



Original Article

Temporal Change in Phenotypic Behaviour in Patients with Crohn's Disease: Do Indian Patients Behave Differently from Western and Other Asian Patients?

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Abstract

Background and Aims: In Western studies, one-third of patients with Crohn's disease have stricturing or penetrating disease at presentation and one-half will progress to complicated disease in 20 years. Asian studies indicate that the Asian disease phenotype may be different. Our aim was to study the disease behaviour in Indian patients with Crohn's disease.

Methods: In this hospital-based study, we analysed [Montreal classification] disease phenotype, presence of perianal disease, need for intestinal surgery, and changes in the Montreal classification over time in Crohn's disease patients from our database.

Results: In the 178 patients (median age 35, interquartile range [IQR] 21 years; 97 males) with Crohn's disease, the proportion of various features was as follows. More patients had ileo-colonic [L3: 43.8%] than ileal [L1: 27.5%] or colonic [L2: 28.7%] disease. Perianal disease was seen in 11.8% at baseline. Non-stricturing, non-fistulising disease [B1] was seen in 74.7%, 65.7%, 50%, and 44.4% at baseline, at 5, 10 and 15 years, respectively. Stricturing disease [B2] was seen in 21.4%, 21.9%, 28.9%, and 33.3%; penetrating disease [B3] in 3.9%, 11.4%, 21%, and 16.7%; and intestinal surgery was required in 10.7%, 20%, 34.2%, and 55.5%, respectively. Kaplan-Meier analysis showed no association between progression of disease and patient age or the location of the disease.

Conclusions: Gender distribution and predominant ileo-colonic location of disease were similar to earlier Asian reports on Crohn's disease. Perianal disease was less frequent than reported in Western and other Asian studies. One-fourth of Indian patients had aggressive disease at diagnosis, but the tendency to progress towards aggressive disease over time was less pronounced than in Western patients.

Key Words: Crohn's disease; India; Montreal classification; natural history

1. Introduction

Studies from the West have shown that the location of disease in Crohn's disease [CD] tends to be stable over time but its behaviour

tends to vary not only between patients but also in the same patient at different times.¹ After 15–20 years, the disease is reported to progress to a more aggressive phenotype in about half the patients.² The stricturing and penetrating phenotypes are associated with a more

complicated disease course, resulting in higher morbidity and surgery rates.³

The first attempt to classify disease behaviour was the Vienna classification⁴ which was later modified as the Montreal classification;⁵ the latter is now commonly used for classifying disease phenotype in CD. For paediatric patients, the Paris modification⁶ is used; this incorporates growth retardation and has the option of combining B2 and B3 disease.

The few Asian studies, from China⁷ and Korea,⁸ suggest that Asian patients with CD may behave differently from Western patients. There are epidemiological and phenotypic differences in CD between Chinese and Caucasian patients, including male predominance, lack of familial clustering, higher proportion of upper gastrointestinal tract involvement, and lower frequency of ileal disease in Chinese patients.⁷ Similarly Korean patients differed in gender distribution, disease location, and occurrence of perianal fistula; they may also have a more favourable clinical course, as indicated by a lower intestinal resection rate.⁸

No data are available on the phenotype and disease behaviour of Indian patients with CD, in whom we studied the disease behaviour pattern using the Montreal classification and changes over time.

2. Patients and Methods

This retrospective analysis used the Crohn's disease patient database of the Division of Gastroenterology in Mumbai, maintained since 2005. The diagnosis of CD was based on combination of clinical, histological and radiological, surgical, and serological parameters⁹ or the Lennard Jones criteria.¹⁰ Patients

with uncertain diagnosis or incomplete data or follow-up were excluded. Records of 216 patients were screened [last patient in May 2014] and 178 were included in the study. Follow-up was done at scheduled visits or by telephone calls, letters, or email. Age at diagnosis, gender, baseline behaviour, location of disease, perianal involvement, and treatment including surgery were noted. The disease phenotype was classified as per the Montreal classification. Their subsequent course was noted at 5, 10, 15, and 20 years, and changes in Montreal class were noted along with requirement for surgery.

The study design was approved by the institutional review board.

