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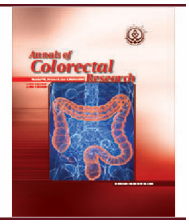

Left-Sided Diverticulosis is a Risk Factor for Distal Colon Polyps

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Abstract

Background: Previous small to mid-sized studies have found an inconsistent relationship between diverticulosis and colon polyps. We assessed the odds of polyps in patients with left-sided diverticulosis (LDV) compared with patients without LDV, and if a predilection for polyps existed in the distal colon (DC) versus the proximal colon (PC).
Methods: In this case-control, retrospective study, records of all patients in the Cleveland Clinic undergoing average-risk, screening colonoscopy between January 2011-August 2017 were identified. Baseline characteristics were described. Multivariate logistic regression analysis was performed to identify odds of polyps in PC and DC after adjusting for clinical and colonoscopic factors.
Results: A total of 50,703 patients (mean age=60 years; 48% male) were included; 38.9% of patients had LDV. Compared to patients without LDV, those with LDV more often had adenomas (33.2% vs 27.8%; P<0.001), hyperplastic polyps (HPs) (18.3% vs 16.2%; P<0.001), and sessile serrated polyps (SSPs) (4.8% vs 4.3%; P=0.011). LDV was associated with adenomas in the DC (OR, 1.59; 95%CI, 1.52, 1.67) more than the PC (OR, 1.15; 95%CI, 1.10, 1.21), with HPs equally in the PC (OR, 1.27; 95%CI, 1.20, 1.34) and DC (OR, 1.28; 95%CI, 1.19, 1.38), and with SSPs in the DC only (OR, 1.50; 95%CI, 1.34, 1.67).
Conclusion: LDV is associated with significantly increased risk of adenomas, HPs, and SSPs, but this association is stronger for adenomas in the DC. Careful inspection of the DC should be encouraged in patients with LDV. More research is needed to understand this phenomenon.

Keywords: Diverticulosis, Polyps, Distal colon, Adenomas, Colorectal cancer surveillance, Sessile serrated polyps, Sessile serrated polyps detection rate, Adenoma detection rate

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Introduction

The prevalence of diverticular disease increases with age (1). Alterations in the colonic wall, age-related motility disorders, obesity, and certain nutritional habits contribute to the development of diverticulosis (2, 3). In Western populations, left-sided diverticulosis (LDV)—descending colon and sigmoid colon—is far more prevalent than right-sided diverticulosis (4). The estimated prevalence of diverticular disease ranges from 10% in people below the age of 40 to 70% among those above 65 years of age (5). As with prevalence of diverticular disease, the prevalence of colonic polyps and colorectal cancer (CRC) also increases with advancing age (6, 7). Other common risk factors between diverticulosis and colorectal cancer include slowed colonic transit time, increased saturated fatty acids in the diet and decreased dietary fiber intake (7). In addition, structural and molecular changes involved in the development of diverticulosis may predispose the colonic mucosa to chronic microinflammation, which in turn may induce carcinogenesis in the colonic regions affected by diverticulosis (8).

Although the majority of scientific literature demonstrates a moderate to strong association between LDV and adenomatous polyps (9-13), there are a few studies which suggest otherwise (14, 15). A few small-to-mid sized studies have examined the relationship between LDV and the location of colonic polyps, and these studies reported mixed results (9, 16). If there is an association between LDV and sidedness of colon polyps it has significant implications for ensuring a high-quality examination is performed. Due to the smaller sample size of the previous studies, which have inadequately controlled for patient and colonoscopic characteristics, there is a need for a large, well-adjusted analysis to more definitively analyze the nature of association between LDV and colonic polyps. In this large, single-center study, we aim to re-examine the relationship between LDV and colonic polyps (adenomas, sessile serrated polyps (SSPs), and hyperplastic polyps). We also sought to assess the location of said polyps within the colon of patients with LDV.

Materials and Methods

Study Population and Setting

All adults (≥50 years of age) who underwent screening colonoscopy at Cleveland Clinic from January 1, 2011 through June 30, 2017 were eligible for inclusion. Patients who underwent colonoscopy for diagnostic or surveillance purposes, or had non-average risk for CRC were excluded. The study was conducted with approval by the institutional review board (IRB). Informed written consent was not obtained given the retrospective nature of this study.

