# Improving outcomes of inflammatory bowel disease

Thesis Defense in Partial Fulfillment of the Requirements for the Degree of Master of Medical Sciences in Clinical Investigation (MMSCI)

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## Overview of the thesis papers

Inflammatory bowel disease (IBD) is an autoimmune disease that involves the gastrointestinal tract and can affect multiple organ systems in the human body. It is classified into two main types, Crohn's disease (CD) and ulcerative colitis (UC).

Taking care of patients with IBD can be faced by multiple challenges, including symptomatic treatment, medication monitoring, managing interaction of IBD with other comorbidities, and preventing long term complications, like implementing colorectal cancer (CRC) screening.

Additionally, in the last two decades, there have been advances in managing these patients in terms of treatment, as well as improvement in diagnostic and screening techniques.(1) Consequently, this raised more challenges, such as changing in body habitus of these patients,(2) and increased the demand to examine the quality of the enormous amount of data that become available.

Our research group has tackled multiple areas of these challenges. I will be presenting two projects of our research works in this thesis. While in the first paper we analyzed the existing data to find the evidence behind using advanced visual technology in performing colonoscopy for CRC screening in patients with IBD. In the second paper, we studied the effect of obesity on the outcomes of hospitalized patients with UC.

# Project 1

## Meta-analysis of virtual based chromoendoscopy compared to dye spraying chromoendoscopy standard and high-definition white light endoscopy in patients with inflammatory bowel disease at increased risk of colon cancer

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**Abstract**

**Background**: Patients with inflammatory bowel disease (IBD) have an increased risk of colorectal cancer. We sought to assess the comparative efficacy of virtual chromoendoscopy (VCE) vs high definition white light endoscopy (HDWLE) or dye-spraying chromoendoscopy (DCE) through a meta-analysis and rating the quality of evidence.

**Methods:** A systematic review of the literature was performed through February 15, 2019. Primary outcomes were number of patients in whom dysplasia was identified and number of dysplastic lesions identified in these patients. We included only randomized control trials (RCTs) and performed meta-analysis using RevMan5.3.

**Results:** Of the 3205 studies identified, 11 RCTs were included, with a total of 1328 patients. Per patient analysis, VCE was not statistically different compared with DCE (risk ratio [RR] 0.77; 95% CI, 0.55–1.08) or HDWLE (RR 0.72; 95% CI, 0.45–1.15). However, per dysplasia analysis, VCE was not statistically different compared with DCE (RR 0.72; 95% CI, 0.47–1.11) and inferior compared with HDWLE (RR 0.62; 95% CI, 0.44–0.88). The quality of evidence was moderate in the HDWLE and low to moderate in the DCE studies.

**Conclusion:** Based on this meta-analysis, VCE was as good as HDWLE and DCE in identifying dysplasia per patient analysis. However, per dysplasia analysis, VCE was inferior compared with HDWLE and no different from DCE. Further studies need to examine the efficacy of each individual VCE technique.

**Key Words:** inflammatory bowel disease, colorectal cancer screening, virtual chromoendoscopy, colonoscopy, dysplasia

## Introduction

Colorectal cancer (CRC) remains a feared complication of long-standing colitis from ulcerative colitis (UC) and Crohn's disease (CD) colitis. Even though the overall risk associated with long-standing colitis is variable in the literature, studies report the risk to be as high as 18% at 30 years.(3) Although pharmacologic therapy appears to have decreased this risk of cancer over time, the risk remains in those who have at least one third of the colon involved.(4) To reduce the risk of CRC, multiple societies have recommended ongoing screening and surveillance of these patients.(3,5–8) However, the ideal modality to screen for CRC and identify early dysplastic changes that allow the clinician to decide between endoscopic resection and surgery remains unclear.

The historical standard for CRC screening in inflammatory bowel disease (IBD) has been white light endoscopy (WLE) with biopsies in a 4-quadrant sampling every 10 cm, with a minimum of 32 samples.(9) However, this method provides a very limited sampling of the colon surface area, potentially missing areas of dysplastic changes.(10,11) To improve the screening of patients with IBD for CRC and address newer technologies to aid in CRC screening, the surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) consensus statement was developed to provide guidance on the use of WLE and chromoendoscopy.(6) Dye-spraying chromoendoscopy (DCE) has the benefit of covering the entire surface area of the colon and highlighting areas of suspected dysplasia, allowing for more targeted biopsies and removal of visible dysplasia that may have been considered unresectable under standard WLE.(12) However, chromoendoscopy requires the spraying of methylene blue or indigo carmine throughout

the colon, requires expertise in its use, and can be time consuming, as well, compared with WLE.(13)

Though DCE has been advocated as the new standard of care, the overall benefit of this modality over high definition WLE is questionable.(13) In more recent years, there has been a push toward using technological advances to evaluate the colon to better highlight areas of dysplasia and determine if the dysplasia is resectable or not.(14) Virtual chromoendoscopy (VCE) has been evaluated with many techniques to date, including narrow band imaging (NBI),(15–20) iSCAN,(21,22) fuji intelligent color enhancement (FICE),(23,24) and autofluorescence imaging (AFI).(25) Each of these methods uses proprietary technology to highlight areas of dysplasia. The overall benefits of these advances compared to standard definition white light colonoscopy (SDWLE), high definition white light colonoscopy (HDWLE), and dye-based chromoendoscopy is less clear.

To that end, we sought to perform a systematic review and meta-analysis of randomized control trials of VCE compared to DCE, SDWLE, HDWLE.

## Methods

### Protocol and Registration

We conducted this systematic review and meta-analysis guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA). The population of interest, interventions, control, outcomes (PICO), and type of studies to be included were prespecified in a protocol before starting the systematic search.

### Search Methodology

A systematic literature search was performed through February 15, 2019, with the assistance of a medical librarian at Harvard Medical School with specific expertise in meta-analysis methodology. PubMed, EMBASE, and Web of Science were queried for studies comparing CRC screening in ulcerative colitis or CD colitis with VCE and DCE, WLE, or compared with other VCE techniques. When evidence was present, studies were evaluated based on study design. The complete search strategy is reported in supplemental table 2.

### Study selection

### Inclusion criteria

Included studies that utilized VCE, including NBI, iSCAN, FICE, or AF in patients with ulcerative colitis or CD colitis in the evaluation of dysplasia when screening for CRC. To be included, studies needed a comparator arm of DCE, HDWLE, SDWLE, or directly comparing a second VCE method. Trials were included only if they reported number of patients who were diagnosed with at least one dysplastic lesion or number of dysplasia per patient. Studies that used a crossover design with patients undergoing two

colonoscopies separated by several weeks were included, but data from only the first procedure were assessed.

**Exclusion criteria**

Non-IBD related studies and non-human studies of VCE were excluded. Studies reporting data only as dysplasia per colonoscopy in which patients underwent multiple colonoscopies and studies that utilized tandem colonoscopies were excluded. Similarly, studies without any comparator arm were also excluded.

**Data extraction**

Multiple reviewers reviewed the initial search criteria followed by two reviewers (ME and CY) independently reviewing all search results for improved accuracy. Initial results were reviewed by title to determine potential eligibility for inclusion. If a screened title was eligible or potentially eligible for inclusion, then the abstract or full article was reviewed in detail. Any disagreement was resolved by the evaluation of a third reviewer (JF) using a modified Delphi method. Data items were collected and confirmed by two authors (ME and JF) and included the last name of the first author, year of publication, population being studied (CD or UC), sample size, age, percentage of female, type of colonoscopy technique, and all relevant outcomes reported in each study.

**Outcome measures**

Our outcomes included (1) number of patients with dysplastic lesions identified with VCE compared with nonvirtual based modalities and (2) number of dysplastic lesions detected in each group. The comparator arms included DCE, SDWLE, HDWLE, or other VCE-based methods. A per-protocol analysis was utilized when extracting the data. Procedure times were also compared. If the study reported the procedure time by median and

interquartile range (IQR), we assumed that the data were normally distributed and hypothesized that the median was equal to mean and IQR was equal to 1.35 standard deviations.(26)

**Risk of bias and quality of evidence assessment**

We used the Cochrane risk of bias tool (Higgins 2011) for included randomized control trials (RCT). Domains include random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Concordance between two authors (ME and JF) for “low”, “high” or “unclear” risks of bias were recorded (Supplemental table 3).

Funnel plot was used as a visual tool to evaluate for potential publication or other possible biases across the studies. If publication bias was present, we used the trim and fill method to estimate and adjust for the missing studies in the meta-analysis. Quality of evidence was also assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.(27) The overall certainty in the evidence was assessed using the GRADE domains including risk of bias, inconsistency, indirectness, impression, and other publication bias considerations. Evidence was then graded as high, moderate, low, or very low. In GRADE, randomized control trials are considered high-quality evidence but can be rated down based on issues in any of these mentioned domains.

**Statistical Analysis**

Comparative studies were analyzed using pooled risk ratio (RR) and 95% confidence intervals (CI) were calculated based on the DerSimonian-Liard random-effects model. Heterogeneity was assessed using $I_2$ statistic with values > 50% suggesting significant

heterogeneity. Regarding procedure time, we used pooled mean difference and 95% CI of the comparative studies. Statistical analysis was performed using RevMan, version 5.3 (Cochrane Collaboration, Copenhagen, Denmark), R version 3.3.2 (to assess for publication bias), and using GradePro/GDT software (McMaster University, 2015).

