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# Co-existing inflammatory bowel disease and Barrett's esophagus is associated with esophageal dysplasia: a propensity score-matched cohort

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## ABSTRACT

**Background and study aims** Barrett's esophagus (BE) and inflammatory bowel disease (IBD) predispose to the development of dysplasia and cancer. It is unclear if the inflammatory cascade seen in IBD affects disease progression in BE. We aimed to determine if patients with BE who have co-existing IBD had a higher risk of dysplasia, nodular disease, or longer segments than BE patients without IBD.

**Patients and methods** This was a multicenter, retrospective propensity score-matched cohort study. We compared rates of dysplasia, nodular disease, and segment length in patients with BE and IBD (cases) to patients with BE who did not have IBD (controls). Controls were 1:1 propensity score matched with controls for age, sex, body mass index (BMI), smoking, and hiatal hernia.

**Results** A total of 132 patients were included in the IBD + BE group and 132 patients in the BE group. Patients with IBD + BE had higher rates of esophageal dysplasia compared to controls (15.9 % vs. 6.1 % [adjusted odds ratio [OR]: 2.9, 95 % CI: 1.2–6.9]) and more nodules (9.8 % vs. 3.0 % [adjusted OR: 3.5, 95 % CI: 1.1–11.0]). IBD + BE group was also associated with longer BE segments (43.9 % vs. 12.1 % [OR: 5.7, 95 % CI: 3.0–10.6]).

**Conclusions** Co-existing IBD may increase the risk of dysplasia and esophageal nodules in patients with BE. Our findings may have implications for BE surveillance intervals in IBD patients. Prospective studies are needed to confirm

## Introduction

Barrett's esophagus (BE) is a condition in which normal stratified squamous epithelium of the distal esophagus is replaced by metaplastic columnar epithelium [1]. BE prevalence in the United States ranges from 0.5 % to 2 % [2]. BE carries a risk of progressing to esophageal adenocarcinoma (EAC), but the overall magnitude of this risk is low (< 1 %) in patients without dysplasia [3]. Risk of adenocarcinoma increases in the setting of dysplasia. Low-grade dysplasia (LGD) carries a 0.2 % to 1.2 %

annual risk and high-grade dysplasia (HGD) has an annual risk of 4 % to 8 % of progression to EAC [4, 5].

Several studies have assessed risk factors for progression of BE to dysplasia and EAC. Risk factors have been those that predispose to BE, such as longstanding gastroesophageal reflux disease (GERD), hiatal hernia, older age, obesity, and smoking [6]. Our group anecdotally noted that patients with BE who have IBD seemed to have higher rates of dysplasia than patients with BE who did not have IBD. We hypothesized that IBD may increase the risk of dysplasia and EAC in BE via several potential mechanisms, including upregulation of inflammatory cytokines [7], changes to bile acids [8, 9], and perturbations in the microbiome [10, 11].

The aim of the current study was to assess whether these findings persist when assessed in a larger sample of IBD and BE patients across multiple centers in the United States, when compared to a propensity score-matched group of controls with BE who did not have IBD.

## Patients and methods

This was a retrospective study conducted at four tertiary care academic medical centers in the United States (Virginia Commonwealth University Medical Center, Zucker School of Medicine at Hofstra/Northwell, University of Arkansas Medical Center, and Tufts University Medical Center). The institutional review boards at all participating centers approved this study.

### Patient selection

At all four centers, we queried the medical records database with the ICD-10 code k22.7 to identify patients diagnosed with BE between 2009 and 2019. We reviewed the medical records to assess whether patients met inclusion criteria. Patients were included if they were ≥ 18 years of age with a diagnosis of BE. Patients with BE were excluded from the study if biopsy results did not confirm intestinal metaplasia in the esophagus. Patients were excluded if they had endoscopic or histopathologic evidence of esophagitis. Among patients identified as having a diagnosis of BE, we queried the medical records database with ICD-10 codes K50* for Crohn's disease (CD) and K51* for ulcerative colitis (UC). Patients were excluded from the IBD arm if they did not have an endoscopic biopsy confirming presence of CD or UC and if they had a diagnosis of indeterminate colitis. For patients who the met inclusion criteria, we abstracted information on demographics, endoscopy findings, pathology results, and concomitant IBD therapy. Patients with BE and IBD (IBD + BE) were considered the active study arm. In the BE without IBD group (controls), we performed 1:1 propensity score matching using a maximum caliper adjustment of < 0.25 using nearest-neighbor matching. Cases were matched with controls for the following variables potentially associated with an increased risk of dysplasia in the literature: age, sex, presence of a hiatal hernia, body mass index (BMI), and history/use of tobacco.