Potential Predictors

The patient electronic medical record was searched using the Clarity database®. Information on demographic characteristics (age, gender, race, body mass index (BMI), insurance type, substance use (tobacco and alcohol use), comorbid conditions (diabetes, cirrhosis, dementia, stroke, constipation, coronary artery disease, congestive heart failure), medication use at the time of colonoscopy (aspirin, statin, angiotensin converting enzyme inhibitor, calcium channel blocker, angiotensin receptor blocker, calcium supplements, vitamin D, estrogen, bisphosphonates), and history of cholecystectomy was obtained. Validated natural language processing was used to review colonoscopy and pathology reports, identifying quality of bowel preparation applying the Aronchick scale (17), location of polyp, presence of diverticulosis, provider name, and presence of trainee during the exam. As withdrawal time was unavailable in a significant proportion of colonoscopies examined, this was not studied. Many of these aforementioned characteristics have been associated with polyp pathology.

Outcomes

The primary purpose of this study was to identify the association between LDV and colon polyps (adenomas, sessile serrated polyps, and hyperplastic polyps). The secondary aim of this study was to identify if LDV is associated with location of colonic polyps. For the purpose of this study, polyps were categorized based on polyp pathology and location of the polyp where distal colon (DC) was defined as descending colon to anus, and proximal colon (PC) as cecum to splenic flexure. Given significant differences in the factors that are associated with right- and left- sided diverticulosis (4), along with relative rarity of finding right-sided diverticulosis in the western population, we have chosen to primarily focus our analysis on LDV. Internally validated natural language algorithm was used to extract information regarding polyps and LDV from colonoscopy reports.

Statistical Analysis

Baseline characteristics of patients who underwent a colonoscopy were described, and differences in these characteristics based on the presence of LDV was calculated. Additionally, differences in polyp detection were computed between patients with and without LDV, and by colonic segment. Categorical variables were reported as frequencies with percentages, and the significance of these differences was assessed with chi-square analysis.

After performing univariate logistic regression to identify odds of finding polyps (throughout the colon as well as in DC and PC) in patients with LDV (compared to patients without LDV), multivariate logistic analysis was performed with adjustment of multiple patient and colonoscopy associated factors.

Table 1: Comparison of baseline characteristics between patients with and without left sided diverticulosis

