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ORIGINAL ARTICLE

Predictors of colorectal carcinoma and inflammatory bowel disease in patients with colonic wall thickening

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Abstract

Background and Aim: Colonic wall thickening (CWT) is commonly associated with clinically significant pathologies, but predictive factors of such pathologies are not well known. This study aims to identify the predictors of clinically significant pathologies, such as colorectal carcinoma (CRC) and inflammatory bowel disease (IBD), in patients with CWT.

Methods: Subjects with an abnormal abdominal computed tomography (CT) and a follow-up colonoscopy between 2010 and 2020 were retrospectively reviewed. Patients with CWT in the CT were included and examined in this study. A multivariable logistic regression analysis was performed to assess for factors independently associated with CRC or IBD in these subjects. Receiver operating characteristic (ROC) curve analysis was used to further examine significant parameters in multivariable logistic regression analysis.

Results: Among 403 patients with CWT on CT scans who underwent a colonoscopy, 269 subjects who met the inclusion criteria were identified and studied. On multivariable logistic regression models, elevated platelet count, low hematocrit, and localized CWT were found to be independently associated with CRC, while elevated platelet count and younger age were independently associated with IBD. On ROC curve analysis for CRC, area under the curve (AUC) for hematocrit, platelets, and localized CWT was 0.76, 0.75, and 0.61, respectively. On ROC curve analysis for IBD, AUC for age and platelets was 0.90 and 0.69, respectively.

Conclusion: Elevated platelet count, low hematocrit, and localized CWT can be potentially used as predictors of CRC in patients with CWT. Elevated platelet count and young age can be used to predict IBD in these patients.

Introduction

Computed tomography (CT) is widely used as an imaging modality for the evaluation of abdominal pathologies.[1] Colonic wall thickening (CWT) is a common radiologic finding in abdominal CT.[2] It can be associated with benign or non-pathological conditions, but in many cases it can represent significant pathologies, such as inflammatory bowel disease (IBD) and neoplasia.[3,4] Previous studies have shown an incidence of 7–21% malignancy rate in patients with CWT.[5–9]

No clear consensus exists to date to address the role of colonoscopy in patients with CWT. Some previous studies have suggested performing colonoscopy in these subjects[10,11] but the results remain conflicting.[4,12] Early diagnosis of significant pathologies including colorectal carcinoma (CRC) can optimize management and improve survival.[13] At the same time, colonoscopy is an invasive procedure with few but potential complications, making it difficult for the patients and the clinicians to decide how to proceed. Thus, better defining the need for colonoscopy in patients with CWT will help optimize their management.

Identifying predictive factors of significant pathologies in patients with CWT, such as CRC and IBD, may potentially help improve the optimal use of colonoscopy, resulting in better utilization of health resources and fewer patient complications.[14] Most studies focus on determining the frequency of pathological findings on colonoscopy, but data on risk and predictive factors for such findings are lacking. The aim of this study was to identify the risk factors and predictors of significant pathologies in subjects with CWT.

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Methods

Study design. We examined subjects at MedStar Washington Hospital Center from January 2010 to May 2020 who had an abnormal abdominal CT scan and a follow-up colonoscopy with biopsy. Abdominal CT scans were performed either with PO contrast, IV contrast, or administration of both. Patients who were found to have CWT in the CT scan and had their colonoscopy within 1 month from that CT scan were included in this study and were retrospectively investigated. These subjects were either hospitalized inpatient or seen in an outpatient setting. Biopsy was obtained from the CWT site and pathology results were reported. Patient were excluded if they had pre-existing gastrointestinal (GI) disease, including colon cancer, or IBD, or when bowel lumen was not well distended and not clearly visualized on CT. This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of MedStar Health Research Institute approved this study.