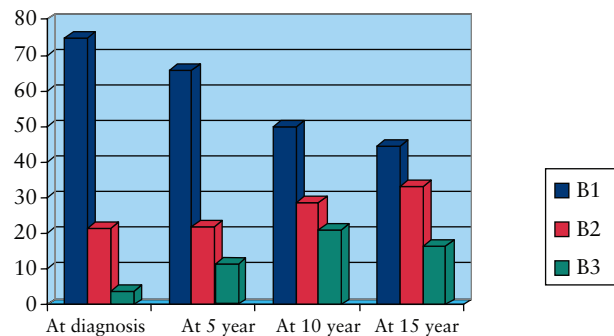


Figure 1. Behaviour at diagnosis, and at 5, 10, and 15 years' follow-up.

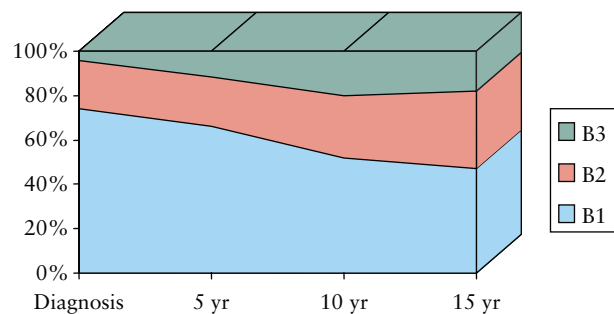


Figure 2. Proportion of patients in B1, B2, and B3 at diagnosis, and at 5, 10, and 15 years' follow-up.

Table 1. Montreal classification at diagnosis [$n = 178$], data as n [%].

A1	A2	A3			
13 [7.3 %]	98 [55.1%]	67 [37.6%]			
L1	L2	L3			
49 [27.5%]	51 [28.7%]	78 [43.8%]			
B1	B1p	B2	B2p	B3	B3p
112 [62.9]	21 [11.8]	38 [21.4]	0	7 [3.9]	0

p, perianal.

Table 2. Disease behaviour, perianal disease, and surgery. at baseline and at 5, 10, and 15 years' follow-up, data as n [%].

Disease behaviour	B0 ^a	B1	B2	B3	Perianal disease	Surgery
Baseline, $n = 178$	0	133 [74.7]	38 [21.3]	7 [3.9]	21 [11.8]	19 [10.7]
Cohort with 5 years' data [$n = 105$] [$p = 0.14$]					[$p = 0.09$]	[$p = 0.51$]
At presentation	0	77 [73.3]	24 [22.8]	4 [3.8]	9 [8.6]	17 [16.1]
5 years	1 [0.9]	69 [65.7]	23 [21.9]	12 [11.4]	17 [16.2]	21 [20]
Cohort with 10 years' data [$n = 38$] [$p = 0.58$]					[$p = 0.15$]	[$p = 0.40$]
At presentation	0	24 [63.1]	11 [28.9]	3 [7.8]	3 [7.8]	8 [21]
5 years	0	21 [55.2]	11 [28.9]	6 [15.7]	8 [21]	12 [31.5]
10 years	0	19 [50]	11 [28.9]	8 [21]	9 [23.6]	13 [34.2]
Cohort with 15 years' data [$n = 18$] [$p = 0.61$]					[$p = 0.5$]	[$p = 0.58$]
At presentation	0	12 [66.6]	6 [33.3]	0	0	6 [33.3]
5 years	0	11 [61.1]	6 [33.3]	1 [5.5]	2 [11.1]	8 [44.4]
10 years	0	10 [55.5]	6 [33.3]	2 [11.1]	2 [11.1]	9 [50]
15 years	1 [5.5]	8 [44.4]	6 [33.3]	3 [6.6]	1 [5.5]	10 [55.5]

p -Values were calculated using chi-square test to compare parameters [behaviour, surgery, perianal disease] at baseline vs 5, 10, and 15 years.

^aPatients had prolonged complete remission without medications.

2.1. Statistical methods

Data were entered into a spreadsheet. Chi-square test was used to compare proportions. KaplanMeier survival analysis was used to study change in behaviour over time and compare it, based on age at diagnosis and location of disease. Log rank test was used to compare survival curves.

3. Results

Of 216 patients screened, 38 were excluded for the following reasons: not fulfilling diagnostic criteria [15 patients], incomplete data [3 patients], incomplete follow-up [4 patients], or change in diagnosis later [16 patients]. The 178 patients included [median age 35, range 4.5 to 76 years, IQR 25 to 46 years; 97 males] had median duration of follow-up of 5 [IQR 1 to 7] years, 105 patients had follow-up of 5 years, 38 patients 10 years, and 18 patients 15 years.

