

Epidemiology, Pathogenesis and Treatment of Ulcerative Colitis in South Asia

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Abstract – Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon and rectum. Its prevalence is on the rise in many non-Western countries and several factors such as changes in lifestyle and improvements in hygiene may account for this. The cultural and ethnic background of South Asia is different from Western countries and other parts of Asia. We have reviewed the scientific literature on UC in South Asia and describe its epidemiology, clinical characteristics, molecular mechanisms, diagnosis and treatment.

Keywords – *Ulcerative Colitis; South Asia; Inflammatory Bowel Disease; Genetics; Pathogenesis.*

I. INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon and rectum. Its prevalence is on the rise in many non-Western countries [1] and several factors such as changes in lifestyle and improvements in hygiene may account for this [2]. Around 1.6 billion of the world's population resides in South Asia (India, Pakistan, Bangladesh, Sri Lanka and Nepal). We have reviewed the epidemiology, clinical characteristics, molecular mechanisms, diagnosis and treatment of UC in South Asia.

II. METHODOLOGY

A bibliographic search of relevant studies published in English before June 2016 was performed in PubMed and Google Scholar. The following medical subject heading (MeSH) terms were searched for titles and abstracts in English: Ulcerative colitis, inflammatory bowel disease, South Asia, developing countries, epidemiology, characteristics and genetics. The "related articles" function was used to expand the literature search. First, article titles and abstracts were screened for relevance and then, full-text articles were manually retrieved to conduct a more detailed search. We did not include unpublished manuscripts and dissertations in this review. Case reports and case series were excluded. Articles retrieved by online database search were reviewed by the authors for relevance to the South Asian population and those studies that included only non-

South Asian populations in the analysis were excluded. The data collected were summarized and organized under several headings.

A. EPIDEMIOLOGY OF UC IN SOUTH ASIA

Although UC was first reported in India in the late 1930s [1], it remained an uncommon disease when compared with gastrointestinal infections. In 1965, Tandon et al. [3] reported that some patients presenting with chronic blood and mucus diarrhoea had non-specific UC. Further cases were then reported from India by Chuttani et al. [4] and Maroo et al. [5]. In 1975, Alam et al. [6] reported cases of UC from Bangladesh. Overall data on the prevalence and incidence of UC in South Asia is scarce. A summary of findings from prevalence and incidence studies of UC in South Asia are shown in Table 1 [7-10].

The 2010, hospital based study from Sri Lanka, was carried out in two districts (out of the nine districts in the country) [7]. These two districts have a combined population of 4.5 million (the population of Sri Lanka is 20 million). Two potential drawbacks of this study are: the two districts studied are the most urbanized areas in Sri Lanka and thus findings may not be applicable to the entire country and those who seek alternative medical treatments would not have been included in the calculations. In 2013, Ng et al using a prospective population based study noted a higher incidence rate of UC in Sri Lanka [8]. Although the

incidence of UC in Sri Lanka seemed to have increased, it is important to note that the higher value was found in a

community based study, whereas the previous study was hospital based.

TABLE 1: SUMMARY OF PREVALENCE AND INCIDENCE STUDIES OF UC IN SOUTH ASIA

Country	Region/City(Ref)	Year	Methodology	Prevalence /100 000	Incidence
Sri Lanka	Gampaha+ Colombo(7)	2010	Hospital based	5.3	0.69
Sri Lanka	Western (8)	2011-12	Community based	NA	0.94
India	North (Haryana) (9)	1986	Community based	42.8	NA
India	North (10)	2003	Community based	44.3	6.02

(NA- Not available in the primary manuscript)

UC: Ulcerative Colitis

The two UC prevalence studies from India, were done 17 years apart and were from Northern India where a majority of the population are Punjabi or Sikhs [9]. In the 2003 study, 51,910 subjects from both urban and rural areas were screened using a cluster sampling method. Both studies reported comparatively high prevalence rates of 42.8 and 44.3 per 100 000 [9,10]. The reported rates had remained stable, unlike in two Southeast Asian countries (Korea and Japan) where a significant rise was noted. [1]. The true prevalence of UC in other regions of India (where ethnicity and lifestyles are different) is still to be determined. The crude incidence rate of 6.02 per 100 000 person years reported by Sood et al is the highest in the Asian region [10]. We could not find published studies on the prevalence and incidence of UC in Pakistan, Bangladesh or Nepal. An epidemiological study done by Ng et al. [8,11] found an increased incidence of UC in countries such as Hong Kong, Japan and Korea. The incidence and prevalence of UC in Western countries is much higher than in Asia [12].

