010 **Exclusion criteria:** Not reported	N = 80118 Age category (yr) = 18-50 13698 (17.11) Perf 5 (10.00%) 50-65 38695 (48.33) Perf 0 (20.00%) 65-80 22954 (28.67) Perf 20 (40.00%) 80+ 4271 (5.90%) Perf 15 (30.00%) Gender Male 38972 (46.68%) Perf 16	50/80118 0.06% (95%CI: 0.05-0.08) or a rate of 6.2 per 10000 colonoscopies	Not reported	Not reported	The study outcome was the diagnosis of colonic Perforation using International Classification of Disease, 9th revision (ICD-9) codes 569.83 and 998.2, defined as perforation of intestine and accidental puncture or laceration during a procedure, 7 d after the day of colonoscopy For every year increase in age, the risk of a

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
			(32.00%) Female 41087 (51.32%) Perf 34 (68.00%)				perforation increased by 7% (95%CI: 5-9) with the incidence of perforation increasing from 2.6 cases per 10000 in the 50-64 year old age group to 31.7 cases per 10000 in the 80+ year old age group Significant risk factors for perforation: age, gender, BMI, albumin level, ICU patients, inpatient setting, and abdominal pain and Crohn's disease as indications for colonoscopy
Samalavicius et al. (2013)	Retrospective multicenter case series study	**Inclusion criteria:** Patients with iatrogenic Full thickness large bowel perforations resulting from colonoscopy within the period January 1, 2007, to December 31, 2011 Representatives of 14 Lithuanian public and private hospitals participated in the survey. **Exclusion criteria:** Not reported	N = 56882 colonoscopies Gender: Female 23 57.5% Male 17 42.5% Mean age 70 (39-85 years)	Diagnostic : 28 of 49,795 patients (0.056%) therapeutic colonoscopies : 12 of 7,087 patients (0.169%) Total incidence: 40/56882 (0.07%)	Not reported	6/40 (15%) deaths All in diagnostic colonoscopy group due to the perforation	All patients underwent surgery either primary repair (70.0 %) or bowel resection (30.0 %). The most common site of perforation is sigmoid colon and rectosigmoid junction, at 70 %. Risk rises when colonoscopy is performed in low-volume practice centers. Urgent surgical management resulted in overall mortality rate of 15.0 % and morbidity of 37.5 %.
Stock et al. (2013)	Retrospective matched cohort.	**Inclusion criteria:** Data collected between January 1, 2000, and December 31, 2008, from a random sample of individuals aged 20 years and older undergoing colonoscopy insured by the AOK in Hesse (N _ 326,652 [18.75% of AOK-insured persons in Hesse in 2000]). **Exclusion criteria:** The examined individual was not insured by the AOK over the 12 months	N = 33,086 individuals who underwent colonoscopy as an outpatient (8658 screening, 24,428 nonscreening) and 33,086 matched controls who did not undergo colonoscopy. Mean age screening = 66 years Mean age non screening = 59 years Female screening =	0.8 (95% CI 0.3-1.7) per 1000 screening colonoscopies 0.7 (95% CI, 0.4-1.1) per 1000 nonscreening colonoscopies	0.5 (95% CI, 0.1-1.2) per 1000 screening colonoscopies 1.1 (95% CI, 0.8-1.7) per 1000 nonscreening colonoscopies	0.6 (0.2-1.3) per 1000 screening colonoscopy 1.6 (1.2- 2.2) per 1000 nonscreening colonoscopy Overall 1.4 (1.0-1.8) per 1000	Adverse events within 30 days of colonoscopy recorded

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
		before the colonoscopy date (this time frame was used to ascertain comorbidity) until 30 days after the colonoscopy date In case of multiple colonoscopies per individual, only the first procedure coded in the insurance data was considered	55% Female nonscreening = 56%				
Warren et al 2009	Population based matched cohort study	**Inclusion criteria:** Random 5% sample of Medicare beneficiaries, age 66 to 95 years, who underwent outpatient colonoscopy between 1 July 2001 and 31 October 2005, matched with beneficiaries who did not have colonoscopy. Inpatient procedures All patients to have continuous enrollment in Medicare Parts A and B and fee-for-service coverage during the year before their colonoscopy and for 30 days after the procedure **Exclusion criteria:** Outpatient procedures Procedures performed in patients at high risk of perforation (diagnosis of diverticulitis, Crohn disease or ulcerative colitis, or colorectal cancer) Incomplete procedure coded by physician Persons younger than 66 years patients who had more than 2 colonoscopies during study period	N = 53220 colonoscopies 10.1% screening, 33.6 % diagnostic and 56.3% procedures involving polypectomy. Male = 22174 (41.7%) Female 31046 (58.3%) Age 66-69y 24.3% 70-74y 31.2% 75-79y 25% 80-84y 14% ≥85 5.5%	0.6 per 1000 procedures	8.7 per 1000 procedures in polypectomy group 2.1 per 1000 Procedures in screening group	Not calculated	all adverse events occurring within 30 days after outpatient colonoscopy that were severe enough to require an emergency department visit or hospitalization were identified. Risk for paralytic ileus was also higher in the polypectomy group (4.8 per 1000 procedures) than in the diagnostic group (1.3 per 1000 procedures) or screening group (1.1 per 1000 procedures). Risk for cardiovascular events was higher in the polypectomy group (23.4 per 1000 procedures) or diagnostic group (15.4 per 1000 procedures) than in the screening group (9.9 per 1000 procedures). For all types of colonoscopies, the most common cardiovascular event was arrhythmia (10.2 per 1000 procedures).