Of the 178 patients, 59 [21.9 %] had received anti-tuberculous treatment and were later diagnosed as having CD. Tissue *Mycobacterium* culture was done from all these patients to rule out drug-resistant tuberculosis, before final confirmation as CD.

More than half the patients [55.1%] were in the age group 17 to 40 years [Montreal A2], followed by A3 [37.6%], and A1 [7.3%] [Table 1]. More patients had ileo-colonic [L3; 43.8%] than ileal disease [L1; 27.5%] or colonic [L2; 28.7%] disease. Perianal disease [p] was seen in 11.8 % of patients at baseline. Three-fourths of patients had non-stricturing, non-penetrating [inflammatory] phenotype, 21.4 % had stenotic, and 3.9% had fistulising phenotype at diagnosis. Upper gastrointestinal [GI] endoscopy was not routinely performed.

Table 2 and Figures 1 and 2 show the disease behaviour, perianal disease, and surgeries at baseline and at 5, 10, and 15 years. At baseline one-fourth of patients had B2/B3 disease; after 10 and 15 years, the corresponding figures were 50% and 56%. However,

Table 3. Location of disease at baseline and at 5, 10, and 15 years' follow-up, data as *n* [%].

Disease location	L0 ^a	L1	L2	L3	<i>p</i> -Value [vs at diagnosis]	L4 modifier
Baseline [<i>n</i> = 178]		49 [27.5]	51 [28.7]	78 [43.8]		12 [6.7]
Cohort with 5 years' data [<i>n</i> = 105]						
At presentation	0	29 [27.6]	30 [28.5]	46 [43.8]		5 [4.7]
5 years	1 [0.9]	31 [29.5]	29 [27.6]	44 [41.9]	0.94	8 [7.6]
Cohort with 10 years' data [<i>n</i> = 38]						
At presentation		11 [28.9]	12 [31.5]	15 [39.4]		2 [5.2]
5 years		14 [36.8]	10 [26.3]	14 [36.8]	0.74	2 [5.2]
10 years		14 [36.8]	8 [21.0]	16 [42.2]	0.56	2 [5.2]
Cohort with 15 years' data [<i>n</i> = 18]						
At presentation		7 [38.8]	6 [33.3]	5 [27.7]		2 [11.1]
5 years		8 [44.4]	6 [33.3]	4 [22.2]	0.91	2 [11.1]
10 years		8 [44.4]	4 [22.2]	6 [33.3]	0.75	2 [11.1]
15 years	1 [5.5]	8 [44.4]	4 [22.2]	5 [27.7]	0.80	1 [5.5]

p-Values were calculated using chi square test, to compare location from baseline vs 5, 10, and 15 years.

^aPatients had prolonged complete remission without medications.

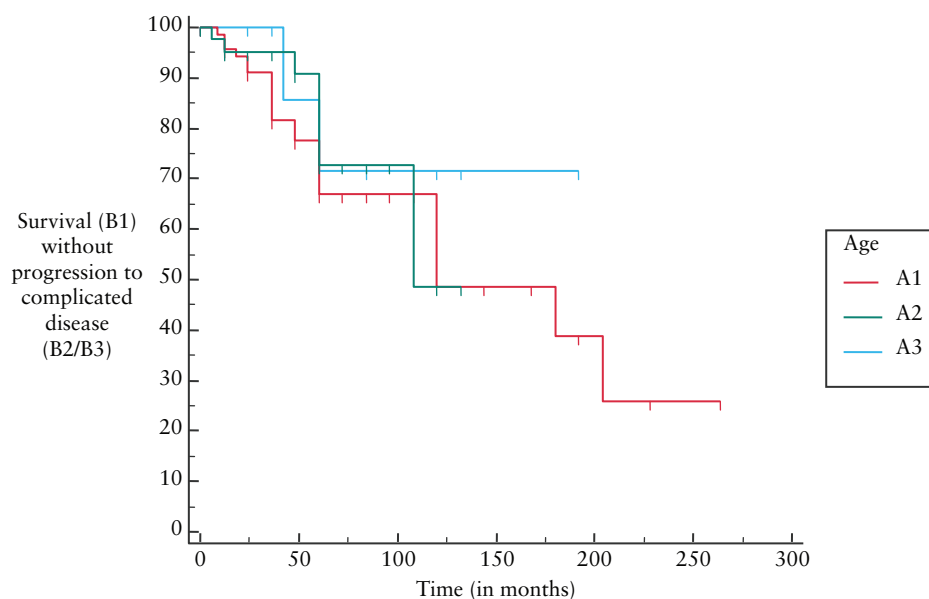


Figure 3. KaplanMeier curves showing change from B1 to B2/B3 disease in relation to age at diagnosis [*p* = 0.56].

