ORIGINAL CONTRIBUTION

Clinical and Genetic Factors Associated With Complications After Crohn's Ileocolectomy

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BACKGROUND: Ileocolectomy is the most common surgery performed for Crohn's disease, and postoperative complications occur frequently. There has been minimal evaluation of complications after ileocolectomy as a function of both clinical and genetic factors.

OBJECTIVE: The purpose of this study was to evaluate both genetic and clinical factors associated with complications after Crohn's ileocolectomy.

DESIGN: This was a retrospective clinical and genetic cohort study.

SETTINGS: This study was conducted at a high-volume tertiary care center.

PATIENTS: We identified 269 patients with Crohn's disease who had undergone 287 ileocolectomies at our institution between July 2008 and October 2018.

MAIN OUTCOME MEASURES: We measured the association of complications with a combination of clinical factors and 6 Crohn's-associated single nucleotide polymorphisms in *NOD2* (rs2076756, rs2066844, and rs2066845), *IRGM* (rs4958847 and rs13361189), and *ATG16L1* (rs2241880).

RESULTS: There were 86 ileocolectomies of 287 (30%) with complications requiring intervention. The single nucleotide polymorphism rs13361189 in the gene *IRGM* was significantly associated with complications on univariate and multivariate analysis. There were 61 patients with a variant at the rs13361189 single nucleotide polymorphism and 26 of them had complications, although only 55 of the 208 wild-type patients had complications (43% vs 26%; OR = 2.1; $p = 0.02$). Other significant factors associated with complication after ileocolectomy were open surgery, placement of a proximal ileostomy, and a greater perioperative decrease in hematocrit.

LIMITATIONS: This study was limited by its retrospective design and inherent selection bias.

CONCLUSIONS: In addition to clinical risk factors, the rs13361189 single nucleotide polymorphism in the *IRGM* gene was independently associated with complications after ileocolectomy for Crohn's disease. The use of such genetic determinants may identify patients at increased risk for surgical complications after ileocolectomy. See **Video Abstract** at http://links.lww.com/DCR/B124.

FACTORES CLÍNICOS Y GENÉTICOS ASOCIADOS CON COMPLICACIONES DESPUÉS DE LA ILEOCOLECTOMÍA DE CROHN

ANTECEDENTES: La ileocolectomía es la cirugía más común realizada para la enfermedad de Crohn y con frecuencia ocurren complicaciones postoperatorias. Ha habido una evaluación mínima de complicaciones

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después de la ileocolectomía, en función de factores clínicos y genéticos.

OBJETIVO: Evaluar factores genéticos y clínicos asociados con complicaciones, después de la ileocolectomía por Crohn.

DISEÑO: Estudio retrospectivo de cohorte clínico y genético.

AJUSTES: Este estudio se realizó en un centro de atención terciaria de alto volumen.

PACIENTES: Identificamos a 269 pacientes con enfermedad de Crohn, sometidos a 287 ileocolectomías en nuestra institución, entre julio de 2008 y octubre de 2018.

PRINCIPALES MEDIDAS DE RESULTADO: La asociación de complicaciones con una combinación de factores clínicos y seis polimorfismos de un solo nucleótido asociados a Crohn en NOD2 (rs2076756, rs2066844 y rs2066845), IRGM (rs4958847 y rs13361189) y ATG16L1 (rs2241880).

RESULTADOS: Hubieron 86 ileocolectomías en 287 (30%) pacientes con complicaciones que requirieron intervención. El polimorfismo de un solo nucleótido rs13361189 en el gen IRGM se asoció significativamente con complicaciones en el análisis univariado y multivariado. Hubieron 61 pacientes con una variante en el polimorfismo de un solo nucleótido rs13361189 y 26 de ellos tuvieron complicaciones, mientras que solo 55 de los 208 pacientes de tipo salvaje (WT) tuvieron complicaciones (43% vs 26%, OR 2.1, p = 0.02). Otros factores significativos asociados con las complicaciones después de la ileocolectomía fueron, la cirugía abierta, la colocación de una ileostomía proximal y una mayor disminución perioperatoria del hematocrito.

