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Epidemiology and Demographic Profile of Inflammatory Bowel Disease in Nepal

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic disease of the gastrointestinal tract. Once thought to be a disease of the developed nations, the burden of IBD has been rising in Asian countries. Inflammatory bowel disease leads to severe impairment in the quality of life of the patients. There have been numerous studies across the globe which have provided new insight into different aspects of this disease. Not only IBD is being diagnosed more but patients are also becoming more aware of this debilitating condition. It is encouraging to see a few studies from Nepal in the recent past. However, the epidemiological and demographic features of IBD remain largely unknown. Through this review, we aim to gain insight into the epidemiology and demographic features of patients with IBD in Nepal.

Keywords
Crohn's disease; epidemiology; inflammatory bowel disease; ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic intestinal condition of unknown etiology. This very entity primarily includes ulcerative colitis (UC) and Crohn's disease (CD).[1] Inflammatory bowel disease results from an abnormal immune response to gut microbiota and environmental factors in a genetically susceptible host.[2] Ulcerative colitis involves colon in continuous manner and almost always involve rectum. On the other hand, CD can involve any part of gastrointestinal tract (GI tract) from mouth to anus, though not in continuous pattern. With growing understanding of the disease, there has been growing knowledge about the epidemiology of IBD across the globe. IBD was considered to be a disease of west mainly because the initial literature comes from those regions.

The estimated burden of IBD in 2017 was 6.8 million globally. There is an increasing trend of IBD globally with age standardized prevalence increasing from 79.5 (75.9-83.5) per 100000 population in 1990 to 84.3 (79.2-89.9) per 100000 in years 2017.[3] Although the incidence might have achieved plateau in Europe in recent times, Asia has experienced a remarkable increase in IBD in the previous 2 decades.[4] In Asia, the overall incidence of IBD is found to be 1.37 per 100000 per year. The annual incidence rates for UC, CD and IBD-undetermined (IBD-U) is 0.76, 0.54, and 0.07 per 100000 population respectively.[5] Ulcerative colitis is found to be twice as common as CD in Asian population.5 Neighboring country India is expected to have the highest burden of IBD.[6]

The epidemiological data from Nepal is less robust and are mainly from hospital-based studies. Here by in this study we aim to review the existing literature regarding the epidemiological and demographic profile of IBD in Nepal.

Epidemiology of IBD in Nepal

The first case of IBD from Nepal was described in literature in 1990.[7] The first case description of CD was reported in 2009 from a surgical specimen of a patient operated upon for intestinal perforation.[8] Another case of CD was reported in year 2013 from a surgical specimen when a 55 year old gentleman had presented with intestinal obstruction.[9] In a study from western Nepal, ulcerative colitis was seen in 10% of the patients undergoing colonoscopies over a period of two years.[10] In another series of 415 patients undergoing colonoscopy for lower gastrointestinal bleed, UC was found to be present in 10.4% of the patients.[11] Since then, there have been five studies that have looked at epidemiological profiles of IBD in Nepal (Table 1 and 2).

In a retrospective study[12] conducted in surgical unit of a hospital in eastern Nepal which included 11 patients with CD, it was seen that incidence rate of CD increased from one case every two year between 2009 and 2015 to four cases per year between 2015 and 2017. This shows that the cases of CD are rising and being diagnosed. However, this figure might be an overestimation as the study was conducted in department of surgery where referral of patients with CD might be high. In a recent multi-center study[13] assessing the epidemiology of IBD on colonoscopy, the incidence of CD was found to be 1.61/1000 colonoscopies per year. This figure may be an underestimation as those cases of CD involving proximal small bowel and upper GI tract might have been missed on colonoscopy. However, there are no other studies which has looked at the epidemiology of Crohn's disease. Most of the studies have predominantly UC patients and only few CD patients. Hence true prevalence and incidence of CD still remains unexplored.