CWT was defined as significant thickening of the bowel wall based on the assessment of the radiologist reading the abdominal CT. Diagnosis of a certain pathology was established according to the physician's judgment taking into account the colonoscopic findings and biopsy results of the thickened bowel. Ischemic colitis was diagnosed based on typical clinical features and risk factors suggestive of intestinal ischemia, along with typical findings on CT angiography and/or colonoscopy. Diagnosis of IBD was established based on characteristic radiologic, endoscopic, and/or histologic findings in a patient with compatible clinical presentation. CRC was diagnosed based on histologic examination of a biopsy obtained from colonoscopy. Inflammatory colitis was diagnosed in patients with nonspecific inflammatory findings on colonoscopy and histologic examination, but in the absence of IBD or ischemic colitis. The groups with normal findings included patients with normal or unremarkable biopsy results from the sample taken at the site of bowel wall thickening. Baseline demographic characteristics and laboratory values were collected from electronic medical records. CWT was found in different parts of the colon, including the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, or rectum. Localized thickening was defined as CWT that was localized and present in only one of the parts of the colon mentioned above, for example, only in the ascending colon, regardless of the length. Subjects who were found to have CRC were further categorized into early stage and late stage, based on the presence of metastasis or not. The main objective of this study was to investigate the risk factors associated with CRC and IBD in patients with CWT. The secondary aim was to assess the predictive value of those risk factors in these subjects.

Statistical analysis. Continuous variables were described by median and interquartile range (IQR), while categorical variables were described using percentages. Pearson's Chi-square test and Mann–Whitney *U* test were used to compare the categorical and continuous variables, respectively. Univariate analysis was performed to examine association of demographic characteristics, laboratory values, and imaging findings with CRC and IBD. Covariates included age, gender, race, body mass index (BMI), smoking status, hematocrit, platelets, blood urea nitrogen (BUN), liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), albumin, and localized thickening. Subsequently, a multivariable logistic regression was performed by including variables found to be statistically significant in univariate analysis to assess the factors independently associated with CRC or IBD in CWT subjects. Stepwise model selection was used for the multivariable logistic regression analysis. Results of the multivariable logistic regression model are reported as odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was used to examine significant parameters in multivariable analysis. Area under the curve (AUC) was calculated to assess predictive value of each parameter. AUC >0.7 was used as a cutoff for strong predictive value. Statistical analysis was performed using SPSS statistics software. A *P*-value ≤0.05 was considered statistically significant.

Results

Features of entire cohort and prevalence of each diagnosis. Overall, 1184 patients with abnormal CT scans who underwent a colonoscopy were identified, and CWT was present in 403 patients (Fig. 1). Of those with CWT, 269 patients (67%) met the inclusion criteria and were selected for further analyses. Subjects were excluded either because of missing data or suboptimal quality of bowel wall imaging on CT scan (89 patients; 22%), or pre-existing GI diseases (45 patients; 11%). In our study, the median age was 58 years (range 44–71), 52% were male, and 77% were of African-American race. The presenting symptoms prompting abdominal CT included abdominal pain (62%), GI bleeding/anemia (11%), weight loss (4%) or other symptoms (23%). A total of 85 patients were diagnosed with inflammatory colitis (32%), 36 with CRC (13%), 19 with ischemic colitis (7%), 12 with IBD (5%), 45 with other pathologies (diverticulosis, tubular adenoma, hyperplastic polyps) (16%), and 74 had normal findings (27%).

Clinical characteristics and factors associated with pathologic findings in patients with CWT. Compared to the 74 patients with normal diagnosis (Table 1), subjects with abnormal findings were found to have an elevated platelet count (265 *vs* 228; $P = 0.03$). There was no statistically significant difference in terms of gender, race, BMI, tobacco use, BUN, AST, ALT, or focality of wall thickening among the two groups ($P > 0.05$). We examined the clinical characteristics and factors associated with CRC, ischemic colitis, IBD, inflammatory/infectious colitis, and other pathologies using univariate analysis. Only CRC and IBD were shown to be statistically significant, and thus the associated factors of CRC and IBD were further examined and presented in this study.

