Factors Predictive of Proximal Disease Extension and Clinical Course of Patients Initially Diagnosed with Ulcerative Proctitis in an IBD Referral Center

Sandro da Costa Ferreira[1], Lilian Rose Otoboni Aprile[1], Rogério Serafim Parra[2], Marley Ribeiro Feitosa[2], Gleici de Castro da Silva Perdoná[3], Omar Féres[2], José Joaquim Ribeiro da Rocha[2], Luiz Ernesto de Almeida Troncon[1]

[1]Department of Medicine, University of São Paulo Ribeirão Preto Medical School, Brazil
[2]Department of Surgery and Anatomy, University of São Paulo Ribeirão Preto Medical School, Brazil
[3]Department of Social Medicine, University of São Paulo Ribeirão Preto Medical School, Brazil

Cite this article as: da Costa Ferreira S, Otoboni Aprile LR, Serafim Parra R, et al. Factors predictive of proximal disease extension and clinical course of patients initially diagnosed with ulcerative proctitis in an IBD referral center. *Turk J Gastroenterol.* 2022;33(4):320-328.

ABSTRACT

Background: *This study aims to determine whether risk factors at the time of diagnosis that are found to be predictive of proximal disease extension in ulcerative proctitis (UP) occur in a cohort of Brazilian patients.*

Methods: *This is a retrospective analysis of data from 97 patients (67% female) with UP (Montreal classification: E1) with at least 12 months of follow-up who were admitted to the Ribeirão Preto Medical School IBD referral center between January 2001 and December 2018. Proximal disease extension, which was defined as E1 progressing to E3 (pancolitis), was evaluated endoscopically during follow-up.*

Results: *A total of 29 (29.9%) patients experienced proximal disease extension. The risk factors at diagnosis associated with proximal disease extension were younger age (<40 years; P = .012), higher Mayo endoscopic score (P < .0001), higher partial Mayo score (P = .0018), and use of oral corticosteroids (P = .0016). During the follow-up period, increased disease relapse rates (P < .0001), immunomodulators (P = .00014) or the use of biological agents (P = .00037), and colectomy (P = .0002) were all significantly higher among UP patients with proximal disease extension.*

Conclusion: *Similar to what has been demonstrated in other studies, Brazilian UP patients with increased clinical and endoscopic severity at the time of diagnosis are likely to evolve with both proximal extension and a more adverse clinical course. Therefore, these patients should be followed-up more carefully.*

Keywords: *Disease progression, inflammatory bowel disease, proctocolitis, ulcerative colitis*

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease affecting the large bowel mucosa, which is clinically characterized by periods of quiescence and relapse.[1] Typically, the inflammation begins in the rectum, which is affected in almost all cases, and may extend continuously to the proximal segments of the colon.[1] Furthermore, inflammation is characteristically restricted to the mucosal surface.[1,2] Disease extension in UC is classified into 3 categories according to the Montreal classification[3]: E1 (proctitis: inflammation restricted to the rectum); E2 (left colitis: inflammation distal to the splenic flexure); and E3 (pancolitis: inflammation proximal to the splenic flexure).[3] Disease severity in UC is classified according to several disease severity scores, which commonly include the Truelove and Witts criteria[4] and the Mayo score.[5,6]

Approximately two-thirds of patients with UC have limited disease (E1 or E2) at the time of diagnosis, whereas the disease is restricted to the rectum in one-third of patients, which characterizes ulcerative proctitis (UP). In most cases, this phenotype progresses with a favorable clinical evolution. However, UC is a dynamic disease, and its progression may involve ascending segments of the colon.[1,7]

In population-based studies, almost 30% of UP cases diagnosed initially as UP will show proximal extension of the disease within 10 years.[8,9] This proximal extension in UP is usually associated with a more aggressive disease course, as evidenced by a greater need for immunomodulators and biological agents, in addition to increased rates of colectomy relative to those who already presented extensive colitis at diagnosis.[10,11] Therefore, proximal disease

Corresponding author: ***Sandro da Costa Ferreira****, e-mail:* ***sandrocferreira1705@gmail.com***
Received: ***February 21, 2021*** *Accepted:* ***June 15, 2021*** *Available Online Date:* ***February 17, 2022***

DOI: ***10.5152/tjg.2022.21124***

extension is an important feature that may be regarded as a major determinant of the long-term course of the disease.[10-12] Thus, it is extremely important not only to identify patients with UP who are at a higher risk of ascending disease progression, but also to monitor these patients more closely and to introduce effective therapies earlier.