Variable	Overall (column %)	No diverticulosis (row %)	Diverticulosis (row %)	P value
Total	50703 (100%)	30997 (61.1%)	19706 (38.9%)	
Age (years)				
50 to 60	29361 (57.9%)	20318 (69.2%)	9043 (30.8%)	<0.001
>60 to 70	15570 (30.7%)	8267 (53.1%)	7303 (46.9%)	
≥70	5772 (11.4%)	2412 (41.8%)	3360 (58.2%)	
Gender				
Female	26300 (51.9%)	16692 (63.5%)	9608 (36.5%)	<0.001
Male	24403 (48.1%)	14305 (58.6%)	10098 (41.4%)	
Race				
White	36933 (72.8%)	21972 (59.5%)	14961 (40.5%)	<0.001
Black	8964 (17.7%)	5792 (64.6%)	3172 (35.4%)	
Other	4806 (9.5%)	3233 (67.3%)	1573 (32.7%)	
BMI				
Underweight	309 (0.7%)	220 (71.2%)	89 (28.8%)	<0.001
Normal	16348 (34.5%)	10613 (64.9%)	5735 (35.1%)	
Overweight	13901 (29.4%)	8476 (61%)	5425 (39%)	
Obese	14308 (30.2%)	8166 (57.1%)	6142 (42.9%)	
Morbid obesity	2493 (5.3%)	1427 (57.2%)	1066 (42.8%)	
Substance use				
Tobacco	18005 (35.5%)	10302 (57.2%)	7703 (42.8%)	<0.001
Alcohol	3132 (6.2%)	1853 (59.2%)	1279 (40.8%)	0.019
Insurance				
Private Insurance	32453 (64%)	21056 (64.9%)	11397 (35.1%)	<0.001
Medicare	15206 (30%)	7892 (51.9%)	7314 (48.1%)	
Medicaid	2547 (5%)	1710 (67.1%)	837 (32.9%)	
Other	497 (1%)	339 (68.2%)	158 (31.8%)	
Comorbidities				
Diabetes	9933 (19.6%)	5855 (58.9%)	4078 (41.1%)	<0.001
Cirrhosis	2661 (5.2%)	1665 (62.6%)	996 (37.4%)	0.118
Dementia	887 (1.7%)	458 (51.6%)	429 (48.4%)	<0.001
Stroke	271 (0.5%)	158 (58.3%)	113 (41.7%)	0.338
Constipation	4798 (9.5%)	2361 (49.2%)	2437 (50.8%)	<0.001
CAD	5499 (10.8%)	2921 (53.1%)	2578 (46.9%)	<0.001
CHF	2254 (4.4%)	1244 (55.2%)	1010 (44.8%)	<0.001
History of cholecystectomy	476 (0.9%)	262 (55%)	214 (45%)	0.006
Quality of bowel preparation				
Inadequate	9328 (18.4%)	5884 (63.1%)	3444 (36.9%)	<0.001
Adequate	41375 (81.6%)	25113 (60.7%)	16262 (39.3%)	
Location				
Tertiary center	10443 (20.6%)	6532 (62.5%)	3911 (37.5%)	<0.001
Community hospital	11698 (23.1%)	7307 (62.5%)	4391 (37.5%)	
Family health center	28562 (56.3%)	17158 (60.1%)	11404 (39.9%)	
Medications				
Aspirin	15056 (29.7%)	8175 (54.3%)	6881 (45.7%)	<0.001
Statin	15775 (31.1%)	8736 (55.4%)	7039 (44.6%)	<0.001
CCB	9457 (18.7%)	5243 (55.4%)	4214 (44.6%)	<0.001
ACE inhibitor	15288 (30.2%)	8532 (55.8%)	6756 (44.2%)	<0.001
ARB	6262 (12.4%)	3352 (53.5%)	2910 (46.5%)	<0.001
Calcium	19088 (37.6%)	11462 (60%)	7626 (40%)	<0.001
Vitamin D	26818 (52.9%)	16264 (60.6%)	10554 (39.4%)	0.017
Estrogen	3970 (7.8%)	2439 (61.4%)	1531 (38.6%)	0.685
Bisphosphonate	4434 (8.7%)	2579 (58.2%)	1855 (41.8%)	<0.001
Specialty				
Gastroenterologists	29217 (57.6%)	17831 (61%)	11386 (39%)	0.778
General surgeons	3366 (6.6%)	2060 (61.2%)	1306 (38.8%)	
Colorectal surgeons	9650 (19%)	5945 (61.6%)	3705 (38.4%)	
Advanced endoscopists	8120 (16%)	4954 (61%)	3166 (39%)	
Fellow present	4323 (8.5%)	2686 (62.1%)	1637 (37.9%)	0.159

Specific factors that were adjusted for in this analysis are listed in appendix 1. All variables had <10% missing values. A post-estimation command was then used to compute adjusted polyp detection rates after controlling for variables in appendix 1. Statistical significance was described as P<0.05. All statistical functions were performed using Stata SE, version 15.0 (StataCorp, College Station, Texas, USA).

Results

Baseline Characteristics of All Included Patients

Our final sample included 50,703 patients. The mean age was 60±8 years, 51.9% were female, and 38.9% had LDV. LDV varied by gender (female-36.5% v. male-41.4%; P<0.001), race (White-40.5% v. Black 35.4% v. 32.7%), and age (50-60 years- 30.8% v. >60 to 70 years- 46.9% v. ≥70 years-58.2%; P<0.001). Other baseline characteristics and differences based on clinical characteristics are tabulated (Table 1).

Differences in Polyp Detection in Patients with and Without LDV—Univariate Analysis

As depicted in Table 2, patients with LDV had a greater prevalence of adenomas (33.2% vs 27.8%; P<0.001), hyperplastic polyps (18.3% vs 16.2%; P<0.001), and sessile serrated polyps (SSPs) (4.8% vs 4.3%; P=0.011) compared to patients without LDV. Additionally, the frequency of proximal adenomas (21.5% vs 17.6%; P<0.001), and proximal hyperplastic polyps (8.3% vs 6.4%; P<0.001), were increased but no significant difference was noted in proximal SSPs (3.5% vs 3.3%; P=0.106). The prevalence of all distal lesions in patients with LDV were increased including adenomas (26.2% vs 17.1%; P<0.001), hyperplastic polyps (14.5% vs 12%; P<0.001), and SSPs (3.9% vs 2.6%; P<0.001).