LIMITACIONES: Este estudio estuvo limitado por su diseño retrospectivo y sesgo de selección inherente.

CONCLUSIONES: Además de los factores de riesgo clínicos, el polimorfismo de un solo nucleótido rs13361189 en el gen IRGM se asoció independientemente con complicaciones después de la ileocolectomía, para la enfermedad de Crohn. El uso de tales determinantes genéticos puede identificar a los pacientes con mayor riesgo de complicaciones quirúrgicas, después de la ileocolectomía. **Consulte Video Resumen** en http://links.lww.com/DCR/B124.
(Traducción—Dr. Fidel Ruiz Healy)

KEY WORDS: Crohn's disease; Genetics; Postoperative complications.

Crohn's disease (CD) is an inflammatory disease of the GI tract that is most commonly seen in Western countries, with a prevalence of ≈249 per 100,000.[1] Although the disease can involve any part of the GI tract, it most commonly affects the terminal ileum, which is involved in more than half of all patients.[2] Up to two thirds of patients with CD require surgical resection of diseased bowel.[3]

Postoperative complications after ileocolectomy for CD are common, with recent studies reporting rates of 20% to 35%.[4–6] Complications include surgical site infection, anastomotic leak, and intra-abdominal abscess.[5–8] Previous studies have identified several clinical risk factors for postoperative complications, including perforating disease, preoperative abscess, steroid use, and malnutrition.[4,6,9,10]

The majority of previous studies have not evaluated the association between genetics and postoperative complications after ileocolectomy, despite increasing evidence that several genes may be associated with adverse disease behavior. More than 150 single nucleotide polymorphisms (SNPs), or allele variants, have now been found to be associated with CD,[11] and studies have revealed possible associations between some of these SNPs (and their associated genes) and increased severity of CD. SNPs in *NOD2* are frequently found in CD and have been associated with early surgery, possibly because of an increased stricturing phenotype.[12] An SNP in *ATG16L1* has been associated with an increased risk of ileal disease, independent of *NOD2* variants.[13] In addition, an SNP in the *IRGM* gene was found to be associated with increased frequency of ileocolectomy.[14] All 3 of these genes encode proteins that participate in the innate immune system and contribute to autophagy that defends against enteric bacteria.[15]

There has been minimal study of the combination of genetic and clinical factors to possibly identify markers in patients with CD who are associated with postoperative complications. Therefore, this study evaluated selected genetic SNPs that have been associated with more severe disease phenotypes in concert with clinical factors to determine which, if any, may predispose the patient with CD to complications after ileocolectomy. We hypothesized that postoperative complications are not only associated with clinical factors but also a genetic predisposition, reflected by certain allele variants in genes contributing to the innate immune system.

PATIENTS AND METHODS

Patient Cohort

A retrospective review was performed on patients who had been prospectively recruited into the Institutional Review Board-approved Colorectal Diseases Biobank at the Pennsylvania State University College of Medicine. Patients were included if they had a diagnosis of CD and had undergone at least 1 ileocolectomy between July 2008 and October 2018. *Ileocolectomy* was defined as resection involving a contiguous region of small bowel and colon. Patients were excluded if diagnosed with any GI cancer or if they underwent total proctocolectomy or total abdominal

colectomy for CD. A total of 269 recruited patients with CD requiring a total of 287 ileocolectomies were identified. There were 16 patients who underwent 2 ileocolectomies over this 10-year time period and 1 patient who underwent 3 ileocolectomies.