The estimates for rates of proximal UP extension and its associated factors, as described in the literature, vary widely due to differences in the methodologies, sample characteristics, and even in the definition of proximal extension.[13,14] Although several predictive factors for this progression have been described, none have been established as definitive. Thus, this study aimed to assess the rate of proximal disease extension in UP and to determine the risk factors at the time of diagnosis that could predict evolution, in addition to verifying the concordance of our results in a cohort of Brazilian patients with those evidenced in large cohorts and in other populations. We also present the results of long-term follow-up of patients with proximal disease extension compared to those who remained classified as UP.

MATERIALS AND METHODS

Study Design

This was a retrospective study of patients with UC with an established initial diagnosis of UP who were admitted to the University Hospital of the Ribeirão Preto Medical School (University of São Paulo, Brazil) between January 2001 and December 2018. All patients were followed-up for at least 12 months. The diagnosis of UC was performed on the basis of clinical, endoscopic, and histopathological reports, and UP was classified according to the Montreal classification[3]: E1–proctitis (involvement limited to the rectum; proximal extent is distal to the rectum–sigmoid junction). This classification was also utilized at regular intervals to establish proximal disease extension to E2–left colitis (involvement of the colonic mucosa not proximal to the splenic flexure); or E3–pancolitis (mucosal involvement reaching any segment proximal to the splenic flexure).[3]

Main Points

- *Ulcerative proctitis (UP) patients diagnosed at younger ages (<40 years old) had significantly higher rates of proximal disease extension than those diagnosed at older ages.*
- *Higher Mayo endoscopic scores, partial Mayo scores, and the use of corticosteroids at the time of diagnosis were significantly associated with proximal disease extension in UP patients.*
- *Proximal disease extension in UP patients was associated with increased incidence of relapse and complications, indicating poor prognosis for the long term. We found that more cases of relapses (>3/year) were associated with a higher risk of UP proximal extension. Moreover, we found that the use of immunosuppressive and biological agents and the colectomy rates were higher in these patients over the follow-up period, despite the optimization of drug therapy.*

Clinical and epidemiological data were obtained from medical records and the following variables presented at diagnosis were recorded: gender, age, race, smoking history, extraintestinal manifestations, initial or recent treatments, clinical disease severity (according to the partial Mayo score), and degree of endoscopic activity (according to the Mayo Clinic endoscopy score).[5,6]

In our service, UC patients are routinely seen at the outpatient clinic at regular intervals (3-6 months) according to their condition, and all are treated based on a step-up approach.[15] We used 5-ASA (5-aminosalicylate) agents (topical and/or oral) for the initial treatment and later as required for non-severe flare-ups, maintenance, and first-line prophylaxis. Corticosteroid therapy was used in patients with moderately to severely active UC, and thiopurines or biological agents [anti-tumor necrosis factor (anti-TNF) and anti-integrins] were used in steroid-dependent or steroid-refractory patients. Medication use, disease relapse, and the need for a colectomy were also evaluated during the follow-up period.

An endoscopy was performed at admission (initial diagnosis) for all patients. The second and subsequent endoscopies were performed at 12- to 24-month intervals, or upon disease relapse, as indicated by the attending physician. Endoscopy was essential to ensure that all patients included in this study had initially limited UC or UP (E1), as well as to define disease proximal progression from the initial extension to diagnosis (defined as a limited UC (E1) and to pancolitis (E3) throughout follow-up.

Patients

Initially, 140 patients diagnosed clinically and endoscopically with UP were included in this study. Among these, 43 patients were excluded for the following reasons: follow-up period of <12 months, loss of follow-up, consent withdrawn, and death unrelated to UC. The remaining 97 patients who completed at least a 12-month follow-up period were divided in 2 subgroups: either with or without proximal disease progression. The demographic characteristics of these patients are shown in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of 97 Patients Initially Diagnosed with Ulcerative Proctitis. Comparison Between Subgroups With and Without Proximal Disease Extension*

Variable	Extension (n = 29)		No extension (n = 68)		*P*
Age (mean ± SD)	44.06 ±16.63		50.25 ±15.08		
	n	%	n	%	
Gender					1.000
Female	19	65.5	46	67.6	
Male	10	35.5	22	32.4	
Skin color					.7400
White	24	82.8	54	79.4	
Mulatto	3	10.3	9	13.2	
Black	2	6.9	5	7.4	
Age at the time of UP diagnosis					**.0120****
<17	3	10.3	2	2.9	
17-40	18	62.1	41	60.3	
>40	8	27.6	25	36.8	
Smoking					.4910
Yes	3	10.3	9	13.2	
No	26	89.7	59	86.8	
Mayo endoscopic subscore#					**<.0001**
1	10	34.5	42	61.8	
2	14	48.3	24	35.3	
3	5	17.2	2	2.9	
Partial Mayo score**					**.0018**
2-4	7	24.1	43	63.2	
5-7	17	58.6	23	33.9	
>7	5	17.3	2	2.9	
Extraintestinal manifestation					.1500
Yes	6	20.7	12	14.8	
No	23	79.3	69	85.2	
Initial use of mesalazine					.3900
Oral mesalazine	8	27.5	20	30.8	
Topical mesalazine	3	10.3	8	12.3	
Oral + topical mesalazine	18	62.2	37	56.9	
Initial use of oral corticosteroids					**.0016**
Yes	25	86.2	28	41.2	
No	4	13.8	40	58.8	