There are relatively more data on ulcerative colitis. Though there is no population-based study, there are five hospital-based studies which have looked at different aspects of ulcerative colitis. In a study conducted in eastern Nepal, the incidence of UC was 1.33 cases/year in period 2009 to 2015 which increased to 5.5 cases per year in the period 2015 to 2017. In a study in the following year by Pathak et al[14], which included 100 cases of UC including 79 new cases, the incidence was found to be 39.5 cases/year. In a study[15] from Gandaki region of Nepal which included 60 patients with UC, the prevalence of UC was found to be 21.9%. All these studies had modest sample size. In a recent multicenter and by far the largest study[13], the incidence if UC was found to be 23.7 per thousand colonoscopies per year. Since this study considered a colonoscopic diagnosis, the number might be slightly overestimation of true incidence (Table 1). However, these studies shows that the incidence of UC is rising Nepal. It appears from the available data that in Nepal, UC is significantly more common than CD. The famous ACCESS study[5] which looked at the incidence and phenotype of IBD in Asia also showed that UC was twice as common as CD.

Age distribution

Inflammatory bowel disease has a bimodal age distribution with the first peak occurring in the third decade of life and the second peak occurring in the 40-70 years age group.[16,17] As far as Asian population is concerned, the median age of IBD diagnosis is 39 (5-81) years. The median age of diagnosis of CD is 34 years in comparison to 42 years in UC. The peak age group of CD diagnosis is 20-24 years with a second smaller peak occurring at 40-44 years. The peak age of UC diagnosis is 30-34 years.[5] Pooled data from the studies from Nepal show the mean age of UC diagnosis to be 34.6-40.6 years with the peak age group being 31-40 years which is similar to the other Asian cohorts (Table 1). However, no

Table 1. Details of ulcerative colitis in studies from Nepal

Studies	*Poudel et al[13]*	*Bhattarai et al[15]*	*Pathak et al[14]*	*Pandit et al[12]*	*Harsh et al[33]*
Year	2021	2020	2019	2018	2015
Data collection year	2017-2019	2017-2020	2017-2018	2009-2017	2014-2015
Study design	Retrospective	Prospective cross-sectional	Prospective Cross sectional	Retrospective	Cross sectional
Number of subjects	352	60	100	19	60
Incidence rate	23.7/1000 colonoscopy/year	21.9% (prevalence)	39.5 new cases/ year	1.33/year (2009-2015) 5.5/year (2015-2017)	N/A
Age(years)	40.6 (mean)	37 ± 3.56	38.04 ± 12.53	45.1 (28-70)	34.6 ± 12.7
Commonest age group (years)	31-40	20-39	26-35	N/A	N/A
Disease duration at presentation	N/A	N/A	N/A	15 (3-48) years	3.7 ± 4.8 years
Male n (%)	245 (58.8%)	36 (60%); (3:2)	51 (51%)	11(57.8%)	31 (51.6%)
E1 n (%)	127 (47.38%)	24 (40%)	41(41%)	1 (5.2%)	23 (38.3%)
E2 n (%)	75 (27.98%)	21 (35%)	46 (46%)	10 (52.6%)	30 (50%)
E3 n (%)	66 (24.62%)	15 (25%)	13 (13%)	8 (42.1%)	7 (11.7%)
EIM n (%)	N/A	21 (35%)	12%	2 (10.5%)	16.7%
Mild n (%)	N/A	19 (31.7%)	41 (41%)	7 (36.8%)	32 (53.3%)
Moderate n (%)	N/A	28 (46.7%)	47 (47%)	5 (26.3%)	23 (38.3%)
Severe n (%)	N/A	13 (21.6%)	12 (12%)	5 (26.3%)	5 (8.3%)
ASUC n (%)	N/A	N/A	N/A	2 (10.5%)	2 (3.3%)

second peak was seen in UC patients unlike in western population. This absence of second peak in UC patients is similar to the findings in ACCESS study. Mean age for CD in Nepal was 36.9 years in a study which included 63 patients with CD.[13] In a previous study including 11 CD patients the median age of CD patients was 55 (28-75) years[12] (Table 2). Studies with larger sample size are required to evaluate proper age distribution for CD.