### Endoscopy procedures

The typical protocol for BE surveillance at all institutions was to perform careful high-definition white light examination (HD-WLE) followed by random biopsies in four quadrants at 1– to 2-cm intervals (i. e. – Seattle protocol biopsies). At all four centers that participated in the study, BE samples are interpreted by gastrointestinal pathologists with expertise in BE and a finding of dysplasia is confirmed by a second pathologist. If an area of nodularity was identified on HD-WLE, then endoscopic mucosal resection was performed to better assess (and potentially treat) that area for dysplasia or cancer before performing Seattle protocol biopsies of the remaining BE segment. Electronic chromoendoscopy was performed at the discretion of the attending gastroenterologist. No other tools to detect dysplasia were used, including distal attachment caps and acetic acid.

### Statistical analysis

All statistical analyses were performed using SPSS v. 26 (SPSS Inc., Chicago, Illinois, United States). Baseline variables in each group were reported as mean ± standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables. We compared baseline variables in the two groups using Student's *t*-test for normally distributed continuous variables, and Fisher's exact test for categorical variables. The primary outcome was the rate of esophageal dysplasia in cases (BE + IBD) versus controls (BE only). Secondary outcomes were BE segment length and rate of nodular disease between cases and controls. The primary outcome was measured using Fisher's exact test. $P < 0.05$ was considered statistically significant. Separate multivariate logistic regression analyses were performed to control for confounding risks factors for dysplasia and nodules.

## Results

We queried the medical records database of 648 patients. A total of 384 patients were excluded from our study for whom we could not confirm an adequate histopathologic diagnosis of either BE or IBD. A total of 264 patients were included (132 IBD + BE matched to 132 controls). Baseline demographics are listed in ▶ **Table 1**. The majority of patients in both groups were white, male, and overweight. In the IBD + BE group, 72 (54.5 %) had CD while 60 patients (45.6 %) had UC. Among patients with IBD, 36 (27.3 %) were not on any disease-specific therapy, while 61 (46.2 %) were on 5-aminosalicyclic acid derivatives, 18 (13.6 %) were on biologic therapy, and 17 (12.9 %) were on immunomodulators (azathioprine or methotrexate).

### Primary and secondary outcomes

The percentage of patients who had any degree of dysplasia was 10.9 % (▶ **Table 2**). Patients in the IBD + BE group had a higher rate of any dysplasia formation compared to the BE group (21 [15.9 %] vs. 8 [6.1 %], $P < 0.01$). In particular, they had significantly higher rates of LGD compared to the BE group (12 [12.1 %] vs. 4 [3.0 %], $P < 0.01$). Patients in the IBD + BE group had a similar rate of HGD compared to the BE group

▶ **Table 1** Patient characteristics.