Clinical characteristics and factors associated with malignancy in patients with CWT. A total of 36 patients (13%) with CWT were diagnosed with CRC (Table 2). The most common indication for CT was abdominal

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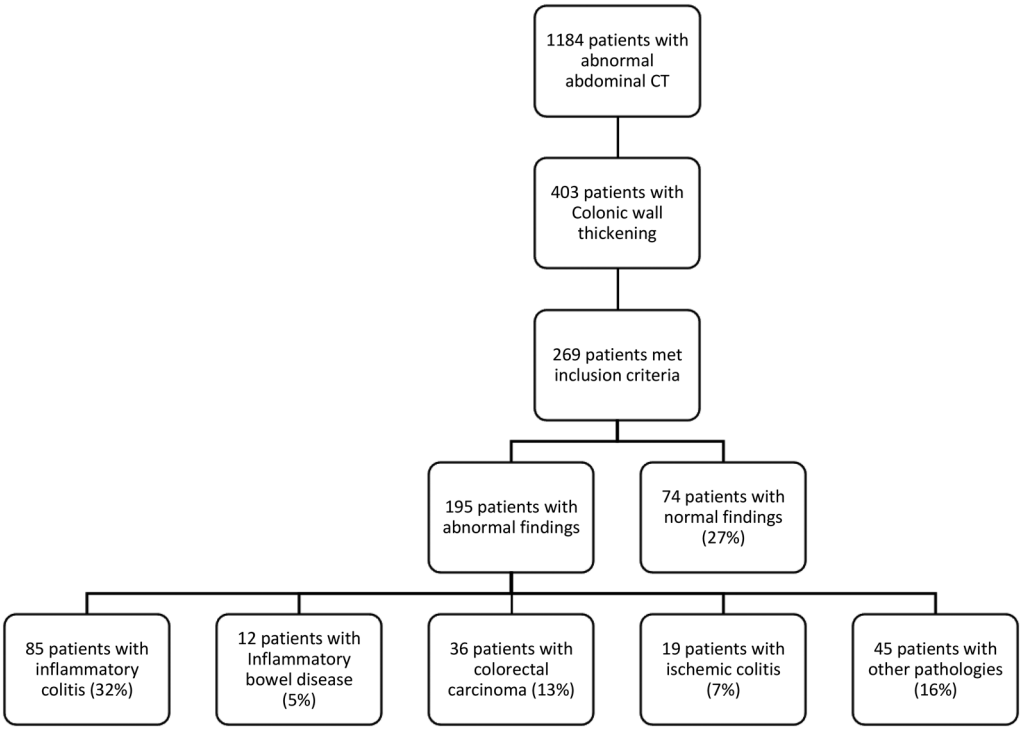

Figure 1 Flowchart of the subjects through the study.

Table 1 Baseline characteristics and laboratory findings of patients with colonic wall thickening with normal *versus* abnormal findings

Characteristics	Normal findings ($n = 74$)	Abnormal findings ($n = 195$)	*P*-value
Age, median (IQR)	54 (29)	60.5 (26)	0.09
Gender, male (%)	35 (47.3%)	104 (53.3%)	0.37
Race, African-American (%)	59 (79.7%)	148 (75.9%)	0.50
BMI ≥30, no. (%)	49 (66.2%)	148 (75.9%)	0.10
Tobacco use, no. (%)	31 (41.9%)	83 (42.9%)	0.92
Hematocrit, median (IQR)	37.8 (31.9, 43.7)	35.8 (30.3, 41.3)	0.50
Platelets, median (IQR)	229 (160, 297)	265 (202, 328)	0.03
BUN, median (IQR)	12 (6, 18)	12.5 (6, 18)	0.29
AST, median (IQR)	20 (10, 29)	20 (23)	0.66
ALT, median (IQR)	24 (14, 34)	23 (14, 32)	0.28
Albumin, median (IQR)	3.4 (2.9, 3.9)	3.2 (2.7, 3.7)	0.10
Localized CWT, no. (%)	144 (73.8%)	56 (75.7%)	0.75

Colonic wall thickening means significant thickening of the bowel wall based on the assessment of the radiologist reading the abdominal CT. Abnormal findings include inflammatory colitis, colorectal cancer, ischemic colitis, inflammatory bowel disease, diverticulosis, tubular adenoma, or hyperplastic polyps.