Notably, the magnitude of difference in polyp detection between patients with and without LDV is greater in the distal colon (adenomas, +9.1%; hyperplastic polyps +2.5%; SSPs, +1.3%) compared to the magnitude of difference observed in the proximal colon (adenomas, +3.9%; hyperplastic polyps +1.9%; SSPs, +0.2%).

Polyp Detection in Patients with LDV—Multivariate Analysis

After adjusting for clinical factors (see appendix 1), compared to patients without LDV, patients with LDV were more likely to have adenomas [OR, 1.16; (95%CI, 1.11, 1.21)], hyperplastic polyps [OR, 1.16

Table 2: Unadjusted polyp detection rate based on presence of left-sided diverticulosis

Variable	Overall polyp detection (%)	Polyp detection in patients without diverticulosis (%)	Polyp detection in patients without diverticulosis (%)	Difference (DV – no DV)	P value
Colonic polyps, overall					
Adenoma	15169 (29%)	8631 (27.8%)	6538 (33.2%)	+5.4%	<0.001
Hyperplastic	8608 (16.5%)	5010 (16.2%)	3598 (18.3%)	+2.1%	<0.001
Sessile serrated	2267 (4.3%)	1328 (4.3%)	939 (4.8%)	+0.5%	0.011
Proximal Polyps					
Adenoma	9679 (18.5%)	5442 (17.6%)	4237 (21.5%)	+3.9%	<0.001
Hyperplastic	3613 (6.9%)	1973 (6.4%)	1640 (8.3%)	+1.9%	<0.001
Sessile serrated	1706 (3.3%)	1011 (3.3%)	695 (3.5%)	+0.2%	0.106
Distal polyps					
Adenoma	10455 (20%)	5293 (17.1%)	5162 (26.2%)	+9.1%	<0.001
Hyperplastic	6583 (12.6%)	3718 (12%)	2865 (14.5%)	+2.5%	<0.001
Sessile serrated	1565 (3%)	802 (2.6%)	763 (3.9%)	+1.3%	<0.001

Table 3: Adjusted Risk of Polyps in Patients with Diverticulosis

Variable	Unadjusted analysis		Adjusted analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Colonic polyps, overall				
Adenoma	1.29 (1.24, 1.34)	<0.001	1.16 (1.11, 1.21)	<0.001
Hyperplastic	1.16 (1.11, 1.21)	<0.001	1.16 (1.1, 1.22)	<0.001
Sessile serrated polyp	1.12 (1.03, 1.22)	0.011	1.11 (1.02, 1.22)	0.02
Proximal polyps				
Adenoma	1.29 (1.23, 1.35)	<0.001	1.15 (1.10, 1.21)	<0.001
Hyperplastic	1.34 (1.25, 1.43)	<0.001	1.28 (1.19, 1.38)	<0.001
Sessile serrated polyp	1.08 (0.98, 1.2)	0.107	1.09 (0.98, 1.21)	0.112
Distal polyps				
Adenoma	1.72 (1.65, 1.8)	<0.001	1.59 (1.52, 1.67)	<0.001
Hyperplastic	1.25 (1.18, 1.32)	<0.001	1.27 (1.2, 1.34)	<0.001
Sessile serrated polyp	1.52 (1.37, 1.68)	<0.001	1.50 (1.34, 1.67)	<0.001

(95%CI, 1.10, 1.22)], and SSPs [OR, 1.11 (95%CI, 1.02, 1.22)]. When characterizing by location, it was noted that the odds for patients with LDV to have distal polyps including adenomas [OR, 1.59 (95%CI, 1.52, 1.67)], hyperplastic polyps [OR, 1.27 (95%CI, 1.20, 1.34)], and SSPs [OR, 1.50 (95%CI, 1.34, 1.67)] was stronger than proximal adenomas [OR, 1.15 (95%CI, 1.10, 1.21)], hyperplastic polyps [OR, 1.28 (95%CI, 1.19, 1.38)], and SSPs [OR, 1.09 (95%CI, 0.98, 1.21)] (Table 3).

The magnitude of difference in polyp detection between patients with and without LDV is greater in the distal colon (adenomas, +9.2%; hyperplastic polyps +2.8%; SSPs, +1.4%) compared to the magnitude of difference observed in the proximal colon (adenomas, +4.1%; hyperplastic polyps +2.1%; SSPs, +0.4%) (Table 4).