| Variables | IBD + BE (n = 132) | BE (n = 132) | *P value* |
|---|---|---|---|
| 1 Race, White, n (%) | 115 (87.1 %) | 113 (85.6 %) | 0.58 |
| Sex, male, n (%) | 89 (67.4 %) | 90 (68.2 %) | NA |
| BMI (kg/m$^2$), mean | 29.0 | 29.1 | NA |
| Charlson CI (SD) | 3.2 (2.1) | 3.0 (2.1) | 0.54 |
| Age, mean (SD) | 57.5 (12.1) | 57.1 (14.9) | 0.79 |
| Hiatal hernia, n (%) | 92 (69.7 %) | 91 (68.9 %) | NA |
| Tobacco use, n (%) | 76 (57.6 %) | 76 (57.6 %) | NA |
| Alcohol use, n (%) | 88 (66.7 %) | 73 (55.3 %) | 0.06 |
| PPI use, n (%) | 122 (92.4 %) | 114 (86.4 %) | 0.11 |
| Aspirin use, n (%) | 46 (34.8 %) | 33 (25.0 %) | 0.08 |
| NSAIDs use, n (%) | 9 (6.8 %) | 15 (11.4 %) | 0.20 |
| Crohn's disease, n (%) | 72 (54.5 %) | | |
| Immunomodulator, n (%) | 17 (12.9) | | |
| Biologics, n (%) | 18 (13.6) | | |
| 5-ASA, n (%) | 61 (46.2) | | |
| No therapy, n (%) | 36 (27.3) | | |

IBD, inflammatory bowel disease; BE, Barrett's esophagus; CI, comorbidity index; SD, standard deviation; NA, not applicable; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; 5-ASA, 5-aminosalicylic acid.

(5 [3.8 %] vs. 4 [3.0 %], $P = 0.73$). Patients in the IBD + BE group had a similar rate of adenocarcinoma compared to the BE group (7 [5.3 %] vs. 6 [4.6 %], $P = 0.78$). Patients in the IBD + BE group had a higher rate of nodule formation compared to the BE group (13 [9.8 %] vs. 4 [3.0 %], $P = 0.02$). Finally, patients with IBD + BE had longer BE segment lengths compared to the BE group (58 [43.9 %] vs. 16 [12.1 %], $P < 0.01$) (▶ **Table 2**). On univariate regression, IBD was the only independent variable associated with dysplasia, OR: 2.9, 95 % CI: 1.0–6.2, $P = 0.05$. On multivariable regression, IBD was the only independent variable associated with dysplasia or nodule formation, OR: 2.9, 95 % CI 1.3–6.9, $P = 0.01$ and OR: 3.5, 95 % CI: 1.1–11.0, $P = 0.03$, respectively. Neither long segment BE, alcohol use, nor Charlson comorbidity index were associated with a statistically significant risk for these outcomes (▶ **Table 3**). Accounting for Barret's segment length, a separate analysis demonstrated that the prevalence of dysplasia was similar between the IBD + BE and BE group in those who has long segment BE (▶ **Table 4**). Subgroup analyses performed for UC and CD separately were similar between groups and are reported in table/supplementary material (**Supplementary Table 1** and **Table 2**).

## Discussion

In this multicenter matched case-control study, we revealed that patients with IBD who have BE have a significantly higher point prevalence of dysplasia and nodular disease, when compared to matched BE patients without IBD. This increased risk was seen with both UC and CD. Intestinal metaplasia is thought to arise as a response to chronic mucosal inflammation and injury of the esophagus, primarily from GERD [12]. IBD patients often have evidence of systemic inflammation with an increase in multiple pro-inflammatory cascades. If the pathogenesis of increased BE severity is related primarily to inflammation, then other inflammatory conditions should theoretically predispose to a more severe BE phenotype. However, the systemic pro-inflammatory state in IBD does not necessarily result in histologic evidence of esophageal mucosal inflammation and thus, other mechanisms may be involved [13, 14].

This is the first study to demonstrate an association between IBD and a more severe BE phenotype. The data were collected from a relatively large cohort of patients across multiple centers in the United States, and propensity score matching was utilized to identify an appropriate group for comparison. Prior studies have demonstrated that long-segment BE is associated with increased risk for dysplasia and increased propensity to progress to esophageal adenocarcinoma [15]. Including only patients with long-segment BE, we again demonstrated that the presence of IBD was associated with a greater risk for dys-

▶ **Table 2** Primary outcomes, IBD + BE vs. BE.