Clinical characteristics gathered from the identified patients included sex, race, age, ASA physical status, BMI, and smoking status at surgery, as well as indication for surgery (abscess, fistula, nonresponsive to maximal medical management, obstruction, or perforation). Immunosuppressive medications used within 2 months of surgery were recorded. Each surgery was categorized as open, laparoscopic, or laparoscopic converted to open. The timing of each surgery was categorized as elective, emergent, or urgent (during a hospital stay for CD but not emergent). Whether a proximal ileostomy (loop or end) was created was also recorded. Preoperative white blood cell count, preoperative albumin, and change from preoperative to postoperative hematocrit were evaluated in association with complications. In addition, white blood cell count, hematocrit, and albumin at the time of discharge were recorded. Postoperative complications (including 30-d readmissions) were identified in the electronic medical chart and classified according to Clavien–Dindo grade.[16]

DNA Samples and Genotyping

All of the patients included in this study had previously donated whole blood samples using standard EDTA collection tubes to be stored in our Colorectal Disease Biobank. DNA was extracted from peripheral blood mononuclear cells using the NucleoSpin Blood L kit (Macherey-Nagel, Bethlehem, PA). DNA concentrations were measured using a NanoDrop 2000 spectrophotometer (Thermo Scientific, Waltham, MA), and working stocks were prepared in 10-mM Tris-HCL. We evaluated 6 SNPs within 3 genes for this study. These included rs2066844, rs2066845, and rs2076756 in *NOD2*; rs4958847 and rs13361189 in *IRGM*; and rs2241880 in *ATG16L1*. These SNPs were chosen because of previous reports associating them with increased severity of CD using various criteria.[12–14]

Samples procured in earlier stages of the biobank were genotyped using a customized DNA microarray developed by Illumina (San Diego, CA).[14] Our laboratory has previously described performing genotyping using this custom microarray run on Illumina's BeadXpress Reader in the Pennsylvania State College of Medicine Genome Sciences Facility.[14] For patient samples that had not been previously genotyped by the custom microarray (147 of the 269), a TaqMan assay was used. TaqMan Genotyping Master Mix (Thermo Scientific) was combined with Predesigned TaqMan SNP Genotyping Assays (C_11717468_20 for rs2066844, C_11717466_20 for rs2066845, C_15863571_20 for rs2076756, C_1398968_10 for rs4958847, C_31986315_10 for rs13361189, and C_9095577_20 for rs2241880), 10 ng of DNA, and water. Polymerase chain reaction was performed using the ABI QuantStudio12KFlex (Applied Biosystems, Foster City, CA).

TABLE 1. Complications by Clavien-Dindo grade

Grade	*Definition*	*n (%)*[a]
I/II	Medical management alone	66 (23%)
III	Required a procedure	11 (4%)
IV	Required intensive care	9 (3%)
V	Postoperative death	0 (0%)

Clavien–Dindo grading system and definitions are from Dindo et al.[16]
[a]Percentage represents the percent of the total number of ileocolectomies (N = 287).

Statistical Methods

The statistical analysis was conducted using R (*www.r-project.org*) and R Markdown (*www.rmarkdown.rstudio.com*). The SNPs in the Cox model were analyzed following an additive genetic association model. Quantitative data were expressed as mean and SE. Univariate analyses were performed using the R package compareGroups. Logistic regression was performed for the multivariate analysis. *P* values of <0.05 were considered statistically significant. To avoid bias created by including patients multiple times if they had multiple ileocolectomies, ORs of complications associated with studied SNPs were then calculated examining only the 269 patients, not the 287 ileocolectomies.

RESULTS

Complications after Crohn's Ileocolectomy

There were 86 ileocolectomies (30%) of 287 that resulted in complications requiring intervention. The complications by Clavien–Dindo grade are shown in Table 1. The top complications were surgical site infection, prolonged ileus leading to vomiting and/or requiring nasogastric tube placement, dehydration requiring readmission, and anastomotic leak and/or intra-abdominal abscess (Table 2). The overall mean length of stay for the entire cohort was 8.9 days, but this included preoperative days in the hospital for acutely ill patients who were optimized before definitive surgery.

