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Stanislav Sitkin, MD, PhD, Associate Professor, Senior Researcher, Department of Internal Diseases, Gastroenterology and Dietetics, North-Western State Medical University named after I.I. Mechnikov, St. Petersburg 191015, Russia. drsitkin@gmail.com

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Observational Study

Real-world disease activity and sociodemographic, clinical and treatment characteristics of moderate-to-severe inflammatory bowel disease in Brazil

Cyrla Zaltman, Rogério Serafim Parra, Ligia Yukie Sasaki, Genoile Oliveira Santana, Maria de Lourdes Abreu Ferrari, Sender J Miszputen, Heda M B S Amarante, Roberto Luiz Kaiser Junior, Cristina Flores, Wilson R Catapani, José Miguel Luz Parente, Mauro Bafutto, Odery Ramos, Carolina D Gonçalves, Isabella Miranda Guimaraes, Jose J R da Rocha, Marley R Feitosa, Omar Feres, Rogerio Saad-Hossne, Francisco Guilherme Cancela Penna, Pedro Ferrari Sales Cunha, Tarcia NF Gomes, Rodrigo Bremer Nones, Mikael Alexandre Gouvea Faria, Mírian Perpétua Palha Dias Parente, António S Scotton, Rosana Fusaro Caratin, Juliana Senra, Júlio Maria Chebli

ORCID number: Cyrla Zaltman 0000-0002-5236-6501; Rogério Serafim Parra 0000-0002-5566-9284; Ligia Yukie Sasaki 0000-0002-7319-8906; Genoile Oliveira Santana 0000-0001-5936-9791; Maria de Lourdes Abreu Ferrari 0000-0002-2122-5538; Sender J Miszputen 0000-0003-4487-5004; Heda M B S Amarante 0000-0001-7449-1138; Roberto Luiz Kaiser Junior 0000-0003-1952-1253; Cristina Flores 0000-0003-1623-4525; Wilson R Catapani 0000-0002-0412-2182; José Miguel Luz Parente 0000-0003-4563-2784; Mauro Bafutto 0000-0001-5585-3957; Odery Ramos 0000-0002-9730-6860; Carolina D Gonçalves 0000-0003-3663-4390; Isabella Miranda Guimaraes 0000-0003-3401-6580; Jose J R da Rocha 0000-0001-7118-0545; Marley R Feitosa 0000-0002-4440-2023; Omar Feres 0000-0003-3593-0526; Rogerio Saad-Hossne 0000-0002-8166-0304; Francisco Guilherme Cancela Penna 0000-0002-2338-5367; Pedro Ferrari Sales Cunha 0000-0003-4384-2606; Tarcia NF Gomes 0000-0003-2897-0327; Rodrigo Bremer Nones 0000-0002-6256-2629; Mikael Alexandre Gouvea Faria 0000-0003-4121-0306;

Cyrla Zaltman, Carolina D Gonçalves, Isabella Miranda Guimaraes, Department of Internal Medicine, Federal University of Rio de Janeiro, Rio de Janeiro 21941-913, Brazil

Rogério Serafim Parra, Jose J R da Rocha, Marley R Feitosa, Omar Feres, Department of Surgery and Anatomy, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto 14049-900, São Paulo, Brazil

Ligia Yukie Sasaki, Department of Internal Medicine, São Paulo State University (UNESP), Medical School, Botucatu 18618-687, São Paulo, Brazil

Genoile Oliveira Santana, IBD Unit, Federal University of Bahia, Salvador 41150-000, Bahia, Brazil

Maria de Lourdes Abreu Ferrari, Francisco Guilherme Cancela Penna, Pedro Ferrari Sales Cunha, Department of Clinical Medicine, Medical School, Universidade Federal de Minas Gerais, Belo Horizonte 30130-100, Minas Gerais, Brazil

Sender J Miszputen, Department of Gastroenterology, Escola Paulista de Medicina, São Paulo 04023-900, Brazil

Heda M B S Amarante, Odery Ramos, Hospital de Clinicas, Universidade Federal do Parana, Curitiba 80060-900, Parana, Brazil

Roberto Luiz Kaiser Junior, Department of Proctology, Beneficencia Portuguesa Hospital/Kaiser Day Hospital, Sao Jose do Rio Preto 15015110, São Paulo, Brazil

Cristina Flores, Department of Gastroenterology and Hepatology Sciences, Hospital de Clínicas, Universidade Federal do Rio Grande do Sul, Porto Alegre 90560002, Rio Grande do Sul, Brazil

Wilson R Catapani, Department of Gastroenterology, Faculdade de Medicina do ABC, Santo Andre 09060-870, São Paulo, Brazil

Mírian Perpétua Palha Dias Parente 0000-0002-0176-717X; António S Scotton 0000-0001-9247-0904; Rosana Fusaro Caratin 0000-0003-0922-8530; Juliana Senra 0000-0001-6787-806X; Júlio Maria Chebli 0000-0003-1527-0663.

Author contributions: Zaltman C, Parra RS, Sassaki LY, Santana GO, Ferrari MLA, Miszputen SJ, Amarante HMBS, Junior RLK, Flores C, Catapani WR, Parente JML, Bafutto M, Ramos O, Scotton AS and Chebli JM provided substantial contributions to the concept and design, acquisition of data, and analysis and interpretation of data; Gonçalves CD, Guimaraes IM, da Rocha JJR, Feitosa MR, Feres O, Saad-Hossne R, Penna FGC, Cunha PFS, Gomes TNF, Nones RB, Faria MAG, Parente MPPD, Caratin RF and Senra J contributed to the analysis and interpretation of data; all authors contributed to the editing of the manuscript, revised it critically for important intellectual content, granted approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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José Miguel Luz Parente, Department of General Medicine, Gastroenterology Unit, University Hospital, Federal University of Piauí, Teresina 64049-550, Piauí, Brazil

Mauro Bafutto, Department of Gastroenterology, Faculdade de Medicina, Universidade Federal de Goiás, Goiânia 74535-170, Goiás, Brazil

Rogério Saad-Hossne, Department of Surgery, Botucatu Medical School at São Paulo State University (UNESP), Botucatu 18618687, São Paulo, Brazil

Tarcia NF Gomes, Department of Gastroenterology, UNIFESP, São Paulo 04040-002, Brazil

Rodrigo Bremer Nones, IBD unit, Gastroenterology Department, Hospital Nossa Senhora das Graças, Curitiba 80810-040, Paraná, Brazil

Mikaell Alexandre Gouveia Faria, Department of Proctology, Kaiser Hospital Dia, São José do Rio Preto 15015-110, São Paulo, Brazil

Mírian Perpétua Palha Dias Parente, Health Sciences Center, Epidemiology Unit, State University of Piauí, Teresina 64001-280, Piauí, Brazil

Antônio S Scotton, Department of Gastroenterology, CMIP Centro Mineiro de Pesquisa, Juiz de Fora 36010-570, Minas Gerais, Brazil