B. DISEASE CHARACTERISTICS OF UC IN SOUTH ASIA

Studies reporting the disease characteristics of UC in South Asian patients are summarized in Table 2 [13-19]. The percentage of patients with extra-intestinal manifestations was significantly higher in India. In addition, the rate of pan-colitis was higher in Indian and Bangladeshi patients. The possible reasons for this are not known. A study by Fernandopulle et al [20] found a high prevalence of *Clostridium difficile* infection among acute severe UC patients from Sri Lanka. Biochemical parameters such as complete blood count and stool full report were not able to predict the presence of infection. Variation in the severity and extent of disease was seen in South Asian studies. Studies conducted in other Asian and Western countries also showed a similar variation across different communities and ethnic groups. Such variations in severity of disease activity

may be attributed to the differences in the genetic background and environmental factors [11].

C. LONG TERM OUTCOME OF UC IN SOUTH ASIA

A retrospective cohort study of 532 Indian patients, found five (0.94%) patients developed colorectal carcinoma and one patient (0.19%) had high grade dysplasia. The reported risk of developing colorectal carcinoma was 0% at 10 years, 2.3% at 20 years and 5.8% for disease duration > 20 years. [17]. In another retrospective analysis of 436 Indian UC patients, eight (1.8%) developed colorectal carcinoma after a mean follow-up of 12.1 years [21]. Senanayake et al. [13] reported cumulative colectomy rates of 1.5%, 4.0%, 5.5%, and 9.3% at 1, 5, 10, and 15 years in a cohort of Sri Lankan UC patient. The cumulative probability of colorectal cancer after 10 and 15 years was 0.47% and 2.36% respectively and the cumulative survival rate after 1, 5, 10, and 15 years was 99.7%, 98.9%, 98.1%, and 94.5%. Pan colitis was significantly associated with disease related deaths [13].

D. DISEASE RELATED KNOWLEDGE OF UC IN SOUTH ASIA

A study conducted at a tertiary hospital in Sri Lanka, showed poor disease related knowledge among UC patients compared to patients in Western countries. A similar pattern was seen in other low income Asian countries [22].

E. RISK FACTORS OF UC IN SOUTH ASIA

Studies on risk factors of UC in South Asians are limited. Gunisetty et al. [16] found those taking food from outside had a higher risk of developing UC than controls. The type of food taken (i.e. vegetarian vs non-vegetarian) was not a risk factor. The source of drinking water (municipal tap water vs boiled or filtered water) did not show a significant association. UC was more prevalent in non-smokers compared to smokers, and there was no association with alcohol consumption [16].

TABLE 2: DISEASE CHARACTERISTICS OF UC IN SOUTH ASIA (EIM – EXTRA-INTESTINAL MANIFESTATIONS, RET- RETROSPECTIVE)

Country	Region (Reference)	Year	N	Design	Proctitis %	Left sided colitis%	Pancolitis%	Severe colitis	Moderate colitis	Mild colitis	EIM
Sri Lanka	Gampaha+ Colombo (13)	2013	348	Ret. Cohort	31.9	43	25.1	35.6	38.8	25.6	NA
Sri Lanka	Colombo (14)	2011	153	Descriptive	30	51.7	18.3	NA	NA	NA	6.8
India	Nationwide (15)	2012	745	Descriptive	18.3	38.8	42.8	NA	NA	NA	51.6
India	South (16)	2012	157	Descriptive	15.3	38.2	46.5	39.5	60.5	NA	NA
India	South (17)	2005	532	Retrospective	44	22.7	33.3	NA	NA	NA	NA
Pakistan	Karachi (18)	1989	189	Descriptive	29	31	13.3	21.1	29.6	42.3	NA
Bangladesh	Dhaka (19)	214	126	Retrospective	45.24	8.73	46.03	NA	NA	NA	NA

Western diets and ex-smoking were found to be significant associations in a multi-center study conducted in Asia [23]. Similarly, a meta-analysis on smoking and inflammatory bowel disease showed a positive association with ex-smoking; current smoking had a protective effect on UC patients [24].