*Proximal extension was defined as E1 progressing to E3; #The Mayo Endoscopic Score: Mayo 0: inactive disease; Mayo 1: Mild activity; Mayo 2: moderate activity; Mayo 3: Severe activity; **Partial Mayo Score: < 2: remission; 2-4: mild activity; 5-7: moderate activity; > 7: severe activity. **(<40 years vs >40 years of age). Variables are expressed as mean ± SD or n (%). Statistically significant results were highlighted in bold.

Ethical Considerations

This study was approved by the local institutional Research Ethics Committee (Protocol No. 3147/2019). All patients agreed to participate in the study and provided informed consent. All procedures were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the 1964 Declaration of Helsinki and its later amendments (or comparable ethical standards).

Statistical Analysis

Statistical analyses were performed with R CRAN statistical software (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as absolute numbers and percentages, and means ± standard deviations (SD). Comparisons between subgroups were performed using the *t*-test for independent samples. Categorical variables were compared with the χ^2 test and Fisher's exact test. Univariate Cox regression was used to identify candidate predictors for inclusion in a multivariate analysis model. Risk factors for progression were expressed as (HR) and 95% CI. Survival analysis was performed using Kaplan–Meier analysis based on the log-rank test. Statistical significance was set at $P < .05$.

RESULTS

Patient Characteristics

Among the 97 patients initially diagnosed with UP who completed the study, 46 (47.4%) were female. The mean age at diagnosis was 37.4 ± 14.74 years, and the duration of follow-up ranged between 25 and 227 months (mean ± SD: 140.1 ± 91.12 months). Seventy-eight (80.4%) patients were white, and active or former smoking was reported in 12 patients (12.4%). Extraintestinal manifestations, mainly articular (e.g., peripheral arthritis and sacroiliitis), but also cutaneous (e.g., erythema nodosum) and hepatobiliary (e.g., primary sclerosing cholangitis) were present in 13 patients (13.4%). Drug treatment at the time of diagnosis included oral mesalazine (28.8%), topical mesalazine (11.3%), or both (56.7%), but 53 (54.9%) patients also required oral corticosteroids.

Throughout follow-up, 29 (29.9%) patients experienced proximal disease extension to pancolitis. Comparisons between the baseline clinical and demographic characteristics of patients with and without proximal disease extension are described in Table 1.

Predictors of Proximal Disease Extension

The univariate analysis revealed the following results:

1. Age at diagnosis: younger age (<40 years of age) at the onset of the disease was significantly associated with proximal disease extension (P = .0012) (Figure 1).
2. Use of oral corticosteroids as an initial medication was significantly more frequent in patients with proximal extension (86.2% vs 41.2%; P = .00016) (Figure 1).
3. Higher initial endoscopic Mayo subscores (Mayo 2: 48.3% vs 36.8% and Mayo 3: 17.2% vs 2.9%; P < .0001) were found in a significantly higher proportion of patients with proximal extension, relative to controls without proximal extension.
4. Significantly higher partial Mayo clinical scores at the time of diagnosis were found in patients with proximal extension when compared those without proximal extension (5.58 ± 3.18 vs 4.45 ± 1.34, P = .0018) (Figure 2).
5. No associations were found between proximal disease extension and gender, skin color, smoking status, or presence of extraintestinal manifestations (P > .05).

The multivariate analysis revealed the following independent risk factors for proximal disease extension: younger age (HR: 2.75; 95% CI: 1.51-6.6; P = .023) and higher Mayo endoscopic subscore (HR: 5.17; 95% CI: 1.33-20.10; P = .018) (Table 3).

Long-Term Follow-up of Patients With Proximal Disease Extension

The durations of follow-up periods for UP patients with and without proximal disease extension were remarkably similar (137.36 ± 86.63 months and 141.90 ± 93.56 months, respectively). Additionally, disease relapse was observed more often in patients with proximal disease extension relative to those without (86.2% vs 20.6%; P < .0001). Also, more relapses (>3/year) were observed in patients with proximal disease extension (20.7% vs 7.2%; P < .0001) (Table 2) (Figure 3).

The need for changes in medical treatment–with the introduction of immunosuppressive and biological agents–in patients with proximal extension of the disease, as compared to those without, was [16 (56.1%) vs 11 (16.1%), P = .00014; 12 (41.4%) vs 7 (10.3%), P = .0037], respectively (Table 2).