Rosana Fusaro Caratin, Scientific Affairs, Takeda Pharmaceuticals Brazil, São Paulo 04709-011, Brazil

Juliana Senra, Clinical Research, Takeda Pharmaceuticals Brazil, São Paulo 04709-011, Brazil

Júlio Maria Chebli, Department of Medicine, University Hospital of Federal University of Juiz de Fora, Juiz de Fora 36036-247, Minas Gerais, Brazil

Corresponding author: Cyrla Zaltman, MD, PhD, Associate Professor, Internal Medicine, Federal University of Rio de Janeiro, Hospital Universitário Clementino Fraga Filho - Rua Prof. Rodolpho Paulo Rocco 255 - 4 andar - Ilha do Fundão, Rio de Janeiro 21941-913, Brazil. c.zaltman@gmail.com

Abstract

BACKGROUND

Understanding the treatment landscape of inflammatory bowel diseases (IBD) is essential for improving disease management and patient outcomes. Brazil is the largest Latin American country, and it presents socioeconomic and health care differences across its geographical regions. This country has the highest increase in IBD incidence and prevalence in Latin America, but information about the clinical and treatment characteristics of IBD is scarce.

AIM

To describe the sociodemographic, clinical, and treatment characteristics of IBD outpatients in Brazil overall and in the Southeast, South and Northeast/Midwest regions.

METHODS

Multicenter, cross-sectional study with a 3-year retrospective chart review component. Patients with moderate-to-severe Crohn's disease (CD) or ulcerative colitis (UC) were consecutively enrolled between October 2016 and February 2017. Active CD at enrollment was defined as a Harvey Bradshaw Index ≥ 8 or a CD Activity Index ≥ 220 or a calprotectin level $> 200 \mu\text{g/g}$ or an active result based on colonoscopy suggestive of inadequate control during the previous year; active UC was defined as a partial Mayo score ≥ 5 . Descriptive statistics were used to analyze all variables.

RESULTS

In a total of 407 included patients, CD was more frequent than UC, both overall (264 CD/143 UC patients) and by region (CD:UC ratios of 2.1 in the Southeast, 1.6 in the South and 1.2 in the Northeast/Midwest). The majority of patients were

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female (54.2% of CD; 56.6% of UC), and the mean ages were 45.9 ± 13.8 years (CD) and 42.9 ± 13.0 years (UC). The median disease duration was 10.0 (range: 0.5-45) years for both IBD types. At enrollment, 44.7% [95% confidence interval (CI): 38.7-50.7] of CD patients and 25.2% (95% CI: 18.1-32.3) of UC patients presented with active disease. More than 95% of IBD patients were receiving treatment at enrollment; CD patients were commonly treated with biologics (71.6%) and immunosuppressors (67.4%), and UC patients were commonly treated with mesalazine [5-Aminosalicylic acid (5-ASA)] derivatives (69.9%) and immunosuppressors (44.1%). More than 50% of the CD patients had ileocolonic disease, and 41.7% presented with stricturing disease. One-quarter of CD patients had undergone CD-related surgery in the past 3 years, and this proportion was lower in the Northeast/Midwest region (2.9%).

CONCLUSION

In Brazil, there are regional variations in IBD management. CD outweighs UC in both frequency and disease activity. However, one-quarter of UC patients have active disease, and most are receiving 5-ASA treatment.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Disease activity; Epidemiology; Treatment

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Core Tip: In this multicenter study from Brazil, a substantial proportion (45%, and less pronounced in the South) of Crohn's disease patients had active disease despite being treated with biologics and immunosuppressors. One-quarter (higher in the Northeast/Midwest region) of ulcerative colitis patients had active disease, with the majority treated with 5-Aminosalicylic acid derivatives. In the largest Latin American country, regional differences were observed regarding inflammatory bowel diseases (IBD) activity and treatment patterns. Findings from this study can further elucidate about variations in clinical practice, ultimately promoting debate among specialists regarding the optimal management of IBD patients.

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INTRODUCTION

Inflammatory bowel diseases (IBDs) comprise mainly Crohn's disease (CD) and ulcerative colitis (UC)^[1]. Signs and symptoms of active IBD may include abdominal pain, rectal bleeding, diarrhea and fatigue^[2]. The global incidence of UC varies from 0.5 to 24.5 *per* 100000 inhabitants, while the CD incidence ranges from 0.1 to 16 *per* 100000 inhabitants^[3,4]. Although the incidence of IBD has been stable in European and North American regions, the incidence and prevalence of IBD is steadily rising across Latin American (LA) countries^[5,6].

Brazil is the largest LA country, with a 2017 Human Development Index of 0.759^[7]. However, socioeconomic and health care disparities reduce this index to 0.578 when it is adjusted for inequality^[7]. These disparities are also observed among Brazilian states or regions. States in the South and Southeast regions have higher socioeconomic levels and a large influence of European immigrant communities than the Northeastern states^[8].

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Epidemiologic information about IBD in Brazil is limited^[4,9,10]. This country has one of the highest increases in IBD incidence among newly industrialized countries, with annual percentage increases of 11.1% in CD incidence and 14.9% in UC incidence from 1988 to 2012^[5,6]. In addition, the incidence of IBD in Brazil was estimated at 0.08 *per* 100000 inhabitants in 1988, but the CD incidence rose from 0.68 (1991-1995) to 3.5 (2001-2005), being observed a peak incidence of 5.5 *per* 100000 inhabitants in 2015^[11]. The same trend can be observed at a regional level, with Sao Paulo State showing the highest IBD incidence when compared to other areas of Brazil^[12-14].

Given the complexity and heterogeneity of IBD, treatment decisions should consider the disease activity and severity, the extent of the inflammatory process, steroid dependency and risk factors for poor prognosis, among other factors^[9,15,16]. Treatments are effective in relieving symptoms and can alter the natural debilitating course of these diseases, and several strategies are available^[1,17].

In Brazil, current treatment options include mesalazine [5-Aminosalicylic acid (5-ASA)] derivatives, steroids, immunosuppressors and biologics therapy, such as antitumor necrosis factor (anti-TNF), anti-integrin drugs, anti-interleukin (IL)12 and IL-23 (only for CD treatment) and Janus Kinase inhibitor (tofacitinib, for UC treatment)^[17-20]. Biologic therapy has been increasingly used, especially for moderate-to-severe IBD or for patients with no response to conventional treatments^[9]. Infliximab^[17,21], adalimumab^[22,23], certolizumab, vedolizumab^[18,20] and ustekinumab^[19,24] are effective for the induction and maintenance of IBD clinical remission. However, some constraints on the Public Health System have been reported regarding access to biologic drugs for UC (e.g., costs and distance from health care facilities), which may compromise the achievement and maintenance of disease control.

Due to the increased incidence and prevalence of IBD and the diversity of IBD treatments in Brazil, this study aimed to describe the sociodemographic, clinical and therapeutic characteristics of IBD outpatients in Brazil overall and in three major geographical regions of Brazil: The Southeast (SE), South and Northeast/Midwest (NE/MW).