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CWT, colonic wall thickening; IQR, interquartile range.

pain (41%). Compared to patients without CRC, patients with CRC were found to be older (68 *vs* 56; $P < 0.05$), had a lower hematocrit (29 *vs* 36; $P < 0.05$), higher platelet count (340 *vs* 249; $P < 0.05$), lower albumin (2.8 *vs* 3.3; $P < 0.05$), and more frequent localized CWT (92 *vs* 72%; $P < 0.05$). There was no statistically significant difference in terms of gender, race, BMI, tobacco use, BUN, AST, and ALT levels among the two groups (all $P > 0.05$). On multivariable logistic regression (Table 3), low hematocrit (OR 0.86; CI 0.80–0.92), elevated platelet count (OR 1.003; CI 1.001–1.005), and localized CWT (OR 4.31; CI 1.06–17.59) were found to be independently associated with CRC in subjects with CWT (all $P < 0.05$). In ROC curve analysis of the independent variables (Fig. 2), the AUC for hematocrit, platelet count, and localized CWT was 0.773, 0.734, and 0.600, respectively. The AUC of multivariable regression analysis was 0.838.

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Table 2 Baseline characteristics and laboratory findings of patients with colonic wall thickening with CRC *versus* no CRC

Characteristics	No CRC ($n = 233$)	CRC ($n = 36$)	*P*-value
Age, median (IQR)	56 (43, 69)	68.5 (53, 83)	0.01
Gender, male (%)	119 (51.1%)	20 (55.6%)	0.61
Race, African-American (%)	180 (77.3%)	27 (75.0%)	0.76
BMI ≥30, no. (%)	168 (72.1%)	29 (80.6%)	0.28
Tobacco use, no. (%)	98 (42.1%)	16 (44.4%)	0.78
Hematocrit, median (IQR)	36.4 (31.9, 40.9)	28.95 (23.9, 33.9)	<0.01
Platelets, median (IQR)	249 (181.5, 316.5)	340 (249.5, 430.5)	<0.01
BUN, median (IQR)	12 (6, 17)	12.5 (8, 17)	0.86
AST, median (IQR)	20 (9.5, 30.5)	20 (5, 35)	0.93
ALT, median (IQR)	24 (14, 34)	18.5 (10, 26)	0.72
Albumin, median (IQR)	3.3 (2.8, 3.8)	2.85 (2.3, 3.3)	<0.01
Abdominal pain, no. (%)	18 (50%)	150 (64.4%)	0.097
Localized CWT, no. (%)	167 (71.7%)	33 (91.7%)	<0.01

Colonic wall thickening means significant thickening of the bowel wall based on the assessment of the radiologist reading the abdominal CT.
ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CRC, colorectal carcinoma; CWT, colonic wall thickening; IQR, interquartile range.

Table 3 Multivariable logistic regression analysis to determine factors independently associated with colorectal cancer and inflammatory bowel disease

	Colorectal carcinoma[†]		Inflammatory bowel disease[‡]	
Variables	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Hematocrit	0.86 (0.80–0.92)	<0.0001	1.14 (0.99–1.30)	0.05
Platelets	1.003 (1.001–1.005)	0.0378	1.009 (1.004–1.014)	0.01
Localized CWT	4.312 (1.06–17.59)	0.0416	—	—
Age	1.019 (0.99–1.05)	0.1438	0.86 (0.79–0.93)	0.01
AST	—	—	0.98 (0.95–1.01)	0.22

[†]Multivariable logistic regression model with colorectal cancer as the outcome.
[‡]Multivariable logistic regression model with IBD as the outcome.
AST, aspartate transaminase; CI, confidence interval; CWT, colonic wall thickening; IBD, inflammatory bowel disease.

Clinical factors associated with early-* versus *late-stage malignancy. Among patients with CRC, 20 (55%) were diagnosed with early-stage malignancy and 16 (45%) with late-stage malignancy with metastases. After comparing these two groups in terms of baseline characteristics, laboratory findings, and imaging findings, no significant differences were found ($P > 0.05$).

Clinical characteristics and factors associated with IBD in patients with CWT. A diagnosis of IBD was made in 12 patients (5%) with CWT. The most common indication for CT in these patients was abdominal pain (83%). When compared to patients without IBD (Table 4), those with IBD were found to be younger (median 30 *vs* 59; $P < 0.05$), had a higher hematocrit (median 40 *vs* 35; $P < 0.05$), higher platelet count (median 377 *vs* 256; $P < 0.05$), and a lower AST (median 14 *vs* 20; $P < 0.05$). No statistically significant difference was found in terms of gender, race, BMI, tobacco use, BUN, ALT levels, albumin, or localized thickening (all $P > 0.05$). On multivariable logistic regression (Table 3), younger age (OR 0.86; CI 0.79–0.93) and higher platelet count (OR 1.009; CI 1.004–1.014) were independently associated with IBD ($P < 0.05$). In the ROC curve of the analysis of the independent variables (Fig. 3), the AUC for age and platelet count was 0.909 and 0.692, respectively. The AUC of multivariable regression analysis was 0.932.