| Variables | IBD + BE, n (%) (n = 132) | BE, n (%) (n = 132) | OR (95 % CI) | *P* value |
|---|---|---|---|---|
| Any dysplasia | 21 (15.9 %) | 8 (6.1 %) | 2.9 (1.2–6.9) | < 0.01[1] |
| LGD | 16 (12.1 %) | 4 (3.0 %) | 4.4 (1.4–13.6) | < 0.01[1] |
| HGD | 5 (3.8 %) | 4 (3.0 %) | 1.3 (0.3–4.8) | 0.73 |
| Adenocarcinoma | 7 (5.3 %) | 6 (4.6 %) | 1.2 (0.4–3.6) | 0.78 |
| Nodule | 13 (9.8 %) | 4 (3.0 %) | 3.4 (1.1–11.0) | 0.02[2] |
| Long Barrett's esophagus | 58 (43.9 %) | 16 (12.1 %) | 5.7 (3.0–10.6) | < 0.01[1] |

IBD, inflammatory bowel disease; BE, Barrett's esophagus; OR, odds ratio; CI, confidence interval; LGD, low-grade dysplasia; HGD, high-grade dysplasia.
[1] $P < 0.01$.
[2] $P < 0.05$.

▶ **Table 3** Binary logistic regression models.

| Model | Variables | Univariate (OR, 95 % CI) | *P* value | Multivariate (OR, 95 % CI) | *P* value |
|---|---|---|---|---|---|
| Model 1: dysplasia | Alcohol | 0.5 (0.2–1.3) | 0.16 | – | –- |
| | Long-segment BE | 0.8 (0.3–1.8) | 0.52 | – | – |
| | Charlson CI | 1.0 (0.8–1.2) | 0.69 | – | – |
| | IBD | 2.9 (1.0–6.2) | 0.05[1] | 2.9 (1.3–6.9) | 0.01[1] |
| Model 2: nodules | Alcohol | 0.7 (0.2–2.1) | 0.54 | – | – |
| | Long-segment BE | 0.7 (0.3–2.2) | 0.59 | – | – |
| | Charlson CI | 0.9 (0.7–1.2) | 0.45 | – | – |
| | IBD | 3.4 (0.9–10.5) | 0.06 | 3.5 (1.1–11.0) | 0.03[1] |

OR, odds ratio; CI, confidence interval; BE, Barrett's esophagus.
Adjusted for use/history of alcohol, long-segment Barrett's esophagus, Charlson CI, and IBD.
[1] $P<0.05$.

▶ **Table 4** Dysplasia risks associated with long-segment Barrett's esophagus, IBD + BE vs. BE.

| Variables | IBD + BE, n (%) (n = 58) | BE, n (%) (n = 17) | OR (95 % CI) | *P* value |
|---|---|---|---|---|
| Any dysplasia | 12 (20.7 %) | 1 (5.9 %) | 4.2 (0.5–34.7) | 0.12 |
| LGD | 10 (17.2 %) | 1 (5.9 %) | 3.3 (0.4–28.1) | 0.21 |
| HGD | 2 (3.4 %) | 0 | 1.0 (0.9–1.1) | 0.31 |
| Adenocarcinoma | 3 (5.2 %) | 1 (5.9 %) | 0.9 (0.1–9.0) | 0.91 |

IBD, inflammatory bowel disease; BE, Barrett's esophagus; OR, odds ratio; CI, confidence interval; LGD, low-grade dysplasia; HGD, high-grade dysplasia.

plasia, indicating another mechanism likely accounts for these findings. Although this is the first study of its kind to show an association between the presence of IBD and dysplasia risk in patients with BE, we have several hypotheses to help explain these findings, including luminal dysbiosis, changes to bile acids, and alteration in gene expression. Whether IBD predisposes to oral dysbiosis along with alterations in bile acids and their impact on altering gene expression in esophageal epithelium warrants further investigation.