MATERIALS AND METHODS

Study design and participants

The Real-world Data of Moderate to Severe Inflammatory Bowel Disease in Brazil (RISE BR) study was a multicenter, noninterventional, cross-sectional study with a 3-year retrospective chart review component. Patients were enrolled consecutively from October 2016 until February 2017 at scheduled clinical appointments at 14 Brazilian IBD reference centers in both the public (9 centers) and private (5 centers) health systems and from across different areas in Brazil: SE (8 centers from the states of Sao Paulo, Rio de Janeiro and Minas Gerais), South (3 centers from the states of Parana and Rio Grande do Sul) and NE/MW (3 from Bahia, Piaui and Goias states, the latter from Midwest region).

Eligible participants had an established diagnosis of UC or CD, were aged ≥ 18 years old and had a previous event suggesting moderate-to-severe IBD at least 6 mo prior to enrollment, irrespective of disease activity at enrollment. Exclusion criteria were presenting indeterminate or unclassified colitis, participation in an interventional study within 3 years prior to enrollment, mental incapacity, unwillingness to participate or language barriers precluding adequate understanding or cooperation with the study protocol. Patients who were hospitalized at enrollment or under off-label treatment with vedolizumab were also excluded.

The study was approved by local ethics committees, and all participants provided written informed consent prior to the study (ClinicalTrials.gov Identifier: NCT02822235).

Data variables

Sociodemographic data (sex, age, educational level, and professional status) and smoking habits were collected from the medical records. The clinical variables related to IBD included the time since IBD diagnosis, Montreal classification (*i.e.*, location and severity/behavior)^[25], steroid status (dependent or refractory), familial history of IBD and the presence of extraintestinal manifestations (EIMs). Steroid-dependent disease was defined in patients who either (1) were unable to reduce steroid use to below the equivalent of prednisolone 10 mg/d within 3 mo of starting steroids, without recurrent disease; or (2) had a relapse within 3 mo of stopping glucocorticoids. Steroid-refractory disease was defined as active disease despite the use of up to 0.75 mg/kg/d

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of prednisolone over 4 wk.

At enrollment, CD activity was assessed by the investigator, and active disease was defined according to one of the following criteria: Harvey Bradshaw Index (HBI) ≥ 8 ^[26] or Crohn's Disease Activity Index (CDAI) ≥ 220 ^[2] or calprotectin $> 200 \mu\text{g/g}$ or colonoscopy suggestive of inadequate control performed during the previous year. UC activity at enrollment was assessed with the 9-item partial Mayo (pMayo) score. This score results from the scores for the three categories of the total Mayo score (bleeding, stool frequency, physician assessment) without the endoscopic subscore^[27]. When available, the endoscopic findings at enrollment were assessed using the Mayo endoscopic subscore, where a score ≥ 2 corresponds to moderate-to-severe UC^[27]. Active UC was defined as pMayo ≥ 5 .

Current and prior IBD treatment (*i.e.*, 5-ASA derivatives, immunosuppressors, biologics, steroids and antibiotics) and the number of previous outpatient visits, surgeries and hospitalizations due to IBD were collected from medical records for the previous 3 years.

Statistical analysis

Overall, 400 patients were expected to be enrolled, irrespective of IBD type. This sample size allowed estimates of disease activity with a 95% confidence interval (CI) and a margin of error $< 5\%$. All analyses were broken down by IBD type (UC or CD) and by geographic region (South, SE and NE/MW).

Descriptive statistics (mean, median, standard deviation and minimum-maximum) were used to analyze sociodemographic, clinical and treatment-related variables. Student's t-test for independent samples or the Mann-Whitney test were used to compare CD and UC patients in terms of quantitative variables. Statistical tests were two-tailed, and significance was set at 5%. There was no imputation of missing values. Statistical analysis was performed using SAS® (version 9.4, SAS Institute, Inc., Cary, NC, United States).

RESULTS

Sociodemographic and clinical characteristics of the sample, overall and by region

Overall, 407 patients – 264 (64.9%) with CD and 143 (35.1%) with UC – were included in the study (Figure 1). The ratio of CD:UC patients was 1.85 for the overall sample, 2.09 in the SE, 1.62 in the South and 1.21 in the NE/MW.

The median age at enrollment was 41.0 (20-72) years for CD and 45.0 (19-84) years for UC ($P = 0.029$), and the majority of patients were female (54.2% and 56.6% in CD and UC, respectively) (Table 1). Approximately 12.5% of the CD patients and 10.5% of the UC patients had a family history of IBD. The median disease duration was 10.0 years for both CD and UC. No statistically significant differences were observed for any sociodemographic or CD or UC clinical characteristics except for age at enrollment.

The South region had a lower prevalence of females with CD (41.2%) than the SE and NE/MW regions did (56.6% and 52.9%, respectively) (Table 1). The median age at CD diagnosis was higher in the NE/MW group (42.0 years) than in the South and SE groups (29.0 and 28.0 years, respectively). The South had a higher proportion of CD patients with higher education (65.2%) and a lower proportion of unemployed CD patients (16.7%) than the SE (28.6%) and NE/MW (30.4%) regions. Most CD patients in the South region were treated at private hospitals (67.6%), while in the NE/MW and SE regions, public hospitals were the most frequent treatment setting (81.1% and 79.4% of patients, respectively). Over 70% of CD patients in the SE region had never smoked, compared to 53.6% in the South and 65.2% in the NE/MW. The presence of EIMs in CD patients was higher in the NE/MW (53.8%) and lower in the South (25.1%).

The NE/MW region had a higher prevalence of females with UC (64.3%) than the SE and South regions did (57.4% and 42.9%, respectively) (Table 1). The median disease duration of UC was higher in the South (14.0 years) and lower in the NE/MW (6.0 years). Half of the UC patients in the South (50.0%) had a higher education, compared to 21.2% in the SE and 6.2% in the NE/MW. The proportion of unemployment among UC patients was higher in the SE (26.6%) and lower in NE/MW (14.8%). Most UC patients in the SE and NE/MW regions were treated at public hospitals (87.2% and 89.3%, respectively), while in the South, private hospitals were the most frequently used treatment settings (85.7% of patients). Over 70% of UC patients in the SE and South regions had never smoked, compared to 45.5% in the NE/MW. The prevalence of EIMs in UC patients was lower in the South (25.0%) and

Table 1 Sociodemographic characteristics and clinical features of Crohn's disease and ulcerative colitis patients by geographic region of Brazil