F. GENETIC FACTORS OF UC IN SOUTH ASIA

A summary of the genetic studies done in UC patients in South Asia are shown in Table 3 [25-29]. Several studies suggest that dysregulated innate immune responses to gut microbiota may play an important role in the pathogenesis of IBD [30, 31]. Genetic alterations in innate immune response genes or pattern recognition molecules (such as Toll like receptors – TLR) have been studied. In a case control study from North India [26], the TLR5 variants R392X and N592S were significantly associated with UC patients. Genotype-phenotype analysis found patients with at-risk TLR5 and TLR4 SNPs had severe disease and were diagnosed at an earlier age. Interestingly, the level of TNF α , IL-6 and IFN γ (innate immune and Th1 type cytokines) were significantly increased in the studied UC patients. Sequencing the NOD2 gene in a cohort of Indian UC patients found eight single nucleotide polymorphisms. These were: rs2067085, rs2066842, rs2066843, rs1861759,

rs2111235, rs5743266, rs2076753, and rs5743291. The latter four were described for the first time in Indians. The SNPs rs2066842 and rs2066843 were in linkage disequilibrium and showed significant association with UC [27]. A case control study by Mahukar et al. [29] failed to find an association between variants in the NOD2 gene or the R381Q IL23R variant in Indian UC patients. Gupta et al [25] found critical variants in the SLC44A4 gene in North Indian UC patients and suggested it to be a susceptibility factor. A meta-analysis by Ng et al. [32] showed new genetic associations in Asian patients compared to the Western population. Furthermore, some well-established associations observed in Western communities were not found in Asians. Interestingly, although genetic studies in South Asians were scarce, the associations that were found in these studies were novel. These variants are not only different from those described in Western population, but also different from those described in other Asian populations.

G. QUALITY OF LIFE IN UC PATIENTS OF SOUTH ASIA

Information on the Quality of life in South Asian UC patients is scarce and is an important area for further study.

TABLE 3: GENETIC FACTORS FOR UC IN SOUTH ASIA (N – NUMBER OF PATIENTS, SNP – SINGLE NUCLEOTIDE POLYMORPHISM)

Country/Place (Ref)	N	Year	Methodology	Genes and SNP's studied	Positive association with UC	Other findings
India North (25)	25	2016	Descriptive	SLC44A4	Yes	Appears to be functionally relevant to UC
India North (26)	328	2015	Case control	TLR1-R80T, TLR2-R753Q, TLR3-S258G, TLR5-R392X, TLR5-N592S and TLR6-S249P	R392X and N592S	The level of TNF α (p=0.004), IL-6 (p = 0.0001) and IFN γ (p=0.006) significantly increased in patients when compared to controls having wild type genotypes for the studied SNPs
India North (27)	318	2013	Case control	NOD2 gene, rs2067085, rs2066842, rs2066843, rs1861759, rs2111235, rs5743266, rs2076753, and rs5743291	rs2111235, rs5743266, rs2076753, and rs5743291	The SNPs rs2066842 and rs2066843 were in significant linkage disequilibrium. Both SNPs showed a significant association with UC
India North - Punjab (28)	298	2007	Case control	SNP5 SNP8, SNP12 and SNP13	SNP5	Sequencing (n = 30) showed two nucleotide polymorphisms: SNP5 (268 Pro/Ser) and rs2067085 (178 Ser/Ser).
India Southern (29)	411	211	Case control	variants in NOD2 and interleukin-23 receptor (IL23R)	None	monomorphic status for three common disease-susceptible variants, R702W, G908R, and 1007fs in NOD2. Three other single nucleotide polymorphisms, P268S, R459R, and R587R, had a comparable minor allele frequency in patients and controls

