

# Capsule Retention in Crohn's Disease: A Meta-analysis

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**Background:** The main factor that limits wider utilization of capsule endoscopy (CE) in Crohn's disease (CD) is the potential risk of retention. The aim of this systematic review was to evaluate capsule retention rates in adult and pediatric CD and determine if retention risk is reduced in established CD (ECD) with patency capsule (PC) or magnetic resonance/computed tomography (MR/CT) enterography.

**Methods:** Studies of CD patients undergoing CE that reported retention were identified. Pooled estimates for retention rates and relative risk in ECD to suspected CD (SCD) were calculated. All hypothesis tests were 2-sided; statistical significance was set at a *P* value of <0.05.

**Results:** In the overall CD cohort, retention rates were 3.32% (95% confidence interval [CI], 2.62%–4.2%); 4.63% (95% CI, 3.42%–6.25%) and 2.35% (95% CI, 1.31%–4.19%) in ECD and SCD, respectively. Retention rates were 3.49% (95% CI, 2.73%–4.46%) and 1.64% (95% CI, 0.68%–3.89%) in adult and pediatric CD, respectively. Retention risk in adult ECD was 3.4 times higher than SCD, but there was no difference in retention risk in pediatric ECD compared with SCD. Retention rates in ECD were decreased after patency capsule (2.88%; 95% CI, 1.74%–4.74%) and MR/CT enterography (2.32%; 95% CI, 0.87%–6.03%).

**Conclusions:** In comparison with older literature, this meta-analysis demonstrates lower CE retention rates in SCD and ECD. Retention rates in pediatric CD were lower than in adult CD. Retention rates in adult ECD were higher than SCD, but there were no differences between pediatric ECD and SCD. Retention rates in ECD were lower after negative PC or MR/CT enterography.

**Key Words:** Crohn's disease, capsule endoscopy, meta-analysis

## INTRODUCTION

Capsule endoscopy (CE) is the only endoscopic modality currently available for visualization of the entire small bowel (SB) mucosa in a minimally invasive manner. It is therefore an ideal tool for diagnostic evaluation of small bowel Crohn's disease (CD). The role of CE in patients with suspected (SCD) and established CD (ECD) has expanded over the years and includes diagnosis of small bowel CD, evaluation of disease activity and response to therapy, objective assessment of mucosal healing, and detection of postoperative recurrence.<sup>1</sup> Interest in evaluating the entire SB and colon with 1 test led to promising results of pilot studies using a colon CE for detection of inflammation.<sup>2,3</sup> In consequence, a novel pan-enteric capsule is being evaluated as a potential tool for monitoring both SB and colonic disease activity in CD.<sup>2,4-7</sup>

The main factor that limits wider utilization of CE is the potential risk of retention. Capsule retention is defined as the presence of the capsule endoscope in the gastrointestinal tract for a minimum of 2 weeks.<sup>8</sup> Retention may be considered a minor adverse event because patients are usually asymptomatic, and in about one-third, the capsule is naturally excreted later than 15 days after ingestion.<sup>9,10</sup> Nevertheless, in some patients it can result in acute obstruction or perforation<sup>11,12</sup> and might require endoscopic and/or surgical intervention for retrieval. Capsule endoscopy retention is dependent upon the underlying SB disorder, ranging from less than 1% in suspected SB bleeding to 21% in the setting of SB obstruction in patients with CD, nonsteroidal anti-inflammatory drug (NSAID)

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enteropathy, SB tumors, SB anastomoses, and radiation enteropathy.<sup>9, 13–15</sup>

In patients with CD, CE retention risk differs widely between suspected and established CD, with a significantly higher risk in ECD. According to earlier studies that predate patency testing, the retention rate in ECD was as high as 13%,<sup>16</sup> whereas recent studies have reported lower retention rates ranging from 2.1% to 7.8%, which may largely be due to avoidance of CE in high-risk patients.<sup>17–20</sup> A previous meta-analysis reported CE retention rates of 3.6% (95% CI, 1.7%–8.6%) in SCD and 8.2% (95% CI, 6.0%–11.0%) in ECD.<sup>21</sup> This study mainly focused on high-risk adult patients, with exclusion of those who had undergone SB patency testing.<sup>21</sup> In comparison, the aim of our meta-analysis was to determine capsule retention rates in the “real-world” scenario in both adult and pediatric CD and determine if the risk can be reduced in ECD with utilization of patency capsule (PC) or dedicated SB cross-sectional imaging (magnetic resonance/computed tomography [MR/CT] enterography).

## METHODS

### Search Strategy

A comprehensive review of the medical literature was conducted for studies that included CD patients (categorized as SCD or ECD) undergoing CE and reported capsule retention (Supplementary Fig. 1). The review of articles, analyses, and inclusion criteria were based on PRISMA recommendations.<sup>22</sup>

### Eligibility Criteria

We considered all clinical studies of CE in CD involving human subjects, both adult and pediatric, from January 2000 to July 2018. Case reports and review articles were excluded. If there was any suspicion of cohort overlap between studies, only the most recent study was included.