	Total		Southeast		South		Northeast/Midwest	
	CD (n = 264)	UC (n = 143)	CD (n = 196)	UC (n = 94)	CD (n = 34)	UC (n = 21)	CD (n = 34)	UC (n = 28)
Age (yr)	41.0 [20-72]	45.0 [19-84]	41.0 [21-72]	44.0 [20-78]	37.5 [20-67]	44.0 [19-66]	41.0 [24-68]	51.0 [26-84]
Female	143 (54.2)	81 (56.6)	111 (56.6)	54 (57.4)	14 (41.2)	9 (42.9)	18 (52.9)	18 (64.3)
Disease duration (yr)	10.0 [0.5-45.0]	10.0 [0.5-31.0]	11.0 [1.0-45.0]	10.0 [0.5-31.0]	8.0 [1.0-30.0]	14.0 [1.0-29.0]	9.0 [1.0-31.0]	6.0 [1.0-22.0]
Age at diagnosis (yr)	29.0 [12-70]	34.0 [14-70]	28.0 [12-70]	33.0 [15-64]	29.0 [18-63]	32.0 [14-64]	42.0 [20-70]	32.0 [18-60]
Educational level ¹								
Not literate	3 (1.4)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)
Primary school	52 (25.1)	38 (38.8)	47 (29.2)	26 (39.4)	3 (13.0)	2 (12.5)	2 (8.7)	10 (62.5)
Secondary school	83 (40.1)	37 (37.7)	66 (41.0)	26 (39.4)	5 (21.7)	6 (37.5)	13 (56.5)	5 (31.3)
Higher education	69 (33.3)	23 (23.5)	46 (28.6)	14 (21.2)	15 (65.2)	8 (50.0)	7 (30.4)	1 (6.2)
Missing	57	45	35	28	11	5	11	12
Professional situation								
Employed	101 (44.3)	53 (42.7)	77 (44.0)	32 (40.5)	13 (54.2)	13 (72.2)	11 (37.9)	8 (29.6)
Unemployed	61 (26.8)	33 (26.6)	44 (25.1)	21 (26.6)	4 (16.7)	3 (16.7)	13 (44.8)	9 (33.3)
Retired	30 (13.2)	15 (12.1)	24 (13.7)	11 (13.9)	5 (20.8)	0 (0.0)	1 (3.4)	4 (14.8)
Student	10 (4.4)	5 (4.0)	8 (4.6)	3 (3.8)	2 (8.3)	1 (5.6)	0 (0.0)	1 (3.7)
Other	26 (11.4)	18 (14.5)	22 (12.6)	12 (15.2)	0 (0.0)	1 (5.6)	4 (13.8)	5 (18.5)
Missing	36	19	21	15	10	3	5	1
Health system								
Public	197 (74.6)	110 (76.9)	159 (81.1)	82 (87.2)	11 (32.4)	3 (14.3)	27 (79.4)	25 (89.3)
Private	67 (33.3)	33 (23.1)	37 (18.9)	12 (12.8)	23 (67.6)	18 (85.7)	7 (20.6)	3 (10.7)
Family history of IBD	33 (12.5)	15 (10.5)	27 (13.8)	10 (10.6)	3 (8.9)	3 (14.3)	3 (8.8)	2 (7.1)
Smoking habits ²								
Current smoker	24 (9.9)	3 (2.3)	20 (10.5)	3 (3.3)	3 (10.7)	0 (0.0)	1 (4.3)	0 (0.0)
Former smoker	47 (19.4)	38 (28.8)	30 (15.7)	21 (23.1)	10 (35.7)	5 (26.3)	7 (30.4)	12 (54.5)
Never smoked	171 (70.7)	91 (68.9)	141 (73.8)	67 (73.6)	15 (53.6)	14 (73.7)	15 (65.2)	10 (45.5)
Missing	22	11	5	3	6	2	11	6
Any EIM ³	54 (37.8)	30 (38.0)	41 (38.7)	21 (42.0)	6 (25.0)	4 (25.0)	7 (53.8)	5 (38.5)
Use of steroids ⁴								
Steroid dependent	31 (14.8)	23 (19.3)	21 (13.8)	9 (11.8)	6 (19.4)	11 (55.0)	4 (15.4)	3 (13.0)
Steroid refractory	16 (7.7)	11 (9.2)	10 (6.6)	7 (9.2)	2 (6.5)	2 (10.0)	4 (15.4)	2 (8.7)
No previous use	87 (41.6)	36 (30.3)	66 (43.4)	22 (28.9)	10 (32.3)	3 (15.0)	11 (42.3)	11 (47.8)
Unknown	75 (35.9)	49 (41.2)	55 (36.2)	38 (50.0)	13 (41.9)	4 (20.0)	7 (26.9)	7 (30.4)
Missing	55	24	44	18	3	1	8	5

Data are shown as *n* (%) or median [range].¹Highest level attended.²Current smokers: patients who were smoking at enrollment and had smoked 100 cigarettes in their lifetime. Former smokers: Patients who were not smoking at enrollment but had smoked 100 cigarettes in their lifetime.³Extraintestinal manifestations observed: For the Crohn's disease population—arthralgia (reported in all regions), arthritis (in the Southeast and

Northeast/Midwest), sacroiliitis (only in the Southeast), erythema nodosum (only in the Southeast), pyoderma gangrenosum (only in the Southeast), uveitis (only in the Southeast), cholelithiasis (only in the Southeast), nephrolithiasis (only in the Southeast), hypertension (only in the Southeast), other (not specified) (reported in all regions); for the Ulcerative colitis population—arthralgia (reported in the Southeast and Northeast/Midwest), arthritis (only in the Southeast), sacroiliitis (in the South and Northeast/Midwest), pyoderma gangrenosum (only in the Northeast/Midwest), psoriasis (only in the Southeast), uveitis (only in Southeast), sclerosing cholangitis (in the Southeast and South), nephrolithiasis (only in Southeast), hypertension (in Southeast and Northeast/Midwest), other (not specified) (in the Southeast and South).

⁴Steroid-dependent disease: Patients who either (1) were unable to reduce steroid use to below the equivalent of prednisolone 10 mg/d within 3 mo of starting steroids, without recurrent disease; or (2) had a relapse within 3 mo of stopping glucocorticoids; steroid-refractory disease: Active disease despite the use of up to 0.75 mg/kg/d of prednisolone over 4 wk. CD: Crohn's disease; EIM: Extraintestinal manifestations; UC: Ulcerative colitis; IBD: Inflammatory bowel diseases.