Discussion

In this large, retrospective, single-center study, we report a significant association between colonic polyps and LDV. After adjusting for demographic, clinical, and colonoscopy-related factors, our study demonstrated that patients with LDV have a 5.4% absolute increase in adenoma detection rate, 2.3% absolute increase of hyperplastic polyp rate, and 0.6% absolute increase in SSP detection rate compared to patients without LDV. Although the risk of having these polyps is increased throughout the colon, patients with LDV seem to have a particularly increased risk of distal colonic adenomas and sessile serrated polyps, compared to the proximal colon. However, hyperplastic polyps seem to occur with an equally increased risk throughout the colon with no preference for distal or proximal colon.

As shown in Table 5, numerous studies in the literature have demonstrated a positive association between diverticulosis (not specifically LDV) and colonic polyps. For example, Gohil et al. found that patients with diverticulosis, had a higher rate of ADR (47.5%) compared to patients without diverticulosis (27.4%) (12). Similarly, Ashktorab et al. found a higher polyp detection rate (70% in diverticulosis vs. 49% in patients without diverticulosis) and adenoma detection rate (43% vs. 25%) (18). However, not all studies have reported positive associations. Meurs-Szojda et al., Peery et al, and Hong et al. demonstrated no association between diverticular disease and colonic polyps (14, 19, 20). As the largest study to-date assessing the relationship between LDV and polyps, our study lends weight to the idea that LDV is an independent risk factor for adenomas, SSPs, and hyperplastic polyps. Furthermore, McCallum et al. demonstrated no significant relationship between diverticulosis and colon cancer (15).

Studies examining diverticulosis and colonic polyps (all locations), have yielded a wide spectrum of conflicting conclusions (Table 6). Morini et al., after adjusting for the influence of age, noted a positive association between diverticular disease and sigmoid colon adenomas [OR: 2.4; 95% confidence interval (CI)=1.3-4.6].(8) A study by Kieff et al., found a similar relationship between extensive LDV and colonic polyps but only in women (21). However, Peery et al. (N=624) found no association between diverticulosis and colorectal adenomas (19). Further, Hirata et al. showed that the prevalence of colonic polyps in patients with diverticular disease in the proximal colon was significantly higher than in patients without diverticulosis. They found an overall 1.7-fold increased risk for colonic polyps in patients with diverticular disease in the proximal colon compared to those without diverticulosis (22). Research published by Wong et al. (N=2,766) and a more recent study by Levine et al. (N=600) yielded a similar conclusion that diverticulosis was not associated with distal colonic polyps (9, 16). Our study, which included 50,703 patients, is the largest study to-date examining this phenomenon. The size of our study allowed us to adjust for multiple confounding factors which were not adjusted in previous studies. Overall our analysis demonstrates that LDV is associated with distal colonic polyps more than proximal colonic polyps.

Pathophysiological mechanisms explaining this association between diverticulosis and distal colonic polyps have been posited. It is known that

Table 4: Adjusted Risk of Polyps by Colonic Location

Variable	DV (95%CI)	No DV (95%CI)	Difference DV minus no DV (95%CI)
Colonic polyps, overall			
Adenoma	33.5% (33.4%, 33.6%)	28.1% (28%, 28.2%)	+5.4% (+5.5%, +5.2%)
Hyperplastic	18.3% (18.2%, 18.4%)	16% (15.9%, 16%)	+2.3% (+2.4%, +2.2%)
Sessile serrated	4.9% (4.9%, 5%)	4.3% (4.3%, 4.4%)	+0.6% (+0.6%, +0.5%)
Proximal polyps			
Adenoma	21.8% (21.7%, 21.9%)	17.7% (17.6%, 17.7%)	+4.1% (+4.2%, +4%)
Hyperplastic	8.4% (8.4%, 8.4%)	6.3% (6.3%, 6.3%)	+2.1% (+2.1%, +2%)
Sessile serrated	3.7% (3.6%, 3.7%)	3.3% (3.3%, 3.3%)	+0.4% (+0.4%, +0.3%)
Distal polyps			
Adenoma	26.5% (26.4%, 26.6%)	17.3% (17.3%, 17.4%)	+9.2% (+9.3%, +9.1%)
Hyperplastic	14.6% (14.5%, 14.7%)	11.9% (11.8%, 11.9%)	+2.8% (+2.8%, +2.7%)
Sessile serrated	4% (4%, 4%)	2.6% (2.6%, 2.7%)	+1.4% (+1.4%, +1.3%)