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SUPPLEMENTARY TABLE 1. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Mortality	Notes
		patients who had 2 colonoscopies less than 60 days apart persons who had their procedure outside of a SEER area Colonoscopies with no corresponding beneficiary in the match group					

SUPPLEMENTARY TABLE 2. Evidence table for the EMR/ESD studies

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
Hiraishi et al. (2010) **Location: Japan**	Prospective Cohort	*Inclusion Criteria:* Patients that underwent ESD for colorectal neoplasia *Exclusion Criteria:* None explicitly stated	N = 25 consecutive patients Age (mean) = 67.4 years Male = 64% Race = NR Mean tumor diameter = 32.2mm Mean removed specimen diameter = 38.2mm Mean procedure time = 42.6 minutes Follow-up period (mean) = 19.8 months	0%	0%	2 patients required additional intervention (surgery). No complications observed. All patients in this cohort had ESD performed with SBK (stag beetle knife).
Moss et al. (2010) **Location: Australia**	RCT, double-blinded	*Inclusion Criteria:* Aged ≥18 years, able to give informed consent and were referred to the Endoscopy Unit for ER of treatment-naïve laterally spreading tumor or sessile lesion ≥20mm in size *Exclusion Criteria:* (1) Previous attempt at removal or hot biopsy of lesion, (2) personal hx of allergy to gelatin, SG or any other type of colloidal plasma expander, Haemaccel (3) use of clopidogrel or aspirin plus dipyridamole within 7 days, or use of warfarin within 5 days of procedure (4) therapeutic dose of unfractionated heparin within 6h or low-molecular weight heparin within 12h of procedure, (5) known clotting disorder, (6) pregnancy, or (7) lactation	N = 80 patients Age (mean) = 69 years Male = 56.3% Race = NR Randomized to receive Normal Saline (NS) or Succinylated Gelatin (SG); patients = 39 NS vs. 41 SG Lesion Size (mean) = 40mm (SG) vs. 35mm (NS) Mean procedure time = 12.0 minutes (SG) vs. 24.5 minutes (NS); p = 0.006	0%	2% (SG) vs. 5% (NS)	3 patients with significant post-procedure bleeding (1 SG / 2 NS) were hospitalized for treatment. Sydney Resection Quotient (SRQ) significantly higher in SG group (10.0 vs. 5.9, p = 0.004). No adverse events reported that were attributable to SG.
Saito et al. (2010) **Location: Japan**	Retrospective, Case-Control	*Inclusion Criteria:* Noninvasive pattern, as determined by magnification chromoendoscopy: ESD = LST-NG lesion ≥20mm (definite), LST-G lesion ≥40mm (relative), or large villous tumor, intramucosal lesion, recurrent lesion or residual intramucosal lesion showing non-lifting sign after EMR EMR/EPMR = Any lesion <20mm (definite), or LST-G lesion ≥20mm and <40mm (definite) *Exclusion Criteria* = None explicitly stated	N = 145 ESD, 228 EMR patients Age (mean) = 64 years Sex = NR Race = NR Tumor size (mean) = 28mm (EMR) vs. 37mm (ESD) Mean procedure time = 29 minutes (EMR) vs. 108 minutes (ESD)	1.3% (EMR) vs. 6.2% (ESD)	3.1% (EMR) vs. 1.4% (ESD)	All complications treated endoscopically. ESD = higher en bloc resection rate (84% vs. 33%, p <0.0001). 33 patients in the EMR group required additional EMR due to recurrence vs. 3 in the ESD group (p <0.0001). Despite a longer procedure time and higher perforation rate, ESD achieved higher en bloc and curative resection rates vs. EMR.

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
Salama et al. (2010) **Location: Australia**	Prospective Cohort	*Inclusion Criteria:* Referred for endoscopic resection of a colorectal neoplasm 20mm or larger *Exclusion Criteria:* None explicitly stated	N = 154 lesions in 140 consecutive patients Age (mean) = 68 years Male = 57.1% Race = NR Lesion type: Sessile (117) vs. Pedunculated (37) Lesion size (mean) = 29mm Mean procedure time = 55 minutes	1.9% (all in Sessile lesions)	1.3% (all in Sessile lesions)	Complete endoscopic removal of lesion in 95% of cases. 20 patients referred to surgery (14%). Endoscopic follow-up data was available in 90% of cases, revealing 5 patients to need endoscopic treatment of residual adenoma to achieve complete clearance of disease.
Seo et al. (2010) **Location: South Korea**	Retrospective Cohort	*Inclusion Criteria:* Underwent EPMR using a submucosal saline injection technique Sessile polyp, ≥20mm *Exclusion Criteria:* Co-existence of synchronous advanced colorectal cancer Non-lifting tumor Encircling lesion > 70% Transfer to outside institution Suspicion of muscle invasion on EUS Recurrent tumor	N = 50 lesions in 47 patients Age (mean) = 60 years Female = 51.1% Race = NR Mean polyp size = 30.1mm	0%	12% (5 during procedure, 1 post-procedure)	All bleeding episodes were managed by endoscopic clip and/or APC. 4 local recurrences were detected at 3-months post-EPMR; 1 occurred at 14-months post-EPMR. Recurrence was significantly higher in malignant polyps (33.3% vs. 3.1%, p = 0.05).
Toyonaga et al. (2010) **Location: Japan**	Retrospective Cohort	*Inclusion Criteria:* Underwent ESD for LST of ≥20mm diameter *Exclusion Criteria:* None explicitly stated	N = 99 LST-NG and 169 LST-G lesions Age (mean) = 68 years (LST-NG) vs. 69 years (LST-G) Male = 52.6% Race = NR Tumor diameter (median) = 28mm (LST-NG) vs. 36mm (LST-G); p <0.0001 Resected specimen diameter (median) = 40mm (LST-NG) vs. 46mm (LST-G); p <0.0001 Procedure time (median) = 69 min (LST-NG) vs. 60 min (LST-G)	5.1% (LST-NG) vs. 0.59% (LST-G); p = 0.027	0% (LST-NG) vs. 0.59% (LST-G); p = NS	En bloc resection rate, en bloc R0 resection rate and en bloc curative resection rate similar in both groups (LST-NG: 99%, 98%, and 88%; LST-G: 99%, 98%, and 91%). No recurrence seen in either group. 5/6 perforations were seen intra-procedure and treated with endoscopic clip and antibiotics; one delayed perforation was treated surgically. ESD was effective for both LST-NG and LST-G; however, degree of technical difficulty is higher in LST-NG group.

