International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Clinical Spectrum of Inflammatory Bowel Disease in Kashmiri Population: A Prospective Study in a Tertiary Care Hospital

Waseem Javid[1], Showkat A. Kadla[2], Nisar A. Shah[3]

[1]Senior resident, [2]Head Of Deparment, [3]Professor
[1, 2, 3]Department of gastroenterology GMC, Srinagar

Abstract

Background and objectives: The global incidence of inflammatory bowel disease (IBD), Ulcerative colitis (UC) and Crohn's disease (CD) is on the rise. We don't have any epidemiological or descriptive data especially in Kashmir valley, India. The objective of this study is to identify socio-demographic and clinical characteristics among patients with IBD attending Tertiary hospital in Kashmir, India.

Methods: The current study was a hospital based prospective cross sectional observational study. It was conducted in the department of Gastroenterology, GMC Srinagar, Jammu and Kashmir, India. We applied a Questionnaire for patients diagnosed with IBD. We focussed on the socio-demographic and clinical variables of each patient.

Results: 100 patients with IBD whose age was more than 17 years were included in this study. Fifty seven of them (57%) were UC and forty three (43%) CD. The mean age of patients with UC was 38.7±6.19 years and 35.3±5.62 years for patients with CD. 48% of patients were males and 52% were females. The male/female distribution was 1.48:1 for UC and 1.45:1 for CD. The most common first presentation of UC and CD were bloody stools (63.2%) and pain abdomen (40%) respectively. Extra intestinal manifestations were present in 58% of UC and 42% of CD patients. CD mostly affected the terminal ileum location (L1) (60.5%). CD patients with stricture (18.6%), fistula (11.6) and /or perianal disease (11.6%) were mostly female and younger at diagnosis. Left sided colitis was the most common extension of UC (62%). Most of CD and UC patients were under treatment with different pharmacological agents which includes 5-ASA (71%), followed by Thiopurines (47%), steroids(50%) and anti- TNF therapy(16%). Majority of our patients are on follow up and in remission (97%) and three of UC patients (5.3%) died of COVID -19 infections mostly were elderly with severe disease.

Conclusion: Diagnostic delay is still a big concern, leading to more complicated disease. The higher proportion of complicated CD and extensive UC resulted in a greater need for healthcare resources in this cohort such as hospitalisation, surgery and biological treatment.

Keywords: Inflammatory bowel disease, UC,CD, Thiopurines, Biologicals, COVID-19

Introduction

Inflammatory Bowel Diseases (IBD) are characterised by chronic and recurrent inflammation of the gastrointestinal tract and are classified into two main types: Ulcerative colitis (UC) and Crohn's disease

(CD) [1]. Inflammatory bowel disease (IBD) has been considered as a disease of white people of European descent and has indistinctly been considered a rare entity in South East and South East Asia[2]. The micro biome signature in the Indian IBD population matches that of patients in west, indicating that the players in the pathogenesis of IBD are not different between the west and the east.[3]IBD in the west is characterised by a bimodal age distribution with peaks at age groups 20- 39 and 60-79 years. Secondly, the mean and median age at diagnosis of CD is a decade earlier than that of UC[4]. Another important finding that is visible in the Indian studies is the use of ATT in IBD patients. The dilemma that intestinal TB is a close mimic of CD often leads to a therapeutic ATT trial because CD specific therapy can be disastrous if a patient has ITB[5]. The primary objective of this study is to explore the clinical spectrum of IBD in the Kashmir region. Understanding these factors will not only aid in improving early diagnosis and management strategies for Crohn's disease in Kashmir but also contribute to the growing body of research on IBD in South Asia.

Objective

To study the demographic and clinical profile of inflammatory bowel disease among UC and CD patients attending Gastroenterology department, GMC Srinagar, Jammu and Kashmir, India.