Factors Associated With Postoperative Complications

Clinical and genetic factors were compared between ileocolectomy patients without complications and those with complications. These factors are shown in Table 3. Significant factors associated with complication after ileocolectomy by multifactorial analysis were open surgery, placement of a proximal ostomy, a greater perioperative decrease in hematocrit, and SNP rs13361189 in the gene *IRGM*. All of the stomas were proximal ileostomies, 60 of which were loop and 5 were end. Of the 269 patients, there were 61 with a variant at the rs13361189 SNP, and 26 of

TABLE 2. Types of complications

Complication	*n (%)*[a]
Surgical site infection	19 (6.7%)
Prolonged ileus	15 (5.2%)
Dehydration requiring readmission	11 (3.8%)
Leak and/or intra-abdominal abscess	10 (3.5%)
Other infectious (PNA, CDI, UTI)	10 (3.5%)
Anastomotic or intra-abdominal bleeding	6 (2.1%)
Venous thromboembolism	5 (1.7%)
In-hospital hypovolemia and/or renal failure	4 (1.4%)
Other	6 (2.1%)

PNA = pneumonia; CDI = Clostridium difficile infection; UTI = urinary tract infection.
[a]Percentage represents the percent of the total number of ileocolectomies (N = 287).

them (43%) had complications. In comparison, only 55 (26%) of the 208 wild-type patients had complications (OR = 2.1; $p = 0.02$). Of note, there was no association between preoperative immunosuppressive medications and postoperative complications. The length of stay was longer in the complication group than the no-complication group (mean: 10.6 vs 6.3 d; $p < 0.001$).

Readmission After Ileocolectomy

Of the 287 ileocolectomies evaluated, there were 31 readmissions (11%) within 30 days of discharge. Causes for readmission are included in Table 4. Two patients with an anastomotic leak required radiologic guided drainage, and an additional patient required return to the operating room for drainage and diverting loop ileostomy. An additional operation was performed for wound dehiscence. A comparison of the readmission group to the no-readmission group is shown in Table 5. Significant factors associated with readmission on univariate analysis were open surgery, presence of a proximal ostomy, and a lower hematocrit and albumin level before discharge. However, only the presence of a proximal ileostomy was independently associated with readmissions ($p = 0.03$) on multivariate analysis.

DISCUSSION

The most unique aspect of this study is the evaluation of possible genetic associations with complications after ileocolectomy in patients with CD. The recent discovery of Crohn's-associated SNPs has led to many studies attempting to increase the understanding of the underlying etiology of CD and identify potential markers that could distinguish patient subsets. Although there have been many recent studies attempting to identify genetic associations with various clinical phenotypes, only 1 small study has evaluated the association between SNPs and postoperative complications in CD.[17] Although it did find an association between a variant in *NOD2*, the study evaluated 137 patients, of which only 78 patients underwent ileocolectomy, and <10% of patients were managed with biological medications before surgery.[17] Our study differs in that it provides data from a larger cohort of more surgically uniform patients who underwent ileocolectomy only. In addition, our study was performed over a more recent timeframe, leading to a higher percentage of patients on biological therapy before surgery (51% in our study vs 9.5% in the previous study). This more closely reflects contemporary management, with recent studies on surgical complications measuring preoperative biological therapy rates of 25% to 44%.[4,6,9]

Of the 6 Crohn's-associated SNPs evaluated in our study, only rs13361189 in *IRGM* was associated with increased postoperative complications. IRGM is an immunity-related GTPase that is stimulated by the interferon-ϒ pathway to induce autophagy.[18,19] In general, SNPs in genes involved in the autophagy pathway are more specific to CD (are found less commonly in ulcerative colitis)[20] and have been proposed as potential markers of disease severity in CD.[21] *NOD2* mutations have been associated with younger CD onset, ileal involvement, ileocolectomies, and increased recurrence after surgery.[22] An allele variant in the *ATG16L1* gene is associated with stricturing disease, early disease recurrence, and earlier need for immunosuppressants.[23] Our own group has shown previously that the rs4958847 SNP in the *IRGM* gene is associated with increased frequency of ileocolectomy in CD.[14] The physiological basis of the relationship between the autophagy pathway and CD severity is unclear, but it has been suggested that defects in the autophagy pathway could lead to decreased protection against bacterial infection, as well as chronic inflammation in CD.[24]

