

INFLAMMATORY BOWEL DISEASE IN MALDIVES; A SINGLE CENTER CLINICAL EXPERIENCE

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ABSTRACT

Introduction

Inflammatory bowel disease (IBD), once considered disease of west is also increasingly diagnosed in Asia in recent years. As there are already studies about IBD in Southeast Asia like India, Srilanka, it would be more informative to study the disease in Maldives as being closer to India and Srilanka. This is probably the first study about the disease from Maldives conducted in a single tertiary hospital center. The objectives of the study were to determine the prevalence, clinical characteristics and treatment of IBD in Maldives.

Methodology

A preliminary hospital-based retrospective observational study was performed in ADK multispecialty hospital, a referral tertiary center located in the capital city of Maldives. Patients visiting gastroenterology OPD, who were diagnosed as IBD either Crohn's disease (CD) or Ulcerative colitis (UC) on basis of internationally established standard practice, were recruited in the study after informed oral consents for the duration of three years from January, 2017 to December, 2020. We collected clinical data including gender, age at diagnosis, symptomatology, severity, smoking habits, family history, disease phenotype, and behavior at diagnosis from each involved patients as per clinical proforma prepared for UC and Crohn's disease in separate forms.

Result

Total 41 patients of IBD with 15 CD and 26 UC were recruited during study period. The prevalence of IBD in the country was estimated to be at least 20 per 100000 persons. Ileocolonic phenotype in CD and Extended colitis in UC were more common. Clinically, majority IBD patients presented with moderate to severe form. Biologic agents were frequently used in IBD.

Conclusion

The prevalence of IBD in Maldives is also more or less similar to other Asian countries where as some aspects of clinical characteristics are similar to Western countries. There needs to be nationwide epidemiological study or multi center hospital based prospective or at least cross sectional study for detail and optimal information about various aspects of IBD.

KEYWORDS

Biologic treatment, crohn's disease, clinical characteristics, inflammatory bowel disease, prevalence, ulcerative colitis



INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting dysregulated immune and inflammatory gastrointestinal disorder of unknown etiology. It mainly involves ulcerative colitis (UC), which is limited to the mucosa of rectum and colon, and Crohn's disease (CD), which can affect any segment of the gastrointestinal tract from the mouth to the anus transmurally. The prevalence of IBD in the Western world is about 50–200/100,000 persons for CD and 120–200/100,000 persons for UC.¹ Therefore IBD was known as western disease earlier.² In recent years, the incidence and prevalence rates of IBD have been increasingly noticed in Asia and Africa.³ The exact explanation behind this increasing trend in Asia is yet unknown however it could be due to the westernized lifestyle.⁴ Sood, et al. from an epidemiological study of Punjab of India found the prevalence rate of UC as 44.3/100,000.⁵ In the Central Province of Sri Lanka, the crude prevalence rate of UC and CD were 5.44 and 2.33/100,000.⁶

Republic of Maldives is a small country in Southeast Asia that is located close to South India and Sri Lanka. As of 1st January, 2020, the population of Maldives was estimated to be 393,883 people. Prevalence of IBD in Maldivian people is unknown after many published studies showing increasing trend in Asia. The ADK, 120-bedded a private multispecialty hospital in the capital city has been providing general as well as specialty services to Maldivians for the last 20 years.

So, we conducted this preliminary study in the center to describe the prevalence, clinical characteristics and treatment of IBD in Maldivian patients.

METHODOLOGY

This is a retrospective observational study conducted in Gastroenterology OPD, ADK hospital from patients already known as IBD who came in follow up as well as index patients after investigations who were diagnosed as IBD during the study period from January, 2017 till December, 2020. The diagnostic criteria for IBD were based on international standard practice on a combination of clinical presentations, upper and lower gastrointestinal endoscopy, radiologic (contrast CT enterography in each patient of CD) and histologic findings with opinion from related subject experts too. Patients with indeterminate colitis and diagnostic dilemma were excluded. Clinical data of each patient including gender, age at diagnosis, symptomatology, severity, smoking habits, family history, disease phenotype, and behavior at diagnosis were recorded in separate proforma (prepared in microsoft word file) in Gastroenterology OPD desktop computer. Montreal classification was used for age, disease location and behavior of CD and extension of UC. Clinical severity was categorized as per Truelove and Witt's criteria for UC and Harvey Bradshaw index for CD. Treatment regimens and bowel resection rates were also recorded in our patients.