Despite the optimization of clinical treatment, colectomy was necessary during the follow-up period in 7 patients (24.1%) who showed proximal disease extension and in none of the patients without proximal extension (P = .0002) (Table 2).

DISCUSSION

In this retrospective study of a single reference center in southeastern Brazil, we observed proximal disease extension in approximately one-third (29.9%) of UP patients during an average follow-up of 137.36 ± 86.63 months. We also reviewed the results of long-term follow-up and

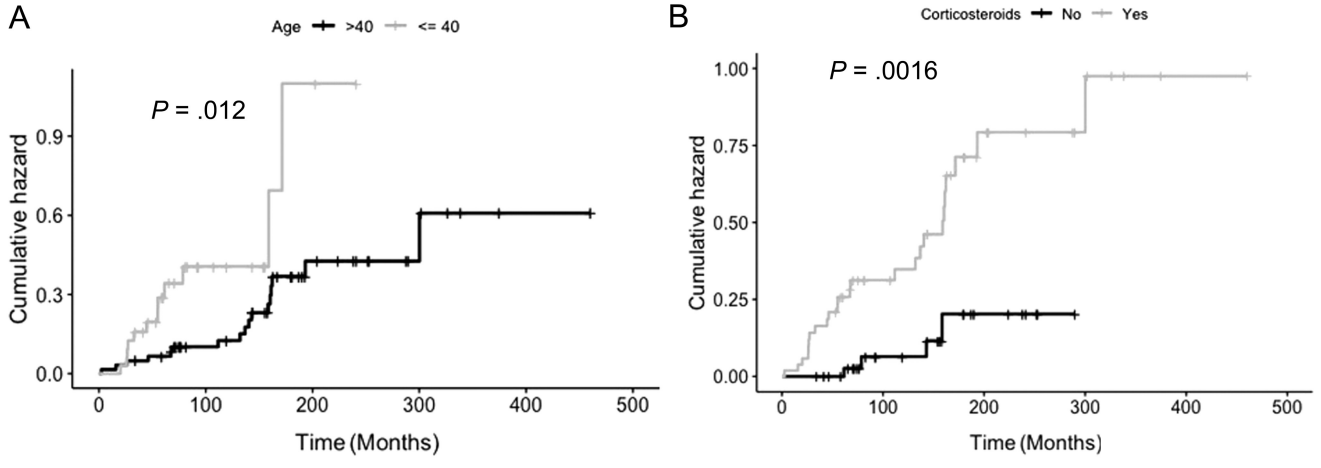

Figure 1. Analysis of the likelihood of disease extension using Kaplan–Meier curves stratified by predictive factors measured at the time of diagnosis. (A) Cumulative disease extension likelihood was significantly more frequent in patients with disease onset before 40 years of age. (B) Cumulative disease extension likelihood was significantly higher in patients with use of corticosteroids at the time of diagnosis.