TABLE 4: SUMMARY OF STUDIES CONDUCTED ON EFFECTIVENESS OF PHARMACOLOGICAL TREATMENT

Country	Author (Ref)	N	Year	Methodology	Study	Conclusion	Other findings
India	Sood (33)	35	2002	RCCT	Azathioprine + sulphasalazine vs sulphasalazine + placebo in remission induction in severe UC	Azathioprine + sulphasalazine had higher remission rates and reduced relapse rates	-
	Sood (34)	25	2003	RCCT	Azathioprine + steroid vs sulphasalazine + steroid in reducing relapse in severe UC	Both groups were comparable in reducing relapse.	Earlier treatment failure in azathioprine group
	Sood (35)	50	2000	RCCT	Role of azathioprine in a combination therapy, in those who relapsed within two months of corticosteroid withdrawal	No effect on remission induction	Reduced relapse noted in azathioprine group
	Sood (36)	14	2002	Prospective	effectiveness of a 3 day course of dexamethasone pulse therapy	13 out of 14 patients underwent successful remission by day 15	-

III. TREATMENT

A. MEDICAL

Nonsteroidal, Steroids and other immunosuppressive medications

There have been a few descriptive studies from South Asia on treatment of UC patients. In a cohort of Sri Lankan UC patients, Subasinghe et al found sulphasalazine alone to be sufficient in 43.8%, sulphasalazine and prednisolone was needed by 34%, and sulphasalazine, azathioprine and prednisolone was used by 22.2% [14]. In a cohort of Indian

UC patients, Makharia et al found sulphasalazine to be used by 26.8% of patients, mesalamine by 96.9%, corticosteroids by 92.4% and azathioprine by 35.9%, at some point during their treatment [15]. As these studies were retrospective and descriptive in nature, it is difficult to interpret the effectiveness of the different medications. In addition, the side effects observed whilst taking these medications were not mentioned.

A summary of the randomized controlled clinical trials done in Indian patients is shown in Table 4 [33-36]. Sood et

al.[33], found a significantly higher number of patients achieved remission earlier in the azathioprine and sulphasalazine group as compared to the sulphasalazine and placebo group. It is important to note that the sample size was small and this may have resulted in bias [33].

In another study Sood et al found a trend towards earlier treatment failure in those who received azathioprine. [34]. In a third trial, azathioprine did not have an effect on remission, but it reduced the proportion of relapses [35]. A prospective trial assessed the effectiveness of a 3 day course of dexamethasone pulse therapy in 14 patients with UC. 13 of the 14 patients underwent successful remission by day 15 [36]. The number of patients included in each of these studies was small.

B. BIOLOGIC THERAPY

Makharia et al reported that only 0.3% of their patients were on a biologic therapy at some point during their treatment [15]. This may be related to the high cost of these medications. There have been no prospective studies on the efficacy of biologic therapy for UC in South Asian patients. Although the use of disease modifying agents was similar, the use of biologics is much less in South Asia compared to western and other Asian countries.

C. SURGERY

In a Sri Lankan study, fifteen UC patients had a colectomy during their follow-up [13]. Of these patients, six had extensive disease, five had left-sided disease, and four had distal disease. Eight of the 15, were performed during the first 2 years of diagnosis and only two were done more than 10 years post-diagnosis. Two patients underwent colectomy due to acute severe UC, two had it after a colorectal cancer was diagnosed and the commonest indication was poor disease control by medical therapy [13].

Another descriptive study from Sri Lanka reported 8.5% (n=13) of their UC patients underwent surgical treatment (i.e., restorative proctocolectomy=12, colectomy with ileostomy =1). The indications for restorative proctocolectomy and ileoanal pouch were: steroid resistance (n=7), atypia on histology (n=4), and sigmoid colon cancer (n=1). Sigmoid colectomy was done on one patient for stricture of the sigmoid colon [14]. A study from India reported 4 % of UC patients underwent surgical treatment [15].

IV. CONCLUSIONS

Most studies on UC from South Asia were from some parts of India and the Western province of Sri Lanka. There

is a lack of large population based studies for reliable assessment of the epidemiological trends of UC in South Asia. Disease characteristics of UC such as the severity, extent of colitis, extra intestinal manifestations show wide variation among different parts of South Asia. Novel genetic associations were identified in some South Asian populations and more focused research on the genetics of UC in South Asians, may shed light on understanding disease pathogenesis better. A scarcity of studies on quality of life, disease related knowledge and risk factors of UC in South Asia was noted. So far, all studies related to treatment efficacy were conducted at the same unit. Most treatment protocols used in the South Asian studies, were based on those developed in the west.

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