Association of Colonic Diverticulosis and Colonic Adenoma: A Cross-sectional Study in Philippine General Hospital

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BACKGROUND AND SIGNIFICANCE OF STUDY

Colonic diverticulosis and colonic adenoma are among the most common endoscopic findings seen in colonoscopy examinations. For the past several years, studies have shown an increasing prevalence of these conditions. Several researches have also suggested that both conditions share common epidemiological features and risk factors such as age, lifestyle-related factors, low-fiber combined with high-fat diet, and smoking[1,2]. A positive association between colonic diverticulosis and colonic adenoma was demonstrated in many studies in various population [3-11]. Some authors even hypothesized that colonic diverticulosis may be a risk factor for the development of colonic adenoma, a known precursor of colorectal malignancy according to the adenoma-carcinoma sequence[12]. For the past several years, there has been a growing interest among researchers to find if there is a relationship between the two conditions. However, the findings in other studies yielded conflicting results.

In Asian countries where the prevalence of colonic diverticulosis is lower compared to the Western countries, results were also conflicting [4,6,7,15]. As to the author's knowledge, no study has been done in the Philippines to investigate the link between colonic diverticulosis and colonic adenoma. Finding an association between diverticulosis and adenoma has potential implications in clinical practice. For instance, when flexible sigmoidoscopy, an acceptable screening procedure, is done and diverticulosis was noted, examination of the proximal colon might be done subsequently despite the absence of distal adenoma. Finding an increased risk of adenoma in patients with diverticulosis might entail a shorter interval of surveillance as compared to those without colonic diverticulosis.

REVIEW OF RELATED LITERATURE

Several years ago, the coexistence of colonic diverticulosis and colonic adenoma reported in various radiologic, endoscopic and autopsy studies was regarded as purely accidental. However, the increasing number of studies showing association between the two conditions led to further investigations [3-11]. The initial case-control study of Morini et. al., involving 150 patients with colonic symptoms and diverticular disease diagnosed by

colonoscopy, showed that the odds of finding an adenoma was significantly higher than matched controls (p value<0.001, OR=3.5)[3]. In a retrospective study in Japan, Hirata and colleagues investigated the prevalence of colonic adenoma in all patients with diverticulosis. They found out that the prevalence of colonic adenoma in patients with diverticular disease was significantly higher than those without diverticular disease (adjusted OR=1.7)[4]. In Korea, Choi et.al. retrospectively analyzed 3007 patients who underwent colonoscopic examination from 2002 to 2004 and found out that patients with diverticular diseases have higher risks of any neoplasia than those without diverticulosis (p=0.03, 37.7% vs 28.2%). No correlation was seen between diverticular diseases and advanced neoplasia. Interestingly, their analysis showed that patients with proximal diverticular diseases had higher risk of proximal neoplasia than other patients ((p<0.01, 24.6% vs 14.3%). Moreover, these patients also had higher risk of proximal advanced neoplasia than others. (p<0.01, 4.5% vs 2%)[5]. Gohil et.al analyzed 300 patients who underwent colonoscopy for various indications. Multivariate analysis revealed that the presence of diverticulosis had an associated odds ratio of 2.3 (p<0.04) in favor of finding at least one adenoma[6]. Another study done by Muhammad et. al., demonstrated that the prevalence of colorectal adenoma with diverticulosis was higher than those without diverticulosis (p<0.001, OR=1.54), This association was found significant for all locations of polyps and all histological subtypes[7]. Another Italian study compared the prevalence of adenoma, advanced adenoma in patients with and without diverticulosis in patients with a positive fecal immunological test. In the univariate analysis, the adenoma detection rate in patients with diverticula was significantly higher than in controls controls (55.9% vs 47.4%; p < 0.011). At multivariate analysis, diverticulosis was an independent risk factor for both adenoma detection rate (OR=1.58; 95% CI, 1.14–2.18; p < 0.006) and advanced adenoma (OR = 1.57; 95% CI, 1.10–2.24; p < 0.013)[8]. On the contrary, at least 4 published studies showed absence of association between colonic diverticulosis and colonic adenoma and/or advanced adenoma. In Netherlands, a cross-sectional study was done in 18 hospitals to investigate association between colonic diverticulosis and colonic polyps. No association was noted when using age-stratified analysis[14]. Peery et. al. studied 624 participants. Diverticula were not associated with increased risk of adenomas compared to those without diverticula (OR=1.0, 95% CI 0.7–1.4). Even in patients with

