

Original Article



Causes of Colectomy in Patients with Ulcerative Colitis: Findings from an Iranian National Registry

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Abstract

Background: Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) marked by rectal and colon inflammation, leading to relapsing symptoms. Its prevalence is increasing, particularly in developed nations, impacting patients' health. While its exact cause remains unclear, genetic and environmental factors are implicated, elevating the risk of colorectal cancer (CRC). Colectomy, though declining, is still performed in select UC cases, necessitating further study.

Methods: We analyzed data from the Iranian Registry of Crohn's and Colitis (IRCC) to examine UC patients undergoing colectomy. We collected demographic and clinical data from 91 patients, focusing on dysplasia. Statistical analyses assessed dysplasia risk factors.

Results: Patients with dysplasia were older at diagnosis and surgery compared to those without dysplasia. Age emerged as a significant risk factor for dysplasia in UC patients undergoing colectomy. No significant associations were found between dysplasia and other factors.

Conclusion: Age plays a crucial role in dysplasia risk among UC patients undergoing colectomy. Older age at diagnosis and surgery may indicate a higher risk of dysplasia and CRC. Clinicians should consider age when managing UC patients and implementing screening protocols. Further research with larger samples is needed to confirm these findings.

Keywords: Colectomy, Dysplasia, Ulcerative colitis

Cite this article as: Momayez Sanat Z, Vahedi H, Malekzadeh R, Kasaeian A, Mohammadi Ganjaroudi N, Sima A, et al. Causes of Colectomy in Patients with Ulcerative Colitis: Findings from an Iranian National Registry. Arch Iran Med. 2024;27(7):350-356. doi: 10.34172/aim.28887

Received: February 2, 2024, Accepted: June 5, 2024, ePublished: July 1, 2024

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Introduction

Ulcerative colitis (UC) stands as a distinctive subtype within the spectrum of inflammatory bowel diseases (IBD), characterized by initial involvement of the rectum, often progressing contiguously to affect the colon.¹ Lesions characteristic of UC manifest superficially, with inflammation predominantly confined to the mucosal and submucosal layers.² UC occurs in a relapsing and remitting form.³ Patients with UC can present with intestinal manifestations such as bloody diarrhea, abdominal pain, tenesmus, and fecal urgency, or extra-intestinal symptoms such as musculoskeletal, cutaneous, and hepatobiliary manifestations.^{4,5}

Over recent years, the prevalence of UC has witnessed a surge, with North America and Europe registering the highest prevalence rate.⁶⁻⁸ Moreover, increased prevalence of UC has been reported in industrialized countries.^{9,10} Previous studies have reported UC prevalence and incidence ranging from 7.6 to 245 and 1.2 to 20.3 cases per 100 000 individuals per year, respectively.¹¹⁻¹⁴ The exact etiologies of UC are unknown, but it is believed that genetics play an essential role in the development of the disease.¹⁵ Reports indicate a four-fold higher risk of UC among first-degree relatives of affected individuals.¹⁴ Additionally, environmental factors exert significant influence on UC progression, with diet, certain medication use, vitamin D levels, stress, and smoking history implicated as potential risk factors.¹⁶ UC is associated with an increased risk of malignancies.¹⁷ Estimates suggest a progressive increase in colorectal cancer (CRC) risk with disease duration, reaching 2%, 8%, and 18% at 10, 20, and 30 years, respectively.¹⁸ Notably, CRC accounts for a significant proportion (10–15%) of mortality in IBD cases.¹⁹ Risk factors for CRC in UC patients include disease extent, duration, concurrent primary sclerosing cholangitis, and family history of CRC.^{18,20-22}

Although the development of new biologic therapies has reduced the need for surgical procedures, a significant number of patients still undergo operations such as colectomy.²³⁻²⁸ Indications for colectomy include failure of medical therapy, increased risk of cancer, fulminant colitis, toxic megacolon, and intensive extra-intestinal manifestations.²⁹

The Iranian Registry of Crohn's and Colitis (IRCC) is a multicenter prospective registry that aims to provide a better understanding of the natural history, phenotype, treatment response, complications, and survival of IBD patients in Iran.³⁰ The colectomy data from this registry have not been reported previously. In this regard, in the current study, we retrospectively examined the baseline characteristics and the presence of identified risk factors for colectomy among all UC patients in the IRCC database.