**Sensitivity and Subgroup Analyses**

Each VCE subgroup was compared to SDWLE, HDWLE and DCE if number of studies permitted.

Due to including abstract articles in our data, we decided to do a secondary analysis excluding these studies.

## Results

The search of the databases and references resulted in 3,205 articles (Figure 1). After first removing duplicate studies, non-human studies, and non-IBD related studies, 82 potential studies were reviewed in depth for inclusion. In total, 11 studies were included in both the final qualitative and quantitative analyses(15–25,28,29). See table 1 for a summary of all of the included trials. In total, 577 patients undergoing virtual colonoscopy evaluation and 751 patients undergoing either WLE or DCE. The VCE arm included NBI, iSCAN, FICE, and AF compared to WLE, indigo carmine or methylene blue DCE. There was no standardized dilution for the DCE. Seven studies were performed in Europe, two in Canada, one in Brazil and one in Japan. Three of the included studies were crossover studies of which only the initial procedure was included, and four studies were only published in abstract form.

## Outcomes

### *Virtual chromoendoscopy compared to dye spraying chromoendoscopy in detecting dysplasia*

Our search found seven RCTs with a total of 482 patients undergoing VCE versus 476 patients undergoing DCE. There was no statistical difference between the two procedures in detecting dysplasia per patient analysis (seven studies, RR 0.77; 95% CI 0.55, 1.08, I2=12%). (Figure 2).

Per dysplastic lesion analysis showed similar findings with no statistical difference between VCE compared to DCE, however, the heterogeneity was significantly high as represented by I2 of 60%. In the subgroup analyses, DCE was superior to AFI in detecting

dysplastic lesions (one study, RR: 0.37; 95% CI 0.21,0.64), while there were no statistical differences between DCE and the other VCE types (NBI, FICE, and iSCAN) (Figure 3).

***Quality of evidence of comparing virtual chromoendoscopy dye spraying chromoendoscopy in detecting dysplasia***

In the studies that examined VCE versus DCE, the quality of evidence was rated moderate when we assessed per patient outcome with serious risk of imprecision. Nevertheless, the quality of evidence was rated low when we assessed per dysplastic lesions outcome with serious risk of imprecision and inconsistency due to crossing the line of unity and elevated heterogeneity, respectively (Table 2).

***Virtual chromoendoscopy compared to high definition white light endoscopy in detecting dysplasia***

We found three RCTs compared VCE to HDWLE, with a total of 169 patients undergoing VCE and 171 undergoing HDWLE. Per patient analysis, there was no statistical difference between VCE (iSCAN and NBI) and HDWLE (three studies, RR 0.72; 95% CI 0.45, 1.15, I2=0%) (Figure 4). Subgroup analysis is provided in supplementary figure 1.

Per dysplastic lesions analysis, HDWLE was superior to VCE (three studies, RR 0.64; 95% CI 0.48, 0.90, I2=0%) (Figure 5). In the subgroup analysis, HDWLE was superior to iSCAN in finding dysplastic lesions (one study, RR 0.55; 95% CI 0.36, 0.83), while, NBI did not show a statistical difference compared to HDWLE (Supplementary figure 2).

***Quality of evidence of comparing virtual chromoendoscopy to high definition white light endoscopy in detecting dysplasia***

The quality of evidence were moderate for both outcomes (per patient and per dysplastic lesions analyses). Evidence were rated down for imprecision (Table 2).

***Virtual chromoendoscopy compared to standard definition white light endoscopy in detecting dysplasia***

We found only one abstract study that compared SDWLE to FICE,(23) and showed FICE is superior in detecting dysplasia compared to SDWLE (One study, RR 3.2; 95% CI 1.59, 6.46) (Figure 5). The study did not report per patient analysis.

***Quality of evidence of comparing virtual chromoendoscopy to standard definition white light endoscopy in detecting dysplasia***

The quality of evidence were low due to serious risk of bias and imprecision (Table 2).

***Narrow band imaging virtual chromoendoscopy compared to non-virtual endoscopy***

Six RCTs studied NBI compared to other colonoscopy techniques (four studies compared NBI versus DCE and two compared NBI versus HDWLE). In both per patient and per dysplastic lesions analyses there were no statistical differences between the two groups (six studies, 643 patients, RR 0.97; 95% CI 0.66,1.42, I2=0%) and (five studies, 614 patients, RR 0.91;95% CI 0.68, 1.22, I2=0%) respectively.(Supplementary figures 3 and 4).

**Procedure Time**

Withdrawal time was reported in five studies(16,19,21,24,25) that compared dye spraying versus VCE, with a total number of 311 undergoing VCE (NBI, FICE, iSCAN, and AF) and 312 undergoing DCE. The pooled mean difference in withdrawal time was -7.19 minutes (95% CI -9.54, -4,83) in favor of VCE. However, the heterogeneity was high (I2=74%), likely due to using different types of VCE (Figure 6). Two out of these five studies reported total procedure time(19,25), and showed similar findings with a mean

difference -7.99 (95% CI -10.6, -5.38) and no significant heterogeneity (I2=0%)(Supplementary figure 5).

**Sensitivity Analysis**

We performed a secondary meta-analysis for the trials that compared VCE to DCE (due to the relatively high number of studies), and we excluded all abstract articles (17,20,21). Also, we removed one patient from the DCE group that had nine serrated polyps, which we included from the Bisschops 2016 study. As per the authors of this study, several lesions were more than 20 mm in size, the patient had serrated polyposis syndrome, and these polyps were likely unrelated to the patient's history of UC.(30)

The results of this analysis still showed no statistical difference between VCE and DCE per patient and per dysplastic lesions analyses (five studies, 628 patients, RR 0.73; 95% CI 0.52,1.04, I2=0%) and (five studies, 628 patients, RR 0.68;95% CI 0.40, 1.16, I2=64%) respectively.(Supplementary figures 6 and 7).

**Risk of Bias in Each Individual Study**

Blinding was an issue and a potential risk of introducing performance and detection bias, given the nature of the trials using colonoscopy and a form of chromoendoscopy. Given that it is impossible to perform these procedures with true blinding, this was judged as an outcome that is not likely to be influenced by lack of blinding of the participants and therefore ranked as "low" risk for bias. Regarding the blinding of the outcome assessors, most of the studies were not blinded to the endoscopists, however, some of them were blinded to histopathologists. The review authors judged the study as "unclear" risk of bias if either the endoscopist or the histopathologist were blinded, and "high" risk if both were

unblinded. The details of bias assessment for the individual and across the studies are detailed in supplementary figures 8 and 9.

**Publication Bias**

Funnel plot was used to assess the publication bias for studies that compared VCE versus DCE in both outcomes, per-patient and per dysplastic lesions analysis (Supplementary figures 10 A and B). In both plots, there was mild asymmetry due to possible publication bias in the small studies. The trim and fill methodology suggested that only one study needed in each outcome for the funnel plot to achieve symmetry (Supplementary figures 10 C and D). The adjusted RR after adding these missing studies (red dots) were not significantly different from the non-adjusted ones. This concluded that there was no high risk of publication bias. (Per dysplastic lesions analysis: adjusted RR 0.8; 95% CI 0.5, 1.2, P-value 0.2, and per patient analysis: adjusted RR 0.8; 95% CI 0.5, 1.1, P-value 0.2). Of note, we did not assess for publication bias in the studies that compared VCE versus SDWLE or HDWLE due to the limited number of studies.

## Discussion

At this time, the ideal technique to screen for CRC in IBD remains elusive. This study analyzed the current literature comparing VCE to dye DCE, HDWLE, and SDWLE. Our meta-analysis data suggest that VCE was not inferior to DCE or HDWLE on a per patient analysis for the detection of dysplasia. On the other hand, per dysplasia analysis showed different results with less dysplasia identified on VCE compared to HDWLE and no difference compared to DCE. This difference between per patient and per dysplasia analyses in the WLE groups can be related to the fact that once dysplasia is detected in a patient, more lesions can be found, especially with the advance in technology and clarity of the VCE and the HDWLE. Regarding SDWLE, we identify only one study that showed superiority of FICE in detecting dysplasia as expected. Even though it is difficult to come up with an accurate conclusion due to the lack of studies, we think that might be irrelevant since most of the colonoscopy practices are moving toward HDWLE instead of SDWLE. Unlike other meta-analyses in the field, (31) (32) (33) (34) (35) we focused only on VCE as a primary procedure of interest and only using randomized control trial data at studies with the highest quality evidence. With this focus on high quality data, we still noted limitations in the overall quality of the evidence supporting VCE when using GRADE methodology. However, given that the risk of CRC in patients with long-standing colonic inflammatory bowel disease remains significant, well-designed superiority studies are needed to better determine how to find dysplasia in patients and to ensure that all potentially dysplastic findings in a given patient are identified and removed.