### Information Sources

Relevant original publications (in English) were identified in MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Web of Science. Prespecified Medical Subject Headings (MeSH) and non-MeSH terms were used for the search and are reported in Supplementary Table 1. Both full texts and abstracts were included. Additional publications were identified through searching the reference lists of retrieved papers. When further information from selected papers was needed, we attempted to contact the authors.

### Study Search Criteria

The abstracts of all retrieved articles were screened by 2 reviewers (S.F.P., M.P., or E.R.). Studies were evaluated for inclusion in the analysis based on review of the entire article. The following inclusion and exclusion criteria were applied:

### Inclusion criteria

Studies that reported:

- (1) the use of CE (small bowel or colon capsule) in patients with CD;
- (2) CE retention in patients with CD;
- (3) CE retention in SB disorders if data could be separately extracted for CD from the manuscript or by contacting the primary authors;
- (4) the use of PC in patients with ECD;
- (5) the use of CT or MR enterography in ECD.

### Exclusion criteria

Studies that:

- (1) did not report CE retention;
- (2) did not use formal criteria (presence of the capsule in the gastrointestinal tract for at least 2 weeks after ingestion) to define CE retention, if specifically stated within the manuscript;
- (3) precluded adequate extraction of data.

Data were separately extracted by 2 of 3 reviewers (S.F.P., M.P., or E.R.). Any disagreements were adjudicated by a third reviewer (D.W. or J.A.L.) and by consensus.

### Search criteria

Capsule endoscopy, or video capsule endoscopy, or capsule, or video capsule, or small bowel capsule, or colon capsule  
AND  
Crohn disease, or Crohn's disease, or inflammatory bowel disease

AND  
Patency capsule, or patency, or retention, or retained, or stricture, or small bowel stricture, or obstruction, or small bowel obstruction, or small bowel stenosis, or stenosis, or CT enterography, or computed tomography enterography, or MR enterography, or magnetic resonance enterography, or small bowel X ray or small bowel follow through

### Data Collection

The reviewers independently extracted the following information: (1) year of publication; (2) type of publication (manuscript/abstract); (3) country(ies) of publication; (4) single or multicenter study; (5) study design (prospective or retrospective); (6) patient demographics (mean age and standard deviation, sex); (7) patients undergoing CE (all CD, SCD, and ECD); (8) patients with CE retention; (9) indication for CE in ECD (evaluation of disease activity, assessment of mucosal healing, evaluation of symptoms, evaluation for postoperative recurrence); (10) risk factors for retention stricture, obstructive symptoms, NSAID use, prior abdominal surgery; (11) patients undergoing PC; (12) results of PC; (13) CE retention after PC; (14) patients undergoing CT/MR enterography; (15) CE retention after CT/MR enterography; (16) duration of CE retention; (17) management of CE retention.

## Study Quality

We planned to assess the quality of included studies using the modified Newcastle-Ottawa Scale for nonrandomized studies, ranging from 0 (low quality) to 5 (high quality).<sup>23</sup>

As far as the overall quality of included studies, we have to emphasize that only a few reported CE retention as the main outcome. In addition, based on our outcome of interest (ie, retention), none of the studies would have had a nonexposed cohort. The method of outcome assessment was not described in several studies. A follow-up of 2 weeks, or until endoscopic or surgical retrieval in symptomatic patients, was considered adequate length of follow-up. However, the majority of studies did not report actual or planned length of follow-up. Based on these limitations, a formal evaluation using a standardized score (such as Newcastle-Ottawa) was not possible.

## Statistical Analysis

Retention rates were estimated using the number of capsule retention events divided by the number of capsules (D.W.) reportedly administered. A continuity correction of 0.5 was added to each 0 cell. The Wilson Score method with continuity correction was used to estimate the 95% confidence interval (CI) for the retention rate for each study. The Wilson Score method was implemented as a result of the observed retention rates being 0 or near 0.<sup>24</sup> The pooled estimates for the various capsule retention rates were calculated using a random-effects model (REM) with the inverse variance method.

The relative risk (RR) of capsule retention in patients with ECD to SCD was estimated for each study. If a study did not specify the number of capsules administered in a particular group (ECD, SCD, etc.), it was assumed that every member of that group received a capsule. Normally, approximated 95% CIs are provided for each RR estimate. The treatment arm continuity correction (TACC) is used in studies where 0 event rates are reported. TACC involves adding the reciprocal of the opposite group size to the cell with 0 events. TACC was chosen over the more typical fixed continuity corrections because of the imbalance in the number of patients with ECD and SCD. The TACC method, together with the Mantel-Haenszel fixed-effect model approach for pooling estimates, has been shown to be less biased than using fixed continuity corrections, such as adding 0.5, in situations where the data are sparse.<sup>25</sup> Studies with 0 event rates for both groups were included in the study to result in a more conservative effect size.<sup>26</sup> These methods were repeated for the adult and pediatric subanalyses. The  $I^2$  and  $T^2$  statistics are provided for each pooled estimate (Supplementary Table 2). All analyses were conducted in R 3.4.2 with the *meta* package.<sup>27</sup> All hypothesis tests were 2-sided, with a  $P$  value <0.05 considered statistically significant.