Previously, the identification of high-risk patients who warrant the institution of biological therapy to decrease the need for surgery or delay recurrence after surgery has been based on clinical criteria alone (smoking status, early age of onset, and stricturing phenotype). However, with increasing data implicating certain SNPs as markers of increased risk for either recurrent surgery or complications after surgery, such determinants could be used to augment clinical criteria and therefore affect clinical and surgical decision-making. Thus, the finding of an association between *IRGM* and increased complications in this study is consistent with the concept that variants in this gene are associated with a more severe phenotype of CD in general and might be used as a marker to identify higher-risk surgical patients. It is unclear why different SNPs in the autophagy pathway are found between our study and others assessing disease severity, but it could be because of genetic differences in populations and variable linkage disequilibrium. A larger multicenter genetic study may help clarify such discrepancies.

The complication rate of 30% after ileocolectomy for CD found in our study is comparable to the 20% to 35% rate of complications cited by current literature.[4–6] In our study, anastomotic leak and/or intra-abdominal abscess

TABLE 3. Factors associated with complication

Characteristics	*No complications (N = 201)*	*Complications (N = 86)*	*Univariate analysis p*	*Multivariate analysis p*
Men, n (%)	90 (44.8%)	39 (45.3%)	1	0.57
White, n (%)	188 (93.5%)	80 (93.0%)	1	0.70
Age at surgery, mean ± SE, y	37.1 ± 1.0	39.7 ± 1.0	0.20	0.46
Smoking at surgery, n (%)	48 (23.9%)	23 (26.7%)	0.71	0.85
Indication, n (%)			0.65	0.30
Abscess	25 (12.4%)	15 (17.4%)		
Fistula	32 (15.9%)	11 (12.8%)		
Nonresponsive	37 (18.4%)	12 (14.0%)		
Obstruction	100 (49.8%)	44 (51.2%)		
Perforation	7 (3.5%)	4 (4.7%)		
Type of surgery, n (%)			0.002*	0.02*
Laparoscopic	109 (54.2%)	27 (31.4%)		
Laparoscopy converted	16 (7.96%)	8 (9.30%)		
Open	76 (37.8%)	51 (59.3%)		
Proximal ileostomy, n (%)	33 (16.4%)	32 (37.2%)	<0.001*	0.002*
Timing of surgery, n (%)			0.53	0.51
Elective	171 (85.1%)	69 (80.2%)		
Emergent	5 (2.5%)	3 (3.5%)		
Urgent	25 (12.4%)	14 (16.3%)		
ASA status, n (%)			0.52	0.86
Class 2	113 (56.2%)	45 (52.3%)		
Class 3	85 (42.3%)	41 (47.7%)		
Class 4	3 (1.5%)	0 (0%)		
BMI, mean ± SE	25.7 ± 0.5	25.7 ± 0.8	0.92	0.80
Immunomodulators, n (%)	49 (24.4%)	22 (25.6%)	0.95	0.82
Biologics, n (%)	105 (52.2%)	41 (47.7%)	0.56	0.28
Prednisone, n (%)	96 (47.8%)	45 (52.3%)	0.56	0.66
IV steroids, n (%)	50 (24.9%)	25 (29.1%)	0.55	0.43
Preoperative WBC, mean ± SE	8.7 ± 0.2	9.5 ± 0.3	0.22	0.86
ΔHCT, mean ± SE	–4.2 ± 0.2	–5.2 ± 0.3	0.06	0.02*
Preoperative albumin, mean ± SE	3.8 ± 0.04	3.8 ± 0.05	0.60	0.49
Length of stay			<0.001*	NA
Mean ± SE	6.3 ± 0.3	10.6 ± 0.7		
Median, d	4	7		
NOD2 SNPs, n (%)				
rs2066845 variants	17 (9.9%)	4 (5.9%)	0.46	0.56
rs2076756 variants	123 (64.8%)	54 (69.3%)	0.72	0.59
rs2066844 variants	43 (23.1%)	19 (25.0%)	0.89	0.48
IRGM SNPs, n (%)				
rs13361189 variants	35 (18.7%)	26 (32.1%)	0.01*	0.049*
rs4958847 variants	36 (23.0%)	23 (33.8%)	0.20	0.56
ATG16L1 SNP, n (%)				
rs2241880 variants	116 (65.2%)	49 (65.4%)	0.32	0.14