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
Khashab et al. (2009) **Location: US**	Retrospective Cohort	*Inclusion Criteria:* Underwent piecemeal resection of a large sessile polyp (≥20mm) Attended subsequent follow-up examination at 3-6 months following the initial resection, and at least 1 year (up to 6-years post-initial resection) after the initial resection *Exclusion Criteria:* Pedunculated polyps Cancerous polyps that underwent subsequent surgical resection Polyps deemed endoscopically unresectable Patients that did not complete all follow-up at this institution, as outlined per inclusion	N = 136 lesions in 132 patients Age (mean) = 67.4 years Male = 50.8% Race = NR Mean polyp size = 32.8mm	0%	4.5%	All patients with bleeding (n = 6) were successfully managed by endoscopy. 24 patients had macroscopically evident residual adenoma at follow-up – 18 at first follow-up, and 6 with a "late" recurrence. Normal macroscopic appearance of the polypectomy site and negative scar biopsy specimen at first follow-up is predictive of long-term eradication.
Luigiano et al. (2009) **Location: Italy**	Retrospective Cohort	*Inclusion Criteria:* Patients that underwent EMR for sessile or flat polyps measuring 20mm or greater in size *Exclusion Criteria:* Lack of follow-up data and/or hospitalization at outside institutions (not enough information available)	N = 148 patients Age (mean) = 69.2 years Male = 63.5% Race = NR Mean polyp size = 30.7mm Lesion Type = 74 Sessile vs. 74 Flat	0.68%	10.1% (13/15 bleeds occurred during procedure)	One early bleed (10 hours post-procedure) and delayed bleed (36 hours post-procedure) were observed. All bleeds (including procedural bleeding) were treated endoscopically – clips (4), injection (7), and APC (4). Perforation required surgical management. Recurrence was observed in 4.2% of patients, and was more often found in patients with giant (>40mm) polyps (p = 0.014).
Conio et al. (2010) **Location: Italy**	Prospective Cohort	*Inclusion Criteria:* Patients with Sessile polyps or Laterally Spreading Tumors (≥20mm) that underwent EMR-C (colorectal) Only benign and resectable (as determined by the endoscopist) lesions were selected for inclusion *Exclusion Criteria:* Ulceration, Induration, depressed lesions and the	N = 282 polyps in 255 consecutive patients (146 sessile polyps vs. 136 laterally spreading tumors) Age (median) = 70 (SP), 64.5 (LST-NG), and 73 (LST-G) years Male = 56.0% Race = NR Median polyp size = 25mm (SG), 30mm (LST-NG), and 30mm (LST-G)	0%	7% (all procedural bleeding)	All bleeding occurred during the procedure and was treated endoscopically. Endoscopic follow-up was available in 200 patients with 216 adenomas and demonstrated a recurrence rate of 4%. Recurrences were treated with

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
		absence of lifting after submucosal injection	Procedure time (median) = 40 minutes			ablation and/or additional resection.
Bahin et al. (2015) **Location: Australia**	RCT, Multi-Center	*Inclusion Criteria:* Patients referred for WF-EMR of a colorectal Sessile or Laterally Spreading lesion (≥20mm) *Exclusion Criteria:* Lesion size less than 20mm Paris Classification of 0-1p appearance Suspected invasive disease WF-EMR of multiple lesions in 1 session Incompletely resected lesion Muscularis propria injury (suspected or confirmed) Occurrence of major intraprocedural bleeding requiring intervention for hemostasis (confounding factor)	N = 347 patients, 172 PEC vs. 175 control Age (mean) = 67.1 years Male = 51.3% Race = NR Median lesion size = 39.5mm (WF-EMR + PEC group), 39.8mm (WF-EMR group), p = 0.13 Mean procedure time = 35 minutes (WF-EMR + PEC group), 30 minutes (WF-EMR group)	0%	6.6% (5.2% PEC vs. 8.0% Controls)	Patients were randomized 1:1 to receive prophylactic endoscopic coagulation (PEC) to determine if it reduced the incidence of clinically significant post-endoscopic mucosal resection bleeding (CSPEB). CSPEB occurred in 9 patients receiving PEC vs. 14 controls (p = 0.3). PEC does not significantly decrease the incidence of CSPEB after WF-EMR.
Lee et al. (2015) **Location: South Korea**	Retrospective Cohort	*Inclusion Criteria:* Patients that underwent ESD with the indication of colorectal carcinoma or adenoma *Exclusion Criteria:* Pathologic result of hyperplastic polyps, inflammatory polyps, neuroendocrine tumors, or no tumor detected Resection with EMR or conventional polypectomy	N = 173 lesions in 170 patients Age (mean) = 65.01 years Male = 61.3% Race = NR Mean tumor size = 25.95mm Resected specimen diameter (mean) = 31.76mm Procedure time (mean) = 77.46 minutes En bloc resection = 88.4%	10.98%	3.47%	Perforation occurred in 19 cases, with 17 being classified as microperforations. Bleeding occurred in six cases, with half being minor and major bleeds. Complications occurred in 26.6% (n = 46) of cases (including post-coagulation syndrome). Surgical intervention was required in 22/46 cases.
Wada et al. (2015) **Location: Japan**	Prospective Cohort, Multi-Center	*Inclusion Criteria:* Patients with colorectal lesions of 20mmn or larger that underwent endoscopic resection *Exclusion Criteria:* Patients that underwent ESD were excluded from the final analysis (all patients were consented to reduce selection bias; however, only interested in EMR or polypectomy outcomes)	N = 1845 colorectal lesions; only 1029 included in the final analysis Age (mean) = 65.2 years Male = 61.9% Race = NR EMR vs. Polypectomy = 866 vs. 163 cases Tumor size (mean) = 26.4mm	0.78%	1.6%	Post-procedure bleeding occurred in 18 cases, all treated endoscopically with endoclips or hemostatic forceps. One case required additional intervention (blood transfusion). Perforation occurred in 8 (EMR) cases, all diagnosed intra-procedure. 7/8 were managed