## RESULTS

### Study Selection

The study flow chart is shown in Figure 1. In total, 368 articles were identified using our search strategy. After reviewing

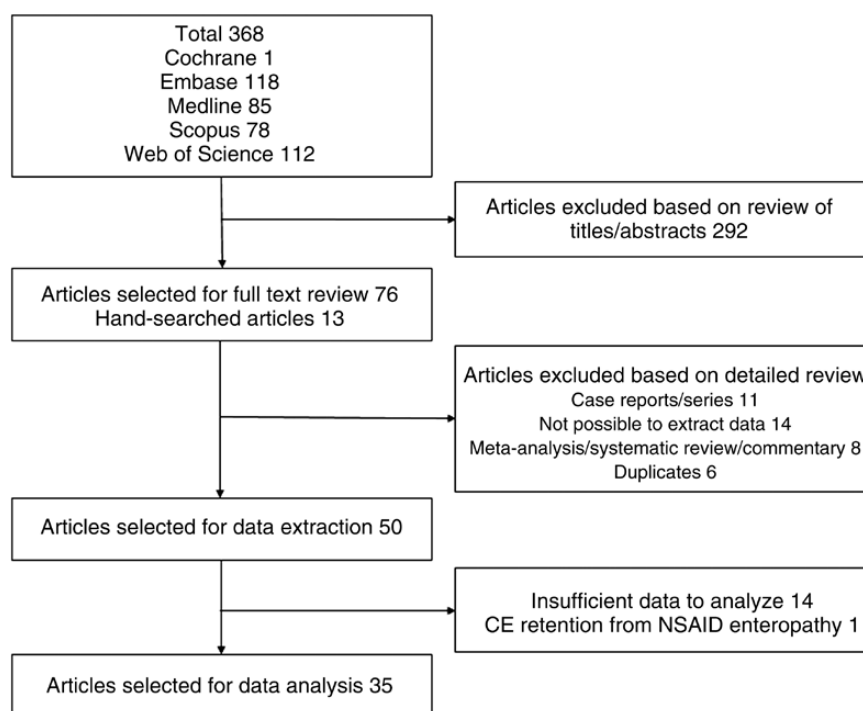


FIGURE 1. Study inclusion diagram.

titles and abstracts, 76 were found to be eligible and reviewed in full text. Thirteen additional articles were identified by bibliographic search of the selected articles. Based on a detailed review of the 89 articles, 35 manuscripts were selected for inclusion in the data analysis (Table 1). The authors of 11 of these studies were contacted for missing data, and we received data for 4 studies (Supplementary Table 3).

The retention rate in the overall CD cohort (SCD and ECD) was 3.32% (95% CI, 2.62%–4.2%; 35 studies) (Fig. 2). The retention rate in patients with ECD was 4.63% (95% CI, 3.42%–6.25%; 32 studies) (Supplementary Fig. 2), and it was 2.35% (95% CI, 1.31%–4.19%; 16 studies) (Supplementary Fig. 3)

in patients with SCD. Patients with ECD were 3.5 times more likely to experience retention than those with SCD (95% CI, 2.12–5.78; 16 studies) (Supplementary Fig. 4).

In the adult and pediatric studies, the estimated retention rate was 3.49% (95% CI, 2.73%–4.46%; 31 studies) (Fig. 3) and 1.64% (95% CI, 0.68%–3.89%; 4 studies) (Fig. 4), respectively. The retention rate for ECD patients was 4.76% (95% CI, 3.4%–6.63%; 28 studies) in adult patients (Supplementary Fig. 5) and 3.45% (95% CI, 1.44%–8.03%; 4 studies) in pediatric patients (Supplementary Fig. 6). In adults with SCD, the retention rate was 2.57% (95% CI, 1.36%–4.78%; 13 studies) (Supplementary Fig. 7), and it was 1.22% in pediatric patients