While this observation is thought-provoking, our results should be interpreted in the context of certain limitations. IBD and BE patients were identified using ICD-10 codes. To address this limitation, we did review the medical record to confirm the accuracy of both BE and IBD diagnoses. Our primary endpoint was the point prevalence of LGD, a diagnosis with considerable disagreement between pathologists. Interestingly, the prevalence of HGD and adenocarcinoma failed to reach statistical significance likely reflecting too small a sample size to detect this difference. Although we identified a strong association between BE severity and IBD, our study was not designed to address the effect of IBD severity and the effect of various IBD therapies on study outcomes. Another limitation is that the number of endoscopies and length of follow up in each group cannot be ascertained from each cohort due the majority of patients being referred to a tertiary care center for management of their BE. Finally, as with any observational study, we recognize that correlation does not imply causation.

## Conclusions

In summary, this is the first study to document an increased risk of dysplasia in BE patients who have co-existing IBD. Our findings may have implications for surveillance intervals in this subgroup of BE patients. Our results could inform risk-benefit discussions with BE in IBD patients who are considering further endoscopic interventions. We believe more studies are needed to confirm these findings, possibly at a population level. Further investigation is also warranted to assess whether other inflammatory conditions predispose to increased BE severity along with translational studies to better understand why IBD may predispose to a more severe BE phenotype.

## Competing interests

Dr. Shah is on the research advisory board for CSA Medical and receives research support from Allergan and Lucid. Dr. Mutha receives research support from Allergan and Lucid. Dr. Trindade is a consultant to Pentax Medical and Olympus American and receives research support from Ninepoint Medical. Dr. Smallfield receives research support from and is on the research advisory board for CSA medical and receives research support from Pentax/C2 Therapeutics and Lucid.

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▶ **Supplementary Table 1** Primary outcomes for UC + BE vs. BE.

| Variables | UC + BE, n (%) (n = 60) | BE, n (%) (n = 114) | OR (95 % CI) | *P* value |
|---|---|---|---|---|
| Any dysplasia | 10 (16.7 %) | 8 (6.1 %) | 3.10 (1.2–8.3) | 0.03[1] |
| LGD | 8 (13.3 %) | 4 (3.0 %) | 4.92 (1.4–17.1) | 0.01[1] |
| HGD | 2 (3.3 %) | 4 (3.0 %) | 1.10 (0.2–6.2) | 0.91 |
| Adenocarcinoma | 3 (5.0 %) | 6 (4.6 %) | 1.10 (0.3–4.6) | 0.89 |
| Nodule | 6 (10.0 %) | 4 (3.0 %) | 3.55 (1.0–13.1) | 0.05[1] |
| Long Barrett's esophagus | 26 (43.3 %) | 16 (12.1 %) | 5.54 (2.7–11.5) | < 0.01[2] |

UC, ulcerative colitis; BE, Barrett's esophagus; OR, odds ratio; CI, confidence interval; LGD, low-grade dysplasia; HGD, high-grade dysplasia.
[1] $P < 0.05$
[2] $P < 0.01$

▶ **Supplementary Table 2** Primary outcomes for CD + BE vs. BE.

| Variables | CD + BE, n (%) (n = 72) | BE, n (%) (n = 132) | OR (95 % CI) | *P* value |
|---|---|---|---|---|
| Any Dysplasia | 11 (15.3 %) | 8 (6.1 %) | 2.79 (1.1–7.3) | 0.04[1] |
| LGD | 8 (11.1 %) | 4 (3.0 %) | 4.00 (1.2–13.7) | 0.02[1] |
| HGD | 3 (4.2 %) | 4 (3.0 %) | 1.39 (0.3–6.4) | 0.67 |
| Adenocarcinoma | 4 (5.6 %) | 6 (4.6 %) | 1.24 (0.3–4.5) | 0.75 |
| Nodule | 7 (9.7 %) | 4 (3.0 %) | 3.45 (1.0–12.2) | 0.05[1] |
| Long Barrett's esophagus | 32 (44.4 %) | 16 (12.1 %) | 5.80 (2.9–11.7) | < 0.01[2] |

CD, Crohn's disease; BE, Barrett's esophagus; OR, odds ratio; CI, confidence interval; LGD, low-grade dysplasia; HGD, high-grade dysplasia.
[1] $P < 0.05$.
[2] $P < 0.01$