Materials and Methods

Study Design

The present study is a cross-sectional, national registry-based study that includes all patients with an established UC diagnosis who were registered in IRCC. UC diagnosis was based clinical, radiological, colonoscopic, and pathologic findings according to international guidelines for IBD diagnosis. The detail of IRCC has been published elsewhere.³⁰ In this registry, a total of 5721 UC patients were enrolled between 2017 and 2022. Among them, 153 patients underwent colectomy, with 91 of these individuals consenting to participate in the present study (Figure 1).

Study Participation and Data Collection

This study targeted UC patients aged 18 or higher who had undergone colectomy regardless of reason. After obtaining informed consent from the patients, demographic and clinical characteristics were collected

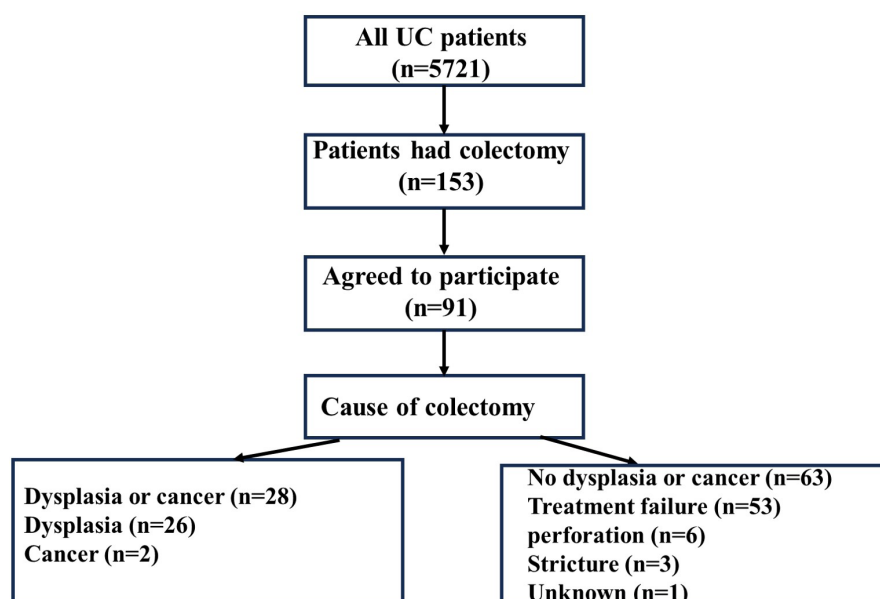


Figure 1. Flowchart of the included patients

from medical records. The collected information included demographic characteristics, disease extent, extra-intestinal manifestations, IBD medication history, cause of colectomy, and type of colectomy (elective vs emergency).

Statistical Analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 16. Descriptive statistics, including mean and standard deviation, were utilized for reporting quantitative variables. The chi-square test was employed for categorical variables, while the independent *t* test was used for continuous variables. Univariate logistic regression was conducted to assess differences between the two groups. Statistical significance was set at $P < 0.05$.

Results

The patients' flowchart, illustrated in Figure 1, outlines the enrollment process, culminating in the inclusion of 91 UC patients in our study. Among these participants, 49 (55.6%) were male. Of the 91 patients admitted, 28 were diagnosed with cancer or dysplasia, while 63 were not. Among the 63 patients whose colectomy was not attributed to dysplasia, 53 (83.9%) experienced treatment failure, 6 (9.4%) encountered perforation, 3 (4.6%) developed strictures, and 1 (1.2%) had an indeterminate cause. The mean age of participants was 54.3 ± 13.6 years in the dysplasia group and 43.6 ± 12.1 years in the non-dysplasia group. Table 1 presents the demographic characteristics of the two study groups based on cause of colectomy (dysplasia vs non-dysplasia), while Figure 2 delineates the age at diagnosis distribution of the two study groups.