All the data recorded in the pre-specified proforma separate for UC and CD in the desktop computer of gastroenterology

OPD were printed and statistical analysis was performed with Statistical Package for Social Sciences version (SPSS 20.0 IBM software, Chicago). Informed consents were taken from all recruited patients for de-identified data collection and the study was conducted as per ethics of the hospital. Ethical clearance was not needed as per local ethics for the retrospective study.

RESULT

By the end of the study period, 41 patients were diagnosed as IBD including new as well as old in our study period. The demography and clinical parameters of patients have been shown in Table 1. There were 15 and 26 patients diagnosed as CD and UC respectively. The mean age at diagnoses of IBD, CD and UC are 31, 25 and 33.1 years with standard deviation of 13.3, 10.5 and 14 respectively. The mean age at diagnosis of CD patients was slightly lesser than that of patients with UC. The youngest age at diagnosis of UC was 6 months old infant who well responded with steroid induction followed by mesalamine for remission. With regard to gender, overall male sex was slightly predominant in IBD (51.2%) and higher in UC (57.7%) than in CD (40%). There were 13.3% active smokers in CD group where as 11.5% ex-smokers in UC group. In addition, we found only 9.7% of IBD patients had a positive family history with 7% in CD and 11.5% in UC groups respectively.

Table 3: Summary of scores of QOL of participants in different domains

Characteristics of IBD	IBD=41	CD=15	UC=26	P
Male sex;n(%)	21(51.2%)	6(40%)	15(57.7%)	.277
Mean age in years(SD)	30(13.3)	25(10.6)	33(14)	.057
Family history;n(%)	4(9.7%)	1(7%)	3(11.5%)	.612
Perianal disease;n (%)	1(2.4%)	1(7%)	0(0%)	
Active Smoker (%)	2(4.8%)	2(13.3%)	0(0%)	
Ex-Smoker (%)	3(7.3%)		3(11.5%)	

Abbreviations. IBD-Inflammatory bowel disease, CD-Crohn's disease, UC-Ulcerative colitis

The Montreal classifications of all patients with IBD in our study are summarized in Table 2, Figures 1 & 2. Colonoscopy in all cases of CD were 100% for ileal intubation however only 80% for severe UC patients category. With respect to the disease phenotype of CD, we found 20%, 20%, 53%, and 7% of cases to be located in L1 (ileum), L2 (colon), L3 (ileo-colon), and L4 (upper GI tract) at diagnosis, respectively. With regard to the disease behavior of CD, B1 (non-stricturing and non-penetrating type), B2 (stricturing type), and B3 (penetrating type) were observed 66.7%, 26.7.0%, and 6.7%, respectively. The ileocolonic and nonstricturing types accounted for the majority of our CD cases. Only one patient that is 6.7% out of 15 CD patients had perianal involvement (P type) in the form of perianal fistula. With regard to the disease extension of UC, we found that the incidences of proctitis (E1), left sided colitis (E2), and extensive colitis (E3) at diagnosis were 23%, 11.5%, and 65.5%, respectively. Extensive UC accounted for the majority of patients in our study.



Table 2. Montreal classifications of IBD

	CD(n=15)	UC(n=26)
UC extent		
E1;n(%)		6 (23%)
E2;n(%)		3 (11.5%)
E3;n(%)		17(65.5%)
CD location		
L1;n(%)	3(20%)	
L2;n(%)	3(20%)	
L3;n(%)	8(53%)	
L4;n(%)	1(6.7%)	
P;n(%)	1(6.7%)	
CD behavior		
B1;n(%)	10(66.7%)	
B2;n(%)	4(26.7%)	
B3;n(%)	1(6.7%)	

Abbreviations. CD-Crohn's disease, UC-Ulcerative colitis, B1-non stricturing and non penetrating, B2-stricturing; B3-penetrating, P-perianal involvement, E1-proctitis, E2- left sided colitis, E3-extensive colitis, L1-Ileum, L2-Colon, L3-Ileocolon, L4-upper gastrointestinal tract