**TABLE 1. Summary of All Studies Included**

Name of Study	Year of Publication	Country	Study Design	Capsule Endoscope
Albert <sup>47</sup>	2005	Germany	Prospective	Small bowel (not specified)
Atay <sup>38</sup>	2009	US	Prospective	Small bowel (not specified)
Pons Beltran <sup>48</sup>	2007	Spain	Prospective	Given M2A
Buchman <sup>49</sup>	2009	US	Prospective	Given M2A
Hara <sup>50</sup>	2006	US	Prospective	Pillcam SB1
Jensen <sup>51</sup>	2011	Denmark	Prospective	Pillcam SB
Kopylov <sup>19</sup>	2015	Israel	Retrospective	Pillcam SB 3, Pillcam colon 2
Nemeth <sup>31</sup>	2016	Israel	Retrospective	Pillcam SB 1/2/3, Mirocam, Endocapsule
Shiotani <sup>52</sup>	2014	Japan	Prospective	Pillcam SB2
Voderholzer <sup>53</sup>	2005	Germany	Prospective	Given M2A
Wiarda <sup>54</sup>	2011	The Netherlands	Prospective	Pillcam SB
Cheifetz <sup>16</sup>	2006	US	Retrospective	SB capsule (not specified)
Hoog <sup>14</sup>	2012	Sweden	Retrospective	Pillcam SB, Mirocam, Endocapsule
Cheon <sup>55</sup>	2007	Korea	Retrospective	Given M2A
Dussault <sup>20</sup>	2012	France	Retrospective	Pillcam SB 2
Signorelli <sup>56</sup>	2006	Italy	Prospective	Given M2A
Ang <sup>57</sup>	2003	Singapore	Prospective	Given M2A
Toy <sup>58</sup>	2008	USA	Prospective	Small bowel (not specified)
Esaki <sup>18</sup>	2014	Japan	Retrospective	Not specified
Cohen <sup>39</sup>	2008	USA	Retrospective	Not specified
Tillack <sup>59</sup>	2008	Germany	Prospective	Given M2A
Delvaux <sup>60</sup>	2005	France	Prospective	Pillcam SB
Niv <sup>61</sup>	2014	Israel	Prospective	Pillcam SB 2
Postgate <sup>62</sup>	2008	UK	Prospective	Pillcam SB
Flamant <sup>63</sup>	2013	France	Prospective	Pillcam SB
Reddy <sup>64</sup>	2004	India	Prospective	Given M2A
Aloi <sup>40</sup>	2013	Italy	Prospective	Pillcam SB
Greener <sup>65</sup>	2016	Multiple	Prospective	Pillcam SB 3, Pillcam colon 2
Spada <sup>66</sup>	2007	Italy	Prospective	Pillcam SB
Nakamura <sup>67</sup>	2015	Japan	Retrospective	Pillcam SB
Fernandez-Urien <sup>9</sup>	2015	Spain	Retrospective	Pillcam SB (only 1 Pillcam colon)
Nemeth <sup>34</sup>	2018	Spain	Retrospective	Pillcam SB1/2/3
Yoshimura <sup>68</sup>	2018	Japan	Retrospective	Not specified
Hanse <sup>69</sup>	2018	USA	Prospective	Not specified
Gonzalez-Suarez <sup>70</sup>	2018	Spain	Retrospective	Pillcam SB, Pillcam colon



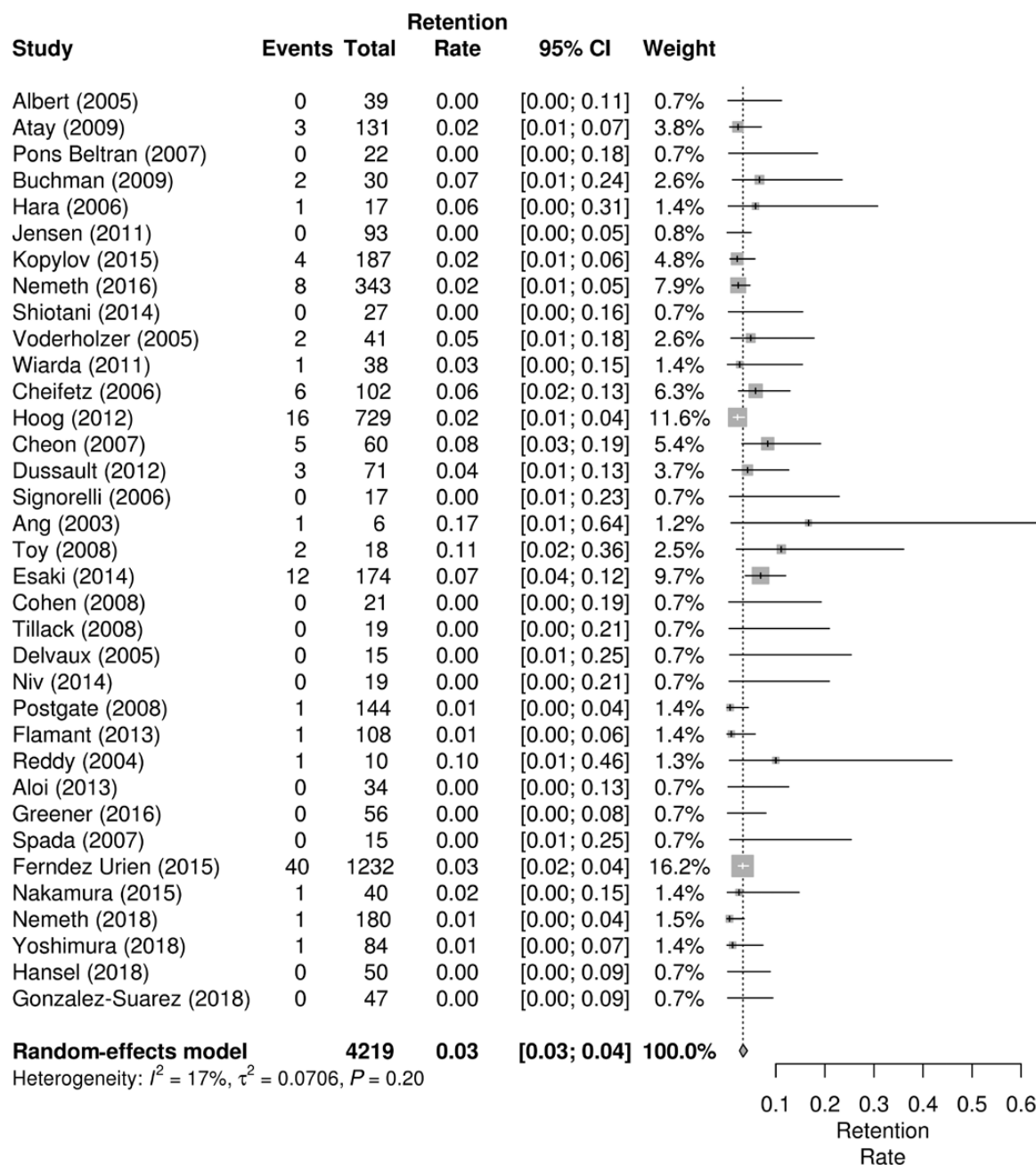


FIGURE 2. Retention rate in overall CD cohort.