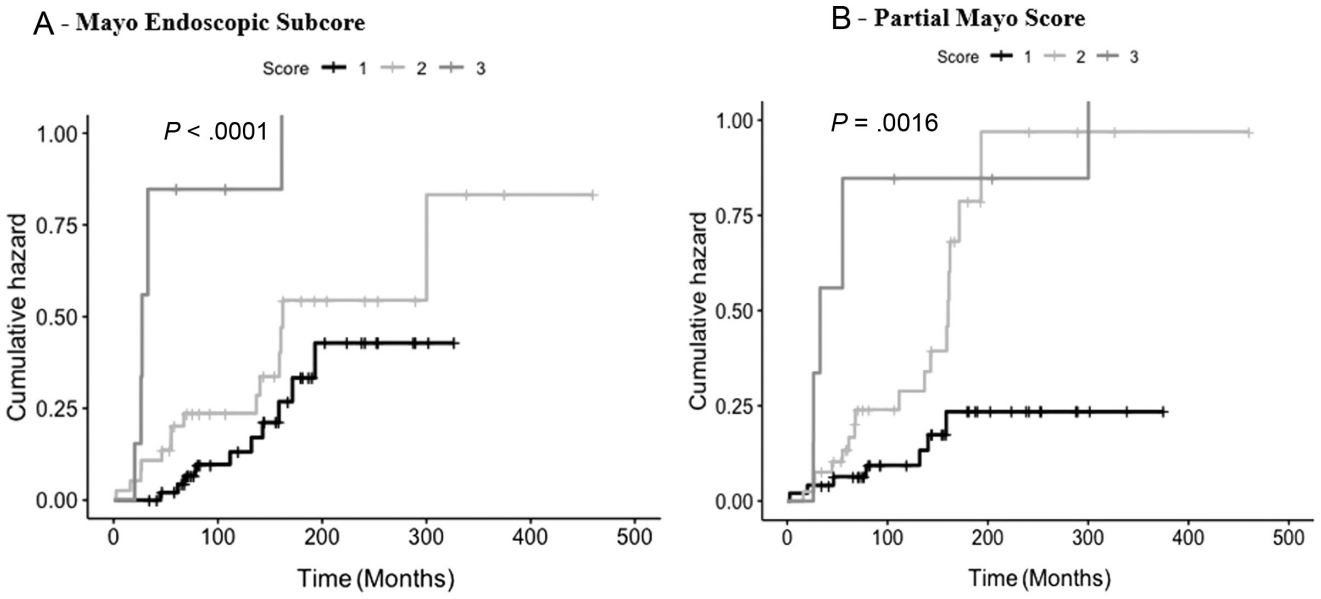

Figure 2. Analysis of the likelihood of disease extension using Kaplan–Meier curves stratified by predictive factors measured at the time of diagnosis. (A) Cumulative disease extension likelihood was significantly associated with patients with higher Mayo endoscopic subscores than patients with lower Mayo endoscopic subscores ($P < .001$). (B) Cumulative disease extension likelihood was significantly associated with patients with higher Mayo partial scores than patients with lower Mayo partial scores ($P = .0018$).

Table 2. Clinical Outcomes and Therapeutic Needs During Follow-Up of 97 Patients Initially Diagnosed With Ulcerative Proctitis: Comparison Between Subgroups With and Without Proximal Disease Extension

Variable	Extension (n = 29)		No Extension (n = 68)		*P*
Follow-Up (Mean ± SD)	137.36 ± 86.63 Months		141.90 ± 93.56 Months		
	n	%	n	%	
Immunosuppressive agents					.00014
Yes	16	56.1	11	16.1	
No	13	44.9	57	83.9	
Biological agents					.00037
Yes	12	41.4	7	10.3	
No	17	58.6	61	89.7	
Flares					<.0001
Yes	25	86.2	14	20.6	
No	4	13.8	54	79.4	
Number of relapses					<.0001
0	4	13.8	54	79.4	
<3	19	65.5	9	13.2	
>3	6	20.7	5	7.4	
Surgical resection					.0002
Yes	7	24.1	0	0	
No	22	75.9	68	100	

*Proximal extension was defined as E1 progressing to E3. Variables are expressed as mean ± SD or n (%).

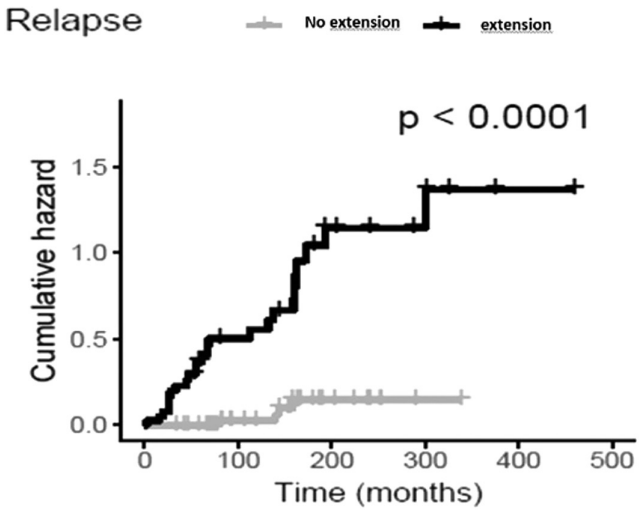

Figure 3. Kaplan–Meier curves of the cumulative rates of relapse of the disease over the long-term during follow-up.

found that many of these patients had an adverse course, indicative of increased disease severity.

Our study was the first to assess the upward progression of UP in this specific Brazilian population from a tertiary referral center in southeastern Brazil. Even with few epidemiological studies published to date, and in addition to factors inherent to the health system itself which make it difficult to obtain accurate data on the epidemiology of inflammatory bowel disease (IBD) in Brazil, there is a clear increase in the incidence and prevalence of IBD, and consequently, of UC.[16-19] In this way, the recent data position Brazil as a country with a significant number of cases, comparable to that of the most developed regions of the world (intermediate prevalence of IBD).[20] Despite our center being a referral center, the shortcomings of the Brazilian healthcare system have forced many patients, whose characteristics require secondary care, to visit our center, and therefore, our "set" of cases may indeed reflect actual disease behavior.