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
						with endoclips, with one case requiring surgical intervention. Risk factors for bleeding were in multivariate analysis were only patients under 60 years of age. Perforation risk factors were en bloc resection and Vienna Classification category 4-5 (high-grade dysplasia and submucosal carcinoma).
Zhang et al. (2015) **Location: China**	Prospective RCT	*Inclusion Criteria:* Patients referred for ESD or EMR for a colorectal tumor Tumor size between 10mm and 40mm *Exclusion Criteria:* Blood disorder Hx of colorectal surgical resection Taking anticoagulant medication Lesions displaying an invasive pattern and/or those lesions that were recurrent or residual tumors Coagulation dysfunction	N = 348 patients, randomized to clip-closure (174) or no clip-closure (174) group Age (mean) = 67.9 (clip-closure group) vs. 64.2 (no-clip closure group) Male = 62.9% Race = NR Tumor size: 10mm-20 mm (n = 111 clip-closure group vs. 107 non-clip closure group) 20-40mm (n = 63 clip-closure group vs. 67 non-clip closure group) Procedure duration (mean) = 38.1 minutes (clip-closure group) vs. 30.9 minutes (non-clip closure group)	0.57%	4.0%	1 patient in the non-clip closure group experienced a perforation during ESD, managed with endoscopic clips. 1 patient in the clip-closure group was found to have a microperforation on CT post-procedure (free air) and was managed conservatively. 14 patients (n = 12 non-clip closure v. 2 clip-closure) experienced delayed post-operative bleeding (p = 0.012). All bleeds were treated endoscopically, no patients in either group required blood transfusion or surgical intervention.
Ahlawat et al. (2011) **Location: US**	Retrospective Cohort	*Inclusion Criteria:* Patients that underwent polypectomy of a ≥20mm colorectal polyp *Exclusion Criteria:* None explicitly stated	N = 183 polyps in 174 patients Age (mean) = 64 years Male = 55% Race = NR Sessile polyps = 84% Polyp size = 73% were 20-30mm	2.2%	9.3%	17 patients had post-polypectomy bleeding – 5 immediate, 12 delayed. All patients with immediate bleeding were treated with endoscopic clips.

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
						For those with delayed bleeds, all required hospitalization (3 needing blood transfusion). Of 4 patients with a post-polypectomy perforation, 3 required surgical intervention. 1 patient was managed with endoscopic clip closure of the perforation. Recurrence of adenoma was noted in 12% of patients on follow up (>1-year post-polypectomy), all managed endoscopically.
Moss et al. (2011) **Location: Australia**	Prospective Cohort, Multi-Center	*Inclusion Criteria:* Patients referred for EMR of sessile colorectal polyps 20mm or larger *Exclusion Criteria:* None explicitly stated	N = 514 lesions in 479 patients Age (mean) = 68.5 years Male = 53% Race = NR Lesion Size (mean) = 35.6mm Procedure Duration (mean) = 25.3 minutes Complete excision achieved in 89.2% of EMR cases	1.3%	2.9%	14 patients were admitted for bleeding post-procedure. 7 were treated conservatively, 6 patients underwent repeat colonoscopy (4 received endoclips or coagulation application), and 1 required an extended right hemicolectomy. 6 patients had a perforation post-procedure. Four patients were stabilized with endoscopic clip; however, $^{1}/_{4}$ required readmission and received conservative management (LOS = 9 days). Two patients required surgical intervention. Risk factors for submucosal invasion were as follows: Paris

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
						Classification 0-IIa+c morphology, non-granular surface, and Kudo pit pattern type V. Predictors of recurrence after effective EMR were lesion size greater than 40mm ($p < .001$), and use of APC ($p = 0.017$).
Binmoeller et al. (2012) **Location: US**	Prospective Cohort	*Inclusion Criteria:* Referred for EMR of large sessile polyp (defined as a lesion with a thickness less than half of the maximum width) Benign adenoma on previous biopsy Benign appearance on high-definition colonoscopy without stigmata of malignancy (ulceration, bleeding, induration, Kudo pit pattern V) Size equal to or greater than 20mm *Exclusion Criteria:* None explicitly stated	N = 60 consecutive patients with 62 sessile colorectal polyps Age (mean) = 65.4 years Female = 53.3% Race = NR Polyp size (mean) = 33.8mm Procedure Duration (mean) = 48.9 minutes Resection time (mean) = 21.4 minutes	0%	5%	Evaluated novel technique of EMR performed with "water immersion" (UEMR). Delayed bleeding occurred in 3 patients and was managed conservatively. Mean follow-up time was 20.4 weeks, with one patient experiencing a recurrence of adenoma.
Fasoulas et al. (2012) **Location: Greece**	Prospective RCT, Multi-Center	*Inclusion Criteria:* LST $\geq$ 30mm detected during colonoscopy, benign appearance, and respectability of the lesion *Exclusion Criteria:* Firm consistency, ulceration, friability, appearance of expansion of normal tissue immediately surrounding the lesion indicating the presence of cancer spreading into the surrounding submucosal space, and converging fold (2 or more) toward the lesion predicting submucosal invasion by cancer cells, even with negative biopsies The presence of a "non-lifting" sign after submucosal injection of solution A lesion with biopsies suspicious for invasive cancer Patients with previous incomplete resections	N = 49 patients (25 in Hydroxyethyl Starch vs. 24 in Normal Saline group) Age (mean) = 68 (HS group) vs. 67 (NS group) Male = 64% (HS) vs. 50% (NS) Race = NR Lesion size (median) = 45mm (HS) vs. 46mm (NS) Recurrence = 20% (HS) vs. 29.2% (NS)	4% (HS) vs. 0% (NS)	4% (HS) vs. 25% (NS)	Evaluated hydroxyethyl starch (HS) vs. normal saline + epinephrine (NS) to determine if HS allowed for prolonged elevation of submucosal cushion for EMR of LSTs. Six patients had mild intraprocedural bleeding successfully controlled endoscopically with epinephrine injection and coagulation by coagrasper (4) or hemoclips (2). One patient had delayed bleeding (self-limited). One patient in the HS group presented with