extensive diverticulosis, increased risk for adenoma was not seen (OR=1.1, 95% CI 0.7–1.8). Furthermore, this study also concluded that diverticulosis was not associated with an increased risk of proximal (OR=1.0, 95% CI 0.6–1.6) or distal adenomas (OR=1.0, 95% CI 0.6–1.7)[15]. In another study by Kieff et. al., analysis of 502 patients showed absence of association between extensive diverticulosis and increased risk of colonic neoplasia and advanced neoplasia after adjusting for age[16]. A large study in mainland China comprising of 17,456 subjects investigated the association of colonic adenoma and advanced adenoma. Adenoma was associated with age and male sex but no relationship between diverticulosis and presence of adenoma or advanced adenoma was after adjusting by age and sex. In stratified analysis according to age and sex, similar results were noted[17]. In view of the conflicting data in literature, this study aims to determine the association of colonic diverticulosis and colonic neoplasia (colonic adenoma and advanced adenoma) in a tertiary hospital.

RESEARCH OBJECTIVES:

General Objectives:

To determine the association of colonic diverticulosis and colonic adenoma

Specific Objectives:

1. To describe the demographic characteristics of patients with colonic diverticulosis and colonic adenoma
2. To determine the association of diverticulosis and colonic adenoma
3. To determine the association of diverticulosis and advanced adenoma

METHODOLOGY

Study design

A review of colonoscopy reports and histopathology reports of patients who underwent colonoscopy at the Philippine General Hospital Gastrointestinal Endoscopy Unit from January 1, 2017- December 31, 2017 was done.

Study Inclusion and Exclusion

All patients who underwent colonoscopy examination in the Philippine General Hospital between January 1, 2017 and December 31, 2017 were eligible for inclusion in the study. Patients with incomplete colonoscopy examination, inadequate bowel preparation, history of prior colonic resection, repeated colonoscopy within one year, colorectal malignancy, inflammatory bowel disease were excluded.

Sample Size Computation

A cross-sectional study was done to determine the association between colonic diverticulosis and colonic neoplasia. Prior data from several studies indicated that the average odds of colonic adenoma increases by 86% (OR=1.86) among patients with colonic diverticula[3-13]. Assuming an event rate under H0 = 0.47, we want to estimate the sample size necessary to achieve a power of at least 80%, in a two-sided test of hypothesis with alpha error probability of 0.05. Assuming further a squared multiple correlation, R^2, of 0.10 (i.e. the variance of colonic diverticulosis explained by the regression relationship with other covariates) and a balanced design (π=0.50) with equal sample frequencies for $X_1 = 0$ and $X_1 = 1$, we will need a sample of 298 patients when using the procedure of Demidenko (2007) with variance correction. We used G*Power to estimate the minimum sample size. As a secondary objective, we also plan to determine the association of colonic diverticulosis and advanced colonic adenoma. Prior data from several studies indicated that the average odds of advanced colonic adenoma increases by 47% (OR=1.47) among patients with colonic diverticula[9,11,15,17]. Following the same assumptions, the computed sample size is 948. The final minimum sample size that will be used is 948.

Definition of Terms

Diverticulosis is defined as presence of one or more sac-like protrusions in the colonic wall irrespective of whether the patient is symptomatic or asymptomatic. Right-sided diverticulosis is defined as presence of diverticula either in the cecum, ascending colon or transverse colon. Left sided diverticulosis is defined as presence of diverticula in the

descending colon, sigmoid colon or rectum. Pancolonic diverticulosis is defined as presence of diverticula in the right and left sections of the colon. Colorectal adenoma/s is/are defined as 1 or more polyps with an adenomatous pattern in histology irrespective of size and location. Advanced adenomas were defined as adenomas more than or equal to 1 cm in size, with villous component or with high grade dysplasia. Data collection process was done in compliance with the Data Privacy Act of 2016.

Data Management and Analysis Plan

The mean, standard deviation and minimum and maximum values of age of the patients were generated and reported according to sex. Frequency distributions were generated for qualitative variables such as indication for endoscopy and location of diverticulosis. The crude Odds Ratio to determine the association of diverticulosis and colonic adenoma was estimated at 95% confidence Level. Likewise adjusted odds ratio (age and sex were accounted for as confounders) was estimated at the same confidence level using logistic regression.