(95% CI, 0.21%–6.73%; 3 studies) (Supplementary Fig. 8). Adult patients with ECD were 3.4 times more likely to experience retention than those with SCD (95% CI, 2.00–5.67; 13 studies) (Fig. 5). In contrast, pediatric patients with ECD did not have a higher risk of retention compared with those with SCD (RR, 4.92; 95% CI, 0.80–30.08; 3 studies) (Supplementary Fig. 9).

The retention rate in patients with ECD after SB imaging was 2.32% (95% CI, 0.87%–6.03%; 4 studies) (Fig. 6), and it

was 2.88% (95% CI, 1.74%–4.74%; 15 studies) after a negative PC (Fig. 7). The retention rate in patients with ECD after either SB imaging or a negative PC was 2.75% (95% CI, 1.76%–4.28%; 19 studies) (Supplementary Fig. 10).

## DISCUSSION

The results of our meta-analysis indicate capsule retention rates of 2% in patients with suspected CD, and 5% in established CD, with a relative risk of retention of 3.5 in ECD

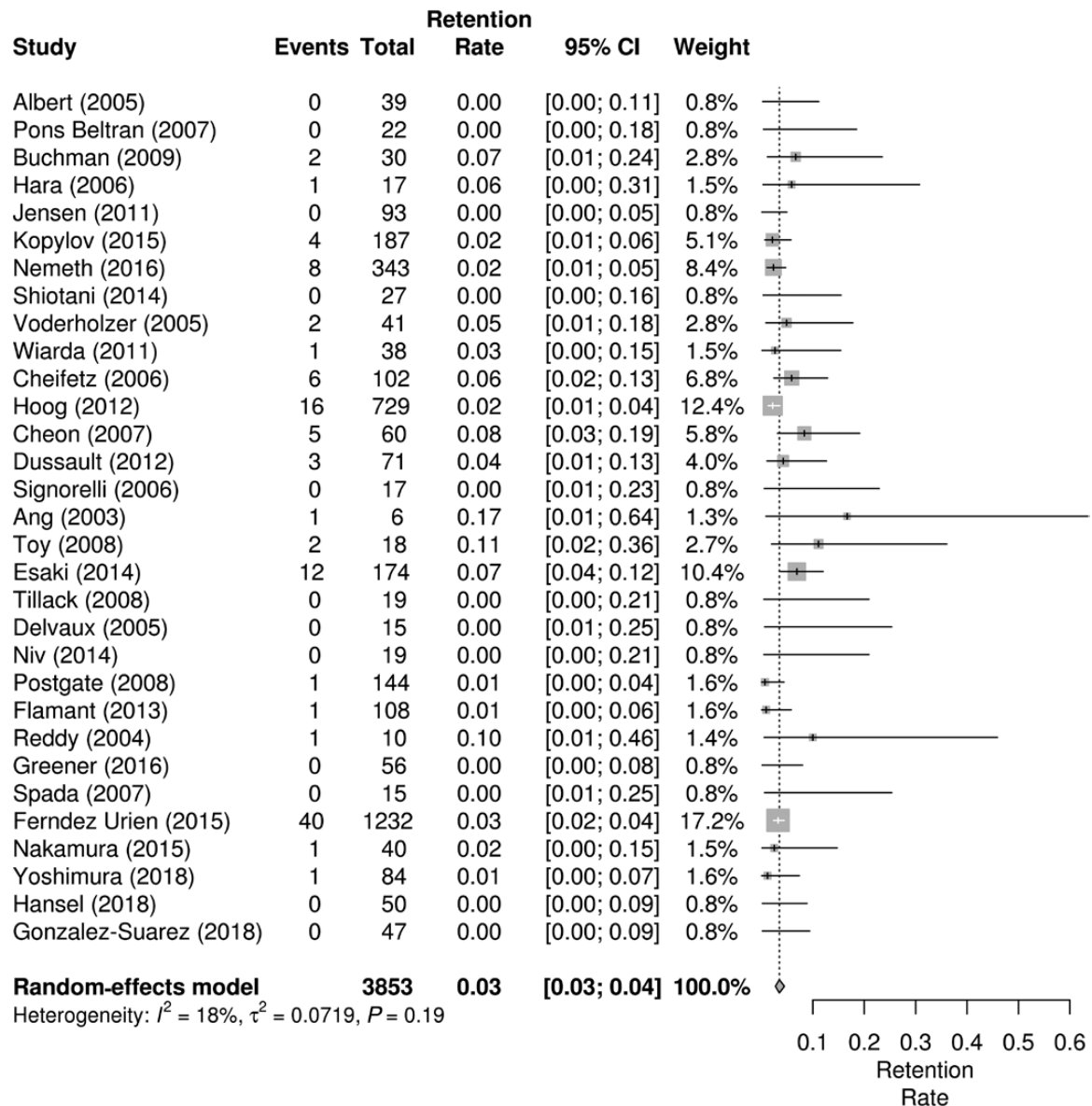


FIGURE 3. Retention rate in adult CD cohort.