Methodology

The current study was a hospital based prospective cross sectional observational study. It was conducted in the department of Gastroenterology, GMC Srinagar, Jammu and Kashmir, India. All consecutive newly diagnosed100 patients from age 17 and above were enrolled over a period of 18 months from December 2019 to June 2021. All participants in the study were included after proper informed written consent and permission was obtained beforehand from the institutional ethics committee **(IEC/GMC/DNB-GE/006).** All patients diagnosed with IBD were hospitalised or referred to Gastroenterology department, GMC Srinagar between 2019 to 2021 were included in the study. IBD diagnosis was based on the typical clinical course of the disease and endoscopic examination with histological confirmation of UC or CD. A prepared Questionnaire was recorded that involved information about demographic aspects (Age, Gender, Income, Residence, Smoking status and Family history) and clinical aspects (IBD type, EIM, Disease severity, The site of colon involvement based on colonoscopic findings and Kind of drugs used).To evaluate some of the EIM in addition to history taking and physical examination some of the laboratory tests and imaging were requested for all the patients. The IBD type was recorded using the previously described and validated Montreal classification for both UC and CD as below:

(Table 1.1) Montreal classification of UC

MONTREAL Classification	EXTENT	Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum
E2	Left sided UC	Involvement limited distal to the splenic flexure

E3	Extensive UC	Involvement extends proximal to the splenic flexure

(Table1.2)Montreal classification of CD

Characteristics	MONTREAL Classification
Age at diagnosis	A1=0-16 years A2=17 -40 years A3=> 40 years
Location	L1=Ileal L2=Colonic L3=Ileo-colonic L4=isolated Upper
Behaviour	B1= Inflammatory B2= Stricturing B3= Penetrating P=Perianal Disease Modifier

INCLUSION CRITERIA

1. Age 17 and above
2. Consecutive new Diagnosed cases of IBD

EXCLUSION CRITERIA

1. Paediatric IBD Cases
2. Patients with IBD-U (IBD Unclassified)
3. Patients with a diagnostic dilemma of CD vs. Intestinal TB
4. Moribund cases with critical illness
5. Pregnant IBD patients
6. Those who lost follow-up
7. Those who refuse to give consent

Results

Demographic characteristics

In our study 100 new cases of IBD were confirmed during the 18 month study. 43(43%) belonged to CD group and 57 (57%) belonged to UC group. The age range was 17 to 82 years. The mean age of onset of IBD recorded in our study was 37.5± 5.93 years (mean ±standard deviation) .Majority of patients belonged to age group of 17-40 years and it was statistically significant (p=0.006). There was no significant age difference between the UC and CD. Individual ages where recorded and data was

compiled according to Montreal Classification (MC). Due to selection bias of age group and ranges used in MC bimodal distribution was not reflected in UC group. In our study 41% CD patients were smokers although statistically not significant. Majority of Study patients were non-smokers (66%).

(Table 2) Demographic characteristics

Characteristic	Value
Total patients	100
CD/UC	43/57
Mean age group	37.5 years

CLINICAL PROFILE:

In our study majority of UC patients presented with Bloody stools (63.2%), followed by chronic Diarrhoea (28.5%), while majority of CD patients had pain abdomen (39.5%) and were diagnosed on being evaluation for anaemia in 15 (34.9%) patients.

(Table 3) Disease presentation of study patients

Disease presentation	CD		UC		Total	P-value
	No.	%age	No.	%age		
Pain abdomen	17	39.5	2	3.5	19%	<0.001*
Chronic diarrhea	6	14.0	16	28.1	22%	
Bloody stools	4	9.3	36	63.2	40%	
EIM	1	2.3	2	3.5	3%	
Anemia	15	34.9	1	1.8	16%	

***Statistically Significant Difference (P-value<0.05)**

In our study majority of CD patients had diagnostic delay of more than 12months (79.1%) in comparison to UC patients who were diagnosed earlier (54.4%), that was statistically significant. This delay may be attributed to Quite revealing symptoms, urban location and better healthcare reach of UC patients.