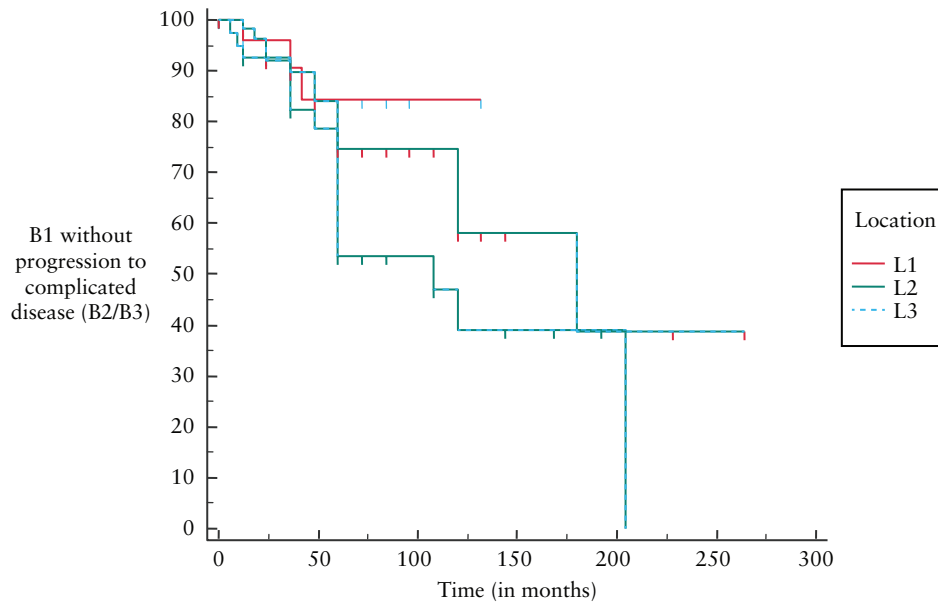


Figure 4. KaplanMeier curves showing change from B1 to B2/B3 disease in relation to location of disease at diagnosis [$p = 0.08$].

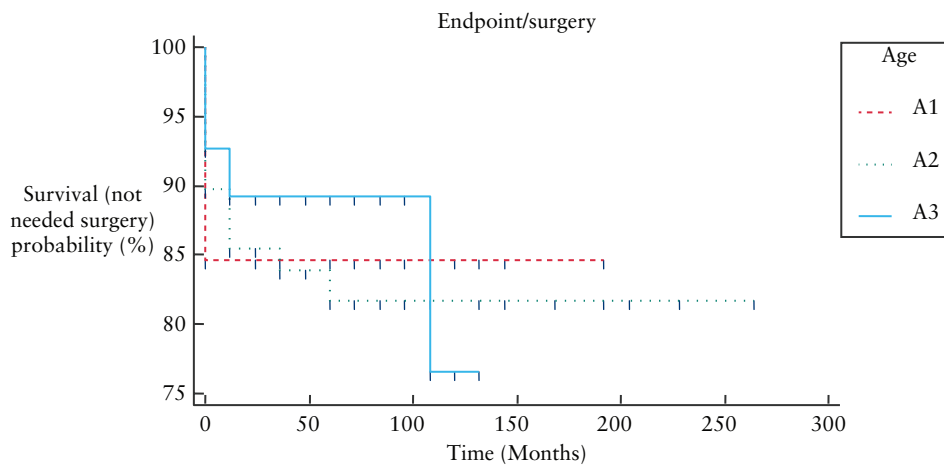


Figure 5. KaplanMeier curves showing need for surgery in relation to age at the time of diagnosis [$p = 0.76$].