With the increasing focus on technological advances to enhance polyp detection, there are now multiple proprietary modalities to perform VCE.(36) Our study included four types of VCE; AF, FICE, iSCAN, and NBI. The subgroup analysis for each of these modalities showed no statistical difference in dysplasia detection per patient analysis with HDWLE and DCE. On the other hand, per dysplasia analysis, FICE was superior to SDWLE, AF was superior to DCE and HDWLE was superior to iSCAN. However, all of these results were based on only one study for each subgroup, which is a limitation to the generalizability of these results. Among all the VCE types that we included, NBI had the largest number of trials (total of six trials, two compared NBI to HDWLE and four compared NBI to DCE) and that led us to run a separate analysis to compare it with DCE and WLE and our results showed no statistical difference per patient and dysplasia analysis (Supplementary figures 4 and 5 ). Overall, this data suggests that any screening technique will identify at least some dysplastic finding, albeit not necessarily all dysplastic findings in a patient. Given that each of these modalities is propriety technologies often integrated into the colonoscope by the manufacturer, any VCE or simply using routine HDWLE is likely to be adequate to screening for CRC in patients with inflammatory bowel disease.

The international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease (SCENIC)(37) suggested against the use of NBI for CRC screening when compared to SDWLE, HDWLE, or DCE. The consensus did not make any other recommendations regarding the other types of VCE due to a lack of qualified studies. Since then, our systematic research found one study that compared SDWLE to FICE,(23) a three-armed study that compared iSCAN to HDWLE and DCE,(22) and four

studies compared DCE to AF,(25) FICE,(24) iSCAN,(21) and NBI(17) respectively. With the additional information, our data suggest that overall there is no difference in the modalities when screening for CRC. At this time, there is insufficient data to suggest that VCE is superior to WLE. Nonetheless, there is more evidence to suggest that the lack of difference between DCE and VCE might actually favor the former if one takes in to account the benefit of a shorter procedure time of 7 minutes (Figure 6). In addition to the shorter procedure time, the overall cost of the procedure is also lowered with the avoidance of adding methylene blue/indigo carmine costs as well as the cost of biopsies every 10cm throughout the colon. Despite the findings from the initial SCENIC analysis, when factoring in potential costs savings from time and procedure related costs, one might consider either VCE or just HDWLE to screen for CRC in patients with inflammatory bowel disease.

Our study has several limitations. Given the small numbers in each VCE technique, we have combined them in aggregate, which could explain some of the significant heterogeneity in the DCE vs VCE and the procedure time analyses. Nevertheless, there is the possibility that one modality may in fact be superior. In our subgroup analysis with NBI, which had more studies supporting it, we did not find any difference in our outcomes of interest. The included studies of our meta-analysis, like all the other trials in interventional procedures, have a high risk of detection bias, and they might reflect individual and institutional experiences rather than a generalized result, especially, at least three of the included studies were conducted by a single endoscopist.(22,23,28) Nevertheless, the trend of the results among all the studies were similar and comparable. Also, we included the first period of the eligible crossover studies to avoid the risk of carry-

over effect; however, by doing so, we might have introduced selection bias. Finally, we included four abstracts in our review, and we were not able to adequately assess the risk of their biases and the quality of their results. However, we addressed that by excluding those studies in a secondary analysis in the VCE versus DCE group, and the result continued to show no statistical difference between the two modalities of colonoscopy.

**Conclusion**

In patients with IBD who undergo colonoscopy for colorectal screening, there was no statistical difference in the number of patients who had at least one dysplastic lesion identified between virtual chromoendoscopy and other colonoscopy techniques. Further high-quality studies are needed to confirm these findings and establish which technique is more optimal to use when screening for colorectal cancer in these patients.

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Table 1. Study characteristic of the included randomized control trials.

| Study reference | Year | Study design | Publication | Study setting | Sample size (PP) | Female (%) | Mean age | Mean disease duration | IBD type | Virtual chromo-endoscopy | Comparator |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bisschops | 2016 | Parallel | Full | Canada | 131 | 58(44%) | 52.3 y* | 15 y * | UC | NBI | DCE |
| Cassinotti | 2015 | Parallel | Abstract | Italy | 91 | NA | NA | NA | UC | FICE | SDWLE |
| Feitosa | 2011 | Parallel | Abstract | Brazil | 29 | 19 (65%) | 50 y | 15.6 y | UC/CD 13/16 | NBI | DCE |
| Gulati | 2018 | Crossover | Full | UK | 48 | 18(37.5%) | 44.9 y | 14.5 y | UC/CD 45/3 | FICE | DCE |
| Iacucci | 2017 | Parallel | Full | Canada | 270 | 122(45%) | 48.7 y | 17.7 y | UC/CD/IC 129/136/ 5 | iSCAN | DCE & HDWLE |
| Ignjatovic | 2012 | Parallel | Full | UK | 112 | 47 (42%) | 52.5 y | 21 y* | UC | NBI | HDWLE |
| Lopez-Serrano | 2017 | Parallel | Abstract | Spain | 66 | 34(51.5%) | 48.2 y | 15 y* | UC/CD 54/12 | iSCAN | DCE |
| Pellise | 2011 | Crossover | Full | Spain | 60 | 27(45%) | 48.3 y | 15.9 y | UC/CD 42/19 | NBI | DCE |
| Van Den | 2010 | Crossover | Full | Netherlands | 48 | 13 (27%) | 56 y | 23 y | UC | NBI | HDWLE |
| Vleugels | 2018 | Parallel | Full | Netherlands & UK | 210 | 88(42%) | 56.2 y | 20.8 y* | UC | AFI | DCE |
| Watanabe | 2016 | Parallel | Abstract | Japan | 263 | 127(48%) | 51 y* | 13 y* | UC | NBI | DCE |

*Median

AFI, Autofluorescence imaging; CD, Crohn's disease; DCE, Dey spraying endoscopy; FICE, Fuji intelligent color enhancement; HDWLE, High definition white light endoscopy; IBD, Inflammatory bowel disease; IC, Indeterminate colitis; NA, Not available; NBI, Narrow band imaging; PP, Per protocol; SDWLE, Standard definition white light endoscopy; UC, Ulcerative colitis; UK, United Kingdom; y, years

Table 2. GRADE quality of evidence

| Comparison | Outcome | Certainty assessment | | | | | | Summary of findings | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| | | № of participants (studies) | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Effect | | |
| | | | | | | | | Relative (95% CI) | Absolute (95% CI) | |
| VCE vs. DCE | № of Patients[$] | 921 (7 RCTs) | not serious | not serious | not serious | serious [a] | none | RR 0.77 (0.55 to 1.08) | 42 fewer per 1,000 (from 82 fewer to 15 more) | ⊕⊕⊕◯ MODERATE |
| | № of dysplasia* | 958 (7 RCTs) | not serious | serious [b] | not serious | serious [a] | none | RR 0.72 (0.47 to 1.11) | 75 fewer per 1,000 (from 143 fewer to 30 more) | ⊕⊕◯◯ LOW |
| VCE vs. HDWLE | № of Patients[$] | 340 (3 RCTs) | not serious | not serious | not serious | serious [a] | none | RR 0.72 (0.45 to 1.15) | 56 fewer per 1,000 (from 109 fewer to 30 more) | ⊕⊕⊕◯ MODERATE |
| | № of dysplasia* | 340 (3 RCTs) | not serious | not serious | not serious | serious [c] | none | RR 0.64 (0.45 to 0.90) | 120 fewer per 1,000 (from 183 fewer to 33 fewer) | ⊕⊕⊕◯ MODERATE |
| VCE vs. SDWLE | № of dysplasia* | 91 (1 RCTs) | serious[d] | not serious | not serious | serious [c] | none | RR 3.2 (1.59 to 6.46) | 352 more per 1,000 (from 49 more to 874 more) | ⊕⊕◯◯ LOW |

[$]Number of Patients with dysplasia; *Number of dysplastic lesions; **CI**, Confidence interval; **DCE**, Dye spraying chromoendoscopy; **GRADE**, Grading of Recommendations Assessment; Development; and Evaluation; **HDWLE**, High definition white light endoscopy; **RCT**, randomized controlled trial; **RR**, risk ratio; **SDWLE**, Standard definition white light endoscopy; **VCE**, Virtual chromoendoscopy.

*Explanations*

a. Small number of participants, a small number of events, and wide CI that cross the line of unity
b. High I square ($I^2$) which indicate a high risk of heterogeneity
c. Small number of participants and small number of events
d. Only one abstract study

Figures:

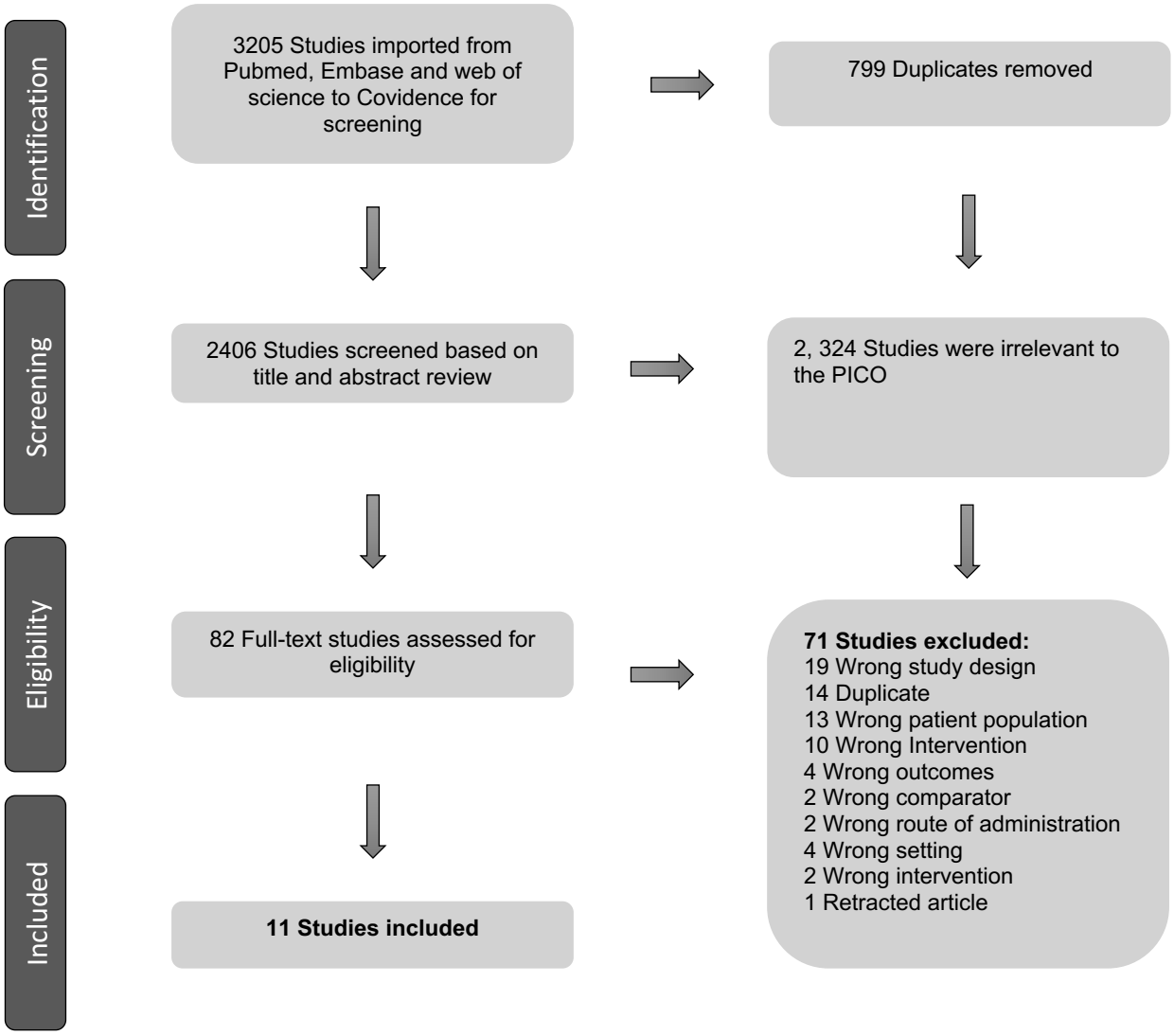


Figure 1. Flow diagram of search results and selection of included studies.

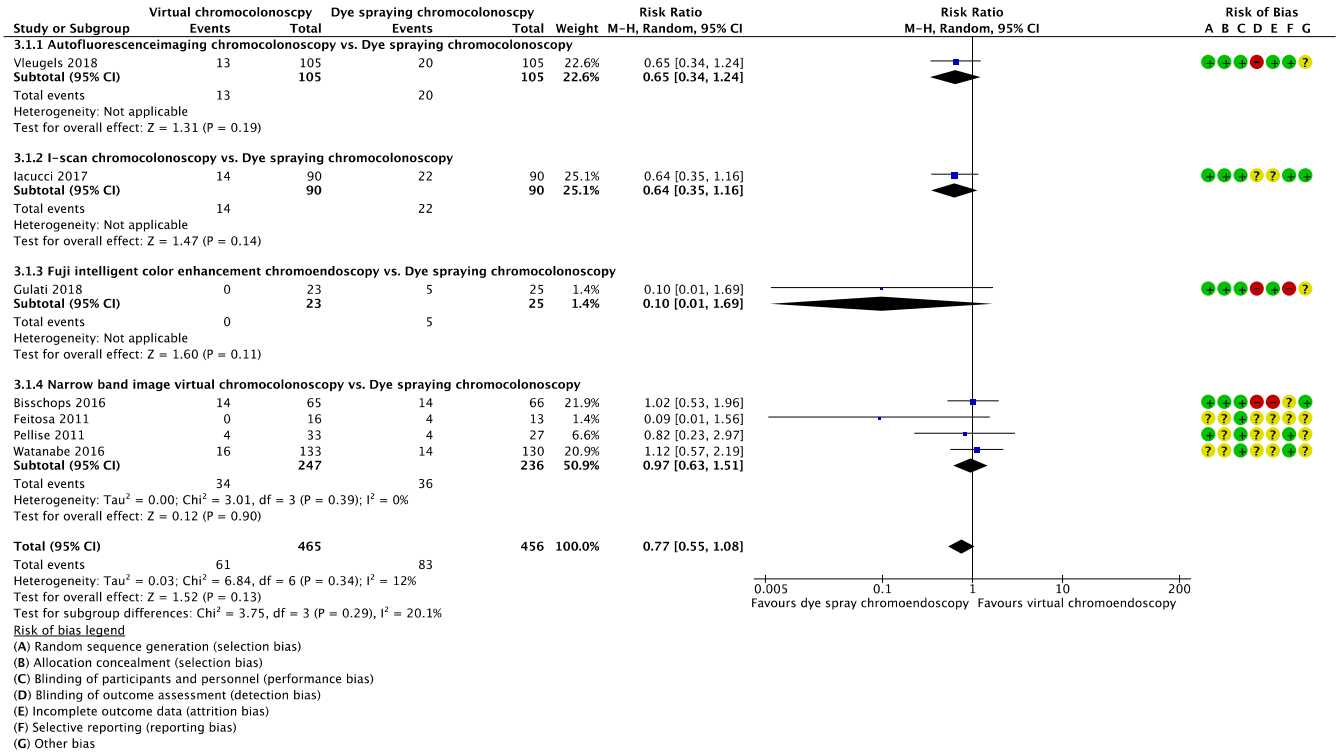


Figure 2. Forest plot comparing virtual chromoendoscopy to dye spraying chromoendoscopy in detecting dysplasia per patient's analysis.

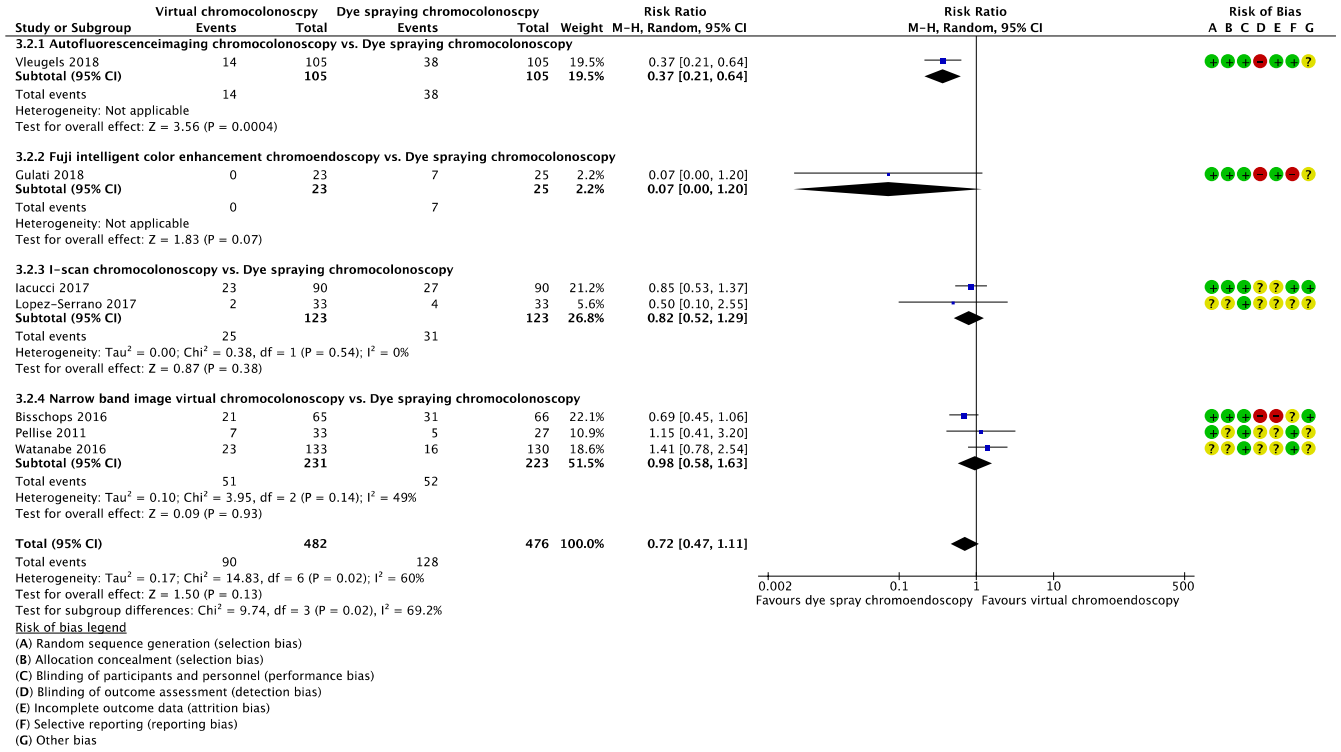


Figure 3. Forest plot comparing virtual chromoendoscopy to dye spraying chromoendoscopy in detecting dysplasia per number of lesions analysis.