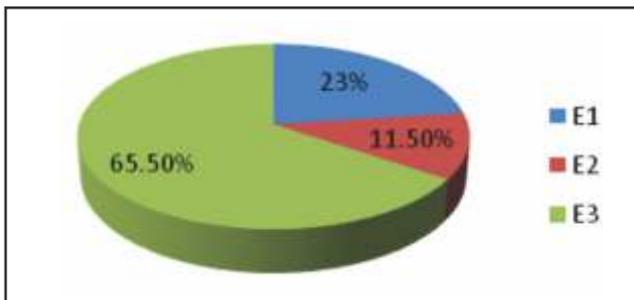


Figure 1: Montreal classification: UC Extension

Abbreviations; E1: proctitis; E2: left sided colitis; E3: extensive colitis

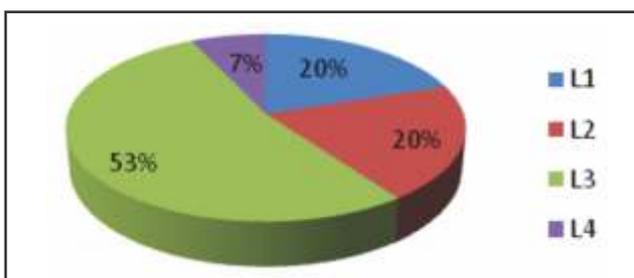


Figure 2: CD location

Abbreviations; L1-Ileum, L2-Colon, L3-Ileocolon, L4-upper gastrointestinal tract

The symptomatology has been mentioned in Table 3. The mean duration of illness at diagnosis for CD was 24.6 months with standard deviation of 45.3 months whereas for UC it was 7.1 months with standard of 6.1 months. Diarrhea was present in 100% of patients with UC whereas only 92.3% of the CD patients had it. 100% and 96.6% of patients of CD and UC had abdominal pain respectively. Bleeding per rectum

was present in all UC patients i.e. 100% whereas only 30.8% in CD patients. Symptoms like urgency, mucoid stool, tenesmus were present in 95.6% in UC patients whereas in CD patients they were significantly lower (15.4 to 38.5%). Weight loss was slightly higher in CD (71%) than in UC (65%). UC patients had more fever predominant (65%) than of CD patients (46%). The incidence of extraintestinal manifestations (EIMs) was 33% in CD and 31% in UC groups. With respect to clinical severity, 80 % of CD and 84.6% of UC patients were moderate to severe at presentation.

Table 3: Symptomatology: Gastrointestinal and EIM

Symptomatology	CD=15	UC=26
Diarrhea	13(92.3%)	26(100%)
Abdominal pain	15(100%)	25(95.6%)
Per rectal bleed	4(30.8%)	26(100%)
Urgency	5(38.5%)	24(95.6%)
Mucus	5(38.5%)	24(95.6%)
Tenesmus	2(15.4%)	23(95.6%)
Weight loss	10(71%)	15(65%)
Fever	6(46%)	15(65%)
Constipation	3(21%)	0(0%)
EIM;n(%)	5(33%)	8(31%)

Abbreviations. CD-Crohn's disease, UC-Ulcerative colitis, EIM-extraintestinal

The treatment regimens and bowel resection rates of IBD patients are summarized in Table 4. Our data showed that 5-ASAs were frequently used in patients with UC than CD with a significant difference (100% vs 73.3%; p=.006). Whereas for corticosteroids use, there was no significant difference (CD: 53.3% vs UC: 65.4%; p=.446). However, with regard to immunomodulators, there was significantly higher use in CD than in UC (67.7% vs. 34.6%, p=.047), and likewise use of the biologic agents mainly Infliximab or Adalimumab in CD was also significantly higher than UC (40.0% vs 11.5%; p=.034). Overall, the bowel surgery in patients with IBD was 7.3%. Patients with CD showed a significantly higher bowel resection rate than those with UC (20% vs 0%, p=.018). By the use of above mentioned single or combined treatment regimens, patients were in remission clinically and biochemically during follow up.

Table 4: Treatment regimens and bowel resection

Treatment Regimens	IBD(n=41)	CD(n=15)	UC(26)	P value
5-ASA;n(%)	37(90.2%)	11(73.3%)	26(100%)	.006
Corticosteroid;n(%)	25(61%)	8(53.3%)	17(65.4%)	.446
Immunomodulator;n(%)	19(46.3%)	10(67.7%)	9(34.6%)	.047
Biologic agent;n(%)	9(22%)	6(40%)	3(11.5%)	.034
Bowel resection;n(%)	3(7.3%)	3(20%)	0(0%)	.018

Abbreviations. IBD-Inflammatory bowel disease, CD-Crohn's disease, UC-Ulcerative colitis, 5-ASA-aminosalicylic acid

DISCUSSION

Recent reports demonstrated that the incidence and prevalence rates of IBD in Asia have been increasing as like