Discussion

To our knowledge, this study is the first and largest study to evaluate for predictive factors of clinically significant GI pathologies, including CRC and IBD, in patients with CWT in North America. Based on the ROC curve analysis, low hematocrit and high platelet count were found to have a strong predictive value for CRC in these patients (AUC >0.7).[15] Similarly, younger age was also found to have a strong predictive value for IBD in these patients (AUC >0.7). A predictive model including these variables could potentially be implemented in clinical practice, which may help guide physicians on how to manage patients with CWT.

CWT as a radiologic finding is frequently used in clinical practice and it can be commonly associated with a clinically significant pathology.[16–18] In our study, 34% of the patients with

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abnormal CT who underwent subsequent colonoscopy were found to have CWT. Of those patients with CWT, 73% had an abnormal colonoscopy and 18% of them had a clinically notable diagnosis of CRC or IBD. Our study population included a high number of African-Americans, which could possibly explain the high prevalence of pathology in patients with CWT, in accordance with previous studies. More specifically, a study by Patel *et al.* revealed a 2.5 times higher likelihood of detecting clinically significant pathology in African-Americans compared to Hispanics.[19] In addition, another study by Padda *et al.* analyzed a cohort of patients in which 60% were Hispanics and 40% were African-Americans and showed a high number of abnormal endoscopic findings in 65.5% of the total cohort with only 9% prevalence of malignancy.[8]

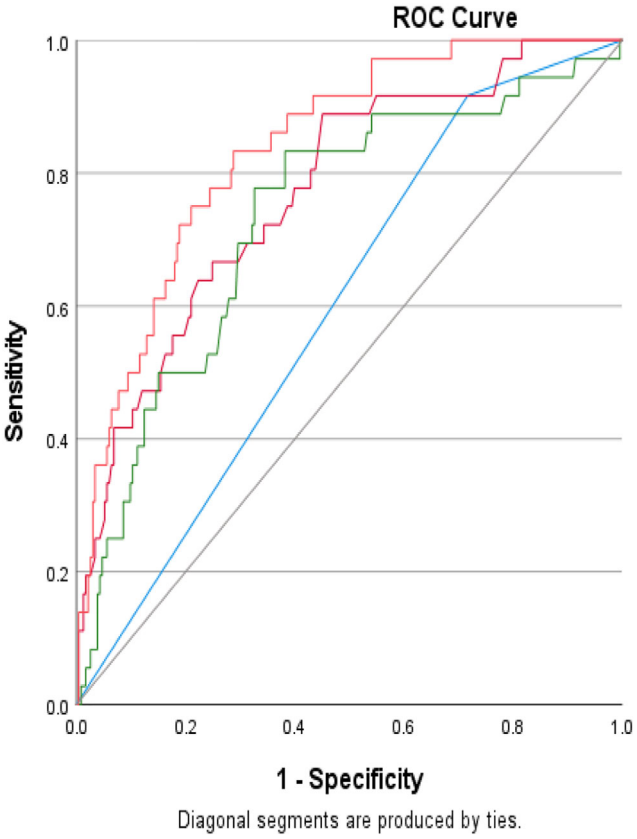

Figure 2 Receiver operating characteristic curve for predicting colorectal carcinoma in patients with colonic wall thickening. Source of the curve: ——, focal thickening; ——, hematocrit; ——, platelet count; ——, multivariable logistic regression; ——, reference line.

The high prevalence of abnormal colonoscopy findings in patients with CWT has also been reported in previous studies. Wolf *et al.* investigated 107 subjects and found that 74.9% of them had some identifiable pathology, including 9.3% with IBD and 7.4% with CRC.[6] It should be noted that this study included only patients who had a CT scan performed for an indication of abdominal pain. In another study, 165 subjects were analyzed; 58% of them had abnormal findings on the colonoscopy, while 22% were found to have CRC.[5] The higher prevalence of CRC in this cohort could potentially be attributed to the higher mean age (66 years) of the total group; however, it could also be due to the fact that it included patients with malignant biopsy from a site different from the one with CWT. In our study, we only included biopsy results from the site of CWT because we wanted to investigate and correlate the CT findings with the specific pathological findings on the colonoscopy with the biopsy at the same site or segment.