(Table 4) Diagnostic delay among study patients

Diagnostic delay	CD		UC		Total	P-value
	No.	%age	No.	%age		
< 6 Months	5	11.6	31	54.4	36%	<0.001*
6-12 Months	4	9.3	9	15.8	13%	
> 12 Months	34	79.1	17	29.8	51%	

Total	43	100	57	100	100%	
Mean±SD	13.1±4.59		7.5±3.74		10.1±4.17	

***Statistically Significant Difference (P-value<0.05)**

The most frequent EIMs were joint 26(26%), Skin and oral (15%) in both UC and CD. A more significant number of patients with skin and oral manifestations (23%) were identified with CD while hepato-biliary disease (5%) prevailed in UC. There was no significant statistical difference in joint, ocular manifestations between the two diseases. The high Occurrence of EIMs can be due to variations in Diet, environment and genetic factors

(Table 5) Extra intestinal manifestations among study patients

Extra intestinal manifestations	CD		UC		Total	P-value
	No.	%age	No.	%age		
Joint	12	28%	14	25%	26%	**0.503**
Occular	2	5%	2	4%	4%	**0.773**
Skin and oral	10	23%	5	9%	15%	**0.045***
Hepato biliary	1	2%	3	5%	4%	**0.821**
No manifestations	18	42%	33	58%	51%	**0.627**

***Statistically Significant Difference (P-value<0.05)**

In our study majority of UC patients were treated with Salicylates (70%) followed by steroids and Immuno-modulators (48%), Biologicals were used for 8.8% patients. Majority (67%) of CD patients were managed with steroids and immuno-modulators, while biologicals were used in 25.6% patients. Patients presenting with severe exacerbations and complications were started on steroids and later proved to be steroid dependent and where tried on Salicylates on long term remission, so in all patients we practically tried Salicylates.

(Table 6) Pharmacological treatment among study patients

Pharmacological treatment	CD		UC		Total	P-value
	No.	%age	No.	%age		
Corticosteroids	29	67.4	17	29.8	48.6%	**0.639**
Salicylate	17	39.5	40	70.17	54.85%	**0.032***
Immuno-modulators	29	67.4	18	31.6	49.5%	**0.021***
Biologicals	11	25.6	5	8.8	16%	**0.023***