Western countries.^{2,7} Wei, et al. from an epidemiologic study of IBD from 1998 to 2008 in Taiwan found that the prevalence of CD increased from 0.19 to 1.78/100,000 and that of UC increased from 0.61 to 7.62/100,000.⁸ As there are not many population-based studies conducted in Asian countries, exact prevalence rates for IBD are yet unknown for Asia. Hospital-based studies would detect only the treatment seeking IBD patients, which might leave out patients who are mild symptomatic or asymptomatic and those who take alternative (ayurvedic or traditional) medicine. Same is true in Maldives and hence the total number of patients of IBD that is 41 during the short period of 3 years collected in ADK hospital, could not reflect the total affected patients in the country. As population of Maldives at present is 393883, we may roughly estimate that the prevalence of IBD in Maldives could be higher than 20 per 100000 persons considering the IBD patients diagnosed in ADK gastroenterology OPD presumably represent around half of total cases in whole country. During the study period of 3 years, I was the single gastroenterologist in the country and that is why suspected patients were supposed to refer to me by physicians. Otherwise, the rest might have been managed in the other two major referral centers or in other Island hospitals/clinics by experienced physicians or some directly did seek treatment from abroad e.g. India, Srilanka, Thailand. Therefore, the prevalence of IBD in Maldives could be comparable to that of India and higher than Srilanka.^{5,6} The sex distribution of IBD has been consistently different worldwide. IBD is a male-predominant disease in Asia, according to previous studies; for example, a study showed male predominance of 59.6% in CD cases and 57.7% of UC cases.⁹ Similarly, a recent large hospital based retrospective study by J. W. Chou et al. from Central Taiwan showed male predominance of 71.1% of all patients with IBD with CD patients (75%) and UC patients (68.2%) respectively.¹⁰ However, our study showed female predominance of 60% in CD and male predominance of 57.7% in UC in line with the several other cohort studies.¹ And there was slight male predominance of 51.2% in IBD overall. Considering the diagnosis of IBD with regard to age, the peak age for CD diagnosis was between 20 and 30 years and that for UC was between 30 and 40 years as seen in the study.¹¹ In the same line, our patients were diagnosed at mean age of 25 years for CD and 33 years for UC with standard deviation of 10.6 and 14 years respectively. A consistent trend was observed that patients with CD had a younger age at diagnosis than did patients with UC. The higher prevalence rate of cigarette smoking also had an association with lower income levels in America, Europe, and Asia.¹² A wide range of prevalence rates of cigarette use was noticed in patients with IBD (CD: 39–72%, UC: 11–23%) and found that nonsmokers were more common among patients with UC than among those with CD.¹³ In our study, there were 13.3% current-active smokers in CD which was similar to Asia-Pacific study (11.6%).⁹ Whereas 12% ex-smokers were there in UC group with no single current smoker implying smoking could be a risk factor for CD and protective for UC as shown in the study.¹⁴ Patients with IBD in Asia tend to have a lower positive family history rate (0.0–3.4%) than those in Western countries (10–25%).^{3,15,16} The rate of positive family history of IBD

(9.7%) in our study is higher than other studies from Asia like a recent study from Taiwan.¹⁰ The study outcome is comparable with recent Asian studies demonstrating an increased positive family history rate of IBD patients, which might be attributable to a higher recognition of IBD.¹⁷ With respect to the disease phenotypes of CD, many studies reported equal proportions of phenotypes in patients with CD, whereas some studies reported that the colonic type (L2) was predominant in Western people. Prideaux et al. demonstrated that the ileo-colonic type (L3) was the most common type of CD in Asia (about 30–50%), followed by the ileal (L1) and colonic type (L2).³ We also identified that the most common phenotype was L3 type (53%), followed by L1 (20%) and L2 (20%) and 7% involving upper gastrointestinal tract (L4). However a study from Taiwan showed L1 was the most common phenotype.¹⁰ Concerning the disease behavior of CD, the non-stricturing and non-penetrating type (B1) was the most common type in Western reports (62–81%) compared with Asian reports (40–69%).^{3,9,18} Our study also showed similar behavior in CD patients as B1 (66.7%) non stricturing type, B2 (26.7%) stricturing type and B3 (6.7%) penetrating type. In the literature, the incidence of perianal involvement ranges from 15.6% to 36.7% in patients with CD.^{3,8} We reported an incidence of only 6.7%. Schwartz et al. demonstrated that 20–40% of patients with CD developed a fistula (mostly perianal fistula followed by enteroenteric fistula) and the cumulative risk of any fistula formation was 50% after 20 years.¹⁹ In our study, 13.4% of patients had a fistula (perianal fistula and enterocolic fistula one-one), which was lower than expectation to the report by Schwartz et al. Different findings have been reported worldwide in regard to the disease extension for UC. Studies from western countries showed proctitis (E1) in 30–60%, left-sided colitis (E2) in 16–40%, and extensive colitis (E3) in 18–35% of patients. Asia-Pacific studies demonstrated more or less equal distributions among these 3 types (32.6%, 34.9%, and 36.2%, respectively).^{3,9} However in our study, the most common type was E3 (65.5%), followed by E1 (23%) and then E2 (11.5%). The prevalence of EIMs in patients with IBD was estimated to be 25–50% in Western countries, and EIMs were more common in CD than in UC.²⁰ Prideaux et al. reported that 3.7–24% of patients with IBD in East Asia had EIMs, and the prevalence was higher in India [3]. Wei et al. reported that EIMs occurred in 1% of CD cases and in 4.5% of UC cases in their hospital-based study in Taiwan.¹⁸ Our study found that 31.7% of patients with IBD had EIMs (33% in CD and 31% in UC), which was higher to that of previous Asian reports but similar to the western reports.