CWT is very important in clinical practice; however, no clear management guidelines exist for these patients. The elevated platelet count was found to be statistically significant in the group of patients with pathologic biopsy results. This finding has significant clinical implications and may potentially help guide clinicians to further investigate these patients with colonoscopy.

In our study, we have investigated any specific predictive factors of significant diagnoses in those patients with CWT and have identified potential predictive factors for CRC and IBD. In the case of CRC, low hematocrit, elevated platelet count, and

Table 4 Baseline characteristics and laboratory findings of patients with colonic wall thickening with inflammatory bowel disease (IBD) *versus* no IBD

Characteristics	No IBD ($n = 257$)	IBD ($n = 12$)	*P*-value
Age, median (IQR)	59.0 (26)	30.50 (14)	<0.01
Gender, male (%)	132 (51.4%)	7 (58.3%)	0.63
Race, African-American (%)	198 (77.0%)	9 (75.0%)	1.00
BMI ≥30, no. (%)	71 (27.6%)	1 (8.3%)	0.19
Tobacco use, no. (%)	109 (42.4%)	5 (41.7%)	0.95
Hematocrit, median (IQR)	35.70 (30, 40)	40.15 (36, 43)	0.02
Platelets, median (IQR)	256 (186, 325)	377 (194, 560)	0.02
BUN, median (IQR)	12 (6.5, 17.5)	10.5 (8)	0.50
AST, median (IQR)	20 (9, 31)	14.5 (10, 19)	0.01
ALT, median (IQR)	23 (13, 33)	20.5 (13, 28)	0.31
Albumin, median (IQR)	3.2 (2.7, 3.7)	3.15 (2.6, 3.6)	0.47
Abdominal pain, no. (%)	10 (83.3%)	158 (61.5%)	0.12
Localized CWT, no. (%)	194 (75.5%)	6 (50.0%)	0.08

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CWT, colonic wall thickening; IBD, inflammatory bowel disease; IQR, interquartile range.

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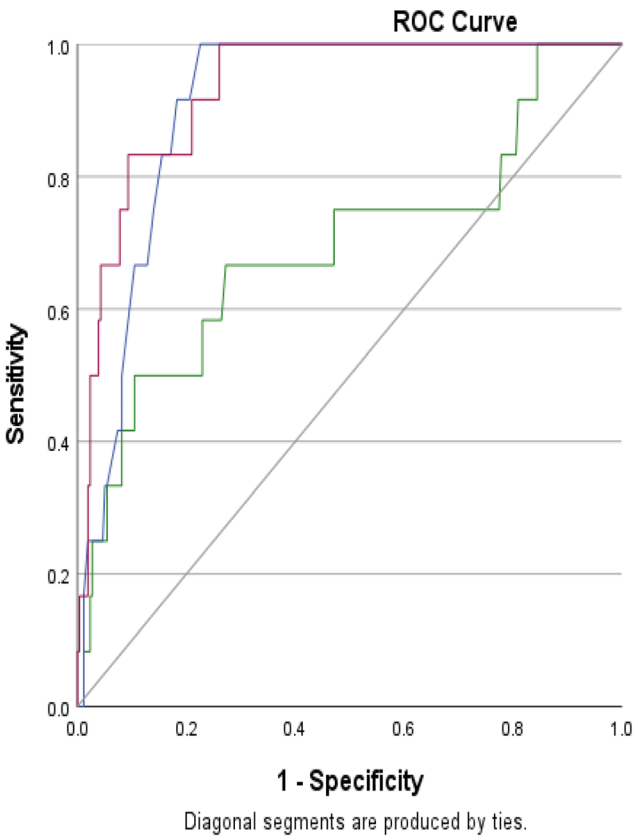

Figure 3 Receiver operating characteristic curve for model predicting inflammatory bowel disease in patients with colonic wall thickening. Source of the curve: ——, platelet count; ——, age (years); ——, multivariable logistic regression; ——, reference line.