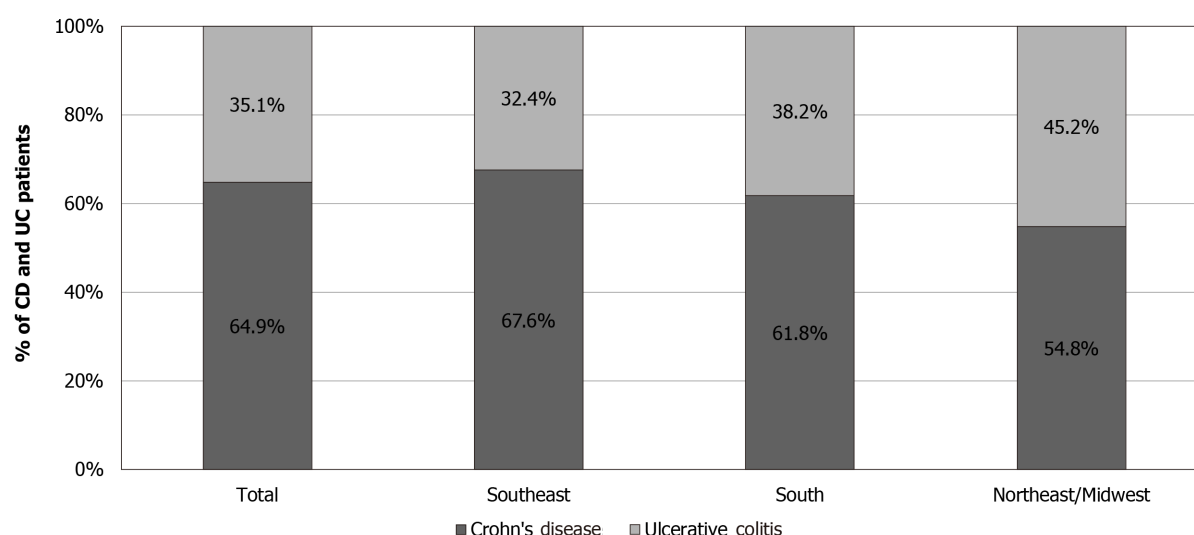


Figure 1 Frequency (%) of Crohn's disease and ulcerative colitis, overall and by Brazilian region. CD: Crohn's disease; UC: Ulcerative colitis.

higher in the SE (42.0%). The presence of steroid-dependent behavior was highest in the South at 55.0% of patients, compared to 13.0% in the NE/MW and 11.8% in the SE.

Regarding the Montreal classification and disease activity at enrollment (Table 2), most CD patients (56.8%) had an ileocolonic location, and this location was most frequent in the SE region (59.2%). The most frequent CD phenotype was stricturing disease (41.7%), and the rate was higher in the SE group (45.4%). A total of 105 (39.8%) CD patients had symptomatic perianal disease. Overall, 44.7% (95% CI: 38.7%-50.7%) of CD patients presented with active disease at enrollment: 17.4% scored HBI $\geq$ 8 or CDAI $\geq$ 220, 15.2% had fecal calprotectin $>$ 200 μ g/g, and 26.1% had a colonoscopy result suggestive of disease activity (presence of ulcerative lesions in any segment of the gut) during the previous year. The proportion of patients with active CD did not vary substantially across the regions. Nevertheless, only half of the patients had undergone CDAI evaluations.

Approximately half of UC patients presented with pancolitis (51.7%), and this prevalence was lower in the NE/MW region (28.6%) (Table 2). Over half (52.1%) of the UC patients had moderate or severe disease according to the Mayo endoscopic subscore (although nearly half of the patients had missing data). Approximately 40% of UC patients were asymptomatic according to the Montreal classification. The median total Mayo score was 2.0 (0.0-10.0, $n = 71$), although data were missing for nearly half of the patients. A quarter of UC patients (25.2%; 95% CI: 18.1%-32.3%) had active disease at enrollment. Active UC was most predominant in the NE/MW (42.9% of patients), compared to 23.8% and 20.2% of patients in the South and SE regions, respectively.

IBD treatment patterns and health care resource utilization

The vast majority of CD and UC patients were on treatment at enrollment (97.0% of CD patients and 96.5% of UC patients) (Table 3). The most common treatments among CD patients were biologics (71.6% of patients), followed by immunosuppressors (67.4%). This pattern was similar across the regions. The most frequent treatment among UC patients was 5-ASA derivatives (69.9% of patients), followed by

Table 2 Montreal classification and activity scores at enrollment by inflammatory bowel diseases type and geographic region

CD classification	CD patients (<i>n</i> = 264)	Southeast (<i>n</i> = 196)	South (<i>n</i> = 34)	Northeast/Midwest (<i>n</i> = 34)
Location ¹				
L1-ileal	67 (25.4)	50 (25.5)	10 (29.4)	7 (20.6)
L2-colonic	42 (15.9)	26 (13.3)	5 (14.7)	11 (32.4)
L3-ileocolonic	150 (56.8)	116 (59.2)	18 (52.9)	16 (47.1)
L4-upper GI tract disease	17 (6.4)	11 (5.6)	2 (5.9)	4 (11.8)
Behavior				
B1-Nonstricturing/nonpenetrating	58 (22.0)	33 (16.8)	9 (26.5)	16 (47.1)
B2-Stricturing	110 (41.7)	89 (45.4)	14 (41.2)	7 (20.6)
B3-Penetrating	91 (34.5)	70 (35.7)	10 (29.4)	11 (32.4)
Perianal disease	105 (39.8)	87 (44.4)	12 (35.3)	6 (17.6)
HBI score	2.0 [0-37]	2.0 [0-37]	2.0 [0-17]	3.5 [0-12]
Missing	34	32	0	2
CDAI	137.0 [-25-495]	141.0 [-25-495]	NA	93.0 [-22-292]
Missing	187	137	34	16
Active CD ²	118 (44.7)	89 (45.4)	13 (38.2)	16 (47.0)
HBI ≥ 8 or CDAI ≥ 220	46 (17.4)	UNK	UNK	UNK
Fecal calprotectin > 200 µg/g	40 (15.2)	UNK	UNK	UNK
Colonoscopy result suggestive of disease activity during the previous year	69 (26.1)	UNK	UNK	UNK
UC classification	UC patients (<i>n</i> = 143)	Southeast (<i>n</i> = 94)	South (<i>n</i> = 21)	Northeast/Midwest (<i>n</i> = 28)
Extension				
E1-distal UC	43 (30.1)	27 (28.7)	8 (38.1)	8 (28.6)
E2-left-sided	26 (18.2)	12 (12.8)	2 (9.5)	12 (42.9)
E3-pancolitis	74 (51.7)	55 (58.5)	11 (52.4)	8 (28.6)
Severity				
S0-asymptomatic	57 (39.9)	36 (38.3)	9 (42.9)	12 (42.9)
S1-mild UC	32 (22.4)	25 (26.6)	3 (14.3)	4 (14.3)
S2-moderate UC	40 (28.0)	25 (26.6)	7 (33.3)	8 (28.6)
S3-severe UC	14 (9.8)	8 (8.5)	2 (9.5)	4 (14.3)
Mayo endoscopic subscore (<i>n</i> = 71)				
Normal	16 (22.5)	9 (19.1)	1 (12.5)	6 (37.5)
Mild disease	18 (25.4)	13 (27.7)	2 (25.0)	3 (18.8)
Moderate disease	28 (39.4)	20 (42.6)	3 (37.5)	5 (31.3)
Severe disease	9 (12.7)	5 (10.6)	2 (25.0)	2 (12.5)
Missing	72	47	13	12
Total Mayo score	2.0 [0.0-10.0]	3.0 [0.0-9.0]	2.5 [0.0-10.0]	2.0 [0.0-8.0]
Missing	72	47	13	12
Partial Mayo score	1.0 [0.0-9.0]	1.5 [0.0-9.0]	1.0 [0.0-9.0]	1.5 [0.0-8.0]
Active UC ²	36 (25.2)	19 (20.2)	5 (23.8)	12 (42.9)

Data are shown as *n* (%) or median [range].