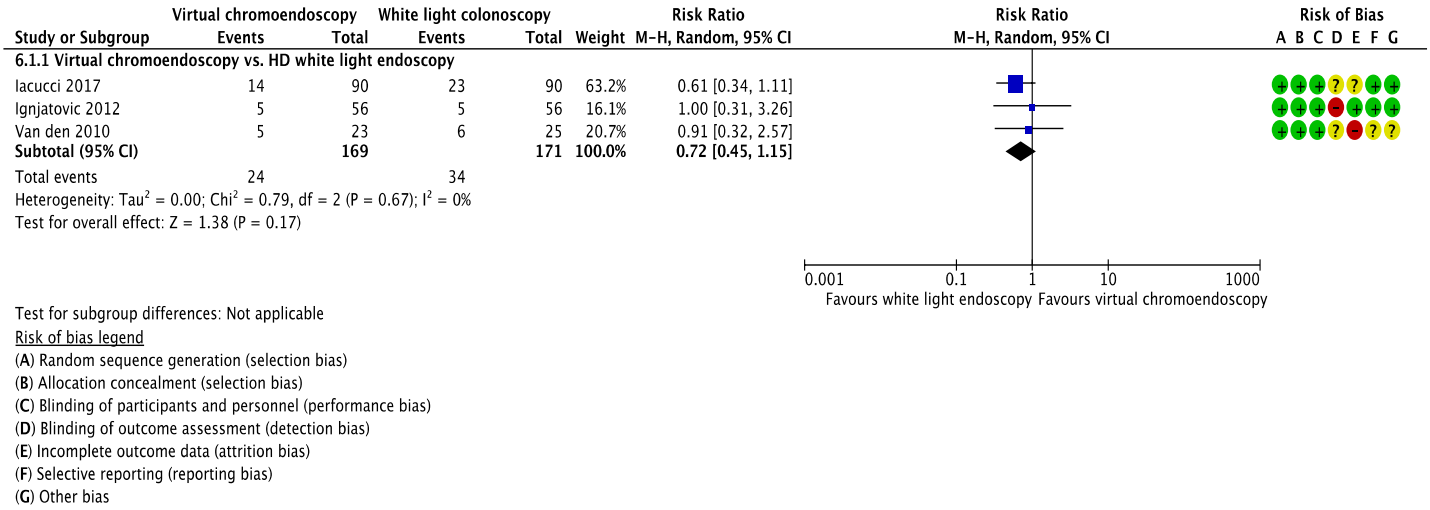


Figure 4. Forest plot comparing virtual chromoendoscopy to white light colonoscopy (high definition) in detecting dysplasia per number of patient's analysis.

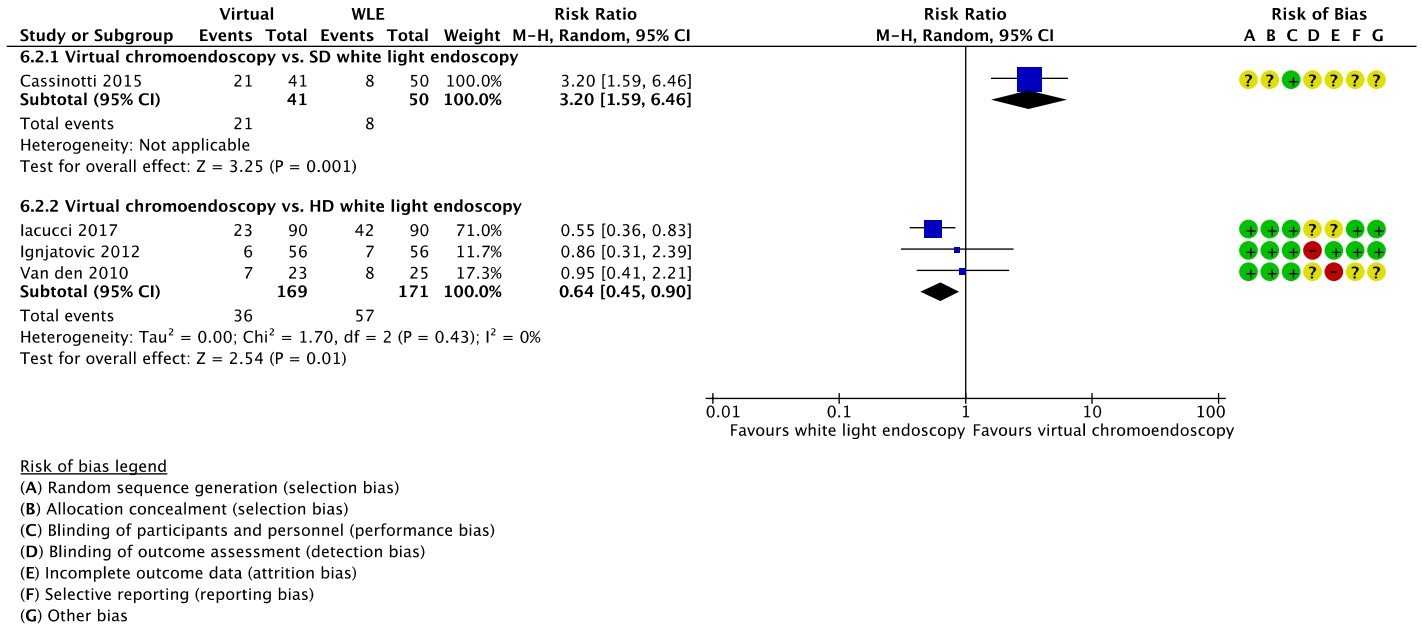


Figure 5. Forest plot comparing virtual chromoendoscopy to white light colonoscopy (standard and high definition) in detecting dysplasia per number of lesions analysis

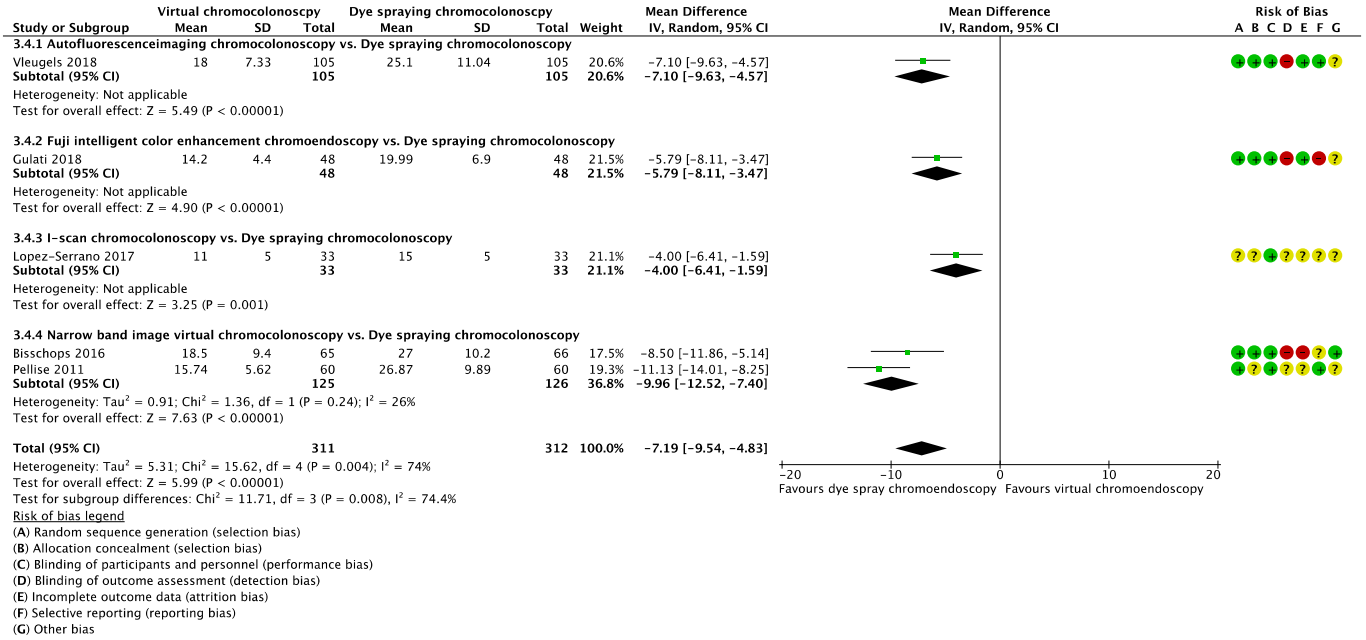


Figure 6. Forest plot of withdrawal time measured by pooled mean difference between virtual chromoendoscopy vs. dye spraying chromoendoscopy.

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# Project 2

## The association of obesity on hospitalized patients with ulcerative colitis

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Acquisition of data: El-Dalla, Stein, Feuerstein

Analysis and interpretation of data: El-Dallal, Raita

Drafting of the manuscript: El-Dallal, Stein, Feuerstein

Critical revision of the manuscript for important intellectual content: El-Dallal, Stein, Rita, Feuerstein

Statistical analysis: El-Dallal, Rita

Study supervision: El-Dallal, Feuerstein

Each author has approved the final draft of this manuscript

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**Abstract**

**Background:** Obesity is the fifth leading risk for mortality in the world, and it has increased among patients with ulcerative colitis in recent years. We examined the impact of obesity on hospitalized patients who were admitted primarily with a diagnosis of ulcerative colitis.