localized CWT were independent risk factors in patients with CWT. Low hematocrit and elevated platelet count were found to have a strong predictive value in ROC curve analysis (AUC >0.7) as well. Anemia is known to be associated with malignancy[20]; it is also common practice that asymptomatic men and postmenopausal women with iron deficiency anemia are recommended to undergo colonoscopy.[21] Surprisingly, GI bleeding or anemia was the indication for CT only in 16% of the CWT patients with CRC in our study. Platelets have been associated with the development and progression of malignancies.[22] Many studies have suggested that platelet count could serve as potential marker in the diagnosis and prognosis of gastrointestinal cancer[23–25] because tumor cells produce factors that can promote platelet production.[26] In addition, activated platelets can release growth factors that lead to cancer cell growth.[27]

Even though the high prevalence of CRC in patients with CWT has been reported in multiple studies, only very few of them investigated the predictors of CRC. Akbas *et al.*[28] examined a cohort of 116 patients in a tertiary center and detected malignancy detected in 52 of them. They identified low hemoglobin and high platelets as possible risk factors for malignancy, which is in accordance with our study. The high percentage of cases with malignancy could be explained by the fact that this center had a large number of referred patients with an overall higher average age (63 years).

Another risk factor, localized CWT, is frequently associated with malignant processes, since most neoplasms of the GI tract present as a focal area of bowel wall thickening.[29] Bowel tumors may appear either as symmetric and regular or as asymmetric and irregular thickening.[30] On the other hand, localized and diffuse thickening of the bowel wall is usually caused by benign conditions.[30] Previous studies have suggested a correlation between localized CWT and neoplasia. Cai *et al.*[16] found four subjects with neoplasia that was localized in all cases, while Karacin *et al.*[7] showed that 63% cases of localized CWT had neoplasia and that focal and asymmetric CWT are independent risk factors for neoplasia. In our study, even though localized CWT did not have a strong predictive value based on the ROC curve, it was found to be independently associated with CRC based on our multivariable logistic regression.

Other factors associated with CRC in our univariate analysis included older age and low albumin levels. Advanced age is a known factor associated with CRC.[31] Albumin levels are also expected to be low in malignancy, possibly secondary to malnutrition, but also due to the body's systemic inflammatory response to malignancy resulting in hypoalbuminemia.[32] However, this significant association was not confirmed in our multivariable analysis.

For IBD, younger age and higher platelet count were identified as independent risk factors in patients with CWT in our study. Younger age was also found to have a strong predictive value for IBD in the ROC curve analysis (AUC >0.7). The age of onset for many patients with IBD is between 15 and 30 years, although it can present at any time with a possible smaller second peak during the fifth to seventh decades.[33] Elevated platelet count is a well-recognized marker of IBD activity, with associated elevation in thrombopoietin levels which stimulate platelet production.[34] Interleukin 6 levels have also been shown to contribute to reactive thrombocytosis in IBD.[35]

This study has several limitations. Our cohort included only patients with abnormal CWT who underwent colonoscopy within 30 days. As a result, CWT on abdominal CT in patients without further colonoscopic evaluation within 30 days was not examined. Thus, it is possible that physicians made the clinical decision to proceed with a colonoscopy based on certain clinical concerns, and hence these patients were more likely to demonstrate pathologic findings on colonoscopy. Furthermore, due to the retrospective nature of our study, potential bias and incomplete data collection may be present. Finally, our results are from a single-center academic setting with a disproportionate percentage of African-American patients compared to other centers and thus might not be generalizable to other clinical settings.

In summary, the present study is the first and largest study from North America to evaluate for predictive factors of significant GI pathologies, specifically IBD and CRC, in patients with CWT. High platelet count was found to be associated with abnormal pathology in patients with CWT, while elevated platelet count, low hematocrit, and localized thickening were found to be predictive of CRC. Additionally, high platelet count, young age, and low AST level were associated with IBD. These data could potentially be useful to clinicians and patients with their decision to proceed with colonoscopic evaluation. Further studies

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with larger study populations, including populations with increased race/ethnic diversity, will be necessary to better identify more precise predictors of IBD and CRC in patients with CWT.

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