Table 2 delineates the pharmacological regimens administered to the patients. Interestingly, no significant difference was observed between patients whose initial treatment involved biological agents and those who received other medications. Furthermore, no statistically significant association was found between the duration of medication use and the occurrence of dysplasia. Mesalazine emerged as the most commonly prescribed initial drug, with a notable proportion of patients with dysplasia having received this medication. Among those who progressed to the second and third stages of drug therapy, none of the six individuals treated with Infliximab were diagnosed with dysplasia. Conversely, only one out of fifteen patients who received Azathioprine exhibited dysplasia. The primary reason for transitioning from the initial drug regimen was treatment failure in 44 patients, while adverse drug reactions prompted a change in medication for 11 individuals, and non-compliance was cited as the reason in 2 cases.

Table 3 show the extra-intestinal manifestations in the two groups. Statistical analysis showed no statistically significant difference between the two groups in any of the extra-intestinal manifestations.

According to the findings derived from the univariate

Table 1. Baseline Characteristics of the Study Population

Variable		All Cases with Colectomy (n=91)		P Value
		No Dysplasia (n=63)	Dysplasia (n=28)	
Age	<55 years	51	15	<0.001
	>55 years	12	13	
BMI	Mean (SD)	24.5 (3.4)	25.7 (3.1)	0.35
Age at diagnosis	Mean (SD)	29.2 (12.1)	36.2 (14.1)	<0.001
Duration of disease	Mean (SD)	14.5 (8.6)	18.1 (8.7)	0.077
Gender	Male	33	17	0.46
	Female	30	11	
Marital status	Single	10	3	0.74
	Married	52	25	
Education level	Less than 12 years	8	9	0.09
	12 years	32	11	
	More than 12 years	23	8	
Ethnicity	Persian	44	24	0.43
	Kurd	1	1	
	Lor	6	1	
	Turk	11	2	
	Baluch	1	0	
Blood group	A	19	7	0.66
	AB	3	1	
	B	14	6	
	O	20	9	
	Unknown	6	4	
Extension of disease	Left colitis	4	2	0.96
	Pancolitis	56	23	
	Unknown	2	1	
UC diagnosis	Inpatient	8	4	0.83
	Outpatient	55	24	
Type of colectomy	Elective	57	26	0.99
	Emergent	6	2	
Smoking	Yes	9	7	0.36
	No	54	21	
Opium use	Yes	1	1	0.55
	No	62	27	
Alcohol use	Yes	3	1	0.81
	No	60	27	
History of blood transfusion	Yes	45	12	0.12
	No	18	16	
History of CMV colitis	Yes	2	0	0.34
	No	61	28	
Family history of UC	Yes	21	7	0.42
	No	42	21	

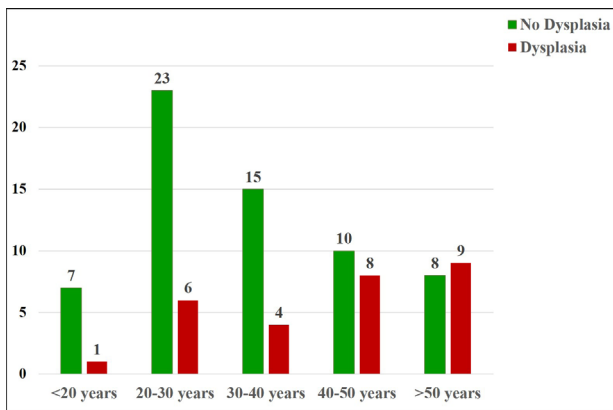


Figure 2. Age at diagnosis

Table 2. Treatment Steps of the Study Population

Steps of Treatment	Dysplasia	No Dysplasia or Cancer
First		
Azathioprine	2	0
Mesalazine	52	20
Sulphasalazine	8	5
Second		
Azathioprine	10	1
CinnoRA®	4	4
Infliximab	5	0
Mesalazine	5	3
Sulphasalazine	8	1
Third		
Azathioprine	2	0
CinnoRA®	5	1
Infliximab	1	0

analysis, as depicted in Table 4, several factors were found to be significantly correlated with an increased risk of dysplasia or cancer in UC patients undergoing colectomy. Notably, age (OR=1.06), age at the time of diagnosis of the disease (OR=1.04), and age at the time of surgery (OR=1.06) demonstrated statistically significant associations with the heightened risk of dysplasia or cancer.

However, other demographic and clinical variables, including gender (OR=1.40), marital status (OR=1.47), duration of disease (OR=2.61), education level (OR=0.87), BMI (OR=1.11), smoking (OR=1.76), and non-steroidal anti-inflammatory drugs, did not exhibit a significant association with dysplasia in UC patients undergoing colectomy.