***Statistically Significant Difference (P-value<0.05)**

DISCUSSION

India appears to be on the epidemiological crossroads where infectious diseases as well as diseases until now considered to be diseases of the western world are both being witnessed[6]. The study of IBD epidemiology in India has been hampered by several factors including a lack of universal accessibility to health care, hospital based studies, the absence of standardized case definitions, relevant databases and registries with appropriate validation and prospective data collection[7]. It is considered that the magnitude of UC is twice that of CD in Asia in comparison to the western world.. The present study showed a predominance of patients with UC. A similar finding was described by Gasparini et al who registered 53.84% of cases of UC and 46.16% of CD[8]. This dominancy was also noted in other epidemiological studies in India and worldwide[9-11]. However, it should be noted that there was an increase in the incidence of CD over the years in developed countries. A recent systemic review showed the ratio of UC: CD exceeding one in all regions[12].IBD occurs predominately in young adults. The average age of patients in this study (37.5±5 years) was similar to that found in most studies. The average age at diagnosis of IBD ranged between 30 and 40 years old and the average for CD (35.3±5.62) was lower than that for UC patients (38.7±6.19). Parente et al, in the epidemiological study carried out in Piaui, found a similar mean age at diagnosis (32±13.6 years for CD and 36±14.8 years for UC)[13]. In developed countries the highest incidence of CD was found in individuals between 20 and 29 years of age, and of UC between 20 and 39 years of age[14,15]. This difference may be related to geographical, cultural and diagnostic delay[16].In concordance with other Indian studies, ours showed male predominance in UC and CD group. The IBD task force survey documented that the male: female ratio was 1.4 and 1.3 for UC and CD respectively[4]. Likewise, the scholarly article on CD from three Indian centres demonstrated a male: female ratio of 1.843.The overall incidence of UC in western world is independent of gender. In CD less consistent findings have been reported with some cohorts suggesting a female predominance in the incidence of CD and others fail to find any gender difference whatsoever[14]. These findings contrast with those from Asia where male gender was associated with higher risk of Both CD and UC. In mainland china the risk ratio of CD and UC in males versus females is 1.15:1 and 2.4:1 respectively[15].The male preponderance can be due to either a relatively incidence in comparison to the western world or a manifestation of socio referral gender bias..Most of our UC patients presented with bleeding and Diarrhoea (62%), while, significant number of CD patients had pain abdomen and Anaemia under evaluation (84%).This is in concordance with data from Bryce perler et al, who conducted the study among IBD patients in the Ocean state Crohn's and colitis area registry (OSCCAR), a community cohort[20]. One of our patients in UC group presented with EIM (Pyoderma gangrenosum) and was diagnosed on referral from dermatologist. Most studies indicate that the prevalence of EIMs in Indian patients is more or less similar to the western scenario. Studies by kedia et al, from AIIMS Delhi revealed the overall prevalence of single and Multiple EIMs in UC and CD was 33.2 versus 38.3% and 6.9 versus 4.7% respectively. The commonest EIM noted in both IBD groups was peripheral arthopathy[14].Unlike western data ,where PSC and other hepato-biliary manifestations has been described as varying from 2.4 to 7.4%[21], the prevalence of PSC in our study was 2.3 and 4% in CD and UC respectively. This is not surprising because the frequency of PSC in UC from Indian studies varied from 1.3 to 3.9%. The probable reason for this low prevalence of PSC may be due to overall low prevalence rate of coexisting autoimmune liver pathology in Indian subjects which accounts for only 1.7 – 7.5% of all cases of CLD in Indian reports[4]. Genetic predisposition is part of the pathogenesis of

IBD[22]. The prevalence of IBD in patient's relatives, in developed countries, varies from 7% to 12% with predominance among CD patients and concordance between the types of IBD[49]. In our study, 9% of individuals with IBD had a family history of these diseases, with a reasonable concordance regarding the type of IBD among relatives. The probable reason for this may be consanguineous marriages in our area.In our study, the time interval between the onset of symptoms and definitive diagnosis in CD patients was in average of 13.1±4.9 months and statistically greater than average of those with UC 7.5±3.9. Our findings are in accordance with Ferreira et at with CD diagnosis delayed by average of 15±4.6 months in comparison to UC where it is10±3.2 months[22]. There is no consensus about the most common location and behaviour of CD : Ileocolonic disease (L3) (17 to 58%) and terminal ileum(L)(11 to 58% of cases) are the most common location , with a lower percentage of involvement of the upper GIT (L4), regardless of the association with other sites[25-26]. Inflammatory behaviour is the most reported (42 to 81%)[50], with greater proportions when the disease duration was shorter. Studies have shown perianal disease in 10 to 46.6% of Patients [12]. Our finding are in accordance with those in medical literature: most common involvement terminal ileum (60.5%) followed by ileo-colonic (25.6%), inflammatory behaviour (58.1%) and perianal involvement in 11.6% patients. Individuals with strictures, fistulas or perianal disease, as expected, had a longer disease duration compared with those with inflammatory behaviour. Unlike the stability noted in the location of CD over time, it is common to notice the progression or regression of the extent of inflammation in UC when following up. In this study, it was found that 62% of our patients had left sided colitis and procto-sigmoiditis (E1 and E2) while 38% had pan colitis (E3). The findings were similar to Sood et al reported that 47% patients had left sided colitis, 27% pancolitis and 25% with proctosigmoiditis in a north Indian IBD cohort[3].There is evidence that the extent of UC is related to the need for hospitalisation and colectomy, as well as age at diagnosis, risk of colorectal cancer and association with Primary sclerosing cholangitis[26]. In our study patients with extensive colitis were with higher number of cases associated with hospitalisations and greater need for immune-modulators and biological treatment. Colectomies and complications such as toxic mega-colon were also more prevalent among these patients. However, due to its small number, it was not possible to verify a statistical difference between them.Several factors lead to IBD patients to hospitalisation: the need for diagnostic tests, disease activity and surgery[26]. Studies have shown various hospitalisation rates worldwide, which were higher in CD than in UC. Among the cases of this study the hospitalisation rates were comparable with UC patients being slightly on higher side (71.9% VS 60.5%). The high rate reflects a greater number of patients with extensive UC and complicated CD.The treatment of IBD has undergone significant changes in the last 20 years, since the introduction of biological therapy, initially for CD treatment and years later for UC[26] Studies that demonstrated the ineffectiveness of salicylate use for CD[25] led to the recent reformulation of the treatment consensus for this disease, reserving salicylate prescription only in mild colonic presentation. Most of our patients had robust clinical and endoscopic outcome with steroids and immunosuppressant (67%) even though surgical intervention was needed in 18.6% and biological (Adalimumab) were given in 25.6%.The largest study from three centres in India reported that 37% of all patients required surgery. The medications used were 5-ASA compounds in 78%, steroids in 42%, AZA in 29% and biological in about 20% of all patients[19]. The use of biologicals among our population exposes the lack of affordability and insurance cover for our patients.Regarding UC treatment, most of the UC patients were treated with steroids, mesalamine and more severe ones with steroids and immunosuppressants. We had almost an almost equal distribution of mild, moderate and severe diseases with slightly more severe cases. The use of