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
						macroperforation following the procedure (42mm lesion) and was managed surgically. HS provided a more prolonged submucosal elevation (p = 0.001), and a shorter procedure time (p = 0.013) than NS (with similar safety profile).
Lee et al. (2012) **Location: South Korea**	Prospective Cohort	*Inclusion Criteria:* Patients referred for resection of colorectal tumors 20mm or larger *Exclusion Criteria:* Colorectal tumors with endoscopic findings such as hardness, ulceration, friability, and spontaneous bleeding (indicative of massive submucosal invasion)	N = 140 tumors in 135 patients (EMR group) vs. 69 tumors in 67 patients (EMR-P group) vs. 314 tumors in 309 patients (ESD group) Age (mean): 63 (EMR) vs. 62 (EMR-P) vs. 61 (ESD) Sex (ratio, male: female) = 1:0.57 (EMR) vs. 1:0.64 (EMR-P) vs. 1:0.80 (ESD) Tumor size (mean) = 21.7mm (EMR) vs. 23.5 (EMR-P) vs. 28.9 (ESD) En-bloc resection rates = 42.9% (EMR) vs. 65.2 (EMR-P) vs. 92.7% (ESD) Recurrence rates = 25.9% (EMR) vs. 3.2% (EMR-P) vs 0.8% (ESD)	0% (EMR) vs. 2.9% (EMR-P) vs. 8.0% (ESD)	0% (EMR) vs. 2.9% (EMR-P) vs. 0.64% (ESD)	Perforation occurred in 2 cases of EMR-P and 25 in ESD. Endoscopic clipping was performed for 20/25 ESD cases, and both of the EMR-P cases. 2 ESD perforations required surgical intervention, with the remaining (3) cases managed conservatively. Delayed bleeding occurred in 2 patients in the EMR-P and 2 in the ESD groups. All bleeding was controlled with conservative management.
Terasaki et al. (2012) **Location: Japan**	Retrospective Cohort	*Inclusion Criteria:* Patients that underwent endoscopic treatment of an LST greater than 20mm diameter *Exclusion Criteria:* None explicitly stated	N = 267 consecutive patients (61 ESD vs. 28 Hybrid ESD vs. EMR vs. 108 EPMR) Age (mean) = 65.0 (ESD) vs. 70.3 (Hybrid ESD) vs. 65.5 (EMR) vs. 69.4 (EPMR) years Sex (ratio, male: female) = 38:23 (ESD) vs. 17:11 (Hybrid ESD) vs. 40:30 (EMR) vs. 59:49 (EPMR) Tumor size (mean) = 42.1mm (ESD) vs. 31.7mm (Hybrid ESD) vs. 24.2mm (EMR) 37.4mm (EPMR); p = 0 0017 Recurrence rates = 0%	0% (ESD) vs. 7.1% (Hybrid ESD) vs. 1.4% (EMR) vs. 1.9% (EPMR)	11.5% (ESD) vs. 0% (Hybrid ESD) vs. 7.1% (EMR) vs. 9.3% (EPMR)	Hybrid ESD was defined as the use of a snare during the final stage of a procedure (following ESD for resection). Perforation occurred in 0 ESD, 2 Hybrid ESD, 1 EMR and 2 EPMR patients. All perforations were managed endoscopically. Delayed bleeding occurred in 7 ESD, 0 Hybrid ESD, 5 EMR and 10 EPMR patients. All

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
			(ESD) vs. 0% (Hybrid ESD) vs. 1.4% (EMR) vs. 12.1% (EPMR)			delayed bleeding events were managed endoscopically and/or conservatively.
Longcraft-Wheaton et al. (2013) **Location: United Kingdom**	Prospective Cohort	*Inclusion Criteria:* Patients referred for resection of large and difficult colonic polyps of at least 20mm or larger *Exclusion Criteria:* Polyps less than 20mm Polyps with features suggestive of malignancy	N = 220 patients Age (mean) = 68 years Male = 61.4% Race = NR Polyp size (mean) = 43mm SMSA scoring system (size/ morphology/site/access) = level 3 (9-12), level 4 (>12); levels 3 and 4 considered difficult lesions; SMSA level 3 (32%) vs. level 4 (63%)	0.45%	2.7%	Six patients experienced delayed bleeding and required hospitalization, blood transfusion, or endoscopic intervention. No patients with post-EMR bleeding required surgical intervention. One patient experienced a microperforation, managed endoscopically. Complications were independent of lesion size and location, but were affected by the SMSA score (p = 0.018). Complete endoscopic clearance was achieved in 90% of this cohort with first endoscopic resection attempt.
Repici et al. (2013) **Location: Italy**	Prospective Cohort	*Inclusion Criteria:* All LST's 30mm or larger located within 15mm of the anal verge with no previous attempt at endoscopic resection in patients in patients 18-80 years of age *Exclusion Criteria:* Lesion infiltrating the submucosal layer as diagnosed by EUS, previous endoscopic resection attempts, ASA Class-III or higher, and disturbance of coagulative parameters	N = 40 consecutive patients Age (mean) = 65.3 years Male = 67.5% Race = NR Polyp size (mean) = 46.8mm Procedure time (mean) = 86.1 minutes Recurrence = 2.5%	2.5%	5.0%	Bleeding occurred in 2 patients, with intraprocedural hemostasis being successfully achieved with thermocoagulation and clipping. Perforation occurred in 1 patient and was endoscopically treated with clipping. En bloc resection rate was 90%, with curative resection in 80%.
Xu et al. (2013) **Location: China**	Retrospective Cohort	*Inclusion Criteria:* Patients with LST's that underwent ESD (lesions over 20mm, and those that were difficult to remove en	N = 137 lesions in 135 patients Age (mean) = 64.5 years Female = 50.4% Race = NR	2.2%	3.6%	Three patients experienced perforation following ESD. 2/3 were treated