Table 5: Studies examining the relationship between Diverticulosis and Colon Polyps

Author	Year	Sample size	Findings	Association
Gohil et al. (12)	2012	300	The frequency of colonic diverticula was 39.2%. ADR was 47.5% for patients with diverticulosis and 27.4% for patients without diverticulosis.	Positive
Muhammad et al. (13)	2014	2223	The prevalence of polyps was higher in patients with versus without diverticulosis (odds ratio (OR) 1.54; 95 % confidence interval (CI) 1.27-1.80, P=0.001).	Positive
Rondagh et al. (30)	2011	2310	In patients aged below 60 years, polyp prevalence was higher in those with compared to without diverticulosis 39.1% (79 of 202 patients) versus 19.6% (176 of 898 patients), adjusted odds ratio (OR) 1.87, 95% confidence interval (CI) 1.26-2.78, and P=0.002.	Positive
Ashktorab et al. (18)	2015	1986	A higher prevalence of polyps (70 vs. 49%; OR=2.3; 95% CI: 1.9-2.8) and adenoma (43 vs. 25%; OR=2.0; 95% CI: 1.7-2.5) in the diverticular vs. non-diverticula patients.	Positive
Peery et al. (19)	2015	624	Diverticula on colonoscopy were not associated with an increased risk of adenomas (odds ratio (OR) 1.0, 95% confidence interval (CI) 0.7-1.4) or advanced adenomas (OR 0.8, 95% CI 0.4-1.5).	None
Kieff et al. (21)	2004	502	Compared to women with few or no distal diverticuli, women with diverticulosis were more likely to have any neoplasia and advanced neoplasia, both distally (34.6%vs 16.3%; P=0.03, and 23.1%vs 5.7%; P=0.003) and proximally (30.8%vs 14.9%; P=0.049, and 11.5%vs 4.3%, P=0.13)	Positive (in women only)
Meurs-Szojda et al. (14)	2008	4241	No association was found between patients with polyps and those with and without diverticulosis (P=0.478)	None
Hong et al. (20)	2018	17,456	Multivariable logistic regression analysis did not find an association between right-sided diverticulosis and adenomas (P=0.185)	None

Table 6: Studies examining Diverticulosis and location of Colon Polyp

Author	Year	Sample size	Findings	Association
Morini et al. (11)	2002	630	Prevalence of adenomas located in the sigmoid colon was significantly higher in patients with diverticula than in controls (64.1% vs 41.8%; P<0.05).	Dominance in sigmoid colon
Hirata et al. (22)	2008	672	Prevalence of colonic polyps in patients with diverticular disease in the proximal colon was significantly higher than in patients without diverticulosis. They found an overall 1.7-fold increased risk for colonic polyps in patients with diverticular disease in the proximal colon compared to those without diverticulosis	Dominance in proximal colon
Wong et al. (9)	2016	2766	Association noted between CRC and left-sided diverticulosis (P=0.034 by trend).	Left-sided dominance
Azzam et al. (1)	2013	3649	Diverticula were predominantly left-sided (sigmoid and descending colon) in 62%, right-sided in 13% and in multiple locations in 25%. There was an association between the presence of diverticulosis and adenomatous polyps (P<0.001),	Left sided dominance
Levine et al. (16)	2017	600	Prevalence of adenomatous polyps reduced in regions of diverticulosis compared to the same colonic segment unaffected by diverticulosis (7 vs. 17% for rectosigmoid (P=0.005); 5 vs. 18% for descending (P<0.0001); and 17 vs. 27% for ascending colon (P=0.0495))	Non-dominance in areas of diverticulosis

the concentration of bacterial content increases distally, with approximately 10^8 bacteria per g (dry weight) of ileal contents and up to 10^{12} bacteria per g (dry weight) of colonic contents, including bacterial species known to degrade biliary steroids in the feces and convert it into toxic carcinogenic metabolites (23, 24). Stefansson et al. speculated that increased carcinogenic material become trapped within diverticula, and that this prolonged contact with mucosa could lead to increased colonic neoplasia (10). Morini, et al. tested this hypothesis by administering rifaximin to patients with LDV and controls. If bacterial inflammation or toxin production was the cause of colonic neoplasia in patients with LDV, rifaximin treatment would have reduced cellular proliferation. However, increased cellular proliferation was noted in patients with LDV despite rifaximin treatment, suggesting factors other than bacterial load may be responsible for increased neoplasia associated with LDV (25). Similar to this

study, Tursi, at al. also found increased cellular proliferation in areas with diverticulosis. In this study, the proliferation rate in patients with LDV was found to be on par with patients with ulcerative colitis (26). Ultimately further studies are needed to investigate the reason for the increased cellular proliferation in patients with DV.