The clinical course of UC is difficult to predict, ranging from long periods of remission to multiple relapses, thus characterizing a chronic recurrent disease. This condition may also present as severe acute colitis, and may have increased risks of colorectal cancer and colectomy rates and death.[1,12] A factor that is linked to increased UC severity is the extent of colonic involvement, which is therefore considered an important prognostic indicator.[2,21] Patients initially presenting with distal disease who developed proximal extension over time have been shown to have a more serious disease, with a higher risk of colectomy, even when compared to those with extensive UC at the time of diagnosis.[2,11] However, the frequency and risk factors for proximal extension in patients with UP remain poorly defined, mainly due to differences in study design, methodologies, population characteristics, treatment strategies, and the very definition of proximal disease extension.[9,14,22,23]

Previous retrospective studies with a design similar to ours have reported UP proximal extension rates ranging from 16% to 51%.[14,22,24,25] On the other hand, a systematic meta-analysis of 30 studies found that the combined global rate of UP proximal extension was 22.8%, with rates of 17.8% in 5 years and 31% in 10 years.[26] Furthermore, the rate of extension from proctitis (E1) to pancolitis (E3) was found to reach 17.8% (95% CI: 11.2-27.3).[26]

Our observed rate of UP proximal extension of the disease was very similar to that from a large Inflammatory Bowel Disease South-Eastern Norway (IBSEN) study (28%) in 843 patients in southeastern Norway over a 5-year follow-up period.[27] Also, a retrospective study by Kim et al[13] demonstrated a proximal extension rate of 27.6% in 98 patients with UP. Another retrospective study of 169 patients by Walsh et al[24] reported a 31% rate of UP proximal extension over an average follow-up period of 4.3 years.[24]

We found that UP patients diagnosed at younger ages (<40 years old) had significantly higher rates of proximal disease extension than those diagnosed at older ages. Studies that investigated young age at diagnosis as a risk factor for proximal UP extension are scarce and have shown discrepant results.[24,28,29] A retrospective study of 66 UP patients followed up for 35 years demonstrated that proximal disease extension was significantly greater in patients aged <25 years at disease onset, with cumulative extension rates of 33.8% and 52.2% in 10 and 20 years, respectively.[30] Similarly, higher rates of UP proximal extension (ranging from 38% to 65%) have been reported, particularly in pediatric populations.[31-33]

Age was found to be the main factor associated with higher rates of proximal extension, which were significantly increased in patients younger than 18 years.[26] However, a retrospective study found no association between younger ages at the time of diagnosis and the risk of UP proximal extension.[24] Our data corroborate the findings

Table 3. Data from Multivariate Analysis for Independent Risk Factors for Proximal Disease Extension in Ulcerative Proctitis Patients*

Variable	HR	95% CI	*P*
Age			
>40 (63)	Reference		
≤40 (34)	**2.76**	**1.152-6.6**	**.023****
Mayo endoscopic subscore#			
1 (51)	Reference		
2 (39)	1.56	0.647-3.8	0.32
3 (7)	**5.17**	**1.327-20.1**	**.018****
Need for oral corticosteroids			
Yes (53)	0.27	0.038-1.9	.188
No (44)	Reference		

#Events: 29; Global *P*-value (Log-Rank): 3.2093e−06 AIC: 207.9; Concordance Index: 0.83. *Proximal extension was defined as E1 progressing to E3. #The Mayo Endoscopic Score: Mayo 0: Inactive disease; Mayo 1: Mild activity; Mayo 2: Moderate activity; Mayo 3: Severe activity. **Factors associated with proximal disease extension in multivariate analyses. HR, hazard ratio; 95% CI (absolute numbers of patients in each category). Statistically significant results were highlighted in bold.

of other studies on the risks of proximal disease extension in UP diagnosed in younger patients (<40 years vs >40 years of age).[13,28,33] Thus, UP should not be seen as a self-limiting disease, particularly in younger patients, and it should be strictly monitored and appropriately treated.

We observed significant associations between higher Mayo endoscopic scores, partial Mayo scores, and the use of corticosteroids at the time of diagnosis and proximal disease extension in UP patients, which align with the findings of several studies.[7,13,24,29,30] Taken as a whole, these findings indicate that the greater the severity of UP at the time of diagnosis, the greater the likelihood of the disease spreading proximally, which may indicate a poor long-term prognosis in these patients.

Contrary to what was described in other studies,[7,21,29] we were unable to identify any significant association between UP proximal extension and sex, absence of smoking, and extraintestinal manifestations, including primary sclerosing cholangitis. We also found that a higher number of relapses (>3/year) was associated with greater risk of UP proximal extension. Moreover, we found that the use of immunosuppressive and biological agents and colectomy rates, despite the optimization of drug therapy, were greater in these patients over the follow-up period. Ultimately, our results corroborate those of other studies. It seems, then, that when relapses of UC are associated with proximal disease extension, patients may follow a refractory course with greater therapeutic needs, such as the use of immunosuppressors, biological agents, or even surgery.[7,9,13,14,24,29,34]

Some limitations of the present study should be addressed. Firstly, this was a retrospective study including patients followed-up at a single reference university hospital. Secondly, our sample size, although sufficient for multivariate analysis, was relatively small. Finally, the unavailability of biomarkers, such as C-reactive protein and fecal calprotectin, during the follow-up period may limit the conclusions that can be drawn. Despite these limitations and taking into account local peculiarities, such as population genetics and characteristics of the health system, we were able to show that Brazilian patients with UP follow a course similar to that already demonstrated in previously published large-scale studies with different populations, thus corroborating these findings.[13,25,26,30,34,35] We also emphasize the fact that this study is original in the sense that proximal extension of proctitis has not yet been addressed in a Brazilian population of UC patients.