Discussion

UC is a subgroup of IBD, which causes inflammation, production of reactive oxygen species (ROS), and increased epithelial cell turnover, resulting in low-grade dysplasia, high-grade dysplasia, and consequently CRC.³¹⁻³³ The relationship between UC and CRC has

Table 3. Comparison of Extra-intestinal Manifestations in the Two Groups

Extra-Intestinal Manifestation	Dysplasia (n=28)	No Dysplasia (n=63)	P Value
Articular disease	1 (3.8)	2 (7.6)	0.941
Autoimmune hepatitis	1 (3.8)	0 (0.0)	0.248
Ophthalmologic disease	1 (3.8)	3 (4.8)	0.857
Primary sclerosing cholangitis	2 (7.6)	2 (3.2)	0.578
Perianal abscess	0 (0.0)	1 (1.6)	0.928

Table 4. Results of Univariate Analysis

Factor	Odds Ratio	95 % CI	P Value
Age	1.06	1.02–1.11	0.001
Age at diagnosis	1.04	1.00–1.08	0.019
Age at surgery	1.06	1.02–1.11	0.002
Gender (Male/Female)	1.40	0.55–3.57	0.475
Duration of disease	2.61	0.98–6.78	0.07
Marital status (Married/Single)	1.47	0.37–5.86	0.581
Education Level	0.87	0.73–1.03	0.123
Body mass index	1.11	0.96–1.28	0.135
Smoking (Yes/No)	1.76	0.55–5.60	0.361
Non steroid anti-inflammatory drugs (Yes/No)	1.25	0.41–3.78	0.774

been established in previous studies.^{18,34,35} The prevalence of CRC in UC patients was reported at 3.7%³⁶; however, in our study, the prevalence of colorectal dysplasia and cancer was 31.1%. In one meta-analysis, the incidence of CRC in UC patients was reported at 1.58 per 1000 patients per year.³⁷ In a meta-analysis by Eaden et al, the incidence of CRC in UC patients was reported at 2%, 8% and 18% in 10 years, 20 years and 30 years, respectively.³⁸ As a result of the occurrence of CRC, UC patients should be followed up based on surveillance protocols, although with the advent of new therapies including biologic agents, the risk of CRC in UC patients has declined.³⁹⁻⁴¹ If malignant lesions are found in the follow-up tests, surgery is considered an option.^{28,29} Another indication for surgery in UC patients is when patients are not responding to pharmacological treatment.^{29,42} Although with the advent of new therapies and treatment protocols, the need for surgery has declined, a significant number of patients undergo surgery.⁴²⁻⁴⁴

In this study, our objective was to assess the risk factors of dysplasia in UC patients who underwent colectomy. We evaluated 12 factors, among which three factors showed significant associations with an elevated risk of neoplasia in UC patients: patient's age, age at the time of diagnosis, and age at the time of surgery.

Based on the results of this study, UC patients who underwent colectomy due to dysplasia were significantly older than those who underwent colectomy due to other reasons. Moreover, they were significantly older at the time of diagnosis and surgery. This finding implies a higher chance of CRC in older UC patients than young ones. The results of other studies are conflicting. In a

cohort study on UC patients, Gyde et al reported that the highest chance of cancer in a UC patient is expected to occur at around 50.⁴⁵ In another retrospective study by Karvellas et al, UC patients diagnosed after the age of 40 were at higher risk of CRC than UC patients diagnosed before the age of 40.³⁴ Bamba and Nishiyama showed the higher risk of CRC in elderly UC patients.⁴⁶ The increased cancer risk in older patients can be attributed to lead-time bias and pathological processes. The chance of undiagnosed colitis for a longer duration is higher in older UC patients.³⁴ Moreover, carcinogenesis processes develop at advanced ages, like DNA hypermethylation which has a potential role in colonic neoplasia.⁴⁷

Our study revealed no significant association between blood group and the risk of dysplasia in UC patients. This finding aligns with research conducted by Al-Sawat, which found no statistical difference in the relationship between blood group types and CRC risk.⁴⁸ Similarly, Khalil et al observed no significant difference between blood group types and the risk of CRC in their study.⁴⁹