Gender distribution

Immune mediated diseases show a distinct female preponderance with 8 of 10 patients being female.[18] However, this female preponderance is less prominent in IBD. Western data suggest that till puberty female are at lesser risk of developing CD. However, after puberty females are at higher risk compared to males. Male and female have comparable risk for development of UC before 45 years of age. After 45 years, males are at higher risk of developing UC than females.[19] However, in Asia there is male preponderance both for CD (61.4% vs 38.6%) and UC (57.9% vs 42.1%).5 Similar to the findings from Asian studies, there is male predominance in patients with IBD in Nepal. All the studies published from Nepal show male to female ratio >1. Males constitute 51%-60% of all the UC cases in Nepal. Similarly, males constitute 61% to 64% of CD patients in Nepal. There is lack of data on early onset and late onset IBD from Nepal.

Table 2. Details of Crohn's disease in studies from Nepal

Studies	**Poudel et al[13]**	**Pandit et al[12]**
Number of subjects	63	11
Incidence rate	1.61/1000 colonoscopy/ year	0.5/year (2009-2015) 4/year (2015-2017)
Age	36.9 years (mean)	55 (28-75)
Male	39 (61.9%)	7 (63.6%)
B1	N/A	4 (36.3%)
B2	N/A	3 (27.3%)
B3	N/A	4 (36.3%)
L1	N/A	7 (63.6%)
L2	N/A	2 (18.2%)
L3	N/A	1 (9%)
L4	N/A	1 (9%)
P	N/A	1 (9%)
EIM	N/A	1 (9%)
Disease duration at presentation (years)	N/A	6 (3-36)

Phenotypic profiles

According to the extent of involvement of colon on colonoscopy, UC is divided into three categories. E1 indicates involvement of rectum only, E2 indicates involvement till splenic flexure (left sided colitis) and E3 indicates involvement of colon proximal to splenic flexure (extensive or pancolitis).[20,21] Similarly, CD is categorized as L1 if only terminal ileum is involved, L2 if only colon is involved, L3 when both ileum and colon is involved and L4 when only proximal small bowel and/or upper GI tract is involved. Disease behavior wise CD is categorized as B1 if only inflammation is there (non-stricturing/ non-fistulizing), B2 if stricture formation and B3 if there is fistula formation.[20,21] There are relatively more data on UC phenotype than CD in Nepal. In one of the largest multicenter study from Nepal, data available for 268 patients with UC showed E1, E2 and E3 to constitute 47.3%, 27.9%, and 24.6% respectively.[13] In another study comprising of 100 UC patients, the proportion of patients having E1, E2 and E3 were 41%, 46%, and 13% respectively.[14] In other two different studies consisting of 60 patients each showed that E1 and E2 were the commonest phenotype. However in the study by Pandit et al[12] which included only 19 patients with UC, E2 and E3 were the commonest phenotype with only one patient having E1 disease. This finding can be explained based on the fact that these data come from a surgical unit where the more aggressive disease phenotype might have been referred. Pooled data of all these five studies consist of 507 UC patients with E1, E2, and E3 constituting 42.6%, 35.8%, and 21.4% (Table 1). Hence the pooled data show that E1 is commonest phenotype followed by E2 and E3 respectively. Study from western world show that 23-34% UC patients present with E1, 34-51% with E2, and 30-38% with E3 disease.[22] In Asian studies, the proportion of E1, E2 and E3 is found to be 35-37%, 32-45% and 20-31% respectively.[5,23] Hence, it appears that Nepalese patient with UC present with a higher percentage of E1 disease in comparison to studies from West and rest of Asia.

Only a single study with a very small sample size (n=11) from Nepal described the phenotypic features of CD. In that study 7 (63.6%), 2 (18.2%), 1 (9%), and 1 (9%) patient had L1, L2, L3, and L4 disease. Four (36.3%), 3 (27.3%) and 4 (36.3%) patients had B1, B2, and B3 disease respectively. Only 1 (9%) patient had perianal involvement.