**Methods:** We used the National Inpatient Sample data for the year 2016, identify patients with ulcerative colitis, and compared obese and non-obese patients in terms of length of hospital stay, total charges, and mortality. We used multiple imputations to estimate missing values, survey analysis to estimate the outcomes and adjusted for independent variables by implementing the inverse probability of treatment weighting using propensity score.

**Results:** A total of 61,075 admissions with ulcerative colitis were identified. Among these, 6,020 were diagnosed with obesity. Baseline hospital and patient characteristics between the two groups were notable for differences in age and sex (Table 1). Patients with obesity were found to have an increased mean difference of length of hospital stay by 0.57 days (95% CI 0.22 - 0.93, p=0.002) and higher charges by $6341.71 (95% CI 2,499.72 – 10,183.71, p=0.001) compared to non-obese. There was no difference in hospital mortality with an odds ratio of 0.28 (95% CI 0.04 - 2.05 p=0.212) (Figure 2).

**Conclusion:** In a comprehensive review of inpatient admissions primarily for ulcerative colitis in 2016, obesity was associated with an increased length of hospital stay and total charges per admission after adjusting for independent variables.

**Keywords:** Ulcerative colitis; obesity; length of hospital stay; total hospital charges**.**

## Introduction

Obesity is a significant problem in the American healthcare system, with a prevalence of 39.8% and affects approximately 93.3 million US adults in 2015~2016.(38) It has been identified as the fifth leading global risk for mortality in the world.(39) Despite historically lower body mass index (BMI) in patients with inflammatory bowel disease (IBD) compared to the general population; obesity has increased among these patients as well in recent years.(40),(2)

Obesity has been associated with an increase in inflammatory markers such as c-reactive protein, erythrocyte sedimentation rate, and other cytokines.(41–43) There are multiple potential pathways by which obesity may worsen outcomes in IBD. Differences in the microbiome of the gut and increase intestinal permeability may contribute to worsening chronic inflammatory diseases by inducing persistent low-grade inflammatory process.(42) Some studies also suggest a direct involvement of adipose tissue and mesenteric fat in creating a proinflammatory environment for developing IBD in obese patients.(43,44)

Data on the impact of obesity on the clinical course of IBD have shown conflicting results regarding the effect on hospitalization and yearly cost.(45–48) One retrospective outpatient registry of patients with IBD showed no differences in healthcare utilization, including hospitalization, between obese and non-obese patients,(45) while another observational study showed an increase in the yearly cost and hospital readmissions of patients with obesity and IBD compared to the non-obese.(47) Furthermore, disparate results have been seen in Crohn's disease (CD) and ulcerative colitis (UC). While obesity

is strongly associated with CD and may have a rule in developing the disease,(44,49,50) it remains unclear if obesity has an effect on UC.(46,49,51)

Previous work has found that BMI is linked to increased mortality and length of hospital stay, with a similar trend in patients admitted for asthma, chronic obstructive pulmonary disease, cardiovascular disease, and cancer.(52) Given the worse outcomes associated with obesity in other chronic conditions, we examined the impact of obesity on hospitalized patients who were admitted primarily with a diagnosis of UC using the National Inpatient Sample.

## Methods

### Data source

We used the National inpatient sample (NIS) data for the year 2016. The NIS is an all-payer annually collected abstraction of approximately seven million hospital discharges from 46 States in addition to the District of Columbia, representing more than 97% of the US population. It is available publicly through the Healthcare Cost and Utilization Project (HCUP) for research purposes. Since 2012, there have been changes in the sampling strategy of the NIS data to improve its precision and decrease sample error. These strategies including sampling 20% from all participating hospitals instead of sampling hospitals, using the statewide data from HCUP to feed the NIS data, and removing all identifiers of hospitals or States as well as data that are not uniformly available at all the States.(53)

### Patients selection

Patients who had a primary diagnosis of UC were identified by the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) code (K51) in the first two discharge diagnoses. This code was used in multiple previous studies.(54,55) We excluded all subjects less than 18 years of age, or anyone with a diagnosis of underweight (ICD-10 R636) or a BMI less than 20 (ICD-10 Z681). We then defined patients with obesity based on ICD-10 codes of obesity and BMI of more than 30 (Supplementary Table 1) and compared them to other patients in the study population. Weighted Charlson Comorbidity Score,(56–58) which does not include obesity as one of its components compared to other indexes, was calculated for all individuals in the study population based on the ICD-10 code's definition of the included comorbidities and used

to adjust between the obese and non-obese patients. Demography (Age, Race, Sex), the median household income for patient's ZIP Code based on current year, the expected primary payer for the patient hospital stay, patient location (based on six-category urban-rural classification scheme for US counties developed by the National Center for Health Statistics), whether the patient was admitted to the hospital electively, and the type of the facilities that the patients were transferred from (if any) were considered as potential independent variables.

**Missing data**

The randomness of the missing values in our data was evaluated by using the missing data pattern plot to recognize if there is any systematic pattern. We used multiple imputations by chained equations,(59) which is recommended by HCUP to compute missing values in the NIS data.(60) Five imputed datasets were created; we ran the analyses repeatedly on each one of them, and then we combined the result

**Outcomes**

Our outcomes of interest were (1) length of the hospital stay, (2) total charges of hospital admission, and (3) in-hospital mortality.

**Statistical analysis**

R version 3.5.1 (R foundation for statistical computing, Vienna, Austria) was used in the analysis. Descriptive statistics were used to describe the baseline hospital and patient characteristics. We used the chi-square test to compare categorical variables and two-group ANOVA to compare continuous variables; the Kruskal and Fisher tests for variables not fitting a normal distribution, respectively.

We then estimated propensity scores by applying logistic regression models on all five imputed datasets to estimate the log odds of the probability of being obese based on possible independent variables listed above.

The common support of propensity score distribution between the obese and non-obese groups was evaluated by visually using Kernel density and box-and-whiskers plots.

We then calculated the inverse probability of treatment weighting (IPTW) using propensity scores. We evaluate covariate balance between the obese and non-obese groups to confirm adequate balance with acceptable absolute standardized effect sizes below 0.1 standard deviations.(61)

All analyses were performed using survey-adjusted methods accounting for NIS-specific hospital weighting and the IPTW. As a confirmatory measure, we re-estimated propensity scores by using generalized boosting modeling (GBM) and compared the final results to the previous ones.

## Results

### Descriptive analysis

We identified a total of 12,215 patients (61,075 weighted sample size) with a primary discharge diagnosis of UC. Among those, 1,204 patients (6,020 weighted sample size) fulfilled the criteria for obesity based on their BMI or ICD-10 coding of obesity, figure 1. The former patients tended to be older (mean 54 years and standard deviation (SD) 16 vs. mean 51, SD 20, P-value <0.001), were more likely to be female (62% vs. 54%, P-value <0.001), admitted electively to the hospital (28% vs. 20%, P-value <0.001), and have Medicare (37% vs. 32%, P-value 0.03). Overall, patients with UC had a lower Weighted Charlson Comorbidity Score (1.17 for patients with obesity vs. 0.77 for non-obese, P-value <0.001). Other characteristics between both groups are summarized in table 1.

### Missing Data

The total amount of missing data was 6.8%. Most of the missing values were in the race (4.3%), followed by median household income for patient's ZIP Code (1.7%), indicator of a transfer into the hospital (0.5%), elective admissions (0.3%), patient location (0.3%), expected primary payer (0.1%), and sex (0.1%). The missing data pattern plot showed that data appeared to be missing at random (Supplementary figure 1).

### Propensity score and IPTW

After creating propensity scores by using a regression model on all five imputed datasets, the common support was reviewed using Kernel density plots and box-and-whiskers plots and was judged as sufficient to use by the authors (Supplementary figures 2,3,4, & 5). IPTW was calculated for each individual based on their propensity score. The covariate

balance was achieved by using IPTW as observed by absolute standardized effect sizes below 0.1 standard deviations in all the covariates. (Supplementary Table 2, Supplementary Table 3, and supplementary figure 6).

**Outcomes**

The mean length of stay for the entire study population was 4.6 days, with a 95% confidence interval (CI) 4.5 – 4.7. In the unadjusted analysis, we found the length of hospital stay increased in patients with obesity by a mean difference (MD) of 0.7 days (95%CI 0.18 - 1.21, P-value 0.008) compared to patients with no obesity. However, after adjusting for independent variables using IPTW, the MD of the length of stay between the two groups decreased slightly to 0.57 days (95%CI 0.22 - 0.93, P-value 0.002), figure 2, A.

Similarly, the average total charges per admission in our population was $43,238, 95% CI 41,640.1- 44,835.3. The unadjusted analysis showed MD of total charges between the two group was $9,553.54 (95% CI 4,544.81 - 14,562.28, P-value < 0.001), while the adjusted analysis found MD of $6,341.71 (95% CI 2499.72 - 10183.71, P-value 0.001) higher in patients with obesity compared to non-obese, figure 2, B.

In our study, the total number of patients who had hospital mortality was 200 out of 61,075 patients (5 patients in the obese and 195 in the none obese group). There was no significant difference in hospital mortality in both the unadjusted and adjusted analyses with odds ratios (OR) of 0.23 (95% CI 0.03 - 1.7, P-value 0.15), and 0.28 (95% CI 0.04 - 2.05 and P-value 0.21), respectively, figure 2, C.