biologicals to treat UC was 8.8%, higher than other Indian studies (0 to 5%) [19]. This data reflects a greater severity of the disease in our population.This paper demonstrates the similarities and vagaries of demographic and clinical details of the IBD patients in Kashmir, India compared to other studies from north and south of the country and to rest of world. The limitations of the current study are a limited size, short study period and the study being a hospital based one than a community based one. Also significant family history could not be elicited in most cases and the risk of malignancy and other chronic sequel could-not be assessed. Because of all these, a larger community based study recruiting more patients with a longer duration of follow-up is necessary for a better understanding of the disease and to arrive a definite consensus.

CONCLUSION

This is the first study addressing clinical and demographic profile in Kashmir valley, in India as far we know. Most clinical and demographic profile is similar to rest of our country reports. Diagnostic delay is still a big concern, leading to more complicated disease. The higher proportion of complicated CD and extensive UC resulted in a greater need for healthcare resources in this cohort such as hospitalisation, surgery and biological treatment. Given the small sample, it may not be generalised to the wilder population. We believe that this result can indirectly raise consciousness about the importance of investing in disease awareness, access to diagnostic examinations, therapy within the window of opportunity to avoid complications and disability. Research should aim on evolving novel and cost effective remedies which may be helping the patients not only in the Indian subcontinent but also the whole world.

REFERENCES

1. Abraham C, Cho JH. Inflammatory bowel disease. N Eng J Med. 2009; 361(21): 2066-2078.
2. Ahuja V, Tandon RK: Inflammatory bowel disease: the Indian augury. Indian J Gastroenterol 2012; 31: 294-296.
3. .Kumari R, Ahuja V, Paul J: Fluctuations in butyrate producing bacteria in ulcerative colitis patients of North India. World J Gastroenterol 2013;19;3404-3414.
4. Makharia GK, Ramakrishna BS,Abraham P, et al; Indian society of Gastroenterology Task Force on Inflammatory Bowel Disease: Survey of Inflammatory bowel disease in India. Indian J Gastroenterol 2012;31:299-306
5. .PratapMouli V, Munot K, Ananthakrishnan A, et al: Endoscopic and Clinical responses to ATT can differentiate ITB from CD. Aliment PharmacolTher 2017;45:27-36.
6. .Tandon BN, Mathur AK, Mohapatra LN, Tandon HD, Wig KL: A study of the prevalence and clinical pattern of non specific ulcerative colitis in northern India .Gut 1965;6: 448-453.
7. .Kedia S, Ahuja V: Epidemiology of Inflammatory bowel disease in India: The great shift East. InflammIntest Dis 2017;2: 102-115.
8. .GalhardiGasparini R, Sassaki LY, Saad –Hossane R. Inflammatory bowel disesase epidemiology in Sao Paulo state, Brazil. ClinExpGastroenterol. 2018;11:423-429.
9. Ng SC, Shi HY, HamidiN , et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systemic review of population based studies. Lancet. 2017 ;390(10114):2769-2778.