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
		bloc using EMR) *Exclusion Criteria:* Histology demonstrating cancer and invasion of the submucosa or permeating the vessels Presence of invasive type V pit pattern Lesion not amenable to ESD (no lifting elevation at submucosal injection)	Tumor size (median) = 30mm Procedure duration (mean) = 52.3 minutes Recurrence = 0.84% En bloc resection = 94.9% Curative resection = 90.5%			successfully with endoscopic clips. The remaining case was treated surgically. Five patients experienced delayed postoperative bleeding. All cases were successfully managed endoscopically (clips).
Bialek et al. (2014) **Location: Poland**	Prospective Cohort	*Inclusion Criteria:* Large, sessile polyp (type 1s) greater than 20mm which could not be removed in 1 piece LST-G regular type or mix type with a dominant nodule, greater than 20mm Non-granular LST, any size *Exclusion Criteria:* Lesions above 70mm in size	N = 53 (37 ESD vs. 16 Hybrid ESD) Age (mean) = 64.0 years Sex = NR Race = NR Lesion size (mean) = 37mm (overall) Procedure time (median) = 70.0 (ESD) vs. 39.0 (Hybrid ESD) minutes En bloc resection rate = 86.5% (ESD) vs. 87.5% (Hybrid ESD) Curative resection rate = 81.1% (ESD) vs. 87.5% (Hybrid ESD) Recurrence Rate = 1.9%	0%	5.7%	Three patients experienced bleeding post-procedure. 2/3 cases were controlled using electrosurgical hemostatic forceps or hemoclips. One case required admission (LOS = 7 days) and required 2 units of blood to stabilize. Recurrence occurred in one patient at 30-months post-procedure (Hybrid ESD).
Knabe et al. (2014)	Prospective Cohort, Multi-Center	*Inclusion Criteria:* Patients with large, non-pedunculated lesions (larger than 20mm) that were referred for ER *Exclusion Criteria:* ASA class 3 or higher Patients receiving anticoagulation treatment	N = 252 lesions in 243 consecutive patients Age (range, only) = 36 – 86 years Male = 58.0% Race = NR Resected lesion size (median) = 33mm En bloc resection rate = 11.5% vs. Piecemeal resection rate = 88.5%	1.6%	2.5% (4 delayed GIB in adenoma patients vs. 2 in polypectomy patients)	Evaluated a standardized follow-up protocol following ER of large lesions. Four patients with resected adenomas experienced delayed GIB (>48h). All of these cases were successfully managed with clipping and epinephrine injection. Two patients (polypectomy) experienced major GIB (defined as a fall in hemoglobin >2g/dL). Both patients were managed blood transfusion and/or endoscopic therapy (epinephrine).

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
						Four perforations occurred that were all considered intraprocedural and were sealed with immediate clip placement. Evident residual neoplasia was noted after 3-6 months in 31.7% of lesions. After 12 months, 19 late recurrences were detected (16.4%). All residual adenomas were retreated with ER or treated with APC.
Bae et al. (2016) **Location: South Korea**	Retrospective Cohort	*Inclusion Criteria:* Patients who underwent ESD for lesions greater than 30mm in diameter *Exclusion Criteria:* Submucosal or non-neoplastic tumors Neoplastic lesions smaller than 30mm	N = 220 lesions in 218 patients Age (mean) = 63.0 years Male = 57.7% Race = NR Protruding tumor group = 30.5% vs. LST group (69.5%) Tumor size (mean) = 43.8mm (overall) En bloc resection rate = 87.7% Complete resection rate = 74.5% Procedure time (mean) = 75.5 minutes	9.1%	10.9%	All intraprocedural bleeding events (n = 19) were managed successfully with endoscopic hemostasis during ESD procedure. 5 cases of post-procedural bleeding were treated conservatively after hemostasis with APC and/or hemoclip placement. Perforation occurred in 20 cases (no difference among groups). 18 cases were successfully treated using hemoclip, with the rest requiring antibiotic administration and admission for observation. No perforation required surgical management. En bloc resection and complete resection rates were lower in the protruding tumor group vs. LST (p = 0.001). Intra- and post-procedural

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
						bleeding were more frequent in protruding tumors vs. LST's. Protruding tumors and size of greater than 60mm were independently associated with incomplete resection.
Bahin et al. (2016) **Location: Australia**	Prospective RCT, Multi-Center	*Inclusion Criteria:* Referred for the management of LSL ≥ 20mm Underwent wide-field endoscopic mucosal resection (WF-EMR) *Exclusion Criteria:* Suspicion of submucosal invasive carcinoma Surgery within 14 days of WF-EMR Technical failure of WF-EMR attempt	N = 2012 patients Age (median) = 68 years Male = 52.4% Race = NR Lesion size (median) = 30mm Procedure duration (median) = 20 minutes En bloc resection rate = 15.5%	NR	6.7%	A total of 135 cases of clinically significant bleeding (CSPEB) presented to the ED. 134/135 were hospitalized, and intervention was required in 54 patients (40.0%; colonoscopy in 52, angioembolization in 4 patients, surgery in 2 patients). Median time of CSPED = 24-48h. Patients were randomized to training cohort or test cohort (n = 1006 in each). Training cohort determined predictive factors to develop a scoring system to compare with the Test cohort. Predictors included lesion size >30mm (OR 2.5), and proximal colonic location (OR 2.3). The risk score scale comprised of lesion size >30mm (2 points), proximal colon (2 points), major comorbidity (1 point), and absence of epinephrine use (1 point). Probabilities of CSPEB of scores low (0-1), medium (2-4), and elevated (5-6) risk levels were 1.7, 7.1, and

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SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
						17.5% in training cohort vs. 3.4, 6.2, and 15.7% in test cohort.
Burgess et al. (2016) **Location: Australia**	Retrospective Cohort	*Inclusion Criteria:* Referred for the management (EMR) of sessile or laterally spreading colorectal lesions of greater than 20mm in size *Exclusion Criteria:* Patients that did not undergo EMR due to suspicion of malignancy or technical failure	N = 912 lesions in 802 patients Age (mean) = 66.8 years Male = 51.4% Lesion size (mean) = 29.2 Type III-V lesions = 28.9% En bloc resection rate = 13.0% Resected lesion size (en bloc, only) = 23.3mm	0.1%	NR	Lesions classified by deep mural injury (DM) class: I/II intact MP with/ without fibrosis, III target sign, IV/V obvious transmural perforation with/ without contamination). All type III-V were clipped, if possible. A delayed perforation (12-d post-procedure) presented in 1 patient (DM type II) following complete resection of 40mm Paris 0-IIa adenoma and admitted for 9 days. Type III-V lesions were associated with en bloc resection (OR 3.84, p = 0.005) and HGD/ submucosal invasive cancer (OR 2.97, p = 0.014).
Sauer et al. (2016) **Location: Germany**	Prospective Cohort (Case-Series)	*Inclusion Criteria:* Adults, aged 18+ Sessile or laterally spreading adenomatous lesions larger than 20mm *Exclusion Criteria:* Coagulopathy (INR >1.5; thrombocytopenia <100g/L) Dual platelet inhibitor therapy or oral anticoagulation that could not be interrupted Pregnancy or lactation Signs of submucosal tumor invasion Life expectancy of less than 6 months	N = 182 consecutive lesions in 178 patients Age (median) = 70 years Male = 57.9% Race = NR Lesion size (mean) = 41.0mm Procedure duration (mean) = 127.5 minutes En bloc resection rate = 88.4% Curative resection rate = 62.6%	9.3%	2.8%	In 27 procedures (14.8%), technical difficulties (severe fibrosis, or lack of access to the lesion) resulted in conversion to EPMR (n = 24) or referral to surgery (n = 3). Microperforations occurred in 17 patients. All perforations were treated conservatively with hemoclips and antibiotics. Delayed bleeding occurred in 5 cases. All patients were treated endoscopically and successfully achieved hemostasis.