In conclusion, our data reinforce that UP is a dynamic disease that can progress and worsen over time. Younger age, more serious disease at the time of diagnosis (determined endoscopically and clinically), and an initial need of oral corticosteroids were all associated with a significantly higher probability of disease extension over time. In these cases, strict monitoring and more aggressive medical treatment should be considered. Moreover, disease extension is associated with increased incidence of relapse and complications, indicating long-term poor prognosis.

Ethics Committee Approval: The study was approved by the medical ethics committee of Ribeirão Preto Medical School (protocol #3147/2019/03/23/2019).

Informed Consent: All patients agreed to participate in the study and provided written informed consent.

Peer Review: Externally peer-reviewed.

Author Contributions: Consept – S.C.F., L.E.A.T.; Design – S.C.F., L.E.A.T.; Supervision – O.F., J.R.R.R., L.E.A.T.; Resources – O.F., J.R.R.R., L.E.A.T.; Materials – L.R.O.A., R.S.P., M.R.F.; Data Collection and/or Processing – S.C.F., L.R.O.A.; Analysis and/or Interpretation – S.C.F., R.S.P., M.R.F.; Writing Manuscript – S.C.F., R.S.P., M.R.F., L.E.A.T.; Critical Review – R.S.P., M.R.F., L.E.A.T.

Acknowledgments: We thank Patricia Picardi Morais de Castro from the University of São Paulo for the assistance with the statistical analysis.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This research was supported by the Fundação de Apoio e Ensino e Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto (FAEPA).

The content of this manuscript has been presented before at AIBD 2019 and the ECCO 2020 Congress:

Ferreira S., Parra R, Feitosa M, et al. Advances in Inflammatory Bowel Diseases (AIBD) 2019 Annual Meeting Abstracts P022 Factors Associated With Proximal Disease Extension in Ulcerative Proctitis: Experience From an IBD Tertiary Center in Southeastern Brazil. The American Journal of Gastroenterology: December 2019 - Volume 114 - Issue - p S6. doi: 10.14309/01.ajg.0000613056.50597.85.

Ferreira S, Queiróz Marques de Mendonça R, Steltenpool Tonin Borges I, et al. P263 Proximal disease extension in patients with ulcerative proctitis: Associated factors and experience of an IBD tertiary Brazilian centre. European Crohn's and Colitis Organisation Congress 2020. Journal of Crohn's and Colitis, Volume 14, Issue Supplement_1, January 2020, Pages S281-S282, https://doi.org/10.1093/ecco-jcc/jjz203.392.