10. Calderon M ,Minckes N, Nunez S, Ciaponni A . IBD in Latin America : a systemic review . Value Heal Reg Issues.2018:17c:126-134.
11. Yamamoto Furusho J, SaemientoA , Toledo Maurino J , et al . P839 Clinical and sociodemographical characteristics of IBD in mexico: multicentric nationwide study (EPIMEX-IBD). J Crohns Colitis.2018:12:S540-S40.
12. Kotze PG, Underwood FE, Damiao AOMC, et al. Progression of IBD throughout Latin America and the Caribean: a systemic review. ClinGastroenterolHepatol. 2020;18(2):304-312.
13. Parente JM , Coy CS, Campelo V. Inflammatory bowel disease in an underdeveloped region of North-eastern Brazil. World J Gastroenterol.2015;21(4):1197-1206.
14. Bitton A, Vutcovici M, Patenaude VVV, Sewitch S, Brassard P. Epidemiology of IBD in Quebec . Inflamm Bowel Dis.2014(10):1770-1776.
15. KappelmanMD ,Rifasshiman SL, Kleinman K , et al. The prevalence and geographic distribution of Crohns disease and UC in the United States. ClinGastroenterol Hepatol.2007;5(12):1424-1429.
16. Cantoro L, Di SabatinoA ,Papi C , at al. The time course of diagnostic delay in IBD over the last Sixty years: an Italian multicentric study. J Crohn's Colitis.2017;11(8):975-980.
17. Amiot A, PeyrinBiroulet L. Current, new and future biological agents on the horizon for the treatment of IBD. TherapAdv Gastroenterol.2015;8(2):66-82 .
18. Lim WC, Wang Y , Macdonald JK, Hanauer S. ASA for induction of remission or response in Crohns disease. Cochrane Database Syst Rev.2016;7:CD008870.
19. Gomollon F, Dignass A, AmneseV,et al. 3rd European evidence based consensus on the diagnosis and management of Crohns disease 2016:part 1:diagnosis and medical management. J Crohns Colitis.2017;11(1):3-25.
20. Khosla SN, Girdhar NK, Lal S, Mishra DS : Epidemiology of Ulcerative colitis in hospital and select general population of northern India. J Assoc Physicians India 1986;34: 405 -407.
21. Mertz A, Nguyen NA, KatsanosKH , Kwok RM. Primary Sclerosing cholangitis and IBD comorbidity : an update of the evidence . AmmGastroenterol. 2019;32(2):124-133.
22. Turpin W, Goethel L, Bedrani L, Croitoru K. Determinants of IBD Heritablity: genes, bugs and more. Inflamm Bowel Dis.2018;24(6):1133-1148.
23. Moller FT, Anderson V, Wohlfahrt J, Jess T. Familial risk of IBD: a population based cohort study. 1977-2011. Am J Gastroenterol.2015;110(4):564-571.
24. Cosnes J, CattanS , Blain A , et al. Long term evolution of disease behaviour of CD . InflamBowel Dis .2002;8(4):244-250.
25. De barros KSC, Flores C, Harlacher L, Francesconi CFM. Evolution of clinical behaviour in Crohns disease : factors associated with complicated disease and surgery. Dig Dis Sci. 2017;62(9):2481-2488.
26. ArgolloMC ,Kotze PG , Spinelli A, Gomes TNF , Danese S. The impact of biological in surgical outcomes in UC . Best Pract Res Clin Gastroenterol.2018;32-33:79-87.