Using a linked database containing SEER tumor registry data and Medicare claims, diverticulosis was shown to be associated with interval colorectal cancers (24). In the study, the odds of cancer were much higher in the DC than in the PC. As our data demonstrates a significant association between LDV and distal colonic polyps, our research further makes a case for closer examination of DC in patients with LDV. Given the increased odds of finding these polyps in the distal location, spending more time performing mucosal inspection in the distal colon, or considering an interval sigmoidoscopy may be the subject of future research. Given the evidence of the success of chemoprevention of CRC using aspirin, statins, and other non-steroidal anti-inflammatory medications an assessment of their utility in this population may be warranted (27).

Our study is the largest study to-date evaluating the relationship between left sided diverticulosis and distal polyps. The main strength of our study is the size of our study population, allowing a large multivariate model which adjusted for multiple factors found to be associated with polyp growth and CRC. Nonetheless, we recognize several limitations to our study. First, since this is a retrospective review, our analysis is based on findings from patient's electronic medical records and colonoscopic data processed data by verified natural language algorithms. Therefore, our study is prone to data mis-representations and omissions. Second, there may be a selection bias given our inclusion of patients undergoing average risk screening colonoscopies. Patients who underwent colonoscopy for reasons other than screening were not included, and therefore may differ from patients who chose to undergo screening colonoscopies (28). Furthermore, we excluded the patients with inflammatory bowel disease given the diversity of carcinogenic pathways leading to cancer in patients with high risk of colorectal cancer compared to those with average risk of colorectal cancer, in this study, we have only included patients with average risk of colorectal cancer. Since patients with inflammatory bowel disease would be considered as more than average risk of having colorectal cancer. We also could not include the history of appendectomy given the limitations of our institutional resources and the limited clinical significance of adjusting for appendectomy.

Additionally, the specificity of colonoscopy for the detection of diverticulosis is high but the sensitivity is low (29) resulting in misclassification of patients with diverticulosis into the no diverticulosis group. However, that would have minimized our findings of an association between LDV and polyps. While we have attempted to evaluate and adjust for many factors that may influence polyp detection and prevalence, we were not able to control for certain known risk factors such as diet, lifestyle, and carcinogenic exposures. Therefore, our study is prone to residual confounding effects from these factors influencing polyp detection.

With regards to detection of diverticulosis, previous research has shown that computerized tomography (CT) imaging is superior in detecting diverticulosis compared to colonoscopy (29). Therefore, the diverticulosis rate may be under reported in our study. However, most studies evaluating the relationship between diverticulosis and polyps used colonoscopic data. Further, the use of CT imaging data for this purpose is unlikely to be generalizable to an average population. Finally, due to limitations of our natural language algorithm, the extent of the diverticulosis and the specific location of the polyp with respect to the diverticula was not appreciable.

Conclusion

In the largest study to date examining the relationship between left-sided diverticulosis and polyp location, diverticulosis increases the overall risk of colonic polyp formation with a disproportionate increase in distal colonic polyp location. Closer examination of the distal colon is warranted in patients with left-sided diverticulosis. Further studies are needed to explore the pathophysiological mechanisms contributing to this finding.

Appendix-1

Variables included or adjusted for in the multivariate logistic regression include: patient age, gender, race, body mass index, payer status, alcohol abuse, any history of smoking, comorbid conditions using diagnostic codes (diabetes, cirrhosis, dementia, stroke, constipation, coronary artery disease, congestive heart failure), medication use at the time of colonoscopy (aspirin, statin, angiotensin converting enzyme inhibitor, calcium channel blocker, angiotensin receptor blocker, calcium supplements, vitamin D, estrogen, bisphosphonates), history of cholecystectomy, quality of bowel preparation, specialty of the provider, and presence of trainee during the exam.

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