REFERENCES

1. *Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389(10080):1756-1770.* [CrossRef]
2. *Gajendran M, Loganathan P, Jimenez G, et al. A comprehensive review and update on ulcerative colitis. Dis Mon. 2019;65(12):100851.* [CrossRef]
3. *Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749-753.* [CrossRef]
4. *Truelove SC, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. BMJ. 1954;2(4884):375-378.* [CrossRef]
5. *Walmsley RS, Ayres RCS, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut. 1998;43(1):29-32.* [CrossRef]
6. *Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in Ulcerative Colitis. Inflamm Bowel Dis. 2008;14(12):1660-1666.* [CrossRef]
7. *Meucci G, Vecchi M, Astegiano M, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). Am J Gastroenterol. 2000;95(2):469-473.* [CrossRef]
8. *Magro F, Rodrigues A, Vieira AI, et al. Review of the disease course among adult ulcerative colitis population-based longitudinal cohorts. Inflamm Bowel Dis. 2012;18(3):573-583.* [CrossRef]
9. *Burisch J, Ungaro R, Vind I, et al. Proximal disease extension in patients with limited ulcerative colitis: a Danish population-based inception cohort. J Crohns Colitis. 2017;11(10):1200-1204.* [CrossRef]
10. *Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis as a progressive disease: the forgotten evidence. Inflamm Bowel Dis. 2012;18(7):1356-1363.* [CrossRef]
11. *Wanderås MH, Moum BA, Høivik ML, Hovde Ø. Predictive factors for a severe clinical course in ulcerative colitis: results from population-based studies. World J Gastrointest Pharmacol Ther. 2016;7(2):235-241.* [CrossRef]
12. *Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol. 2018;16(3):343-356.e3.* [CrossRef]
13. *Kim B, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Proximal disease extension and related predicting factors in ulcerative proctitis. Scand J Gastroenterol. 2014;49(2):177-183.* [CrossRef]
14. *Qiu Y, Chen B, Li Y, et al. Risk factors and long-term outcome of disease extent progression in Asian patients with ulcerative colitis: a retrospective cohort study. BMC Gastroenterol. 2019;19(1):7.* [CrossRef]
15. *Sairenji T, Collins KL, Evans DV. An update on inflammatory bowel disease. Prim Care. 2017;44(4):673-692.* [CrossRef]
16. *Victoria CR, Sassak LY, Nunes HRDC. Incidence and prevalence rates of inflammatory bowel diseases, in midwestern of São Paulo State, Brazil. Arq Gastroenterol. 2009;46(1):20-25.* [CrossRef]
17. *Lima Martins A, Volpato RA, Zago-Gomes MDP. The prevalence and phenotype in Brazilian patients with inflammatory bowel disease. BMC Gastroenterol. 2018;18(1):87.* [CrossRef]
18. *Parente JML, Coy CS, Campelo V, et al. Inflammatory bowel disease in an underdeveloped region of northeastern Brazil. World J Gastroenterol. 2015;21(4):1197-1206.* [CrossRef]
19. *Gasparini RG, Sassaki LY, Saad-Hossne R. Inflammatory bowel disease epidemiology in São Paulo State, Brazil. Clin Exp Gastroenterol. 2018;11:423-429.* [CrossRef]
20. *Quaresma AB, Kaplan GG, Kotze PG. The globalization of inflammatory bowel disease: the incidence and prevalence of inflammatory bowel disease in Brazil. Curr Opin Gastroenterol. 2019;35(4):259-264.* [CrossRef]
21. *Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44(4):431-440.* [CrossRef]
22. *Monstad I, Hovde O, Solberg IC, Moum BA. Clinical course and prognosis in ulcerative colitis: results from population-based and observational studies. Ann Gastroenterol. 2014;27(2):95-104.*
23. *Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology. 1994;107(1):3-11.* [CrossRef]
24. *Walsh E, Chah YW, Chin SM, et al. Clinical predictors and natural history of disease extension in patients with ulcerative proctitis. Inflamm Bowel Dis. 2017;23(11):2035-2041.* [CrossRef]
25. *Lee JH, Cheon JH, Moon CM, et al. Do patients with ulcerative colitis diagnosed at a young age have more severe disease activity than patients diagnosed when older? Digestion. 2010;81(4):237-243.* [CrossRef]
26. *Roda G, Narula N, Pinotti R, et al. Systematic review with meta-analysis: proximal disease extension in limited ulcerative colitis. Aliment Pharmacol Ther. 2017;45(12):1481-1492.* [CrossRef]
27. *Henriksen M, Jahnsen J, Lygren I, et al. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). Inflamm Bowel Dis. 2006;12(7):543-550.* [CrossRef].
28. *Gonçalves TC, Dias de Castro F, Machado JF, Moreira MJ, Rosa B, Cotter J. Impact of the age of diagnosis on the natural history of ulcerative colitis. Rev Esp Enferm Dig. 2015;107(10):614-621.* [CrossRef]

29. Etchevers MJ, Aceituno M, García-Bosch O, et al. Risk factors and characteristics of extent progression in ulcerative colitis. Inflamm Bowel Dis. 2009;15(9):1320-1325. [CrossRef]
30. Anzai H, Hata K, Kishikawa J, et al. Clinical pattern and progression of ulcerative proctitis in the Japanese population: a retrospective study of incidence and risk factors influencing progression. Colorectal Dis. 2016;18(3):O97-O102. [CrossRef]
31. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 2009;104(8):2080-2088. [CrossRef]
32. Aloi M, D'Arcangelo G, Pofi F, et al. Presenting features and disease course of pediatric ulcerative colitis. J Crohns Colitis. 2013;7(11):e509-e515. [CrossRef]
33. Hochart A, Gower-Rousseau C, Sarter H, et al. Ulcerative proctitis is a frequent location of paediatric-onset UC and not a minor disease: a population-based study. Gut. 2017;66(11):1912-1917. [CrossRef]
34. Reinisch W, Reinink AR, Higgins PDR. Factors associated with poor outcomes in adults with newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2015;13(4):635-642. [CrossRef]
35. Sahami S, Konté K, Buskens CJ, et al. Risk factors for proximal disease extension and colectomy in left-sided ulcerative colitis. U Eur Gastroenterol J. 2017;5(4):554-562. [CrossRef]