¹More than one possible option: L4 includes isolated upper gastrointestinal (GI) tract disease or upper GI tract disease combined with L1, L2 or L3.

²Active disease at enrollment was defined as presenting Harvey-Bradshaw index ≥ 8 or Crohn's disease activity index ≥ 220 or fecal calprotectin > 200 mg/g or colonoscopy suggestive of inadequate control during the previous year (for Crohn's disease patients) and partial Mayo score ≥ 5 (for ulcerative colitis patients). CD: Crohn's disease; CDAI: Crohn's disease activity index; HBI: Harvey-Bradshaw index; UC: Ulcerative colitis; UNK: Unknown; GI: Gastrointestinal.

immunosuppressors (44.1%). Most UC patients in the NE/MW region (96.4%) were being treated with 5-ASA derivatives, while over half (57.1%) of patients in the South region were being treated with immunosuppressors.

Approximately one-quarter (25.4%) of patients had undergone CD-related surgery in the past 3 years, and this proportion was lower in the NE/MW region (2.9% of patients). The median number of CD-related surgeries *per* patient in the previous 3 years was 1.0 (range 1-5). The median number of CD-related hospitalizations in the previous 3 years was 1.0 (range 1-5) *per* patient, and the median number of CD specialist appointments was 11.0 (range 1-45) *per* patient.

Only 2.8% of patients, all from the SE region, had undergone UC-related surgery in the previous 3 years, and the median number of surgeries *per* patient was 2.0 (range 1-2). The median number of UC-related hospitalizations in the previous 3 years was 1.0 (range 1-5), and the median number of UC specialist appointments was 10.0 (range 1-39), which was higher in the South (median 14.0 appointments) than in the SE and NE/MW (median 10.0 and 9.0, respectively). The proportion of patients with at least one hospitalization in the previous 3 years was higher among the CD patients than among the UC patients (38.3% *vs* 19.6%, respectively; $P < 0.001$).

DISCUSSION

The objective of the RISE BR study was to characterize IBD patients in terms of their sociodemographic and clinical features and their treatment patterns. As Brazil is a large country with known inequalities, this study allowed us to understand variations across the South, SE and NE/MW regions.

Although UC is more prevalent than CD in most LA countries^[28], including Brazil^[10,12,13,29], we found a predominance of CD compared to UC, both overall and by region. Nevertheless, our findings are aligned with the CD and UC prevalence (24.1 and 14.1/100000, respectively) reported in a systematic review from LA^[11] and those reported in a recent epidemiological characterization of 579 IBD patients from a Southeastern Brazilian tertiary care center, which found a CD prevalence of 56.1%^[30].

The sociodemographic and clinical features of IBD patients varied across the three Brazilian regions. Females were more predominant in the SE and NE/MW regions (for both diseases), a finding that is in line with previous studies^[13,14,29-31]. In the NE/MW region, the majority of IBD patients had a lower educational level and lower employment status. The latter finding could be attributed not only to the incapacity associated with the disease but also to the difficulty of obtaining work opportunities in the region. In the South, IBD patients were mostly men, had higher education and employment rates and were more likely to be followed up in the private setting than patients in the other regions.

Patients from the SE had fewer EIMs, and a lower proportion had active UC. These findings may suggest socioeconomic disparities among the regions, which can translate into differences in access to and use of health care services and medicines.

A substantial proportion of CD patients (44.7%) showed active disease based on clinical (HBI or CDAI), biomarker (fecal calprotectin) or endoscopic outcomes (presence of ulcerative lesions in any segment of the gut). Similar proportions were found across the three Brazilian regions, although the proportions were somewhat lower in the South region. On the other hand, a quarter of UC patients had active disease based on pMayo or Mayo endoscopic subscores, and this proportion was substantially higher in the NE/MW region (42.9%). These results highlight the importance of adopting treatment targets for IBD that can be used as a "treat-to-target" management strategy, which will ultimately improve disease outcomes^[32].

Most CD patients (56.8%) had ileocolonic disease, and a substantial proportion of patients showed a complicated phenotype (41.7% with stricturing disease), particularly in the SE and South regions. Lima Martins *et al*^[29] reported a lower prevalence of ileocolonic location (30.9%) and a less stricturing phenotype (21.0%).

Table 3 Inflammatory bowel diseases treatment at enrollment and use of health care resources during the previous 3 years by inflammatory bowel diseases type and by geographic region

	CD patients (n = 264)	Southeast (n = 196)	South (n = 34)	Northeast/Midwest (n = 34)
Any CD treatment at enrollment ¹	256 (97.0)	189 (96.4)	33 (97.1)	34 (100.0)
CD treatment at enrollment ²				
5-ASA derivates	39 (14.8)	24 (12.2)	7 (20.6)	8 (23.5)
Biological therapy	189 (71.6)	140 (71.4)	21 (61.8)	28 (82.4)
Infliximab	106 (40.2)	NA	NA	NA
Adalimumab	78 (29.5)	NA	NA	NA
Vedolizumab	4 (1.5)	NA	NA	NA
Certolizumab	1 (0.4)	NA	NA	NA
Ustekinumab	1 (0.4)	NA	NA	NA
Immunosuppressors	178 (67.4)	133 (67.9)	18 (52.9)	27 (79.4)
Thiopurines	165 (62.5)	NA	NA	NA
Methotrexate	14 (5.3)	NA	NA	NA
Corticosteroids	30 (11.4)	21 (10.7)	2 (5.9)	7 (20.6)
Prednisone	29 (11.0)	NA	NA	NA
Hydrocortisone	1 (0.4)	NA	NA	NA
Methylprednisolone	1 (0.4)	NA	NA	NA
Antibiotics	14 (5.3)	9 (4.6)	1 (2.9)	4 (11.8)
Any previous CD-related surgery ³	67 (25.4)	58 (29.6)	8 (23.5)	1 (2.9)
CD-related surgeries <i>per patient</i>	1.0 [1-5]	1.0 [1-5]	1.5 [1-3]	2.0
Any previous CD-related hospitalization	101 (38.3)	71 (36.2)	14 (41.2)	16 (47.0)
CD-related hospitalizations <i>per patient</i>	1.0 [1-5]	1.0 [1-5]	1.0 [1-4]	1.0 [1-3]
Previous CD appointments <i>per patient</i>	11.0 [1-45]	11.0 [1-45]	13.5 [4-43]	10.0 [1-21]
	UC patients (n = 143)	Southeast (n = 94)	South (n = 21)	Northeast/Midwest (n = 28)
Any UC treatment at enrollment ¹	138 (96.5)	89 (94.7)	21 (100.0)	28 (100.0)
UC treatment at enrollment ²				
5-ASA derivates	100 (69.9)	60 (63.8)	13 (61.9)	27 (96.4)
Biological therapy	41 (28.7)	30 (31.9)	7 (33.3)	4 (14.3)
Infliximab	31 (21.7)	NA	NA	NA
Adalimumab	9 (6.3)	NA	NA	NA
Vedolizumab	2 (1.4)	NA	NA	NA
Immunosuppressors	63 (44.1)	41 (43.6)	12 (57.1)	10 (35.7)
Thiopurines	59 (41.3)	NA	NA	NA
Methotrexate	3 (2.1)	NA	NA	NA
Tacrolimus	1 (0.7)	NA	NA	NA
Corticosteroids	26 (18.2)	15 (16.0)	6 (28.6)	5 (17.9)
Prednisone	24 (16.8)	NA	NA	NA
Hydrocortisone	2 (1.4)	NA	NA	NA
Prednisolone	2 (1.4)	NA	NA	NA
Antibiotics	7 (4.9)	6 (6.4)	1 (4.8)	NA
Any previous UC-related surgery ⁴	4 (2.8)	4 (4.3)	0 (0.0)	0 (0.0)