SNP = single nucleotide polymorphism; ΔHCT = change in hematocrit; WBC = white blood cell count; NA = not applicable.
*Data show a significant *p* value of <0.05.

occurred in only 3.5% of surgeries, less than most other studies, which report rates of 8.0% to 10.0%.[4,6] One of these studies excluded patients who received protective ileostomies,[4] and another had ileostomies created in 16% of surgeries,[6] although our study had ileostomies in 23% of the surgeries. However, dehydration requiring readmission was common in our patients, and more than half of those patients who were readmitted for hydration had received diverting stomas. It is recognized that ileostomy creation is a risk factor for readmission because of dehydration.[25] The maximum resected ileum in ileocolectomies complicated by readmission because of dehydration was 26 cm, and only 1 of these patients had a previous ileocolectomy, making dehydration because of severely shortened small bowel less likely. It is difficult to determine the reason for ostomy creation from a retrospective study such as this, but the presence of local fistula/abscess or tissue sepsis was likely a contributing factor that necessitated creation. So although an ostomy may be protective and lead to a lower risk of anastomotic leak, it can lead to other complications, specifically dehydration and readmission.

Open surgery and increased intraoperative blood loss were also found to be associated with postoperative complications in our study. Open surgery (versus min-

TABLE 4. Causes for readmission

Cause	*n (%)*[a]
Dehydration	11 (35%)
Intra-abdominal abscess and/or anastomotic leak	5 (16%)
Wound complications	5 (16%)
Venous thromboembolism	3 (10%)
Ileus or small bowel obstruction	3 (10%)
Clostridium difficile infection	1 (3%)
Incarcerated inguinal hernia	1 (3%)
Malnutrition/failure to thrive	1 (3%)
Pleural effusion	1 (3%)

[a]Percentage represents the percent of the total number of readmissions (N = 31).

imally invasive surgery) has been associated with complications or delay in return of bowel function in other studies.[9,26,27] However, these findings probably simply reflect patients who for various reasons are not good laparoscopic candidates. Increased intraoperative blood loss has not been specifically evaluated in terms of postoperative complications in CD, but a previous study has shown association of overall complication risk with blood transfusion.[4] It is unlikely that such an association is specifically related to transfusion directly but is more likely related to blood loss associated with a difficult operative procedure, such as a phlegmon or adhesions from previous surgery.