Clinical features

The most common presentation of patients with UC in studies from Nepal are bleeding per rectum in 51.7-100% cases, chronic diarrhea in 70-95% cases followed by mucus in stool in 65-73% cases, tenesmus in 63% cases, pain abdomen in 42-55% cases, weight loss in 14-40% cases and fever in 7-30% cases. These findings are in accordance with other study where blood in stool and chronic diarrhea were the commonest presentations.[24,25] In the only study from Nepal looking at the clinical features of CD patients, pain was the most common presentation followed by acute abdomen and rectal bleeding.[12]

Severity at presentation

Severity data are available only for UC patients. Out of five studies, only four studies have reported data on severity of presentation. Mild, moderate, and severe disease were seen in 31.7-53.3%, 26.3-47%, and 8.3-26.3% of the patients in UC. Acute sever colitis was reported in only two studies with two patients in each. Considering all the patients of UC in totality, mild, moderate, and severe cases were seen in 41.4%, 43.09%, and 14.64% of cases. The baseline presentation in patients with UC in Nepal is slightly different from those in other studies where mild, moderate and severe disease were present in 54%, 27% and 15-19% cases.[25,26] Severity data in CD were not reported in any of the studies from Nepal.

Extraintestinal manifestations (EIM)

Inflammatory bowel disease is known to be associated with different extraintestinal manifestations (EIM). The presence of EIM varies from 16-43% in CD and 7-31% in UC in western population.[27–29] In Asian population, as shown in the ACCESS study, EIM was seen in 19% of the patients. In a recent multicenter study from Asia, EIM was found to be present in 11.3% of patients.[30] In a single center study from India, EIM was seen in 38%.[31] The commonest EIM involves the musculoskeletal and musculocutaneous organ system.[32] In the five available studies from Nepal, the presence of EIM was seen to vary from 10.5 to 35%. The commonest EIM was arthralgia. Other EIM were recurrent aphthous ulceration, uveitis and sacroiliitis. Most of the EIMs were reported for ulcerative colitis.

Family history of IBD

Family history of IBD was reported in only one study from Nepal.[33] Out of 60 patients with UC, family history of IBD was present in only one patient (1.6%). No other studies discussed family history. Family history IBD reported from West vary from 5 to 18%.[34,35] Family history is more pronounced in UC compared to CD.[36] However in Asia, family history of IBD is present only in about 3% of cases which is low in comparison to western data.[37–41]

Natural history of IBD

Both UC and CD are progressive disease if left untreated. Ulcerative colitis progresses to involve proximal colon in 10-19% and 30% at 5 and 10 years respectively.42 In long term course, patients with UC may develop benign strictures, colonic dysmotility and anorectal dysfunction.[43] About 12% patients with UC at five years and 16% patients at 10 years require surgery.[44] In CD, disease site appears to be stable over time.[45] Less than 20% patients with ileal involvement will develop colonic involvement after 10 years.[46] And in patients with colitis, disease extension to small bowel is seen in < 20%. If timely treatment is not offered, B1 phenotype may progress to stricturing and penetrating types. However, the natural history of patients with IBD has not yet been explored and data are completely unavailable.

Treatment of IBD

Treatment of both UC and CD consists of induction and maintenance of remission. The treatment has revolutionized over previous decade with invention of biologics and small molecules.[47] Currently upfront use of biologics is being advocated both for induction and maintenance of remission.[48] Only adalimumab (TNF-α antagonist) and tofacitinib (JAK 1and 3 antagonist) are available in Nepal. However, these agents are very expensive and is not in reach of many patients. Thiopurines are safe [49] and effective[50–52] group of drugs used for maintenance of remission in patients not able to afford the newer therapies. Other therapeutic modalities include fecal microbiota transplantation which is found to be equally efficacious and safe in comparison to other targeted therapies.[53] Any kind of data on treatment is lacking from Nepal.

Gap in knowledge

Data regarding risk factors, disease course, treatment and colorectal carcinoma are not available. However, it is encouraging to see many studies being done in this field. These gaps in literature requires further studies considering this aspect of IBD. There is no IBD registry in Nepal. Establishing a registry for IBD patients will make case reporting and data compiling uniform.

CONCLUSION

The grading of spleen and liver stiffness can predict the occurrence of esophageal varices in patients with liver cirrhosis, which makes it an optimal method to use for screening cirrhotic patients for esophageal varices in clinical settings. Thus, this study contributes in recognizing SS and LS as novel parameters in screening of cirrhotic population. This may thereby reduce the number of endoscopic evaluation. A prompt endoscopic evaluation for varices is justifiable at spleen and liver stiffness levels at or above the cut-off values revealed in this study for the presence of esophageal varices.

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CONFLICT OF INTEREST

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