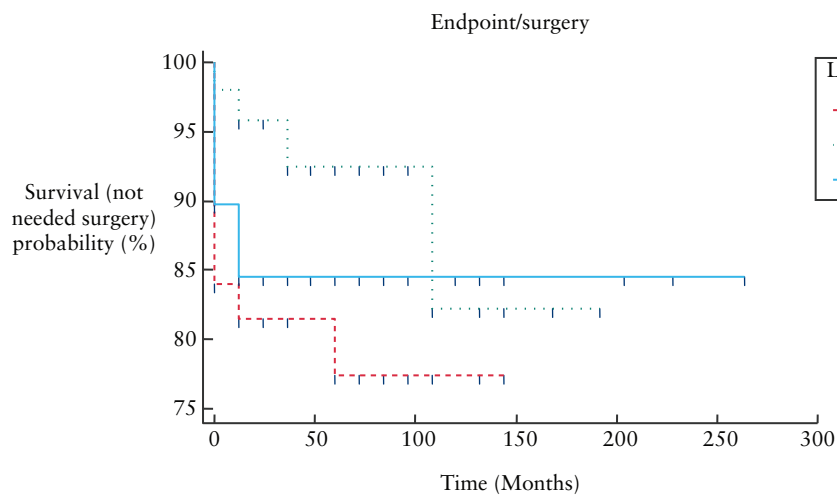


Figure 6. KaplanMeier curves showing need for surgery in relation to location of disease at the time of diagnosis [$p = 0.177$].

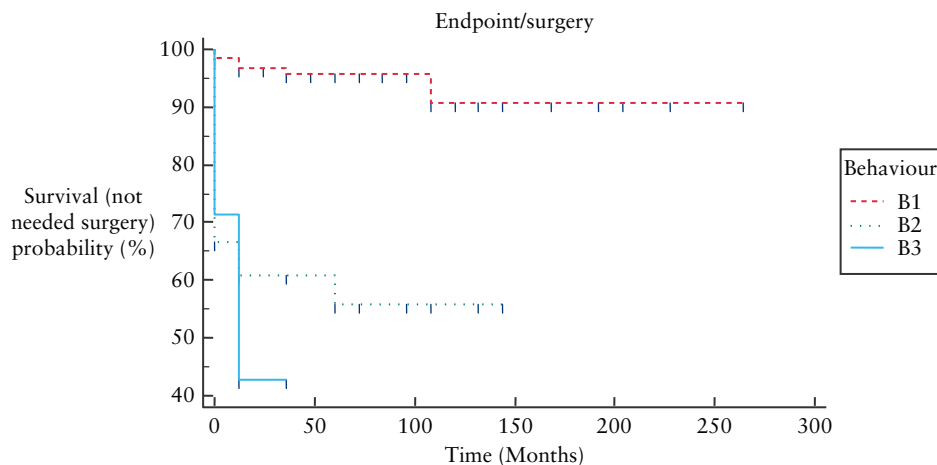


Figure 7. KaplanMeier curves showing need for surgery in relation to behaviour of disease at the time of diagnosis [$p < 0.0001$].

this trend was not statistically significant. Table 3 shows the location of disease; this was stable over time.

KaplanMeier curves [Figures 3 and 4] show that change from B1 to B2/B3 disease was not different between the age groups or between the locations of disease at time of diagnosis.

3.1. Surgery

Of 178 patients, 19 [10.7%] presented with complications requiring surgery which led to the diagnosis of Crohn's disease. After 5 years, 21 of 105 [20%] patients; after 10 years, 13 of 38 [34.2%] patients; and after 15 years, 10 of 18 [55.5%] patients had undergone intestinal surgery. [These figures do not include perianal surgeries.] Seven patients underwent more than one surgery.

Figure 5, 6, and 7 show KaplanMeier curves revealing no association between need for surgery and age or disease location; however B2 and B3 behaviours were associated with need for surgery: B1 vs B2: $p < 0.0001$, B1 vs B3: $p < 0.0001$, B2 vs B3: $p = 0.461$.

4. Discussion

This is the first study reporting changes in Montreal phenotype from India. We report the temporal change in Montreal phenotype over 15 years in 178 patients with Crohn's disease.