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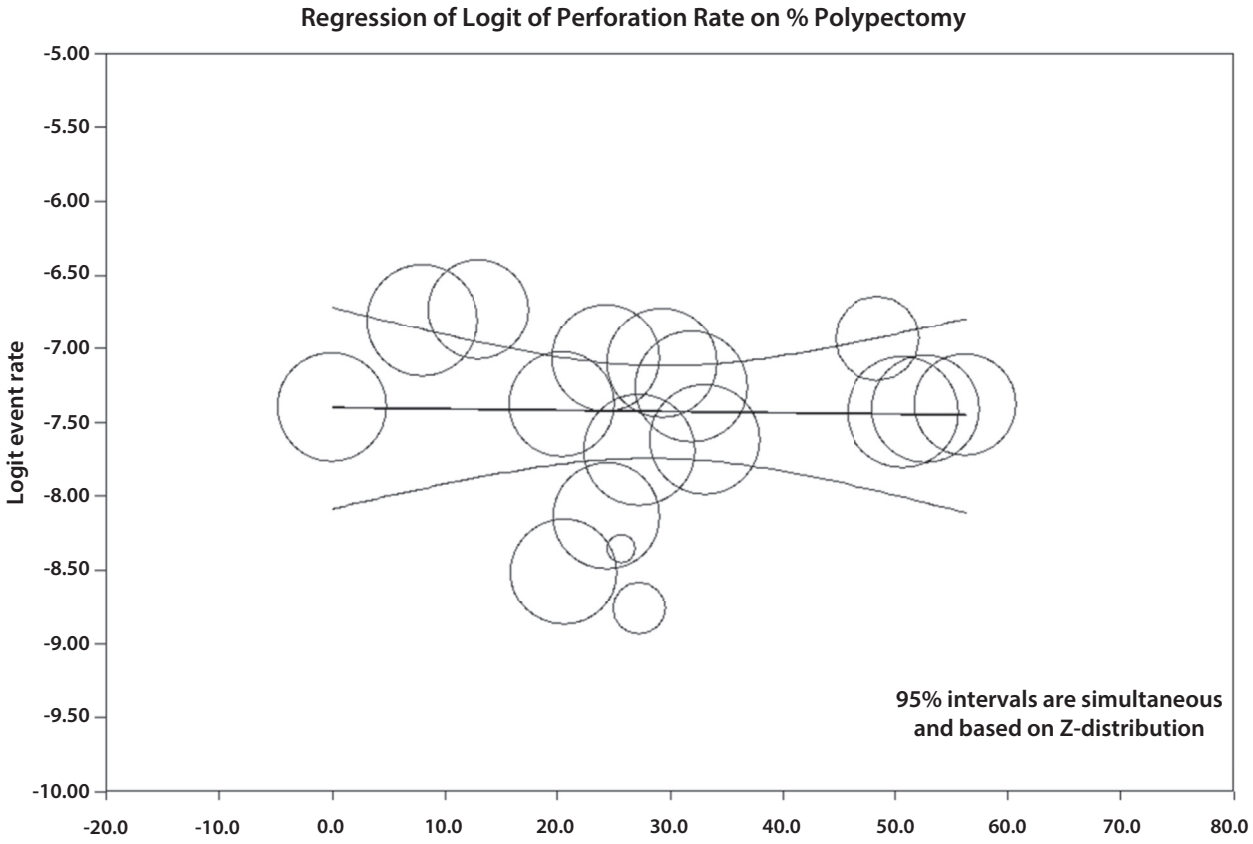
SUPPLEMENTARY TABLE 2. Continued

Author(s)/ Year of Publication	Study Design	Inclusion/Exclusion	Patient Characteristics	Perforation Rate	Bleeding Rate	Notes
Albeniz et al. (2016) **Location: Spain**	Prospective Cohort, Multi-Center	*Inclusion Criteria:* Patients referred for EMR of non-pedunculated colorectal lesions 20mm or larger *Exclusion Criteria:* Lesions smaller than 20mm	N = 1255 lesions in 1214 patients Age (mean) = 67.9 years Male = 63.4% Race = NR ASA of III or IV = 30.5% Lesion size (mean) = 30.5mm En bloc resection rate = 24.6%	1.4%	3.7%	17 cases of perforation were reported, 16/17 were successfully treated endoscopically. One patient was referred for surgical management. Delayed bleeding presented in 46 cases, with most (29; 63%) occurring 3-7+ days post-procedure. Patients were treated endoscopically and/or with blood transfusion. No patient required surgery. Predictors significantly associated with delayed bleeding presentation were age 75+ (OR 2.36), aspirin use (OR 3.16), ASA classification III or IV (OR 1.90), and lesion size of 40mm or larger (OR 1.91). Based on these factors, a predictive score was created indicating low risk (0-3) vs. average risk (4-7) vs. high risk (8-10). High-risk patients experienced a probability of 40% chance of presenting with delayed bleed.



Main results for Model 1, Random effects (MM), Z-Distribution, Logit event rate

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-7.1507	1.6157	-10.3174	-3.9840	-4.43	0.0000
Age	-0.0091	0.0185	-0.0454	0.0272	-0.49	0.6225
% Female	0.0062	0.0203	-0.0337	0.0460	0.30	0.7615
% Polypectomy	-0.0009	0.0068	-0.0143	0.0125	-0.14	0.8916

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 0.38, df = 3, p = .9445

Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.1430, Tau = 0.3782, I^2= 96.39%, Q =360.46, df =13, p = .0000