UC-related surgeries <i>per patient</i>	2.0 [1-2]	2.0 [1-2]	-	-
Any previous UC-related hospitalization	28 (19.6)	13 (13.8)	9 (42.9)	6 (21.4)
UC-related hospitalizations <i>per patient</i>	1.0 [1-5]	1.0 [1-2]	2.0 [1-5]	1.0 [1-2]
Previous UC appointments <i>per patient</i>	10.0 [1-39]	10.0 [1-39]	14.0 [4-38]	9.0 [1-17]

Data are shown as *n* (%) or median [range]. Percentages were calculated for the total group of patients.

¹Any inflammatory bowel diseases treatment ongoing or initiated at the study appointment.

²More than one possible option: patients could have combined treatment.

³The most common surgeries were fistulectomy/anal fistulectomy (20.4% of patients), partial colectomy (12% of patients) and enterotomy and/or enterorrhaphy with suture/resection (12%).

⁴Two total colectomies and two enterostomy closures.

CD: Crohn's disease; 5-ASA: 5-Aminosalicylic acid; NA: Not available; UC: Ulcerative colitis.

However, Parra *et al*^[30] found a predominance of ileocolonic location (53.0%) and penetrating phenotype (52.0%) in the SE region that was higher than that usually reported by European studies^[33]. Other studies, including ones from Hungary, the Netherlands, Australia and Asia, reported proportions of ileocolonic disease ranging from 38.8% to 45%^[34]. Parente *et al*^[35] reported a frequency of colonic location of 36.0% and a frequency of nonstricturing/nonpenetrating disease of 69.0% in the Northeast region. In our study, 47.1% of patients from the NE/MW region had nonstricturing/nonpenetrating disease, 47.1% showed ileocolonic location, and 32.4% had colonic location (approximately two times higher than the prevalence in the other two regions). The higher proportions of CD patients with a worse phenotype that we observed in our study – compared to others – could have resulted from differences in study populations, as we included patients that had a previous moderate-to-severe episode and that were followed at IBD referential centers – which, in general, receive patients with more complicated disease.

UC patients seemed to present less severe disease than CD patients, while most CD patients were receiving standard care with immunosuppressive drugs. Although the median disease duration was quite similar for both IBD types (approximately 10 years), in the NE/MW region, the disease duration for UC patients was lower (6 years). The median age at diagnosis in CD patients in this region was higher than that in other regions, exceeding 40 years old. The extent of UC influences the disease behavior and prognosis of the disease^[35]. In a 7-year follow-up study, approximately half of UC patients had inflammation that extended to the proximal transverse colon and beyond (pancolitis), a suggested risk factor for colectomy^[36]. For the three geographic regions, the results were similar to other Brazilian studies^[14,30,31], with UC patients in the NE/MW showing predominantly left-sided disease (42.9%), while patients from SE had more frequent pancolitis, which is aligned with findings from Uruguay (a 40.0% prevalence of extensive UC in Montevideo)^[37]. Even so, the rates of UC-related surgeries, including colectomies, and UC-related hospitalizations were low in the SE region. This may be because the reference IBD surgery centers in Brazil (*i.e.*, centers that perform a high number of IBD surgeries) are located in the South and SE regions.

One quarter of CD patients underwent surgery (fistulectomy being the most common) and had, on average, one hospitalization due to the disease in the previous 3 years, with no variations observed across the three regions. A very small percentage of UC patients underwent surgery (colectomy or closures of enterostomy) and had, on average, one hospitalization over the past three years. Hospitalization rates were substantially higher in the centers in the South, but for both CD or UC patients, few hospitalizations and surgeries were observed across the three regions during the previous three years.

Several risk factors for higher activity and a worse prognosis have been described, including genetics, environmental factors and factors related to early diagnosis and treatment^[38,39]. Family history is a window to both the genetic background and shared environment, and some authors suggest that having a relative with IBD is an important risk factor for the onset of IBD^[13,40]; however, this is a controversial issue, especially in a country with a mixed ethnic background such as Brazil^[35,41]. A systematic review with pooled data from several countries (excluding LA) showed a prevalence of family history ranging from 11%-13%^[42]. In our study, approximately 12% of CD patients (higher in SE) and 10% of UC patients (higher in South) reported a family history of the disease. One study conducted in northeastern Brazil showed that 7.9% of UC patients had a family history^[14]. Similarly, in a case-control study

conducted in the southeastern region of Brazil, 9.0% of the 145 CD patients had a family history, although this finding was not statistically associated with CD (OR = 1.51; 95%CI: 0.64-3.54)^[38]. Based on these results, we hypothesize that genetic background may play a smaller role in the increase in IBD incidence in Brazil, in addition to characteristics such as a high education level, urban residency, smaller family size and use of treated water^[38,43].

Smoking is an environmental factor that negatively affects the prognosis of some types of IBD, although evidence is also conflicting^[13,14,35,38]. In our sample, 9.9% of CD patients and only 2.3% of UC patients were current smokers, with similar rates across regions. Public health strategies that promote smoking cessation can partially explain the low rate of smoking observed if we consider that approximately 19% of CD patients and 29% of UC patients were former smokers. Although one should be cautious regarding this interpretation due to the volume of missing data regarding smoking status, this variable may be particularly relevant as smoking cessation might slow CD development and attenuate its severity, in contrast to UC, where smoking is considered a protective factor against the development of disease^[44].

Treatment is a major determinant of IBD prognosis, and several treatment strategies are available in Brazil^[1,22]. Considering that the study included moderate-to-severe patients, it is not surprising that almost all patients were on treatment at enrollment. UC patients were predominantly prescribed 5-ASA derivatives (approximately 70%), while biologics (71.6%) and immunosuppressors (67.4%) were the most common treatments among CD patients. A systematic review of studies from LA reported that less than 13% of UC patients used anti-TNF drugs, with the most common treatment being mesalazine (5-ASA compound), a lower-cost medicine^[28].