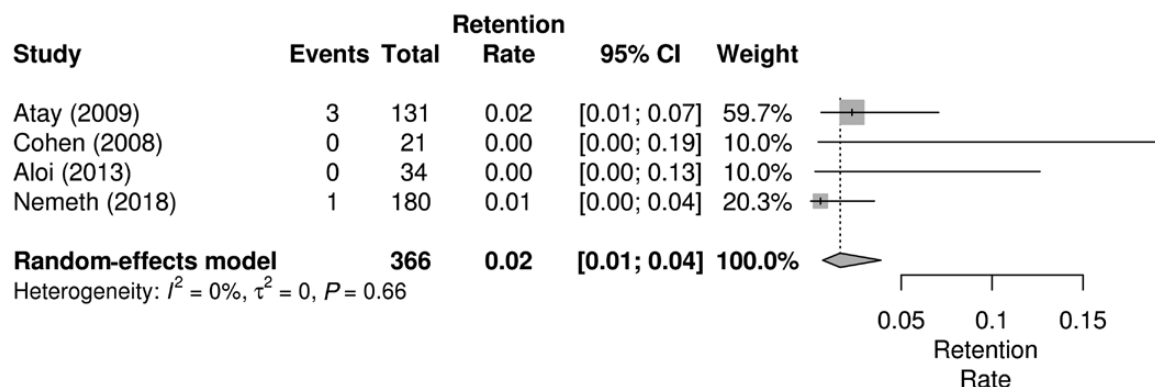


FIGURE 4. Retention rate in pediatric CD cohort.

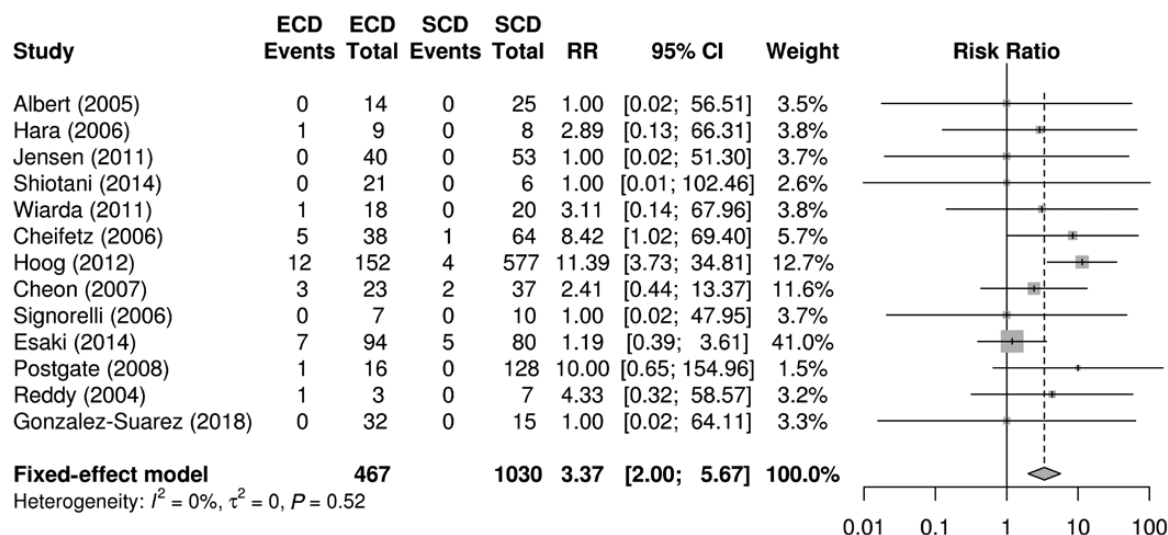


FIGURE 5. Relative risk for retention in adults with suspected CD vs established CD.

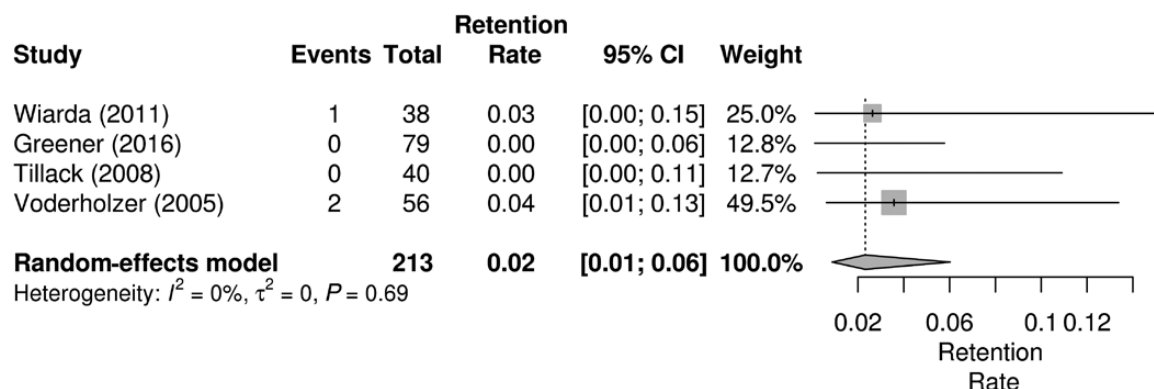


FIGURE 6. Retention rate in patients with established CD after small bowel imaging.