RESULTS

A total of 990 patients were included in the study. The mean age is 53.5 years and 54% are males (Table 1). Indications of colonoscopy are shown in Table 2. Gastrointestinal bleeding history, bowel movement changes and screening colonoscopy are among the most common indications of colonoscopy. A total of 128 patients (13%) have diverticulosis. Fifty percent of these are located on the left of the colon (Table 3). A total of 167 (16.9%) were found to have adenoma. Of these patients 35 (21%) were advanced. Majority of these advanced adenoma has villous histology, followed by presence of high grade dysplasia and size more than or equal to 1 cm (Table 4). The odds of finding colonic adenoma is higher for those with diverticulosis than those without (Crude OR = 1.3 (95% Confidence Interval: 0.82-2.08). Adjusting for Age and sex of patients, the adjusted OR is 0.98 (95% CI: 0.60-1.58, p value=0.92) which indicates that frequency of adenoma was not higher in patient with colonic diverticulosis compared to those without. Sex as a possible modifier for colonic diverticulosis and colonic adenoma association was explored. Based on logistic regression analysis, the odds of adenoma in

male was lower in those with diverticulosis as compared to those without although results did not reach statistical significance (OR= 0.67,95% CI: 0.32-1.35, p value=0.25). On the other hand, the odds of adenoma in female was higher in patients with diverticulosis as compared to those without (OR=1.4,95% CI: 0.74-2.76, p value=0.28). For advanced adenoma, the odds were higher in patients with colonic diverticulosis as compared to those without although was not. (Crude OR= 1.4, 95% CI: 0.57-3.47), Adjusting for age and sex, the adjusted OR was 1.00 which means that the odds for adenoma was the same for those with and without diverticulosis (Adjusted OR= 1.00, 95% CI: 0.39- 2.53, p value-0.98). To check if sex was a modifier, logistic regression analysis was done controlling for age. The odds of advanced adenoma in male sex was a little higher in patients with colonic diverticulosis than those without although was not statistically significant (OR =1.1, 95% CI: 0.35-3.43, p value=0.89). In contrast, the odds of advanced adenoma in females was lower in those with diverticulosis (OR= 0.82, 95% CI:0.16-4.05, p value= 0.81).

Table 1. Age and sex distribution of 990 patients

Sex	N	Mean	SD	Min	Max
Male	456	52.64	13.76	21	86
Female	534	54.22	13.38	19	86
Total	990	53.49	13.57	19	86

Table 2. Distribution of 990 patients according to indication for colonoscopy

Indication	Number	Percent
1 Screening	180	18.18
2 Bowel Movement changes	206	20.81
3 GI bleeding	364	36.77
4 Surveillance	33	3.33
5 Abdominal Mass	68	6.87
6 Abdominal Pain	96	9.70
7 Anemia Workup	11	1.11
8 Metastatic workup	12	1.21
9 Others	20	2.02
Total	990	100.0

Table 3. Distribution of patients who had diverticulosis according to location

Location	Number	Percent
Left	68	53.13
Right	33	25.78
Bilateral	27	21.09
Total	128	100.00

Table 4. Distribution of advanced adenoma according to type

Type of Advanced Adenoma	Number (%)
More1cm	4 (11.7)
Villous Histology	20 (58.8)
High Grade Dysplasia	10 (29.4)
No Info	1 (2.9)
Total	34

Table 5. Cross tabulation of Diverticulosis and Adenoma

Diverticulosis	Colonic Adenoma		
	Present	Absent	Total
Present	26	102	128
	20.31	79.69	100.00
Absent	141	721	862
	16.36	83.64	100.00
Total	167	823	990
	16.87	83.13	100.00