With regard to treatment for IBD, 5-ASAs and corticosteroids were more frequently used worldwide. In the present study, 5-ASAs were the preferred and first regimen for the treatment of IBD (90.2%), with higher in UC than CD (100% vs 73.3%, $p=0.006$), which was consistent with other studies.^{21,22} Concerning the use of immunomodulators, our present study demonstrated that immunomodulators were prescribed significantly higher in patients with CD than UC (67.7% vs 34.6%, $p=0.047$) which was comparable to the findings of other reports.^{10,22} With respect to the use of biologic agents, 40.0% of our patients with CD and 11.5% of



patients with UC ($p=.034$) received biologic treatments either Infliximab or Adalimumab, which were comparable with previous Western and Asian reports for UC (1–2% vs. 9%) but higher for CD (3–25% vs. 8–11%).^{22,23} The higher use of biologic agents in Maldives in comparison to many fellow South Asian countries could be due to good insurance coverage by Government to its citizens irrespective of expensiveness of the treatment. In spite of good efficacy of biologic agents for IBD, there might be lower use of such therapy in some poor countries where people need to pay themselves for expensive biologic agents.²⁴ Biologics as well as 5-ASA are neither manufactured nor available in the market of Maldives at present and have to purchase from neighbor countries through the government facilitating agency and insurance companies on doctor's prescription basis which sometimes delay in treatment and as a result of which chance of incomplete remission or relapses are occasionally observed. The bowel resection rate in our patients with CD was only 20% which is lower than the reports from Korea (35.5%), Europe (38–61%) and Japan (55%) after a 10-year follow-up.²⁵⁻²⁷ There was no history of surgical treatment in our UC patients that might be due to small sample size, short study period and a single center study missing other patients in the country who did not visit to us. The mean duration of illness at diagnosis for CD was 24.6 months whereas for UC it was 7.1 months which showed early and timely diagnosis for IBD unlike other South Asian countries like Nepal.²⁸ It is probably because of high health seeking behavior of Maldivian people and good insurance coverage as like in western country. With regard to clinical severity at presentation, 80% of CD and 84.6% of UC patients were moderate to severe at presentation unlike the other Asian study showing majority with mild presentation.²⁹

CONCLUSION

The prevalence of IBD in Maldives could probably be similar to that of other Southeast Asian countries like India and even higher than Sri Lanka. The diagnosis of IBD is relatively early as like in western countries. Biologic agents are frequently used in IBD particularly CD as like in Western countries. Ileocolonic phenotype in CD and Extended colitis

in UC are more common which are different than most of the other studies in Asia and Western countries. Majority of IBD patients clinically presented in moderate to severe forms. Prospective or cross sectional multicenter hospital and population-based studies at national level are needed to identify prevalence, clinical characteristics and optimal treatment strategy of IBD in Maldives with more clarity.

Key Messages: In Maldives

- 1) IBD is as common as other Southeast Asian countries
- 2) Many characteristics of IBD are similar to Southeast Asian countries like India, Sri Lanka, Nepal and some with Western countries
- 3) Needs further prospective or cross sectional nationwide multicenter studies of IBD to get more realistic conclusion in regard to characteristics of IBD in Maldivian population.

LIMITATIONS OF THE STUDY

A single hospital based study with a short duration, small number and retrospective in nature are limitations of the study.

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CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

FINANCIAL DISCLOSURE

The author has no funding source to declare

AUTHOR CONTRIBUTION

I am the single author for designing, conducting and writing this study. There are no other authors involved to carry out the study except timely advice from colleagues.

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