vs SCD. Despite the higher risk in ECD, it is important to recognize that overall the retention rates in both SCD and ECD are significantly lower than in the older literature. We believe our results more accurately reflect CE retention, as compared with the earlier meta-analysis by Rezapour et al.<sup>21</sup> Our inference is based on the main strength of our analysis, which is that it included a larger number of studies and therefore a higher number of patients and events, resulting in narrower confidence intervals in our results. In addition, we had a more robust collection of data, and both our main and subanalyses were focused on CD, with exclusion of other SB disorders.

Our results confirm that prior testing with PC or cross-sectional imaging is effective in reducing CE retention in ECD (2.75%; 95% CI, 1.76%–4.28%). Additionally, we found no difference between PC and CT/MR enterography, although there were only 4 studies with small numbers of patients that reported data on cross-sectional imaging. The studies also differed in the type of cross-sectional imaging performed (CT enteroclysis [1 study],

MR enteroclysis [2 studies], and MR enterography [1 study]) and the definition of a “critical stenosis” that would preclude CE. Although retrospective data suggest that PC may be more effective than CT/MR enterography,<sup>28</sup> head-to-head comparison trials would be helpful to determine if either of these modalities is more effective in the prevention of CE retention. Based on the available data, we were unable to confirm if combined testing with both modalities can further reduce CE retention risk, as indicated in a prior study.<sup>29</sup>

In a large study by Bawardy et al., the overall retention risk was only 0.3% among a large cohort of more than 5000 patients who underwent CE for various indications. None of the patients with CE retention had undergone prior PC. In all patients with CE retention, high-risk findings, including partial SBO, were identified on retrospective review of the CT/magnetic resonance enterography (MRE) images. This reinforces the need for a careful review of the imaging studies by experienced radiologists to avoid CE retention.<sup>30</sup> Additionally, studies

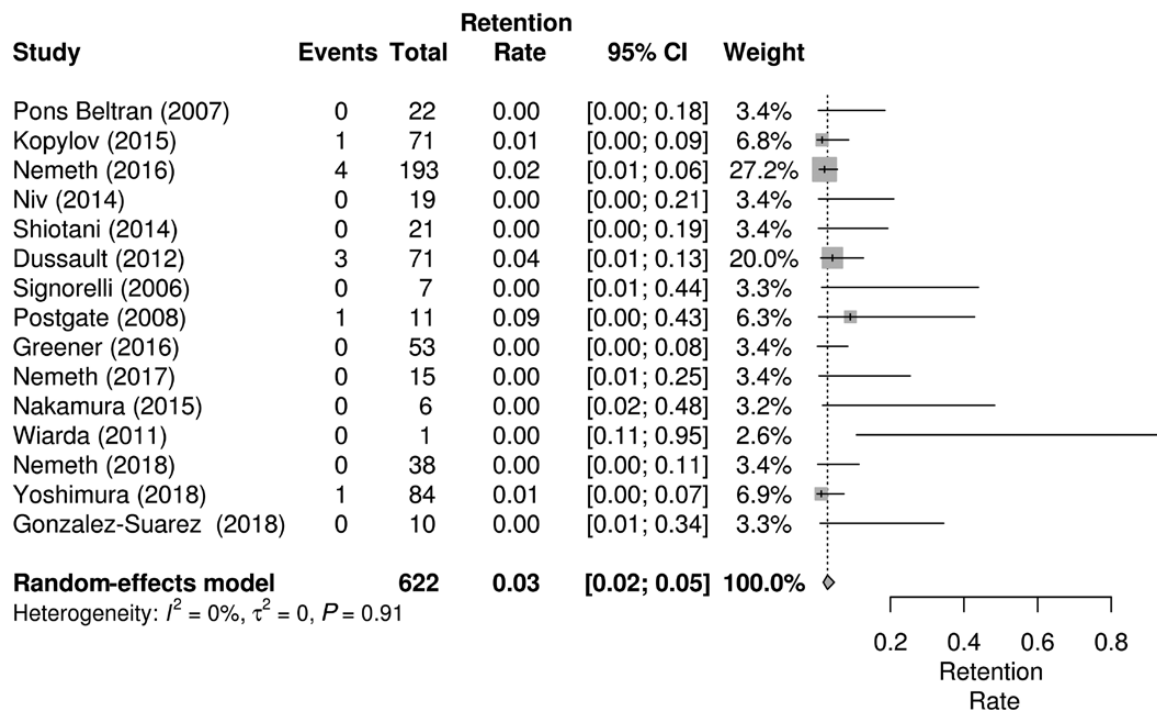


FIGURE 7. Retention rate in patients with established CD after negative patency capsule.

have shown that CT/MRE may fail to detect NSAID-related diaphragm disease, which is a common diagnosis in patients undergoing evaluation for SCD and is associated with a high risk of CE retention.<sup>13</sup>