TABLE 5. Factors associated with readmission

Characteristics	*No readmission (N = 256)*	*Readmission (N = 31)*	*Univariate analysis p*	*Multivariate analysis p*
Men, n (%)	113 (44%)	16 (52%)	0.45	0.99
White, n (%)	240 (94%)	28 (90%)	0.44	0.80
Age at surgery, mean ± SE, y	37.5 ± 0.8	40.6 ± 2.6	0.16	0.33
Smoking at surgery, n (%)	61 (24%)	10 (32%)	0.69	0.91
Indication, n (%)			0.29	0.14
Abscess	34 (13%)	6 (19%)		
Fistula	40 (16%)	3 (10%)		
Nonresponsive	45 (18%)	3 (10%)		
Obstruction	128 (50%)	16 (52%)		
Perforation	9 (4%)	3 (10%)		
Type of surgery, n (%)			0.04*	0.19
Laparoscopic	128 (50%)	8 (26%)		
Lap converted	20 (8%)	4 (13%)		
Open	108 (42%)	19 (61%)		
Proximal ileostomy, n (%)	52 (20%)	13 (42%)	0.01*	0.03*
Timing of surgery			0.29	0.42
Elective, n (%)	217 (85%)	23 (74%)		
Emergent	32 (13%)	7 (23%)		
Urgent	7 (3%)	1 (3%)		
ASA status, n (%)			0.52	0.55
Class 2	143 (56%)	15 (48%)		
Class 3	110 (43%)	16 (52%)		
Class 4	3 (1%)	0		
BMI, mean ± SE	25.8 ± 0.4	25.1 ± 1.1	0.63	0.36
Immunomodulators, n (%)	64 (25%)	7 (23%)	1	0.45
Biologics, n (%)	132 (52%)	14 (45%)	0.57	0.53
Prednisone, n (%)	124 (48%)	17 (55%)	0.57	0.61
IV steroids, n (%)	64 (25%)	11 (35%)	0.28	0.62
WBC before discharge, mean ± SE	10.7 ± 0.2	12.0 ± 0.9	0.07	0.13
HCT before discharge, mean ± SE	34.1 ± 0.3	32.1 ± 1.0	0.02*	0.47
Albumin before discharge, mean ± SE	3.2 ± 0.03	3.0 ± 0.1	0.01*	0.78
NOD2 SNPs, n (%)				
rs2066845 variants	19 (7%)	2 (6%)	1	0.34
rs2076756 variants	155 (61%)	22 (71%)	0.33	0.55
rs2066844 variants	56 (22%)	6 (19%)	1	0.54
IRGM SNPs, n (%)				
rs13361189 variants	52 (20%)	9 (29%)	0.25	0.18
rs4958847 variants	52 (20%)	7 (22%)	0.81	0.11
ATG16L1 SNPs, n (%)				
rs2241880 variants	147 (57%)	18 (58%)	1	0.37

SNP = single nucleotide polymorphism; HCT = hematocrit; WBC = white blood cell count.
*Data include a significant *p* value of <0.05.

In addition, although statistically significant in our study, the drop of an additional point of hematocrit in the complication group may not be clinically significant in and of itself. Thus open surgery, stoma placement, and perioperative bleeding are all factors that could indicate a complex patient with aggressive or severe disease. Although low albumin was not associated with complications in our study, a lower albumin before discharge was associated with readmission on univariate analysis. This supports previous studies that show lower albumin and worse nutritional status influence postoperative outcomes.[9,28] Our study may not have found a strong association between nutrition and postoperative outcomes because operative management of patients with IBD increasingly includes optimizing them before undergoing ileocolectomy, often with nutrition supplementation.[29] We have no standard protocol for preoperative nutritional optimization at our institution, but ad hoc optimization does occur and therefore probably contributes to some preselection in this study.

There were some limitations to this study. First, the retrospective nature of this study allowed for preselection bias to play a role in the clinical factors assessed. However, because the genetic status of the patients was unknown at the time of surgery, the genetic portion of this study does not experience this limitation. This study is also much smaller than larger-scale genome-wide association or genetic population studies, which prohibit subgroup analyses of different categories of complications because of the small overall percentage of individual categories. Finally, the single-center nature of this study only represents a small subgroup of the overall population undergoing ileocolectomy. Such studies need to be replicated in larger, broader-based populations.

CONCLUSION

Our evaluation of 287 ileocolectomies performed for CD found a complication rate of 30%, which is comparable to the prevalent literature. An evaluation of factors associated with these complications revealed clinical factors that likely reflect the severity of disease in these patients with CD. In addition, the SNP rs13361189 in the *IRGM* gene was independently associated with postoperative complications. This study adds to increasing evidence that allele variants involved in the autophagy pathway identify patients with CD with increased risk for more aggressive disease behavior. This is one of the first studies to evaluate genetic factors associated with complications after Crohn's ileocolectomy and suggests that genetic SNPs involved in the autophagy pathway, such as rs13361189, could be used in addition to clinical risk factors in preoperative patient education, as well as perioperative decision-making and management.

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