Our results by estimating propensity score using GBM were similar with length of stay MD 0.56 days (95% CI 0.14 - 0.97, P-value 0.008), total charges MD $5657.59 (95% CI:

1439.66 - 9875.52, P-value 0.009), and no significant difference in hospital mortality with OR 0.56 (95% CI 0.08 - 4.07, P-value 0.57).

Also, when we performed a complete case analysis (without imputation), we found similar results, however, with smaller P-value as the sample size decreased (Length of stay MD 0.56, 95% CI 0.09 - 1.03, P-value 0.02, total charges MD 6834.84, 95% CI 2213.61 - 11456.06, P-value 0.004, and odds ratio of death 0.27, 95% CI 0.04 - 1.97, P-value 0.2).

## Discussion

In this article, we studied the impact of obesity on the outcome of hospitalized patients with UC using the NIS data. Our results show that obesity is associated with increasing length of hospital stay and total hospital charge per admission even after adjustment for other comorbidities. These results were consistent in subgroup analyses that stratified patients based on the presence of a simultaneous diagnosis of CD or other types of colitis, being overweight, or being younger than 65 years old.(Supplementary figures 7 & 8). Nevertheless, we did not find a significant difference between hospital mortality between obese and non-obese patients, likely due to the low mortality rate in our cohort, and generally, in patients with UC.(62)

The increase in length of hospital stay, and the disproportionate higher hospital charges is likely multifactorial due to the complex nature of obesity, which could affect both medical and surgical management for patients with UC. The proinflammatory process induced by obesity could complicate the clinical picture of patients with UC, interfere with the biological treatment dosing or worsen some of the side effects of systematic steroid use, like hyperglycemia. In addition, obesity has been found to increase IBD related surgery in patients with UC,(2) and multiple studies have shown that obesity is an independent risk factor for postoperative complications including wound infections, postoperative myocardial infarction, stoma problems, and other postsurgical complications,(63–65) which might be contributors for increased length of hospital stay and to more degree, hospital charges. In fact, several studies have shown that obesity by itself increases hospitalization costs in general(66) as well as in a variety of surgical and medical admissions.(67–71)

These results are in alignment with other studies that focused on outpatient settings and showed an increase in annual charges, the number of hospitalized days per year, and surgery complications.(2,47,72) A cohort study that used the Nationwide Readmissions Database to estimate the burden of obesity on patients with IBD showed that the obese group spent a median of 8 days with a median charge of $17,277 compared to 5 days and $11,847, respectively in the non-obese group.(47) Nonetheless, Christian et al. found that obesity is one of the predictors of early hospital readmission within 30 days for patients with IBD and by increased readmission by an OR of 1.72 (95% CI 1.20 – 2.47).(48)

Our study has some limitations, including that it was done using administration data of sampled hospitals discharges in the United States, and interpreting the results out of this context should be avoided. Furthermore, we used the diagnostic ICD-10 codes to identify the patient population, and our results are dependent on the accuracy of these codes; however, we used verified codes that have been used in many other studies. Identifying patients with obesity was a challenging part of our project, as obesity is known for under-coding.(73) Obesity defined by BMI has been accepted in population-based studies and was found as a better predictor for cardiovascular mortality compared to other obesity indicators.(74,75) We also used ICD-10 codes E66 to identify obesity, which has been verified in a study and found to have a specificity of 98% and sensitivity of 7.7%, which represents that obesity would be accurate if it coded; nevertheless, it suffers from under-coding in general.(73) Nonetheless, because we used two definitions of obesity in our cohort, there were occasional discrepancies between the two definitions, i.e., some subjects could be defined as obese based on the ICD 10 code, while coded as overweight

using the BMI definition. For that reason, we excluded patients with overweight in the sensitivity analysis, and the results showed no differences from the primary analysis.

Patients with UC already have an increased risk of coronary artery disease,(76–78) diabetes,(79) and stroke(80) regardless of their body weight. In our study, we showed that obesity increases the healthcare cost of hospitalized patients with UC, which probably secondary to worsening their medical and surgical conditions. Further studies are needed to study the etiology of these phenomena and the best way to manage it using a multidisciplinary approach, including nutrition, lifestyle changes, and possibly alternating some of UC related medications.

**Conclusion:**

In a comprehensive review of inpatient admissions primarily for ulcerative colitis in 2016, obesity was associated with an increased length of hospital stay and total charges per admission after adjusting for independent variables, including demographics and comorbidities. Future studies are needing to understand obesity's impact on disease management better and identify methods to improve care in patients with ulcerative colitis.

**Acknowledgment**

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**Table. 1.** Baseline characteristics of patients with UC comparing obese and non-obese patients

| Characteristics | Non-obese | Obese | P-value |
|---|---|---|---|
| Total number (Weighted) | 11,011 (55,055) | 1204 (6020) | |
| Age (mean (SD)) | 51 (20) | 54 (16) | <0.001 |
| Elective (%) | 10,685 (19.5) | 1,665 (27.7) | <0.001 |
| Female (%) | 29,720 (54) | 3,720 (61.9) | <0.001 |
| Expected primary payer (%) | | | 0.03 |
| 1. Medicare | 17,780 (32.3) | 2195 (36.5) | |
| 2. Medicaid | 7,825 (14.2) | 810 (13.5) | |
| 3. Private insurance | 25,145 (45.7) | 2,625 (43.6) | |
| 4. Self-pay | 2,310 (4.2) | 220 (3.7) | |
| 5. No charge | 285 (0.5) | 5 (0.1) | |
| 6. Other | 1,640 (3) | 165 (2.7) | |
| Patient Location: NCHS Urban-Rural Code (%) | | | 0.73 |
| 1. "Central" counties of metro areas of >=1 million population | 16,305 (29.7) | 1,700 (28.2) | |
| 2. "Fringe" counties of metro areas of >=1 million population | 15,515 (28.3) | 1,655 (27.5) | |
| 3. Counties in metro areas of 250,000-999,999 population | 10,895 (19.9) | 1,230 (20.4) | |
| 4. Counties in metro areas of 50,000-249,999 population | 4,930 (9) | 565 (9.4) | |
| 5. Micropolitan counties | 4,215 (7.7) | 525 (8.7) | |
| 6. Not metropolitan or micropolitan counties | 2,995 (5.5) | 345 (5.7) | |
| Race (%) | | | 0.01 |
| 1. White | 40,075 (76) | 4,375 (76.7) | |
| 2. Black | 5,110 (9.7) | 645 (11.3) | |
| 3. Hispanic | 4,700 (8.9) | 495 (8.7) | |
| 4. Asian or Pacific Islander | 915 (1.7) | 25 (0.4) | |
| 5. Native American | 255 (0.5) | 30 (0.5) | |
| 6. Other | 1,680 (3.2) | 135 (2.4) | |
| Indicator of a transfer into the hospital (%) | | | 0.48 |
| 0. Not transferred in | 51,969.9 (94.8) | 5,705 (95.3) | |
| 1. Transferred in from a different acute care hospital | 2,130 (3.9) | 225 (3.8) | |
| 2. Transferred in from another type of health facility | 715 (1.3) | 55 (0.9) | |
| Median household income for patient's ZIP Code (%) | | | 0.03 |
| 1. 0-25$^{th}$ percentile | 12,165 (22.5) | 1,435 (24.1) | |
| 2. 26$^{th}$ to 50$^{th}$ percentile | 13,170 (24.4) | 1,580 (26.5) | |
| 3. 51$^{st}$ to 75$^{th}$ percentile | 14,215 (26.3) | 1,595 (26.7) | |
| 4. 76$^{th}$ to 100$^{th}$ percentile | 14,505 (26.8) | 1,355 (22.7) | |
| Weighted Charlson score (mean (SD)) | 0.77 (1.37) | 1.17 (1.59) | <0.001 |
| Concurrent diagnosis of CD and other colitis (%) | 2,125 (3.9) | 300 (5.0) | 0.06 |
| Overweight (%) | 775 (1.4) | 270 (4.5) | <0.001 |
| Older than 65-year-old (%) | 1,6025 (29.1) | 1,775 (29.5) | 0.8 |

Abbreviations: SD, Standard deviation; NCHS, National Center for Health Statistics.