A large study by Nemeth et al. that compared a nonselective strategy of PC in all CD patients vs selective administration in those with suspected obstruction or abdominal surgery found no difference in retention risk (1.6 vs 1.3%,  $P = 0.9$ ).<sup>31</sup> Due to significant heterogeneity in our included studies and lack of a consistent approach toward performance of PC, we could not determine which patients with ECD would benefit from patency testing. Given the high risk of CE retention in this cohort, the inability to distinguish high-risk from low-risk patients based on clinical presentation alone, and the indisputable effectiveness of patency testing, the safest approach would be to pursue patency testing before CE in all ECD patients. From a practical standpoint, PC may be the preferred test, as it is much more cost-effective, lacks subjective variation in interpretation of SB findings, and avoids adverse effects of intravenous contrast and radiation exposure. CT/MRE would be preferred in patients who also require imaging to assess for penetrating complications, followed by additional testing with PC in high-risk patients with a history of NSAID use, SB surgery, obstructive symptoms, or radiologic evidence of SB luminal narrowing.

Interestingly, a few studies have demonstrated safe performance of CE after a positive PC.<sup>31–33</sup> In a pediatric study, 33 of 71 patients (46%) had a positive PC.<sup>34</sup> Subsequent cross-sectional

imaging confirmed SB stenosis in 8 (8/33, 24%) patients in whom CE was not performed. There was no evidence of SB stenosis in 14 (14/33, 42%), and 7 patients underwent subsequent CE. In 4 additional patients, CE was performed without cross-sectional imaging after re-evaluation of symptoms. There were no cases of CE retention.<sup>34</sup> The discriminative power of a positive PC in predicting CE retention is limited by inaccurate localization of the PC within the small bowel (true positive) or colon (false positive) with the PC scanner and abdominal x-ray. Performance of a low-radiation spot CT scan in patients with a positive PC can eliminate false-positive results, allowing safe performance of CE.<sup>29, 34–36</sup>

There are limited data on CE retention in pediatric CD. The main concern of utilizing CE in children is the smaller SB luminal diameter, <21 mm (mean) in patients younger than age 8 years as compared with 23 mm in those older than age 15 years,<sup>37</sup> which may be further compromised by inflammation and fibrostenotic CD complications. Contrary to this concern, we found lower retention rates of 1% and 3% in pediatric SCD and ECD, respectively, than adults. There was also no significant difference in CE retention in pediatric ECD compared with SCD. These findings may reflect the shorter duration of CD and lower likelihood of fibrostenotic complications in this cohort. One of our limitations was inclusion of only 4 pediatric studies and inability to distinguish high-risk from low-risk patients.<sup>38–40</sup> Despite lower retention rates, management of retention in pediatric patients with endoscopic retrieval or surgery does carry both safety and long-term implications. Pediatric



patients should therefore be judiciously screened, with consideration of both cross-sectional imaging and PC before CE.<sup>34,41</sup>

However, the concern for retention should not preclude CE utilization, as long as patients have undergone appropriate patency testing. It is important to recognize that the majority of CD patients with a retained CE do not require surgical management. Most patients remain asymptomatic, with spontaneous passage of the capsule, or can be managed with purgatives, medical management with steroids or biologics, or endoscopic retrieval using a standard endoscope or device-assisted enteroscopy.<sup>33,42</sup> Moreover, capsule retention can provide evidence of strictures that may not be evident on other tests, and thus guide management of symptomatic patients. Endoscopic retrieval of retained capsules also allows localization and dilation of SB strictures and avoidance of surgery.<sup>43-45</sup>

Although there are reports of asymptomatic CD patients with CE retention followed conservatively for 36 to 38 months after ingestion, it is recommended that CE retention be identified and managed electively, to avoid infrequent but major adverse events of SB obstruction and perforation.<sup>11,16,46</sup>

There are several limitations of our meta-analysis. A formal quality assessment could not be completed, as only a few studies have reported CE retention as the main outcome, and the method of outcome assessment and length of follow-up were not reported in the majority of studies. As most of our analyses were based on incidental information rather than the main outcomes of the studies, the effect of publication bias is unclear. There were only a small number of studies available to pool in many subanalyses, and some included studies in which no events (ie, retentions) were observed. There was significant heterogeneity among cohorts, including a lack of a consistent approach toward patency testing. Unless explicitly stated otherwise, we also made the assumption that studies had used formal criteria for CE retention, which may have led to a falsely inflated CE retention rate. Furthermore, either there was no standardized approach toward management of CE retention or it was not reported in most studies, and therefore these data could not be systematically reviewed. Lastly, although PC is effective in reducing retention of capsules 26 × 11 mm or smaller in dimension, its utility in decreasing the retention risk of capsules with larger dimensions (31 × 11 mm) is not known.

In conclusion, CE retention rates in clinical practice are lower than in earlier studies, likely due to the prudent performance of SB patency testing when indicated. Our meta-analysis confirms the utility of PC and cross-sectional imaging in lowering CE retention in established CD. Our results also indicate lower retention rates in pediatric compared with adult CD and, in contrast to adults, no difference in CE retention with SCD and ECD in the pediatric cohort.

## SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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