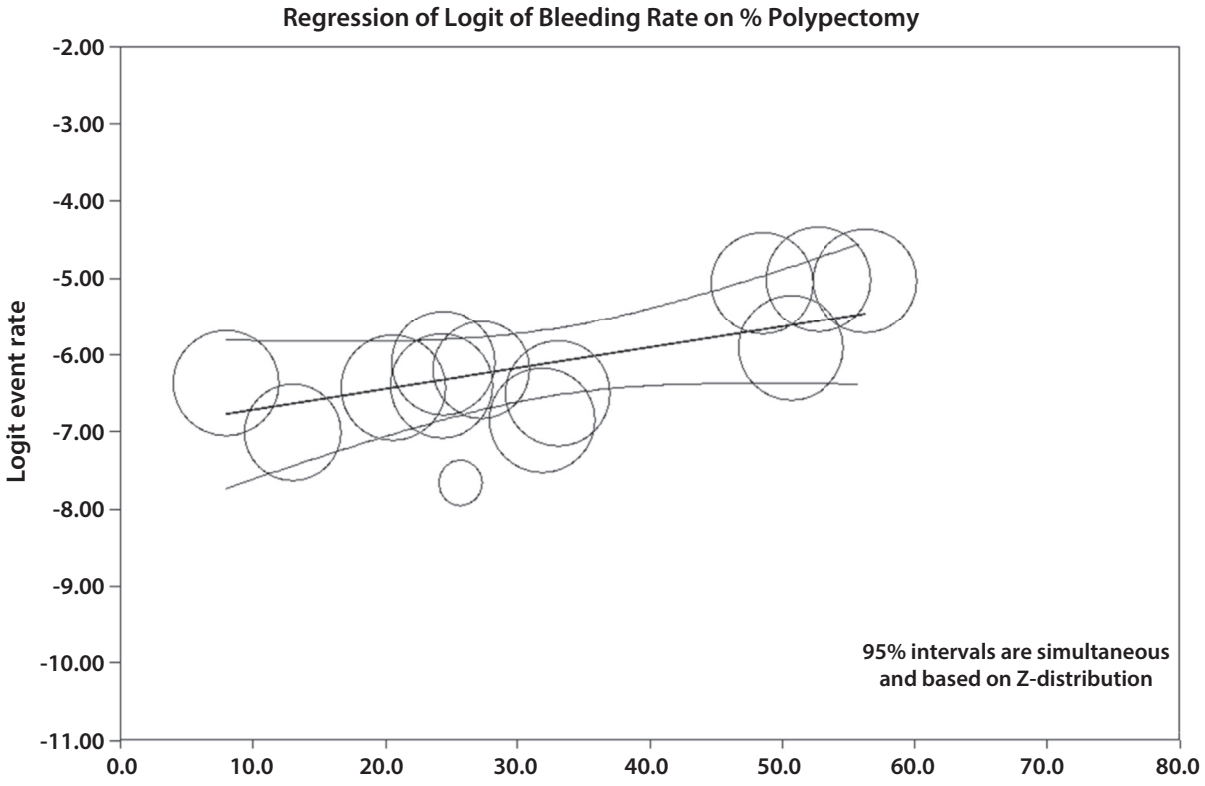
Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.1204, Tau = 0.3470, I^2= 96.92%, Q =519.93, df =16, p = .0000

Proportion of total between-study variance explained by Model 1
R^2 analog = 0.00 (computed value is -0.19)

A

Supplementary Figure 1. Meta-regression of postcolonoscopy perforation (A) and bleeding (B) from population-level studies with percentage of cohort undergoing polypectomy (% polypectomy) as a mediator covariate, following adjustment for age and gender. Data analyzed with a random-effects model, and 95% confidence intervals shown.



B

Main results for Model 1, Random effects (MM), Z-Distribution, Logit event rate

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-6.7319	2.1293	-10.9053	-2.5586	-3.16	.0016
Age	0.0231	0.0304	-0.0365	0.0826	0.76	.4478
% Female	-0.0327	0.0290	-0.0895	0.0241	-1.13	.2597
% Polypectomy	0.0271	0.0113	0.0050	0.0492	2.41	.0160

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 15.81, df = 3, p = .0012

Goodness of fit: Test that unexplained variance is zero

Tau^2 = 0.2338, Tau = 0.4836, I^2= 98.85%, Q =780.63, df =9, p = .0000

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau^2 = 0.3099, Tau = 0.5567, I^2= 99.49%, Q =2360.26, df =12, p = .0000

Proportion of total between-study variance explained by Model 1

R^2 analog = 0.25

Number of studies in the analysis 13

Supplementary Figure 1. Continued.

Main results for Model 1, Random effects (MM), Z-Distribution, Logit event rate

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided p-value
Intercept	-3.6700	0.7529	-5.1457	-2.1943	-4.87	.0000
EMR/ESD: ESD	-2.1856	0.3313	1.5364	2.8349	6.60	.0000
Location: Asian	-0.2927	0.3225	-0.9248	0.3395	-0.91	.3642
Size of polyp	-0.0271	0.0216	-0.0695	0.0152	-1.26	.2093

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 66.95, df = 3, p = .0000
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.0993, Tau = 0.31 51, I^2 = 28.78%, Q = 33.70, df = 24, p = .0902

Comparison of Model 1with the null model

Total between-study variance (intercept only)
Tau^2 =1.1099, Tau = 1.0535, I^2 = 84.72%, Q = 176.69, df = 27, p = .0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.91

A Number of studies in the analysis 28

Supplementary Figure 2. Meta-regression of EMR/ESD-related perforation (A) and bleeding (B) with type of procedure (ESD vs EMR), location (Asian vs Western), and mean diameter of polyp as mediator covariates. Data analyzed with a random-effects model. *ESD*, Endoscopic submucosal dissection.

Main results for Model 1, Random effects (MM), Z-Distribution, Logit event rate

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided p-value
Intercept	-4.4941	0.9033	-6.2645	-2.7237	-4.98	.0000
EMR/ESD: ESD	-0.4048	0.3457	-1.0824	0.2728	-1.17	.2416
Location: Asian	0.0242	0.3291	-0.6208	0.6692	0.07	.9413
Size of polyp	0.0357	0.0254	-0.0142	0.0855	1.40	.1610

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 3.69, df = 3, p = .2968
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.1848, Tau = 0.4299, I^2 = 60.17%, Q = 62.76, df = 25, p = .0000

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.2171, Tau = 0.4659, I^2 = 66.53%, Q = 83.65, df = 28, p = .0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.15

B Number of studies in the analysis 29

Supplementary Figure 2. Continued.