In our study, the ethnicity of the patients was not a risk factor for occurrence of dysplasia in UC. Ethnicity can play an important role in the development of UC.^{12,50-52} Studies showed that ethnicity can also affect the incidence and prevalence of CRC.^{53,54} In a study by Damas et al, the prevalence of IBD-related dysplasia was significantly affected by ethnicity.⁵⁵

In our study, we did not find smoking to be a significant risk factor for dysplasia in UC patients. However, our sample size was small, so caution is advised in interpreting these results. The impact of smoking on UC remains controversial, with current smoking being potentially protective while former smoking may pose a risk.⁵⁶ Smoking is thought to be a risk factor for CRC. A recent meta-analysis showed former smokers, and current smokers to be at higher risk of CRC.⁵⁷ In a recent retrospective cohort study, former smokers were at increased risk of colorectal neoplasia in the UC population, while passive smoking had no significant effect.⁵⁸ Due to the divergent impact of smoking on the UC severity and risk of CRC, we suggest further studies to assess the pooled results of cigarette smoking on CRC among UC patients.

In this study, positive family history of UC was not significantly associated with increased risk of CRC in UC patients. This finding is consistent with the result of a cohort study by Askling et al in which although a positive family history of CRC was associated with increased risk of CRC in the IBD population, no significant relation was found for family history of IBD.²²

Our study did not find a significant difference in the prevalence of extra-intestinal manifestations of UC between patients with cancer and those without, contrary to previous findings indicating an increased cancer risk in IBD patients with extra-intestinal manifestations.⁵⁹ We believe the small sample size of our study is one of the reasons which necessitate the result to be considered

with caution. In addition, data of some patients were not available. We recommend more high-quality, studies with larger sample size and in multicenter settings to assess the relationship between the extra-intestinal manifestations of IBD and CRC.

Conclusion

In summary, we discovered a correlation between dysplasia and advanced age at diagnosis and operation. According to these results, older UC patients may be at increased risk of CRC. It is recommended that clinicians treat certain patient groups as high-risk individuals and that specific screening and surveillance strategies are implemented for them.

Acknowledgements

The authors thank Digestive Disease Research Institute (DDRI) of Tehran University of Medical Sciences for logistic support for setting up the Iranian Registry of Crohn's and Colitis (IRCC). All authors contributed solely as volunteers. We are grateful to the employees of the IRCC cohort for their contribution to data gathering.

IRCC members that contribute to this study include:

AbdolRasool Hayatbakhsh, Abdossamad Gharavi, Afshin Shafaghi, Ali Beheshti Namdar, Amineh Hojati, Amir Hossein Faraji, Amirabbas Hasan Zadeh, Arash Kazemi Veisari, Elham Mokhtari Amirmajidi, Fatemeh Farahmand, Forough Alborzi, Hasan Ali Metanat, Hayedeh Adilipour, Hosein Alimadadi, Jalaluddin Naghshbandi, Katrin Behzad, Kourosh Mojtahedi, Ladan Goshayeshi, Mahdi Pezeshki Modares, Mahmoud Hoseinian, Mahmoud Yousefi Mashhour, Masoud Dooghaie Moghadam, Mehdi Saberi Firoozi, Mehri Najafi, Mitra Ahadi, Mohammad Reza Farzanehfard, Nadieh Baniasadi, Sahar Rismantab, Sanaz Gonoodi, Seyed Mohammad Valizadeh Toosi, Tarang Taghvaei, Vahid Hosseini, Taghi Amirani, Abazar Parsi, Shahsanam Gheibi, Saied Matinkhah, Baran Parhizkar, Roozbeh Rabiee, Mohammadreza Seyyedmajidi, Mandana Rafeey, Ali Gavidel, Mahdi Saberi Firoozi.

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Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to the institution's opposition but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no conflict of interest.

Consent for Publication

Not applicable.

Ethical Approval

This study was ethically approved by the Ethics Committee of Digestive Disease Research Institute of Tehran University of Medical Sciences (reference number: IR.TUMS.DDRI.REC.1401.028). All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from all subjects.

Funding

This work was supported by Deputy of Research of the Ministry of Health and Medical Education, and Digestive Diseases Research Institute (DDRI).

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