DISCUSSION

For several years, the association of colonic diverticulosis and colonic adenoma was not clearly established. Several studies theorized that the link between the two can be related to a common risk factor such as dietary factors. A low fiber diet can increase colonic diverticulosis and colonic adenoma[18]. Painter hypothesized that a low fiber diet can create excessive segmental contraction in the colon which can further increase intraluminal pressure resulting in mucosal herniation and formation of diverticula[19]. Burkitt hypothesized that low fiber diet decreases fecal bulk, concentrates carcinogens, slows colonic transit time and increased contact time between carcinogens and the luminal epithelium [20]. Another proposed theory is that there is an upward shifting of cellular proliferation of colonic mucosa in patients with diverticulosis which appears 3-fold higher than controls. This pattern was also observed in patients with ulcerative colitis, a chronic inflammatory condition of the colon associated with colorectal neoplasms[21]. Despite a common plausible mechanism, the association of colonic diverticulosis and colonic adenoma has not been established with conflicting results. A positive association was observed in some studies while others did not show any association at all. A meta-analysis done by Jaruvongvanich et. al. in 2016 showed an association between colonic diverticulosis and colonic adenoma. No association between diverticulosis and advanced colonic neoplasms was noted. Those who have colonic diverticulosis have 1.67-fold increased odds of developing colonic adenomas compared to those without colonic diverticulosis [22]. This meta-analysis however did not include the studies done by Meurs-Szojda et.al. and Hong et.al which have negative results. The latter studies adjusted for age and sex in the analysis which was not done in studies with positive association. Furthermore, the pooled analysis has significant heterogeneity (I^2=83%) which can be attributed to differences in study design, study population and outcome of interest.

In this study, the overall prevalence of colonic diverticulosis and colonic adenoma was 13 % and 16.9 %, respectively. The prevalence of diverticulosis was lower compared to the epidemiologic studies in Singapore (45%) and Japan (20-25.8%)[23-25]. Colonic adenoma prevalence was slightly higher compared to a study in China (13.2%)[17]. In terms of diverticulosis distribution, our study shows that diverticulosis is predominantly distributed in the left side of the colon. This is in contrast to the epidemiologic studies

showing a predominant right sided distribution of colonic diverticulosis among Asian countries. Many believe that the shift in distribution of diverticulosis from a predominant right to a left-sided distribution may be due a change to a Western type of diet.

The results of this study did not show a statistically significant association between diverticulosis and colonic adenoma. However, it appears that those with diverticulosis have increased odds of having a colonic adenoma compared to those without diverticulosis. After adjustment for age and sex, the odds ratio decreased from 1.3 to 0.98. The same pattern was observed regarding the association of diverticulosis and advanced colonic adenoma. The 1.4 fold increased in odds was not seen after adjustment according to age and sex. Sex as a possible modifier of association was investigated as well. Although, no significant association was noted, it appears in this study that the odds of adenoma in females is higher in patients with colonic diverticulosis than those without. The observed association was not seen in males. This trend is consistent with the findings of Kieff et. al. wherein they found out that the presence of extensive diverticulosis in females increased the odds of finding an adenoma compared to those with few or none[16]. Whether association of colonic diverticulosis and adenoma can be modified by female sex is not clear from this preliminary work.

There are limitations in this study. The study design was retrospective in nature in which other variables which can modify the association of diverticulosis and adenoma were not taken into account due to unavailability of information such as type of diet and family history of colonic neoplasia. Including these variables in the analysis will make conclusions more robust. The second limitation was the modest sample size. Although statistical analysis for the overall relationship of diverticulosis and adenoma/advanced adenoma did not reveal a statistically significant association, the study power was limited as suggested by the wide confidence intervals of the estimates. The wide confidence limits do not allow exclusion of either a protective risk or an increase in risk in patients with diverticulosis compared to those without. In summary, the results of our study suggest that there’s no statistical significant association between diverticulosis and adenoma/advanced adenoma. However, there is insufficient evidence to conclude absence of association due to limited power of the study. We therefore recommend to increase the sample size in future research to increase the power of the study. We

likewise recommend further investigation regarding association of diverticulosis and adenoma in relation to female sex.

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APPENDIX

Data Collection form

Patient Number	
Age	
Sex	
Male	
Female	
Indication	
Screening - 1	
Bowel movement changes - 2	
GI bleeding -3	
Surveillance -4	
abdominal mass -5	
abdominal pain -6	
anemia workup -7	
metastatic workup-8	
Others-9	
Diverticulosis	
Present-1	
Absent -2	
Location of Diverticulosis	
Right-1	
Left-2	
Bilateral-3	
Adenoma	
Present-1	
Absent-2	
Advanced Adenoma	
Present – 1	
Absent -2	
Type of Advanced Adenoma	
Size >=1 cm	
With villous histology	
High grade dysplasia	