When considering Brazilian regions, the proportion of biologics users in the SE (71.4%) was similar to that previously reported by Parra *et al.*^[30]. All CD patients from the NE/MW region, a region with a higher proportion of patients with active CD, were taking medication. Notably, the proportion of UC patients with active disease was also higher in this region (42.9%) compared to the other regions, but even though the large majority of patients were medicated with 5-ASA derivatives (96.4%), the proportion of biologics users was much lower than that in the SE and South regions. In 2015, da Silva *et al.*^[14] reported that UC patients from two reference centers in Bahia state (Northeastern) were even less frequently prescribed biologic drugs (only 1.5% of the 267 patients). Together, these findings suggest that NE/MW UC patients may face some barriers regarding access to more advanced therapies, such as biologics therapy, which is not currently available for UC patients as part of the Brazilian public reimbursement system^[14]. Greater access to medical care and therapy for IBD patients in the South region (who were mainly recruited from private centers) may contribute to improving clinical, endoscopic and other outcomes in IBD patients.

One of the major strengths of this study was the number and diversity of IBD settings included, which covered the more densely populated regions of Brazil. In fact, the sociodemographic characteristics found in our study, overall and by region, corroborate the findings observed in other studies.

One of the study limitations is its cross-sectional nature, making it difficult to interpret associations between IBD activity at enrollment and sociodemographic and clinical features and treatments. Methodological and setting differences can partially explain the inclusion of more severe cases in our study, particularly among CD patients, when compared with other regional/single-center studies. In fact, the study sample included IBD patients from reference centers (including tertiary care centers) from both public and private settings with moderate-to-severe disease and an average of ten years of disease duration, which may reflect a heavily treated population, more prone to refractoriness, or with a more progressed/severe IBD but also represent a subgroup with higher medical needs. Since the scope of this study was to capture information in the outpatient setting only, one may not exclude the potential bias associated with exclusion of hospitalized patients, where information on more severe cases could have been captured. Capturing information on hospitalizations would require another sampling approach that would affect the study's recruitment rate. Due to the way data capture was designed, it was not possible to obtain robust information regarding treatment combinations (challenging to know whether treatments were done concomitantly or not). Moreover, some of the medical and treatment histories were captured from chart reviews, resulting in a substantial volume of missing data for some variables. Therefore, one should be cautious in interpreting the treatment patterns and medical data captured from this study. Finally, the small samples obtained for the South and NE/MW regions limited comparisons among the three regions.

CONCLUSION

In conclusion, this study provided a picture of IBD in private and public settings in three important regions of Brazil. CD patients predominated over UC patients. Some differences were observed across the regions regarding sociodemographic characteristics. The SE region presented a higher proportion of females and higher levels of education and employment. Sao Paulo, which is located in the SE, is the most developed state in Brazil, with higher economic activity and greater opportunities for employment. Based on public health system records from 2012-2015, the state of Sao Paulo recorded the highest IBD incidence, namely, 6.14 and 7.16 *per* 100000 inhabitants/year for CD and UC, respectively^[12].

A substantial proportion of the CD patients had active disease (though the proportion was less pronounced in the South) and were being treated primarily with biologics and immunosuppressors. A quarter of the UC patients had active disease (the proportion was considerably higher in the NE/MW), and most were treated with 5-ASA derivatives. Although the Brazilian public health system is free and universal, patient access to specialized care is frequently delayed and difficult. Furthermore, biological therapy, until very recently, was available through the government health system only to CD, which could justify the low use by UC patients. As the prevalence of infectious disease – an IBD risk factor in Brazil^[43] – is high in NE/MW region, the physicians from primary health care and also specialists from other areas (*e.g.*, dermatologists, rheumatologists), should be informed and aware about IBD, in order to perform an earlier diagnosis and/or referral to centers with expertise in IBD. We suggest that, with more timely diagnosis of UC and with the improvement of patient access to biologic drugs in this region, a better control of UC activity can be achieved. Future studies in this region should also address other IBD risk factors such as education level, local geographic features, urban residency, family size and use of treated water, on a context of public health strategy.

By characterizing the sociodemographic and clinical features of the IBD population across different settings and regions, describing the treatment patterns and the use of health care resources, the findings from this study can further contribute to understanding practices and variations, with the ultimate goal of promoting discussion among specialists regarding the optimal management of IBD patients in Brazil.

ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel diseases (IBD) incidence and prevalence has been consistently increasing in Latin American countries. Brazil is the largest country in South America, with regional sociodemographic and health care disparities that can impact IBD epidemiology and treatment.

Research motivation

IBD incidence and prevalence have been increasing in Brazil but the information about IBD epidemiology and setting is still scarce in this continent-sized country. On the other hand, multiple treatments are currently available but some constraints on the access to biologic drugs have been reported. A real-world characterization of the IBD patient profile, disease activity and uptake of IBD treatments in Brazil is required to support the optimization of IBD management.

Research objectives

This study aimed to describe the sociodemographic, clinical and therapeutic characteristics of IBD outpatients in Brazil, overall and by three major geographical regions of Brazil: The Southeast (SE), South and Northeast/Midwest (NE/MW).

Research methods

A multicenter, cross-sectional study with a 3-year retrospective chart review component was conducted in 14 Brazilian IBD reference centers. Adult patients with moderate-to-severe Crohn's disease (CD) or ulcerative colitis (UC) were consecutively enrolled between October 2016 and February 2017, during routinely scheduled in-office appointments. Active IBD at enrolment was defined as presenting, for CD patients, Harvey Bradshaw Index ≥ 8 , Crohn's Disease Activity Index ≥ 220 ,

calprotectin level > 200 µg/g or an active result based on colonoscopy suggestive of inadequate control during the previous year, and, for UC patients, presenting a partial Mayo score ≥ 5. Descriptive statistics were used to analyze study variables, overall and by geographical region.

Research results

We observed that, in Brazil, CD was more frequent than UC, overall and by region. Almost half of CD patients and one quarter of UC patients presented active disease at enrolment and, while CD patients were commonly treated with biologic drugs, UC patients were mostly treated with 5-Aminosalicylic acid (5-ASA) derivatives and immunosuppressors. CD patients showed a worse phenotype, namely ileocolonic disease and stricturing disease, and one-quarter had undergone CD-related surgery in the past 3 years. In the South, IBD patients were mostly men, had higher education and employment rates and were more likely to be followed up in the private setting than patients in the other regions. In the NE/MW region, the majority of IBD patients had a lower educational level and lower employment status. In this region, more UC patients had active disease compared to the SE and South regions, but the proportion of biologics users was much lower than that in the other regions.

Research conclusions

In Brazil, CD frequency, activity and severity outweighs those of UC. Nevertheless, one-quarter of UC patients have active disease, and most are receiving 5-ASA treatment. Regional variations in IBD management were observed, with the NE/MW region presenting more UC patients with active disease and less treated.

Research perspectives

Findings from this study can elucidate about differences in clinical practice across Brazilian regions, thus promoting discussion among specialists regarding the optimal management of IBD patients.

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