Our data show certain similarities to those reported in other Asian studies; the age of onset in our study was 31–40 years in more than half of our patients and there was no second peak. Some Western studies^{11,12,13} have reported two peaks, whereas others have not found this^{14,15}; Asian studies have shown either a smaller second peak^{7,16} or no second peak.^{17,18} Our cohort had nearly equal gender distribution [males:females 1.2:1]. In most Western reports, women are equal or higher in proportion^{12,13,19}; one European study²⁰ and most Asian studies^{18,21,22} have shown male predominance [1.7:1:2.9:1]. We found the ileo-colonic region to be the most commonly affected site, as noted in other Asian studies^{3,8,16,23}; Western studies report isolated colonic disease as the most common type.^{19,24,25}

Perianal disease at the time of diagnosis was present in 12% of our patients, which is similar to other reports from India.^{26,27} In contrast, other Asian studies have reported much higher occurrence of perianal disease at diagnosis [Hong Kong 33%,^[3] Korea 37%,^[8] China 59%^[22]]. Figures from Western studies vary from 16% to 27%.^{28,29}

At baseline, the disease behaviour phenotype [75% B1, 21% B2, 4% B3] is similar to that seen in most Western studies and in a

Table 4. Studies on natural history of Crohn's disease based on Montreal classification.

		Baseline	5 years	10 years	15 years
Present study	B1	74.7 %	65 %	50 %	44.4 %
	B2	21.3 %	21 %	28.9 %	33.3 %
	B3	3.9 %	11 %	21%	16.6 %
Chow <i>et al.</i> ³ 2007	B1	67 %	50 %	43 %	
	B2	30 %	45 %	43 %	
	B3	3 %	5 %	14 %	
Thia <i>et al.</i> ²⁹ 2010	B1	81 %	64%	58%	
	B2	5 %	12%	15%	
	B3	14%	24%	17%	
Tarrant <i>et al.</i> 2008 ²⁸	B1	73%	56%	44 %	
	B2	17 %	25%	31 %	
	B3	10 %	20%	25 %	
Lovasz <i>et al.</i> ³²	B1	57%			
	B2	20%			
	B3	23%			
Solberg <i>et al.</i> ³⁶	B1	62		47	
	B2	27		31	
	B3	11		22	
		EE	WE	A	
Vegh <i>et al.</i> ³⁷ [2011]	B1	57%	73%	79%	
	B2	27%	17%	11%	
	B3	16%	10%	10%	
Burisch <i>et al.</i> ³⁸ [2010]	B1	68%	68%		
	B2	19%	21%		
	B3	13%	12%		

EE, Eastern Europe; WE, Western Europe; A, Australia.

national survey by the Indian Society of Gastroenterology.²⁷ A multicentre Indian study by Das *et al.*³⁰ reported a more complicated phenotype [51% B1, 24% B2, 25% B3], but both these Indian studies^{27,30} indicated disease behaviour at inclusion, not at baseline.

Western studies have shown that a large proportion of patients change their behaviour pattern to a more aggressive type [B2 and B3] after 5, 10, and 15 years of follow-up.² In the older studies based on the Vienna classification, more patients were reported as having B3 as this category included perianal disease. Table 4 shows studies on disease phenotype based on the Montreal classification. The study from Korea by Ye *et al.*⁸ reported similar behaviour phenotype at time of diagnosis as our study. Chow *et al.*³ reported more patients with aggressive

disease at baseline and more likelihood of disease progression than in our study. Lakatos *et al.*³¹ noted a change in disease behaviour in 31% of patients with initial non-stricturing non-penetrating disease, after mean disease duration of 9 ± 7 years; we noted change to more aggressive disease at 10 years in only 20% of patients. Western studies^{28,32} have also shown faster progression as compared with our data. A limitation of our study was the small number of patients at 10 and 15 years and a shorter median duration of follow-up.

In our study, surgery rates are 10.7%, 20%, 34.2%, and 55.5% at diagnosis, at 5 years, at 10 years, and at 15 years, respectively. Surgery rates have been described in wide ranges in various studies, but overall they are less in Asian studies^{7,8} as compared with Western studies.^{33,34,35}

In summary, there are similarities in our data with other Asian studies: age of onset, absence of a second peak, gender distribution, and location of disease. Our patients differed from Western and other Asian patients in lower occurrence of perianal disease. The location of disease in our patients remained stable over time. One-fourth of our patients with Crohn's disease had aggressive behaviour at presentation; however, fewer patients progressed to stricturing or penetrating behaviour than those seen in Western reports. The surgical rates were also less than in a majority of reported studies.

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Conflict of Interest

Nothing to declare.

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