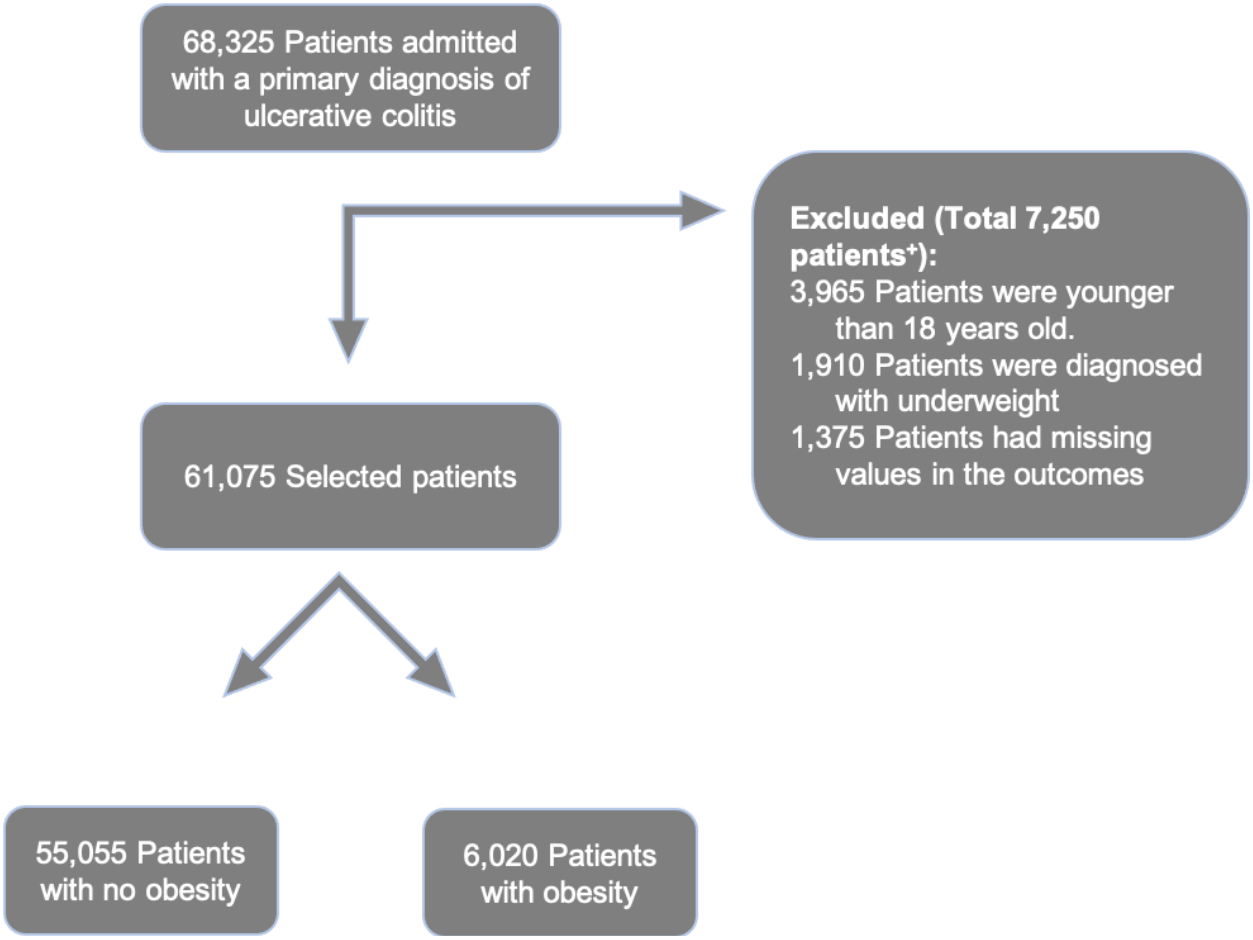


**Figure 1.** Flow chart of study population.
+ Total excluded discharges surpass the actual of excluded patients due to overlap.

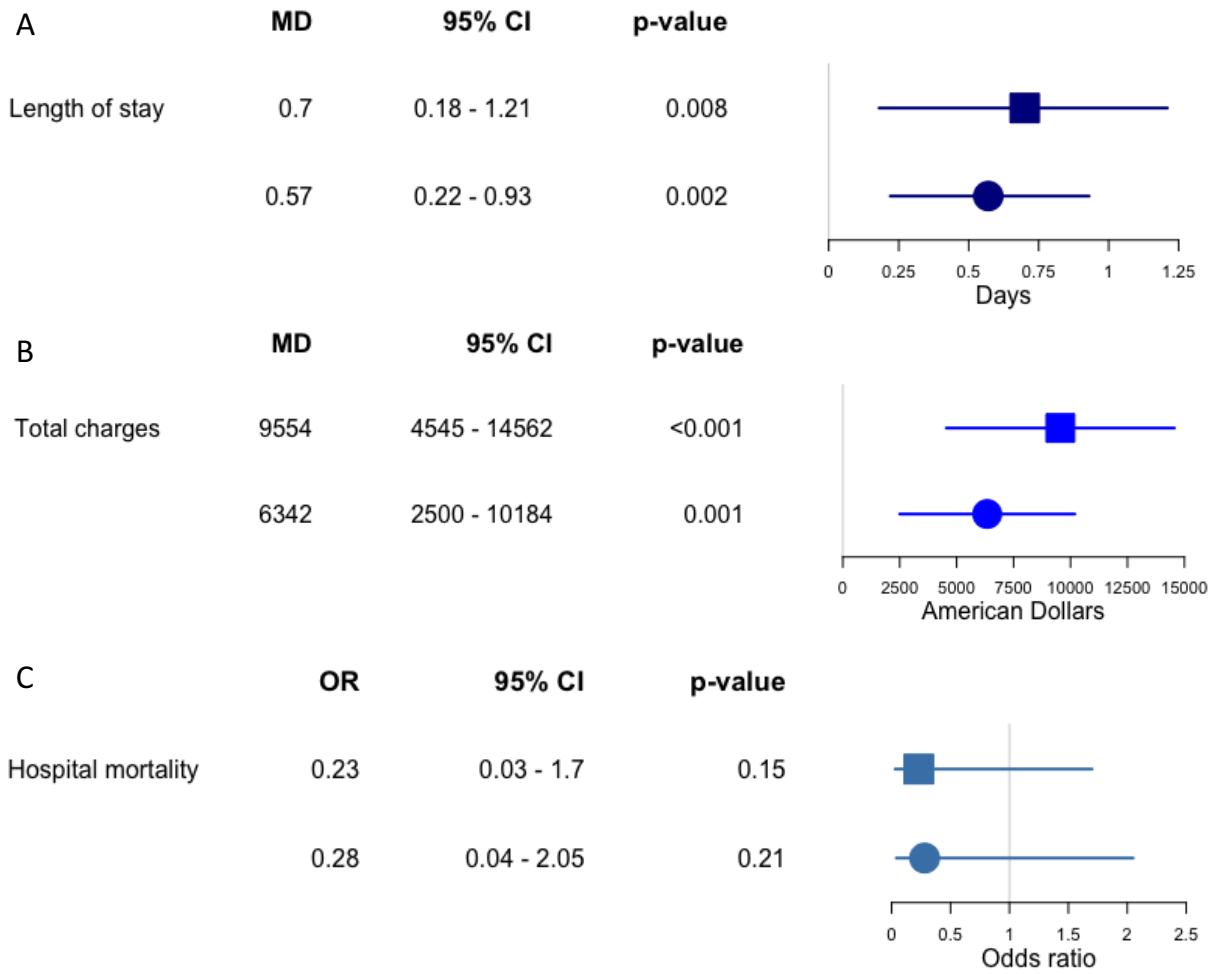


**Figure 2.** Outcomes plots of hospitalized patients with ulcerative colitis comparing obese and non-obese patients in (A) the length of stay, (B) total charges and (C) hospital mortality.
■ Represent unadjusted analysis and ● represent adjusted analysis.
Abbreviations: 95%CI, 95% confidence interval; MD, mean difference; OR, Odds ratio

**Summary of Paper 1 and Paper 2 conclusions**

In this thesis project, we discussed two challenges regarding managing patients with inflammatory bowel disease. In the first paper, we conducted a meta-analysis to compare virtual based chromoendoscopy to white light colonoscopy and dye spraying chromoendoscopy. Our findings concluded that there is no difference between virtual based chromoendoscopy and dye spraying chromoendoscopy in detecting patients with dysplastic lesions. However, dye spraying chromoendoscopy required prolonged procedure time with an average of seven minutes difference between the two techniques. In comparing virtual based chromoendoscopy to high definition white light colonoscopy, there was no difference between both techniques in detecting patients with dysplastic lesions, but high definition white light colonoscopy detecting more dysplastic lesions per patient. Also, we presented our assessment of the risk of biases, and we found that the quality of the presented evidence range between low to moderate based on the current available studies.

In the second paper, we study the effect of obesity on the hospitalization outcomes for patients who were admitted primarily for ulcerative colitis using one of the biggest national inpatients data. Our results found that obesity is associated with an increase of length of hospital stay and total charges of hospitalization. These results did not change after we excluded patients who were older than 65 years old (as they might have worse outcomes) or have a concurrent diagnosis of Crohn's disease or overweight.

**Discussion and perspectives:**

Our findings in the first project, as well as in a previous meta-analysis that was done by our group,(13) highlighted the improvement in visualizing colonic lesion by using advances in camera technology and raised the question if dye spraying chromoendoscopy should continue as the more favorable technique for CRC screening in patients with IBD.(6)

Nonetheless, these findings were driven mainly by one trial (Lacucci 2017), and that could be interpreted to be due to individual or institutional performance rather than superiority of one procedure over the other. For that reason, we are conducting a randomized control trial at Beth Israel Deaconess Medical Center to compare HDWLE to DCE. The study was approved the IRB and registered at ClinicalTrials.gov, Identifier: NCT04191655. The total sample size is estimated to be 500 participants, and currently, we reached 128 patients,however, the study is now on hold due to the COVID-19 situation.

Also, after our results proved the association of worsening outcome of hospitalized patients with UC in the second paper, and similar results in patients with CD [in press], now we are discovering the possibility of studying the long-term effect of change in body weight on the outcomes of IBD management.

Furthermore, I continued to work with my mentor, Dr. Feuerstein, on other challenges to improve the outcomes of IBD patient and we recently published a meta-analysis to compare interactive versus proactive therapeutic drug mentoring for adult patients with IBD,(81) and another review to study the evidence behind using marijuana in managing symptoms for patients with IBD [in press].

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